The protein interaction network of *Treponema pallidum* – a minimal proteome

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"Asking naïve questions is one of the most successful ways of really moving ahead."

Craig Venter, 17.10.05 (ZDF online)

für Maren

Diese Arbeit wurde in der Arbeitsgruppe von Dr. Peter Uetz am Institut für Toxikologie und Genetik (ITG) des Forschungszentrums Karlsruhe (FZK), Mitglied der Helmholtz-Gemeinschaft, angefertigt.

I. Abstract

Genome sequencing projects provide a wealth of knowledge about the inventory of the respective organism. However, life evolves through an incredible complex interplay of all gene products of an organism. Only high-throughput approaches can cope with this complexity and only integration of various large-scale datasets into a comprehensive systems biology framework will eventually provide insights on the organization of life's complexity. Large-scale protein interaction datasets make a major contribution to this ultimate aim.

In this thesis, a proteome-wide binary protein interaction map for *Treponema pallidum*, the Syphilis spirochete, is presented. About 1,000,000 protein combinations were tested in an array-based yeast-two-hybrid system. 3,684 protein interactions were identified, from which a filtered set of 1,634 interactions was selected. 726 (70% of the proteome) and 601 (58% of the proteome) distinct proteins were incorporated in these two networks. In parallel to this study, the Y2H interaction map of *Campylobacter jejuni* was analyzed (Parish *et al.*, *pers. comm.*). These two bacterial networks are the first proteome-wide binary interaction maps for bacteria, and constitute the most comprehensive available binary interaction maps for any living organism.

Biological insights from all levels of the network can be gained ranging from the topology, over protein complexes, to individual proteins.

Bioinformatical predictions support a significant fraction of the interactions. However, in concordance with other studies only a limited overlap with other interaction datasets is observed (max. 5%).

The network topology shows scale-free properties and an optimization of the network for information processing is demonstrated by the central position of regulatory proteins.

Protein domains are the interacting entities. The protein domain network of *T. pallidum* shows the wide range of interactions of the TPR domain and an interesting link of peptidoglycan metabolism and the flagellum.

The network demonstrates, for the first time, that different genomic locations are linked by protein interactions, e.g., a region flanking FliS is associated to a region flanking TP0048 via six interactions among six proteins – a link probably involved in motility related processes.

The interaction network provides starting points for the investigation of the pathogenesis of Syphilis. Several interactions for pathogenicity-related and (predicted) essential proteins were identified.

Based on their interactions, functions of proteins can be predicted ("guilt-by-association" approach). These predictions include a function of TP0183 in "DNA replication, recombination, and repair" and a function of TP0496 in linking tRNA metabolism and DNA replication.

Several associations of functional categories are found including a striking self-association of DNA metabolism and motility proteins.

For assessing the functional relevance of proteins for motility, a whole-genome motility phenotyping for *Escherichia coli* was conducted. 3,985 mutant strains were tested and 159 showed reduced motility. A majority were known motility proteins. The intersection with a large-scale motility dataset for *B. subtilis* indicated that most well conserved genuine motility proteins are already known. However, intersection with the interaction dataset indicated the presence of additional group-specific or regulatory motility proteins – one example is the protein TP0658.

Based on its interactions with flagellin proteins (FlaB1, FlaB2, FlaB3) a flagellin-related function for the conserved hypothetical protein TP0658 (DUF180/COG1699) was anticipated. TP0658 has homologs in at least 34 sequenced genomes and its interaction with flagellin is conserved in at least four species (including *Bacillus subtilis* yviF-hag, *Campylobacter jejuni* Cj1075- Cj0720c, and *Helicobacter pylori* HP1154-flaA and HP1377-flaA). TP0658 binds an epitope of FlaB1 comprising a peptide from Leu_{231} to Asp_{247} (the c_s loop of flagellin). This

interaction epitope is conserved in *B. subtilis* and other bacteria. One well-conserved Asparagine residue of flagellins (Asn_{237} of FlaB1 and Asn_{255} of its *B. subtilis* homolog *hag*) is crucial for binding of TP0658/YviF. A *B. subtilis* ΔyviF mutant showed strongly reduced motility, which was rescued by YviF over-expression. Co-expression of TP0658 and FlaB1 in *E. coli* suggests that TP0658 stabilizes flagellin and thus appears to act like the known flagellin assembly factor, FliS. It is suggested that TP0658 is another assembly factor for flagellin proteins, complementing the function of FliS or replacing it in certain subsets of bacterial species.

A second detailed analysis revealed the *in vivo* "house-cleaning" function of YjjG. House-cleaning enzymes protect cells from the adverse effects of non-canonical metabolic chemical compounds. The *Escherichia coli* nucleotide phosphatase YjjG (B4374, JW4336) functions as a house-cleaning phosphatase *in vivo*. YjjG protects the cell against non-canonical pyrimidine derivatives such as 5-fluoro-2'-deoxyuridine, 5-fluorouridine, 5-fluoroorotic acid (5-FOA), 5-fluorouracil (5-FU), and 5-aza-2'-deoxycytidine. YjjG prevents the incorporation of potentially mutagenic nucleotides into DNA as shown for 5-bromo-2'-deoxyuridine (BrdU). Its enzymatic activity *in vitro* towards non-canonical 5-fluoro-2'-deoxyuridine monophosphate (5-FdUMP) is higher than towards canonical thymidine monophosphate (dTMP). The closest homolog in humans, HDHD4, does not show a protective effect against non-canonical nucleotides, excluding an involvement of HDHD4 in resistance against non-canonical nucleotides used for cancer chemotherapy.

Finally, the Y2H system was used to analyze the properties of transcription activation domains. Eukaryotic transcription activation domains are not well defined on the proteome scale. As a prerequisite of two large-scale Y2H studies, ~6000 yeast proteins have been analyzed for transcriptional activity using a yeast one-hybrid system. 451 transcriptional activators were identified. Here, their transcription activation strength was determined using fusions to the Gal4 DNA-binding domain and a His3 reporter gene which contained a promoter with a Gal4-binding site. Among the 132 strongest activators, 32 are known transcription factors while another 35 have no known function. Although zinc fingers, helix-loop-helix domains and several other domains are highly over-represented among the activators, only few contain characterized activation domains. Some striking correlations were found: the stronger the activation activity, the more acidic, glutamine-rich, proline-rich, or asparagine-rich the activators were. About 29% of the activators have been previously found to specifically interact with the transcription machinery, while 10% are known to be components of transcription regulatory complexes. Based on their transcriptional activity, localization, and interaction patterns, at least four previously uncharacterized proteins are suggested to be bona fide transcriptional regulators (namely YFL049W, YGL066W/Sgf73, YKR064W, and YCR082W/ Ahc2).

II. Zusammenfassung

Genomsequenzierungsprojekte liefern eine umfassende Übersicht über die Gene eines Organismus, aber erst das unglaublich komplexe Zusammenspiel aller Genprodukte lässt Leben entstehen. Dieser Komplexität kann nur mit Hochdurchsatzansätzen begegnet werden und nur die Integration zahlreicher umfassender Datensätze in einem Systembiologiekontext wird schlussendlich Einblicke in die Organisation der Komplexität des Lebens liefern. Großflächige Protein-Interaktionsdatensätze werden einen großen Beitrag zu diesem Ziel liefern.

In dieser Arbeit wird eine Proteom-weite, binäre Proteininteraktionskarte für *Treponema pallidum*, den Erreger der Syphilis, präsentiert. Ungefähr 1.000.000 Proteinkombinationen wurden in einem Matrix-basierten Hefe-Zwei-Hybrid-System getestet. Insgesamt 3.684 Proteininteraktionen wurden identifiziert. Von diesen wurde ein gefilterter Satz von 1.634 Interaktionen ausgewählt. 726 (70% des Proteoms), resp. 601 (58% des Proteoms) Proteine waren in diesen Netzwerken enthalten. Zeitgleich wurde eine Hefe-Zwei-Hybrid Interaktionskarte für *Campylobacter jejuni* (Parish *et al.*, *pers. Komm.*) erstellt. Diese beiden bakteriellen Netwerke stellen die ersten Proteom-weiten binären Interaktionskarten für Bakterien und die umfangreichsten binären Interaktionskarten für einen lebenden Organismus insgesamt dar.

Einblicke in die Biologie können auf allen Ebenen des Netzwerkes gewonnen werden: von der Topologie, über Proteinkomplexe, bis hin zu individuellen Proteinen.

Ein signifikanter Anteil der Interaktionen wird durch bioinformatische Vorhersagen gestützt. In Übereinstimmung mit anderen Studien wurde jedoch nur eine begrenzte Überlappung (max. 5%) mit anderen Interaktionsdatensätzen gefunden.

Die Netzwerktopologie zeigt skalenfreie Eigenschaften und eine Optimierung des Netzwerks für die Informationsverarbeitung wird durch die zentrale Position, die von regulatorischen Proteinen eingenommen wird, demonstriert.

Proteininteraktionen basieren auf der Interaktion von einzelnen Proteindomänen. Das Domäneninteraktionsnetzwerk für *T. pallidum* zeigt z.B. das weite Spektrum an Interaktionen der TPR Domäne und eine interessante Verbindung zwischen dem Peptidoglykanmetabolismus und der bakteriellen Flagelle.

In dieser Arbeit wird zum ersten Mal gezeigt, dass verschiedene genomische Lokationen über Proteininteraktionen verbunden sind, z.B. ist die Region um FliS mit der Region um TP0048 über sechs Interaktionen zwischen sechs Proteinen verknüpft – diese Verbindung steht wahrscheinlich mit der bakteriellen Motilität in Verbindung.

Das Interaktionsnetzwerk liefert Ansatzpunkte für die Untersuchung der Pathogenität der Syphilis. Es wurden zahlreiche Interaktionen für Pathogenitäts-relevante und (vorhergesagte) essentielle Proteine identifiziert.

Basierend auf den Interaktionen können Vorhersagen über die Funktion von Proteinen getroffen werden. So kann z.B. eine Funktion für TP0183 bei der „DNA Replikation, Rekombination und Reparatur“ und für TP0496 eine verbindende Funktion zwischen tRNA Metabolismus und DNA Reparatur vorhergesagt werden.

Zahlreiche Assoziationen von funktionellen Kategorien wurden gefunden; diese beinhalten eine Selbstassoziation von DNA Metabolismus Proteinen und Motilitätsproteinen.

Um die funktionelle Relevanz von Proteinen für die bakterielle Motilität zu ermitteln, wurde das gesamte Genom von *Escherichia coli* auf einen Einfluss auf die Motilität getestet: 3.985 Mutantenstämme wurden getestet und 159 zeigten eine reduzierte Motilität. Ein Großteil waren bekannte Motilitätsproteine. Ein Abgleich mit einem großflächigen Motilitätstest für *Bacillus subtilis* wies darauf hin, dass die meisten stark konservierten Motilitätsproteine bereits

bekannt sind. Es existieren allerdings zusätzliche Gruppen-spezifische oder regulatorische Motilitätsproteine – ein Beispiel hierfür ist das Protein TP0658.

Basierend auf seinen Interaktionen mit allen Flagellinproteinen (FlaB1, FlaB2 und FlaB3) konnte eine Funktion des konserviert-hypothetischen Proteins TP0658 (DUF180/COG1699) im engen Zusammenhang mit diesen Flagellinproteinen angenommen werden. TP0658 hat Homologe in wenigstens 34 sequenzierten Genomen und seine Interaktion mit Flagellinproteinen ist in wenigstens vier Spezies konserviert (einschließlich *Bacillus subtilis* yviF-hag, *Campylobacter jejuni* Cj1075- Cj0720c und *Helicobacter pylori* HP1154-flaA and HP1377-flaA). TP0658 bindet ein Epitop von FlaB1, welches ein Peptid von Leu_{231} bis Asp_{247} (c_s Schleife des Flagellins) einschließt. Dieses Interaktionsepitop ist in *B. subtilis* und anderen Bakterien konserviert. Ein stark konserviertes Asparagin (Asn_{237} von FlaB1 und Asn_{255} seines *B. subtilis* Homologes *hag*) ist essentiell für die Bindung von TP0658/YviF. Eine *B. subtilis* ΔyviF Mutante zeigt eine stark verminderte Motilität, die durch Widereinführen von YviF wiederhergestellt werden kann. Die Koexpression von TP0658 und FlaB1 in *E. coli* legt nahe, dass TP0658 das Flagellinprotein stabilisiert und damit eine ähnliche Funktion wie der bekannte Assemblierungsfaktor, FliS, ausführt. Es wird vorgeschlagen, dass TP0658 ein weiterer Assemblierungsfaktor für Flagellinproteine ist, welcher die Funktion von FliS komplementiert oder in einer gewissen Untergruppe von bakteriellen Spezies ersetzt.

Eine zweite detaillierte Analyse zeigte eine "Hausreinigungsfunktion" des Proteins YjjG *in vivo*. "Hausreinigungsenzyme" schützen Zellen vor den schädlichen Einflüssen von nicht kanonischen metabolischen Molekülen. Die *Escherichia coli* Nukleotidphosphatase YjjG (B4374, JW4336) arbeitet als „Hausreinigungsphosphatase" *in vivo*. YjjG schützt die Zelle vor nicht kanonischen Pyrimidinderivaten wie 5-Fluor-2'-desoxyuridin, 5-Fluor-uridin, 5-Fluor-orothsäure (5-FOA), 5-Fluor-uracil (5-FU), and 5-Aza-2'-desoxycytidin. YjjG verhindert die Inkorporation von potentiell mutagenen Nukleotiden wie es anhand von 5-Brom-2'-desoxyuridin (BrdU) gezeigt wurde. Seine enzymatische Funktion gegenüber nicht kanonischem 5-Fluor-2'-Deoxyuridinmonophosphat ist höher als gegenüber nicht kanonischem Thymidinmonophosphat (dTMP). Das am nächsten verwandte homologe Protein im Menschen, HDHD4, zeigt keinen schützenden Effekt gegen nicht kanonische Nukleotide. Dieses schließt eine Funktion von HDHD4 bei der Resistenz gegenüber nicht kanonischen Nukleotiden bei der Chemotherapie von Krebs aus.

Schließlich wurde das Hefe-Zwei-Hybrid System zur Analyse der Eigenschaften von Transkriptionsaktivierungsdomänen verwendet. Eukaryotische Transkriptionsaktivierungsdomänen sind im Proteom-weiten Maßstab schlecht definiert. Als Voraussetzung für zwei großflächige Y2H Studien wurden ~6000 Hefeproteine auf Transkriptionsaktivierung in einem Hefe-Ein-Hybrid System analysiert. 451 Transkriptionsaktivatoren wurden identifiziert. In dieser Arbeit wurde ihre Aktivierungsstärke gemessen. Hierfür wurden Fusionen dieser Protein mit der Gal4-DNA-Bindungsdomäne und ein His3-Reporter unter der Kontrolle eines Gal4-Promoters verwendet. Unter den 132 stärksten Aktivatoren waren 32 bekannte Transkriptionsfaktoren, während 34 keinerlei bekannte Funktion hatten. Obwohl Zinkfinger, Helix-Drehung-Helix und zahlreiche andere Domänen hochgeradig überrepräsentiert im Satz der Aktivatoren waren, trugen nur wenige eine bekannte Aktivierungsdomäne. Einige interessante Korrelationen wurden entdeckt: je stärker die Aktivatoren waren, desto saurer, Glutamin-reicher, Prolin-reicher und Asparagin-reicher waren sie. Für ca. 29% der Aktivatoren wurde zuvor eine spezifische Interaktion mit der Transkriptionsmaschinerie gezeigt und 10% sind bekannte Komponenten von Transkriptions-regulierenden Komplexen. Basierend auf ihrer Transkriptionsaktivierungsstärke, Lokalisation und des Interaktionsmusters wurde für wenigsten vier zuvor uncharakterisierte Proteine eine wirkliche Transkriptions-regulierende Funktion vorhergesagt (dieses sind: YFL049W, YGL066W/Sgf73, YKR064W und YCR082W/ Ahc2).

III. Parts of this thesis have been or are being published

Titz, B., M. Schlesner, and P. Uetz. 2004. What do we learn from high-throughput protein interaction data? *Expert Rev Proteomics* **1**: 111-21.

Titz, B.*, S. Thomas*, S.V. Rajagopala, T. Chiba, T. Ito, and P. Uetz. 2006. Transcriptional activators in yeast. *Nucleic Acids Res* **34**: 955-67.

Titz, B.*, S.V. Rajagopala*, C. Ester, R. Hauser, and P. Uetz. 2006. A novel conserved assembly factor of the bacterial flagellum. *J Bacteriol.* **188**: 7700-7706.

Rajagopala, S.V., B. **Titz**, and P. Uetz. 2007. Array-based yeast two-hybrid screening for protein-protein interactions. In *Yeast Gene Analysis* (ed. M. Stark and I. Stansfield). Elsevier. *in press*

Rajagopala, S.V.*, B. **Titz***, J. Goll, J. Parish, M.T. McKevitt, T. Palzkill, H. Mori, R.L. Finley, Jr., and P. Uetz. Functional genomics of bacterial motility. *in preparation.*

Titz, B.*, R. Häuser*, A. Engelbrecher, and P. Uetz. The Escherichia coli protein YjjG is a House-Cleaning Nucleotidase in vivo. *submitted*

Titz, B.*, S.V. Rajagopala*, R. Häuser, J. Goll, K. Wohlbold, M.T. McKevitt, T. Palzkill, and P. Uetz. The protein interactome of *Treponema pallidum*. *submitted*

* equal contribution

IV. Table of Content

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VII. Supplementary Tables

VIII. Abbreviations

3-AT	3-Aminotriazole
AD	activation domain
bGal	beta-Galactosidase
coAP/MS	co-affinity purification / mass-spectrometry
coIP	co-immunoprecipitation
DBD	DNA-binding domain
GO	gene ontology
GST	glutathione-S-transferase
HA	haemagglutinin
HTS	high-throughput screening
LIMS	laboratory information management system
LT	medium depleted from leucine and tryptophane
LTH	medium depleted from leucine, tryptophane and histidine
MS	mass spectrometry
OD	optical density
ORF	open-reading frame
PIM	protein interaction map
SD	standard deviation
SEM	standard error mean
TIGR	The Institute of Genome Research (Rockville, USA)
TPA	*Treponema pallidum*
UPS	univector-plasmid-fusion system
Y2H	yeast-two-hybrid
YEPD	yeast full medium

1. Introduction

1.1. The Starting Point

Today more than 300 bacterial and about 20 eukaryotic genomes have been completely sequenced and these sequencing projects provided us with a wealth of information about these organisms. Theoretically, most gene products of these genomes can be predicted from their sequence. Nevertheless, the biochemical activities and biological roles of many gene products remain unclear. Surprisingly, even in new genome sequences about 1/3 of the genes cannot be annotated functionally, either because there is only ambiguous homology or because homologous genes lack sufficient annotation.

In order to turn the significant number of uncharacterized open reading frames into biological knowledge, high-throughput functional analysis appears to be a perfect tool. Although high-throughput screening (HTS) usually will not yield a detailed understanding of a protein's function, it often provides first evidence for function and therefore an in-route to further characterization.

Currently established HTS methodology includes expression profiling using DNA microarray technology, systematic knock-out studies, high-throughput localization studies and protein-protein interaction mapping approaches (Ge et al. 2003). Eventually, only the combination of all these approaches together with integration into a comprehensive systems biology framework will let us understand how life can evolve from the intrinsic complexity of biological systems.

In this thesis, the protein interaction network of *Treponema pallidum*, the bacterium causing Syphilis, is presented. Already, a glimpse on this network gives an impression of the complexity of this organism with only about 1000 genes. The network itself reveals biological building principles; even well understood protein complexes like the bacterial flagellum appear to be still more sophisticated; functions of individual proteins can be elucidated by analyzing their molecular context; and finally, the interactions of pathogenicity factors can provide new insights for the Syphilis disease.

1.2. Background

Treponema pallidum

Treponema pallidum subspecies *pallidum* is the causative agent of veneral syphilis, a sexually transmitted disease. *T. pallidum* belongs to a group of bacteria called spirochetes. These are Gram-negative bacteria, which are characterized by their helical to sinusoidal shape. *T. pallidum* has an outer and a cytoplasmic membrane, a thin peptidoglycan layer, and periplasmic flagella. Outside its host, *T. pallidum* only survives for a short period and cannot be cultured continuously *in vitro*. Other members of the spirochete group are *Borrelia* and *Leptospira*. Other *Treponemes* that cause human diseases include *T. pallidum* subspecies *pertenue*, the causative agent of yaws, and *T. pallidum* subspecies *endemicium*, the causative agent of endemic syphilis.

Genome

The genome of *T. pallidum* was sequenced in 1998 by "The Institute of Genome Research" (Fraser et al. 1998). An overview (status: August 2006) is given in Table 1 (Peterson et al. 2001)

Feature	Value
Genome size	1138012 bp
G+C content	52.77%
Protein coding genes	1039
…with role category	580 (55.82%)
…conserved hypothetical	176 (16.93%)
…hypothetical	283 (27.23%)
tRNA genes	45
rRNA genes	6

Table 1 *T. pallidum* genome summary

Strikingly, a large number of ORFs (176) is conserved in other bacterial species, but still does not have a functional assignment ("conserved hypothetical" proteins) and an even higher number of ORFs (283) is uncharacterized and specific to *T. pallidum*. These two groups of proteins will be of special interest in this study, since the functional characterization of the former group will reveal functions valid for several species and characterization of the latter is the basis to understand specific features of *T. pallidum*. An overview of the functional classifications of all ORFs is shown in Fig. 1.

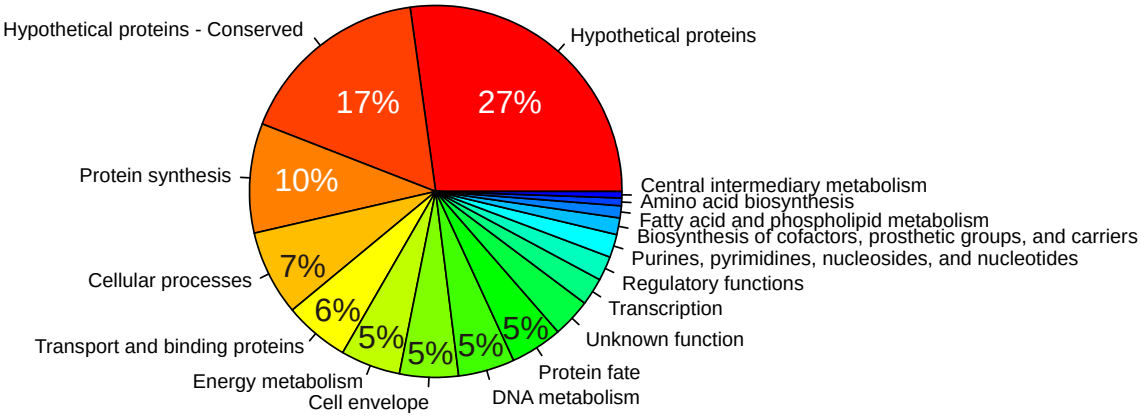


Fig. 1 Genome of T. pallidum – functional classifications. TIGR roles were taken from the TIGR-CMR database (Peterson et al. 2001).

The most abundant functional categories of proteins with known function are "protein synthesis" (9.5%), "cellular processes" (7.4%), and "transport and binding" (5.7 %).

T. pallidum contains a basic set of genes involved in transcription and translation (Fraser et al. 1998). This set includes RNA polymerase genes, several sigma factors (both rpoS for the stationary phase and σ^{32} for heat-shock response were not identified), and proteins necessary for elongation and termination. The major DNA replication proteins are present. Unlike *B. burgdorferi*, topoisomerase IV, which is involved in chromosome segregation, is lacking. DNA repair in *T. pallidum* includes the major known pathways of *uvr* excision repair, mutL/mutS mismatch repair, *mutY*, and *dat*. RecBCD is missing, but the *recF* pathway of recombination is conserved. As an obligate human parasite, *T. pallidum* has only limited biosynthetic capabilities. *T. pallidum* is unable to synthesize enzyme co-factors, fatty acids, and nucleotides *de novo*. In contrast, it has a large number of transporter proteins to obtain the required factors from its host. 57 ORFs forming 18 distinct transporters have been identified in the initial genome sequencing study; these include ABC transporters for the import of sugars. *T.*

pallidum has all enzymes of the glycolytic pathway, but none of the enzymes of the tricarboxylic acid cycle or oxidative phosphorylation. It contains a minimal set of regulatory genes that include two two-component systems and several putative transcriptional regulators of unknown specificity. Even though, *T. pallidum* does not have a sugar-specific PTS (phosphotransferase system), it contains enzymes of this pathway, which probably function as regulators.

However, the outstanding feature of *T. pallidum* is its limited genome size with 1,039 genes compared to ~4,500 in *Escherichia coli* or *Bacillus subtilis*. This strong genome reduction, which resulted in the loss of essential enzymes, explains the strict dependency of *T. pallidum* on its human host.

Syphilis

Venereal syphilis was first reported in Europe in the late 1400s, coincident with the return of Columbus from the New World. The disease quickly reached epidemic proportions in Europe and spread across the world during the early 16th century. Since the introduction of penicillin, effective therapies have been available. However, syphilis remains an important global health problem.

The World Health Organization estimates 12 million syphilis infections worldwide for 1999 (Table 2) (World Health Organization 2001). Whereas the incidence is below 5 per 100,000 in the majority of Western European countries, there has been an alarming increase of the rates in the newly independent states of the former Soviet Union; in 1996, 120-170 cases per 100,000 have been reported. In Africa, syphilis prevalence among pregnant women varies from 2.5% (Burkina Faso) to 17.4% (Cameroon).

Region	Male	Female	Total
North America	0.054	0.053	0.107
Western Europe	0.069	0.066	0.136
North Africa & Middle East	0.167	0.197	0.364
Eastern Europe & Central Asia	0.053	0.052	0.105
Sub Saharan Africa	1.683	2.144	3.828
South and South East Asia	1.851	2.187	4.038
East Asia & Pacific	0.112	0.132	0.244
Australia & New Zealand	0.004	0.004	0.008
Latin America & Caribbean	1.294	1.634	2.928
Total	5.29	6.47	11.76

Table 2 Estimated new cases of Syphilis (in million) among adults for 1999. Source: World Health Organization (2001)

In Germany (like in other industrial states), the infection rate of Syphilis declined strongly, especially since the seventies of the last century (Robert Koch Institut 2003) (Fig. 2). However, since the nineties the incidence is steadily increasing and reached a level of 2.8 infected persons per 100,000 in 2002. The majority of these are men having sex with men (MSM). The higher infection rate in Eastern Europe was also found to have an influence on Syphilis in Germany. In addition, Syphilis has an importance when coinfection with HIV occurs. In 2006 an outbreak of Syphilis among heterosexuals in the region of Aachen has been reported by the Robert Koch Institut (Robert Koch Institut 2006); during this "outbreak" 138 cases were reported in total.

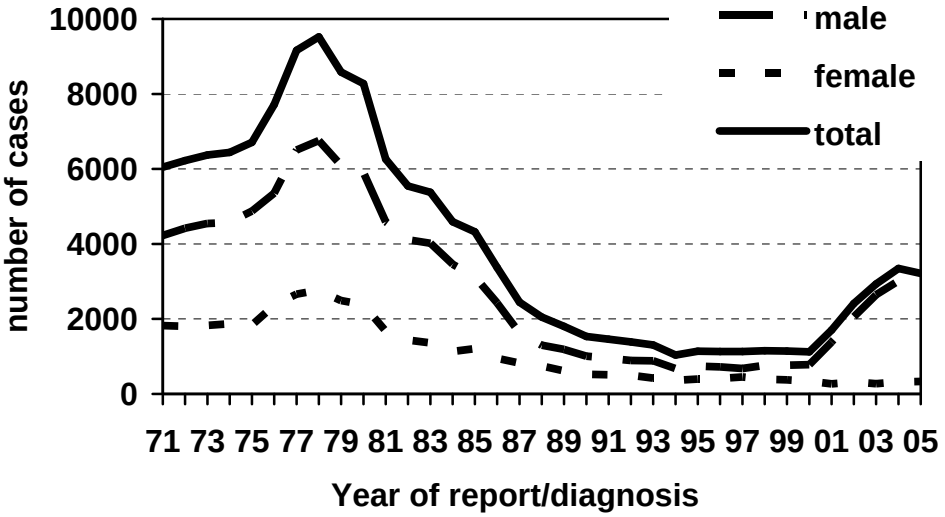


Fig. 2 Syphilis cases reported in Germany. Source: Robert Koch Institut. In 2001, a new law on reporting of infectious diseases ("Infektionsschutzgesetz", IfSG) has been issued explaining the increase of the reported number of cases. Source: Robert Koch Institut

Syphilis is characterized by multiple clinical stages and long periods of latent, asymptomatic infection. It is acquired by sexual intercourse or by transmission from the mother to the baby (Goh 2005). Sexual transmission is probably by inoculation into tiny abrasions from sexual trauma. This results in erosion, then an ulcer, which is called "chancre" and appears 9-90 days after infection. The chancre is classically painless and indurated and may not be apparent and recognized by the patient. This ulcer is commonly accompanied by a regional lymphadenopathy. Systemic dissemination results in immune response against *T. pallidum* leading to secondary syphilis. Immune complexes are formed which may be deposited in organs such as kidney or joints. Secondary syphilis presents with generalized rash affecting soles and palms, generalized lympadenopathy, and oro-genital mucosal lesions. This is followed by a latent stage that develops into tertiary syphilis in 40% of untreated patients. This stage is characterized by gummatous, cardiovascular, and neurological involvement; the latter two are also classified as quartary syphilis. Gummatous syphilis can involve the organs and the supporting structure and can lead to destructive lesions and organomegaly. Late neurosyphilis can lead to stroke syndromes and general paresis. Cardiovascular syphilis can lead to angina and aortic aneurysm.

Diagnosis is by identification of *T. pallidum* by dark field microscopy, direct fluorescent antibody stain, staining in histological specimen, and by serological tests.

Treatment is done by intramuscular injection of benzathine penicillin either as a single dose or weekly in two or three doses. In patients allergic to penicillin, doxycycline, tetracycline, or azithromycine can be used alternatively.

Despite several attempts, the development of an effective vaccine for Syphilis was not successful (Brinkman et al. 2006). However, in principle the development of a vaccine should be possible, because in a proof-of-principle study the immunization of rabbits with large-numbers of gamma-irradiated treponemes was successful (Miller 1973). Although, the applied protocol is impractical for human vaccine development, it is hoped that new vaccines based on recombinant proteins or peptides can overcome the encountered challenges (Brinkman et al. 2006).

Molecular Pathogenesis of Syphilis

T. pallidum has only few outer membrane proteins and does not have lipopolysaccharide. Due to the lack of these immune targets, *T. pallidum* is also commonly called the "stealth pathogen" (Radolf et al. 1989; Peeling and Hook 2006). Important pathogenicity factors belong to a family of Tpr proteins, which encode homologs to the major surface protein of *T. denticola* that mediates attachment to the host tissue and function as porins (Edwards et al. 2005). One member of this family is TprK, which is a cell-surface or periplasmic protein and could be a target for opsonic antibodies (Centurion-Lara et al. 1999; Hazlett et al. 2001). TprK has variable regions and variability in these regions is observed with successive passage (Centurion-Lara et al. 2004). Antigenic variation through gene conversion is thought to be a second mechanism of immune evasion. The genome encodes for putative virulence factors similar to known hemolysins and cytotoxins, but a secretion system for these has not been identified.

Infection with *T. pallidum* provokes a strong humoral and cell-mediated immune response. Antibodies against *T. pallidum* are readily detected throughout the course of infection. A certain degree of protective immunity is formed in human as well as in animal models, although this does not completely protect from reinfection. However, the antigens eliciting this protective immune response are not known. A candidate is the previously mentioned protein TprK; immunization with this protein leads to a significant, but incomplete protection against infection in the rabbit model (Centurion-Lara et al. 1999). However, it should be mentioned that this finding has been questioned (Hazlett et al. 2001).

1.3. Approaches for and Lessons from Large-Scale Interaction Mapping

> Parts of this section have been published in Expert Reviews on Proteomics (Titz et al. 2004). The text has been modified and updated.

The aim of this thesis is the analysis of protein-protein interactions of *T. pallidum* at the genome-wide scale. The employed method for identification of protein interactions is the yeast-two-hybrid system, a genetic screen in yeast cells. In the following paragraphs, an overview of protein-interaction mapping approaches and lessons that can be learnt is given.

The Biological Significance of Protein-Protein Interactions

Proteins usually function in the context of other proteins. Protein-protein interactions greatly expand the flexibility of proteins beyond their individual activities. For example, the dimeric transcription factors Myc and Max have to associate in order to recognize their DNA-binding motif. The Myc-Max dimer allows regulation by changing the protein concentration of each protein but also by the expression of competitive inhibitors such as mad which binds to and blocks Max. Such combinatorial regulation expands the evolutionary flexibility too because each genes encoding binding partner can duplicate and these additional proteins can adopt different specificities and eventually biological roles. For an extensive discussion of protein interactions and their biological significance, the reader is referred to standard textbooks of molecular biology.

How Protein-Protein Interaction Data are generated

Although a number of methods are available for high-throughput analysis of protein-protein interactions, the yeast-two-hybrid system (Y2H) and a combination of protein-complex purification and subsequent analysis by mass-spectrometry (coAP/MS) are the most commonly used ones (Fields and Bartel 2001; Mann et al. 2001).

The yeast-two-hybrid-system was developed by Fields et al. (1989). This genetic assay takes place in living yeast cells and employs a transcription factor that can activate a reporter gene

when its DNA-binding domain (DBD) and its transcriptional activation domain (AD) are linked (e.g. the transcription factor GAL4 is used). When both domains are separated from each other, they do not have the capability to activate transcription of the reporter gene. To answer the question whether a protein A interacts with protein B, each protein is fused to one of these transcription factor domains: AD and DBD, respectively. If protein A binds to protein B, an active transcription activator complex is re-established, the reporter gene is transcribed and its gene product can be used to detect the protein-protein interaction. The protein linked to the DNA-binding domain is called bait; the protein linked to the activation domain is called prey. This assay is applied in a high-throughput manner to screen for protein-protein interactions.

Various modifications of this assay were developed (e.g., the use of different transcription activators) and this assay was the first protein-protein interaction assay to be employed at a genome-wide scale. Uetz et al. (Uetz et al. 2000) used a special type of this system, the array-based Y2H system, to screen for interactions in the yeast proteome. In this system individual prey strains are systematically arranged on culture plates with 384 positions, individual bait strains are mated with the prey strains at each position of this array, the positions of these bait-prey combinations are retained throughout the assay, and individual protein-interactions can easily be identified by their reporter-gene activation at a specific positions of the array (Fig. 3).

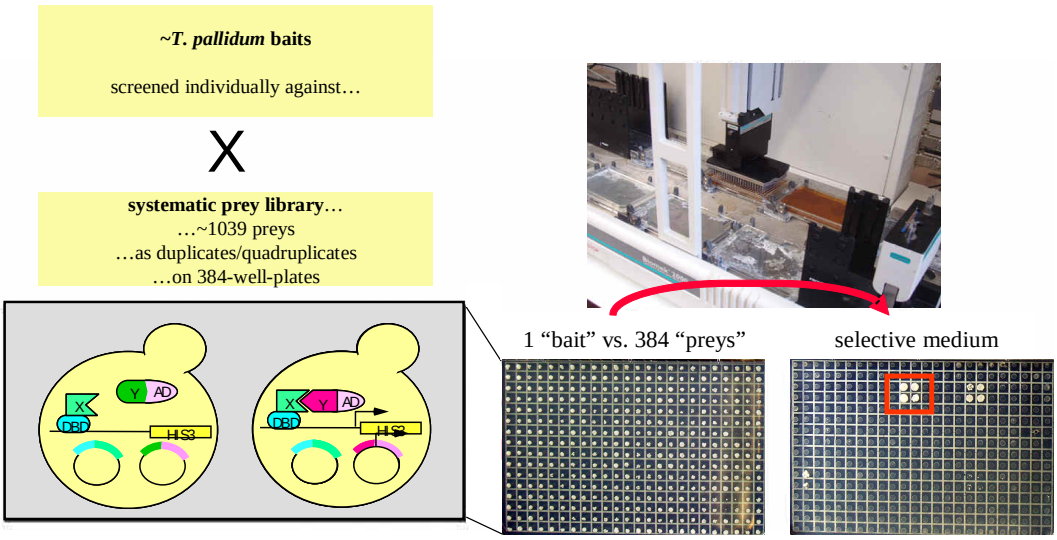


Fig. 3 Array-based yeast-two-hybrid system. This system is based on the procedure employed for interaction mapping of yeast proteins (Uetz et al. 2000) and was used for the generation of the *T. pallidum* interaction map in this thesis. The Y2H system is a genetic screen in living yeast cells, which is based on a split transcription regulator (lower left); only if the two tested proteins interact, an active transcriptional activation complex is formed, which activates a reporter gene. All prey strains of the proteome are arranged on plates with 384 defined positions (lower right) – this set of plates is called "prey array". For each screen, the whole "prey array" is mated with an individual bait strain. After mating each position of the array carries a yeast colony with a specific prey (defined by array position) and always the same bait (from the mating). Handling of colonies is done with a laboratory robot (upper right). Yeast colonies are transferred to selective plates, on which only bait/prey combinations, that activate the reporter gene, can grow. Colony growth at a specific position of the array (lower right) is indicative for a specific protein interaction of the tested bait and the prey at this specific position.

Another method for identifying protein-protein interactions makes use of mass spectrometry (MS) for the identification of protein-interaction partners (Rigaut et al. 1999). In these approaches, which are commonly called co-affinity-purification/MS (coAP/MS) approaches, a purification tag is added to the protein of interest. By means of this tag, this protein is

subsequently purified from a whole cell lysate. Proteins, which interact with the purified protein in the selected cell-type, stick to this protein and are co-purified. These co-purified proteins can be identified by mass-spectrometry to define the set of interacting proteins.

Several genome-wide protein interaction studies have been conducted (Table 3). The first "genome-wide" two-hybrid screen was carried out by Bartel *et al.* (Bartel et al. 1996) for the study of protein interactions in bacteriophage T7. The first genome-wide protein-protein interaction study of a free-living organism has been published by Uetz et al. (Uetz et al. 2000) using the yeast *Saccharomyces cerevisiae*.

At present, these interaction studies cover a wide range of organisms ranging from viruses, over yeast, to human. Note that – despite the recent publication of two coAP/MS studies for *E. coli* (Butland et al. 2005; Arifuzzaman et al. 2006) – only a partial Y2H interaction map (with 261 tested baits) is available for bacteria (Rain et al. 2001).

Some key differences of the resulting two-hybrid and coAP/MS datasets are illustrated in Fig. 4.

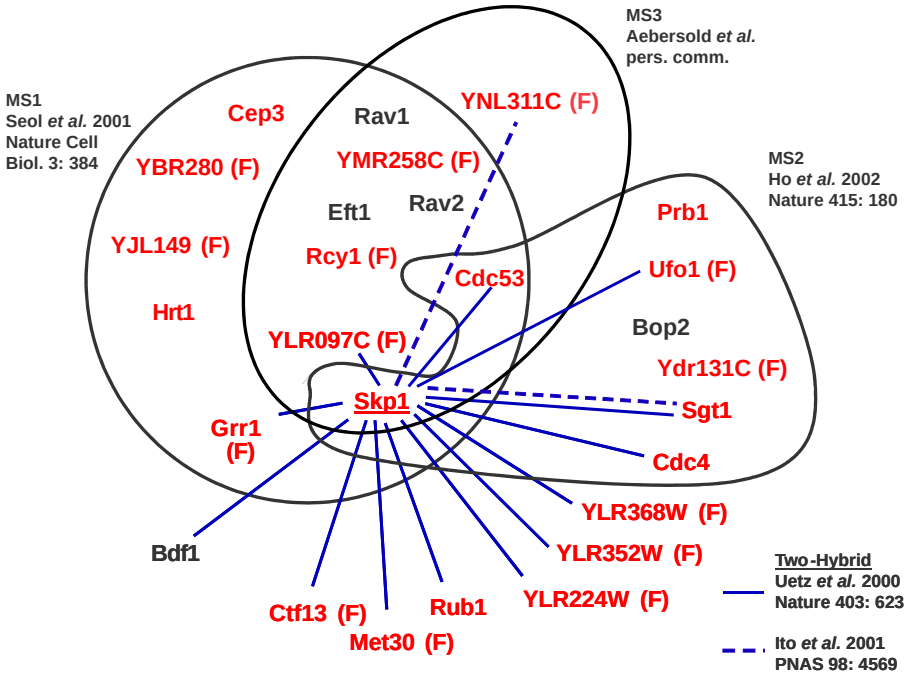


Fig. 4 Interaction data gained by Y2H and coAP/MS are complementary. Skp1 is a protein involved in ubiquitin-mediated protein degradation and has been epitope-tagged for both two-hybrid screens and mass spectrometry analysis. The purified complexes of Skp1 from three independent MS studies and the binary interactions from two Y2H studies are compared. Despite the differences in the data sets, most of the found interactions seem to be plausible: All proteins colored red are known to be involved in protein degradation. Skp1 is directed to its target proteins via so-called F-box proteins, which contain a short peptide motif, the F-box (F). Data from (Uetz et al. 2000; Ito et al. 2001; Seol et al. 2001; Ho et al. 2002) and R. Aebersold (pers. comm.). This figure was published in (Titz et al. 2004).

These experimental approaches for high-throughput interaction analyses have taught us already one important lesson: Y2H and MS datasets are strikingly different but also highly complementary. This difference between datasets – even between datasets derived by a similar method for the same species – is exemplified by two recent coAP/MS studies for yeast (Gavin et al. 2006; Krogan et al. 2006). Goll and Uetz (Goll and Uetz 2006) found, that only 28% of the core complexes from Gavin *et al.* are completely contained in the complexes identified by Krogan *et al.*.

Interestingly, transient interactions are more often found by yeast-two-hybrid analysis, whereas stable interactions (such as those in protein complexes) are more reliably identified by *in vivo* pull-down techniques (Aloy and Russell 2002). This finding is not surprising, given the highly cooperative forces that stabilize a protein complex: many interactions in a complex will not be detected by Y2H analysis as long as only pairs of proteins are tested that are not stabilized by the other subunits of a complex.

Organism (genes)	Method	Interactions (or complexes)	Proteins (% genome)	Reference
Yeast	Y2H	967	1004 (~16%)	(Uetz et al. 2000)
	Y2H	4549	3278 (~55%)	(Ito et al. 2001)
	Co-AP/MS	9421	1665 (~28%)	(Gavin et al. 2002)
	Co-AP/MS	3878	1578 (~26%)	(Ho et al. 2002)
	Co-AP/MS	491 complexes	2760 (~46%)	(Gavin et al. 2006)
	Co-AP/MS	547 complexes	4087 (2708 in core set) (~68%)	(Krogan et al. 2006)
Drosophila	Y2H	20405 (4680 in high confidence set)	7048 (4679 in high confidence set) (~52%)	(Giot et al. 2003)
	Y2H	1814	488 (~4%)	(Stanyon et al. 2004)
	Y2H	2338	1727 (~13%)	(Formstecher et al. 2005)
C. elegans	Y2H	4027	1926 (~10%)	(Li et al. 2004)
Human	Y2H	2800	NA	(Rual et al. 2005)
	Y2H	3186	1705	(Stelzl et al. 2005)
H. pylori	Y2H	1465	732 (~47%)	(Rain et al. 2001)
E. coli	Co-AP/MS	5253	NA	(Butland et al. 2005)
	Co-AP/MS	11511	NA	(Arifuzzaman et al. 2006)
KSHV	Y2H	123	50	(Uetz et al. 2006)
VZV	Y2H	173	55	(Uetz et al. 2006)

Table 3 High-throughput protein-interaction studies. For yeast-two-hybrid (Y2H) screens, the approximate number of binary interactions is shown. For co-affinity-purification/mass-spectrometry approaches, the number of predicted binary interactions based on the spoke model is shown. The table is based on and extends a table from Uetz *et al.* (Uetz and Finley 2005).

No matter how they are generated, interaction data have been used by both experimentalists and theorists for further analysis. A breakdown of such uses is shown in Fig. 5 and discussed below in more detail.

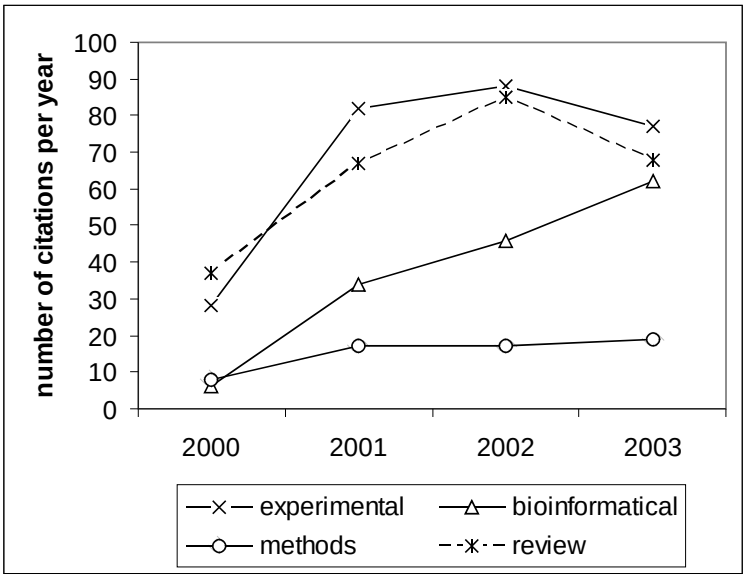


Fig. 5 The use of large scale protein interaction data sets as shown by the number of citations that Uetz *et al.* (Uetz et al. 2000) received during 4 years after publication (grouped into 4 categories). The high level of citation by experimental (small-scale in-depth) studies indicate the usefulness of high-throughput interaction data for more focused analyses. The increasing citation rate by bioinformatics studies, which mainly focus on the high level organization of protein interaction networks, however, illustrates that both a bottom-up, as well as a top-down view of biological systems are encouraged by these high-throughput studies. This figure was published in Titz *et al.* (Titz et al. 2004).

Special Focus: Transcriptional Activation

The yeast-two-hybrid system is based on the reconstitution of a split transcription factor. The underlying principles of transcriptional activation are, therefore, essential for understanding this system. Conversely, the yeast-two-hybrid system can form the basis for a better understanding of transcriptional activation.

Transcriptional regulators that activate transcription are usually composed of a DNA-binding domain (DBD) and an activation domain (AD). The DNA binding domain targets these proteins to a specific binding site in the promoter or enhancer region of a gene and the activation domain mediates transcription initiation (Kadonaga 2004).

Transcriptional activators in yeast were among the first to be studied in detail. In all known cases they recruit additional proteins or whole complexes to the pertinent promoters, eventually leading to the binding of one of the three RNA polymerases. For example, the yeast transcription regulator Gal4 is involved in regulation of galactose metabolism and activates transcription by recruitment of the basal transcription machinery (Ptashne and Gann 1997; Koh et al. 1998; Bhaumik and Green 2001; Bhaumik and Green 2003; Bhaumik et al. 2004).

The Gal4-AD can recruit Tra1, a component of the SAGA complex, to the upstream activating sequence (UAS), where Gal4 itself is bound. SAGA, in turn, recruits the Mediator complex to the UAS. The Gal4-AD can also directly recruit the mediator complex. In any case, the UAS bound Mediator is required for recruitment of general transcription factors (GTFs) to the core promoter and assembly of the pre-initiation complex (PIC).

While DNA-binding domains are extremely well characterized both functionally and structurally, activation domains do not share easily recognizable motifs or structures (Triezenberg 1995): Accordingly, no specific pattern or motif for the identification of an activation domain has been defined in pattern/domain databases such as Prosite (Hulo et al. 2004) or SMART (Letunic et al. 2004). In contrast, more than 50 patterns for DNA binding domains have been documented in the SMART database.

Because the activation properties of transcriptional activators cannot easily be recognized by sequence homology, several studies tried to identify more general sequence features resulting in a number of different activation domain classes (Mitchell and Tjian 1989), e.g. acidic activators (Sadowski et al. 1988), glutamine-rich activators (Courey et al. 1989) and proline-rich activators (Mermod et al. 1989). In addition, a few rather unspecific properties like hydrophobic patches interspersed with hydrophilic residues (Regier et al. 1993) or amphipatic alpha-helices (Giniger and Ptashne 1987) have been identified. These analyses culminated in the finding that even small chemical compounds with a certain pattern of hydrophobic and hydrophilic residues are sufficient for transcriptional activation (Minter et al. 2004).
Only a few proteins have been identified as specific interaction partners of transcriptional activators, including TATA-box binding protein (TBP), TFIIB, TFIIH (Stringer et al. 1990; Ingles et al. 1991; Goodrich et al. 1993; Melcher and Johnston 1995; Koh et al. 1998; Neely et al. 1999), and several others.
An in detail analysis of transcriptional regulators will be presented in this thesis (chapter 3.2).

Reliability of High-Throughput Data

No method is able to identify all protein-protein interactions. That is, each experimental strategy generates a significant number of **false negatives**. The sources of this systematic error are poorly understood. Two-hybrid false negatives might be caused by sterical effects due to the usage of two fusion proteins ("two-hybrid") or involve weak interactions within complexes that require cooperative effects to be stabilized (Aloy and Russell 2002). Conversely, a major bottleneck for mass spectrometry analysis is low abundance proteins and proteins that are only weakly associated with protein complexes and hence tend to get lost during purification.

False positives are usually a more serious problem because they result in erroneous data and thus misleading conclusions. In yeast-two-hybrid studies, some bait constructs activate the reporter gene without interacting with a prey and so may generate large numbers of "technical false positives". On the other hand "biological false positives" represent true interactions that take place in the Y2H system but have no biological relevance (Ito et al. 2002). A case in point are interacting proteins that are usually expressed in different cell types.

Several approaches were used to minimize the number of false positives in high-throughput studies. Uetz et al. (Uetz et al. 2000) discarded yeast-two-hybrid interactions which could not be reproduced and Ito et al. (Ito et al. 2001) defined interacting protein pairs found three or more times as (supposedly reliable) "core" dataset.

More elaborate statistical scores were proposed by Rain et al. (Rain et al. 2001) for the *Helicobacter* interaction map and by Bader et al. (Bader et al. 2004) for yeast and other data sets.

Rain et al. screened bait proteins against a genomic fragment prey library and considered overlapping prey fragments as the most reliable. This approach combines reproducibility and identifies the interacting domain at the same time.

The critical point of any attempt to estimate the number of true and false positives in a HTS interaction study is the choice of the "true positive" data set against which the new interactions are evaluated. Bader et al. (Bader et al. 2004) used the dataset of known protein complexes to derive other parameters that allow the scoring of Y2H data. A similar statistical model was applied to the whole *Drosophila* data set resulting in a high confidence protein interaction network which the authors estimated to retain 40% interactions of "biological significance" (Giot et al. 2003).

Edwards et al. (Edwards et al. 2002) selected known interactions from 3D-structures (RNA polymerase II, proteasome and the Arp2/3 complex), and additionally, complexes from the literature. The crystal structures of complexes approximate the "absolute truth" about stable

protein interactions because they reveal all interactions in atomic detail, at least for the proteins that have been co-crystallized. Based on crystal structures, Edwards et al. found a false negative rate of 51%-96% for yeast-two-hybrid and of 15-50% for in vivo pull-down experiments, respectively. In this context it is remarkable that conventional "low throughput" methods also produce a large fraction of false positives - for example 61% in a pull-down study of RNA polymerase II (Edwards et al. 2002).

Several studies showed that interacting proteins tend to be co-expressed at the mRNA level under various experimental conditions (Ge et al. 2001; Grigoriev 2001). However, while co-expression of the two partners increases the confidence in a protein-protein interaction, it is only an indirect measure of its reliability. While proteins in a complex need to be expressed at similar levels in order to maintain their stochiometric ratios, this is not necessarily true for transient interactions that are often found in Y2H screens.

Overall, it is impossible to reliably estimate the false positive rate of the Y2H system – especially, because all "gold standards" are biased themselves. However, recent large-scale studies found that between 50% and 70% of the identified interactions can be reproduced by an independent method (which also has a certain false-negative rate) (Rual et al. 2005; Uetz et al. 2006). Thus, the question is not, whether these proteins do interact, but whether and under which physiological conditions their interactions are biological meaningful.

The Topology of Protein Interaction Networks

Protein interactions identified on a genome wide scale are most commonly visualized as protein interaction networks. These networks are graphs with proteins as nodes, which are connected by edges (interactions) (Fig. 6 A). This representation is vivid and allows for the analysis of certain graph properties.

Many biological networks, including protein interaction networks and metabolic networks, have a so-called scale-free topology (or at least a scale-free node-degree distribution) (Barabasi and Albert 1999). **Scale-free networks** are characterized by a few highly connected nodes ("hubs") and many less well connected peripheral nodes. The distribution of the node degree k follows a power law ($P(k) \sim k^{-\gamma}$ with power coefficient γ, and probability/frequency of a node degree P(k)) (Jeong et al. 2000; Wagner and Fell 2001) (Fig. 6 A).

The scale-free nature explains several properties of protein interaction networks. For example, highly connected hubs often appear to have central roles in a network, which would make them vulnerable to attack by mutation or drugs. Indeed, Jeong et al. (Jeong et al. 2001) have shown based on the yeast network that the inhomogeneous structure of a network results in tolerance to errors. Random mutations in the yeast genome do not appear to affect the overall topology of the network. By contrast, when the most connected proteins are computationally eliminated, the network diameter increases rapidly (that is, the minimum number of nodes between two arbitrary proteins). Although proteins with five or fewer links constitute about 93% of the total number of proteins in the dataset of Jeong et al., they found that only about 21% of them are essential. By contrast, only some 0.7% of the yeast proteins with known phenotypic profiles had more than 15 links, but a deletion of 62% of these proves lethal. This finding has been confirmed for yeast, the fly, and the nematode networks (Yu et al. 2004; Hahn and Kern 2005). This phenomenon is commonly referred to as the centrality-lethality rule (Jeong et al. 2001). However, this rule has also been disputed in the literature. Coulomb *et al.* state that this observation is an artifact of the underlying biased data – though, it should be noted that their conclusion relies on a single yeast-two-hybrid dataset generated by Ito *et al.* (Ito et al. 2001). He *et al.* (He and Zhang 2006) challenge the notion that the functional importance of a node arises from its structural importance in the network. They explain the basis of this observation by the existence of essential protein-interactions rather than individual essential proteins. The existence of a certain fraction of essential network links would lead to a higher probability for hubs to be essential. In a recent

study, however, Batada *et al.* reinvestigated the importance of hub proteins based on a comprehensive literature curated interaction set for yeast (Batada et al. 2006b); they found a robust correlation of essentiality and connectivity of proteins (Batada et al. 2006a) – however, literature derived interactions were suggested to be highly biased (Coulomb et al. 2005).

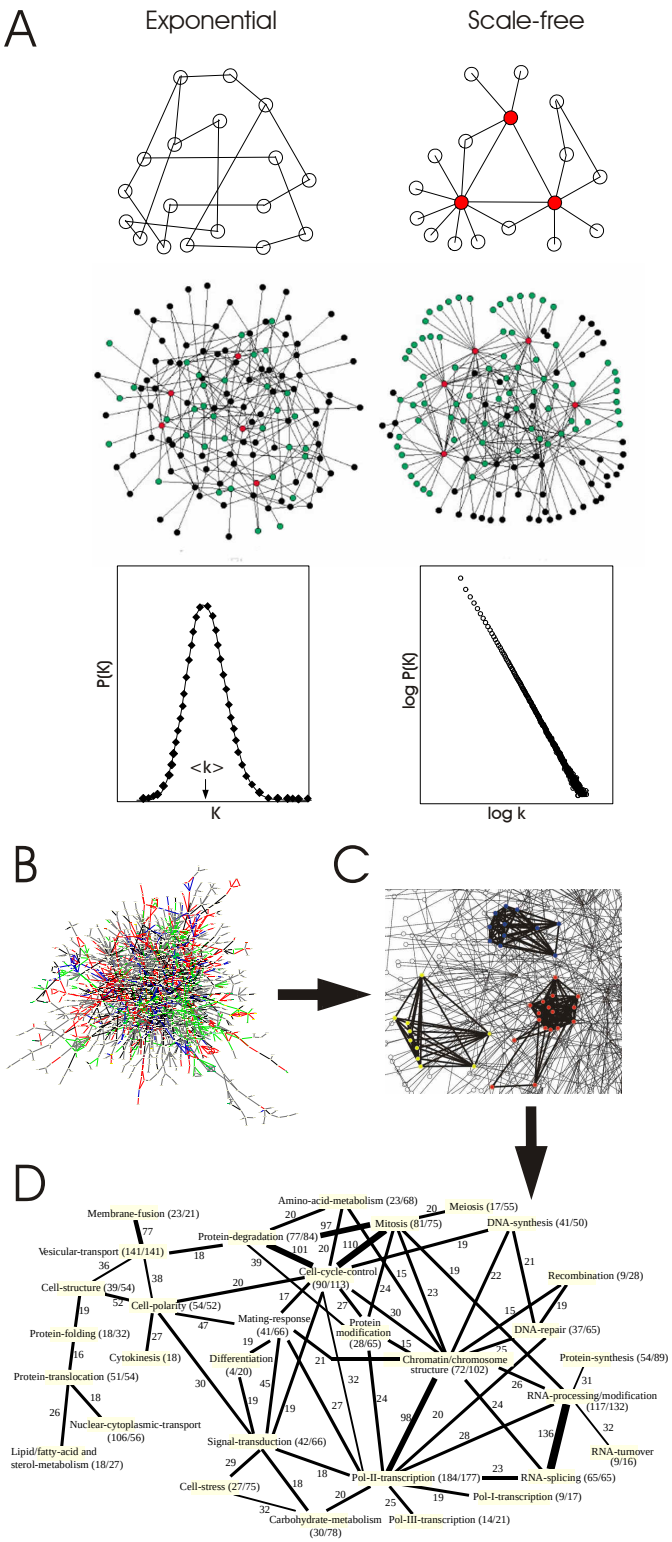


Fig. 6 Network classification and analysis. (A) Protein interaction networks are scale-free networks. In contrast to exponential random networks, in which all proteins (nodes) are regarded as equal, in scale-free networks highly connected proteins are more likely to interact with new proteins added to the network. Exponential networks are therefore statistically homogenous, whereas scale-free networks have a few highly connected

proteins (hubs) and many proteins with few interactions. The signature of scale-free networks is the power law distribution of the node degree (k) (number of interacting partners of a protein), $P(k) \sim k^{-\gamma}$, whereas the node degree follows a Poisson distribution in the exponential network model. Figures taken from (Jeong et al. 2001; Spirin and Mirny 2003). (B-D) The protein interaction network of yeast (B) reveals different levels of organization. (C) Computer algorithms can deduce molecular modules (protein complexes and pathways) directly from the topology of protein interaction networks (Spirin and Mirny 2003). (D) Complex protein interaction networks can be collapsed into a meta-network showing the interactions between functional categories. Numbers in parenthesis denote, first, the number of interactions of a group, and second, the number of proteins in a group. The numbers at the edges denote the number of linking interactions. (B) and (D) after (Schwikowski et al. 2000). Figures reprinted by permission from Macmillan Publishers Ltd. and Copyright 2003 National Academy of Sciences, U.S.A. This figure was published in (Titz et al. 2004).

Experimentally derived interaction networks such as that shown in Fig. 6 B can be extremely complex and biological meaning is not immediately obvious in them. However, biological systems are hierarchically organized into **functional modules** and sub modules (Hartwell et al. 1999). For example, cells produce ATP via a set of modules such as the glycolytic pathway, the Krebs cycle and the protein complexes involved in oxidative phosphorylation. Even if their annotation cannot be used for clustering as shown in Fig. 6 C, several groups have developed algorithms to identify functional clusters ("cliques") in protein interaction networks. For example, Spirin and Mirny (Spirin and Mirny 2003) developed an algorithm that was able to recover many previously known protein complexes (e.g. the anaphase promoting complex) and functional modules, e.g. the yeast pheromone response pathway. In addition, new complexes (e.g. a complex of six proteins including a YIP1 Golgi membrane protein) and new members of complexes (e.g. two 40S small ribosomal subunits in the Lsm splicing complex) were identified, and thereby these methods can provide information about single proteins and their biological context.

The interconnections between different modules can be derived from individual protein interactions and their functional annotation (Fig. 6 D): when all proteins of a certain functional class (or module) are collapsed into one node each, then the protein interactions can be used to visualize their relations. For example, in Fig. 6 D (top middle) the 68 proteins involved in amino acid metabolism are connected by 23 protein interactions. More importantly, this class of proteins also interacts with proteins involved in protein degradation (arguably to generate amino acids!), the cell cycle (which controls almost everything and therefore is highly connected by definition), and, surprisingly, chromatin structure. Unexpected interactions like the one between amino acid metabolism and chromatin structure point to hitherto unnoticed crosstalk between biological pathways and functions, which in this case may be regulatory in nature. The fact that some groups (such as the cell cycle proteins) are highly connected indicates their central regulatory role for most other processes in a cell.

Another method for the detection of complexes in protein interaction networks based on k-cores (Tong et al. 2002) was used to detect a novel nucleolar network in yeast (Bader and Hogue 2002). A k-core is a sub network of the protein interaction network in which each protein is connected to at least k proteins of this sub network, and therefore this set of proteins forms a highly connected complex in the protein interaction network. The identified nucleolar protein interaction network showed a structure corresponding to the known electron microscopic substructure of the nucleolus (Bader and Hogue 2002) (fibrillar component, dense fibrillar component and granular component) which illustrates that the close examination of protein interaction networks can reveal molecular structures, without *a priori* knowledge of protein functions.

Lessons from Single Interactions

The ultimate goal of molecular biology is the mechanistic explanation of specific biological phenotypes. For such explanations, a detailed understanding of single proteins is necessary. Protein interaction data often provide critical information about the molecular behavior of a protein and almost always allow the **formulation of some biological hypothesis**. The chromosome cohesion proteins illustrate this point: a few interactions of the Smc and Scc proteins in yeast and their predicted coil-coil structure suggested a model that explained their ability to hold chromatids together.

Obviously, the lower reliability of high-throughput interaction data has to be taken into account and hypothesis building should start with the most plausible interaction and then proceed to less likely ones. However, the power of interaction mapping is also based on the fact that it is not dependent on previous knowledge of a certain protein and therefore completely unexpected interactions may lead to spectacular new discoveries. For example, interactions between membrane proteins and transcription factors usually have been considered as false positives. However, during the past couple of years in a number of cases it has been shown that such interactions represent novel ways of regulating transcription directly by membrane receptors. Well-studied examples include the SREBPs (Hoppe et al. 2001), the Alzheimer protein APP and the signaling protein Notch (Kimberly et al. 2001). In this way, protein interactions can uncover **new connections** between previously unlinked processes or pathways. Striking examples are "moonlight" proteins. These proteins posses multiple functions that are not due to gene fusions, splice variants or multiple proteolytic fragments. Clf1p, for example, is a protein involved in pre-mRNA splicing or assembly of splicing complexes in yeast. In addition to its interaction with the U5 and U6 subunits of the spliceosome an interaction with the replication initiation protein Orc2p was shown in a two-hybrid assay. This interaction together with a DNA replication phenotype makes Clf1p a protein involved in splicing and in DNA replication initiation, and thus represents a link between these putative unrelated processes (Zhu et al. 2002).

An important goal of proteomics is a **functional assignment** for proteins that cannot be annotated by homology alone. Several approaches for automated functional assignment from protein interaction networks have been developed. The "majority rule" assignment is based on the observation that 70-80% of the interacting proteins share at least one function, therefore an unclassified protein is assigned the most common function in the set of characterized interacting proteins (Schwikowski et al. 2000; Hishigaki et al. 2001). One disadvantage of this simple method is that interactions between two uncharacterized proteins are not taken into account.

Such **predictions also have been experimentally tested**. Kemmeren et al. (Kemmeren et al. 2002) verified the predicted function of 5 proteins that had interactions with known proteins and which were co-expressed as well. For example, a deletion strain of an uncharacterized ORF (YLR270W) shown to interact with a protein required for thermotolerance (NTH1, neutral trehalase gene) indeed showed sensitivity to heat shock.

Ideally, high-throughput interaction data are used by more "traditional" cell-biological studies and this seems to be the case (Fig. 5). For example, Tesse et al. (Tesse et al. 2003) examined the role of Ski8p in Soradia meiosis. A role of Ski8p in meiotic DNA recombination was suggested by the mutational phenotype, but because of its known role in cytoplasmic RNA degradation (non-poly(A) and double stranded RNA) a indirect role of Ski8p was assumed. However, a direct interaction between Ski8p and a protein involved in meiotic recombination, Spo11, in a comprehensive yeast-two-hybrid study (Uetz et al. 2000) led the authors to examine a direct effect of Ski8 on meiotic recombination which was subsequently proven.

Evolution of Protein Interaction Networks

It has been suggested that proteins with more interactions are more conserved than proteins with a smaller number of interaction partners (Fraser et al. 2002). However, Jordan et al. (Jordan et al. 2003) demonstrated that only proteins with the highest number of interactions (the hubs of the protein interaction network) show a slower evolution rate. In a recent study, a negative correlation between evolutionary rate and connectivity was only found in high-throughput interaction data not in a literature curated dataset (Batada et al. 2006a). Thus, the correlation found by Fraser et al. (Fraser et al. 2002) may be an artifact caused by the specific underlying dataset rather than a general phenomenon.

Comparative Interactomics: Predicting Homologous Interactions

Proteins evolve and so do their interactions. If interacting proteins have only weak homology to another pair of interacting proteins, the interaction will support both their functional and evolutionary homology. In order to detect such homologous interactions and pathways, Kelley et al. (Kelley et al. 2003) developed the program "pathblast" (www.pathblast.org) which aligns two protein-protein interaction networks combining interaction topology and sequence similarity. Using this approach, it was possible to show that the protein-protein interaction networks of yeast and *Helicobacter pylori* harbor a significant number of evolutionary conserved pathways. One spectacular example among the conserved sub networks is a group of proteins that is involved in bacterial membrane transport and nuclear-cytoplasmic transport in yeast. This finding indicates that nuclear-cytoplasmic transport may have originated from a homologous system in bacterial plasma membranes.

Pathway comparison cannot only uncover conserved pathways but also identify additional components that have been found in one organism but not in another. We can exploit this information to predict yet unknown interaction partners based on homologs in another model. Such predictions are particularly supported by protein complexes that tend to be well conserved, especially because they usually require several conserved subunits for stability.

With the availability of additional interaction maps, the pathblast algorithm was extended and, for example, used for comparison of the networks of fly, worm, yeast, plasmodium, and *H. pylori* (Suthram et al. 2005).

In addition, new tools for the alignment of biological networks become available, e.g. Flannick *et al.* developed an algorithm which allows the alignment of multiple large interaction networks (Flannick et al. 2006).

Integrating Protein Interaction Data with other HTS Data

Obviously, high-throughput data is not sufficient to explain complex biological processes. However, it has been shown that the combination of several datasets improves their reliability. In addition, different features analyzed by high-throughput approaches can be joined to ameliorate their predictive power significantly.

For example, it has been shown that the intersection of high-throughput interaction datasets contains more interactions from the same MIPS complex which are supposed to be of high quality (Edwards et al. 2002).

A major drawback of this method is that all high-throughput datasets are far from being comprehensive which results in a very small intersection between different data sources, e.g. 133 common interactions between Uetz' and Ito's core data set (Bader and Hogue 2002). Therefore, a very limited number of interactions are marked as "reliable" using this method.

A more elaborate approach is the use of a Bayesian network that allows for the probabilistic combination of multiple data sets. It has been shown that the fraction of false positives and false negatives can be reduced with this method (Edwards et al. 2002). This approach has also been used in a comprehensive study by Jansen et al. (Jansen et al. 2002), in which the high-throughput interaction data sets for the yeast proteome (yeast-two-hybrid and in vivo

pull-down) were combined with genomic features only weakly associated with an interaction (e.g., co-expression of two proteins) to generate a more reliable interaction data set.

In a recent publication, Hwang *et al.* present a method which allows for integration of several biological data sources based on combination of several p-values (Hwang et al. 2005a; Hwang et al. 2005b).

Can a combination of high-throughput data replace traditional experiments?

As we have seen, HTS data is often of lower quality than individually obtained data. On the other hand, HTS data is often better internally controlled because it has been collected under standard conditions. What if all kinds of data are collected under such standardized conditions and are then combined? For example, why don't we study intracellular transport processes by (1) localizing all proteins in organelles such as the Golgi, (2) identify all protein interactions and complexes, (3) measure their transcription (4) degradation, and (5) posttranslational modifications under various conditions, (6) their mutant phenotypes etc.

We can easily collect such data but they will not explain any biological mechanism unless we perform experiments that explicitly address defined causal relations. Most importantly, we are not able to distinguish between cause and effect in advance. For example, just deleting all genes in a genome is useful to investigate which proteins are essential. However, if a protein is not essential under the tested conditions it will not tell us much. For instance, we assume that a protein of previously unknown function (say YHR105W) is involved in vesicular transport, because it interacts only with other transport proteins in two-hybrid assays. However, one screen of a yeast mutant collection (Bonangelino et al. 2002) has not found YHR105W as being defective in transport. For further clarification we do need other hypotheses which reconcile the interaction data and the mutant phenotype and such hypotheses are often not foreseeable by standardized HTS analysis: the interaction screen was most likely not comprehensive (i.e. there are probably false positives and false negatives) and the mutant screen has only looked at one transport phenotype, namely carboxypeptidase Y export, which mainly affects Golgi to vacuole transport. Now we have to study more subtle effects of YHR105W on protein transport, because it is well possible that the interaction has a modulatory role in transport as opposed to being absolutely essential. One needs to remember that most mutations are not deleterious but rather show no or only subtle defects because gene functions can be either substituted on the single gene level by duplicate or redundant genes or a substitution occurs on the network level as an intrinsic property of a scale-free network (see above). Such special circumstances usually cannot be identified by high-throughput screening and thus have to be analyzed by a painstaking hypothesis-driven approach where the hypothesis is refined by each additional experiment.

As an interesting new development, King et al. (Berriz et al. 2003) have devised algorithms to automate such "hypothesis-driven" research. Computer-algorithms can replace human reasoning to a certain extent and it may be possible to push HTS to a degree that its experimental conditions can be refined based on previous experiments and therefore do simulate hypothesis-driven experimentation.

Protein Interaction Networks for Medical Research

Most diseases are caused by malfunctioning proteins in one way or another. However, there are only few known examples of disease-causing defects in protein interactions. The best-studied cases are probably receptors that bind (or do not bind) to peptide hormones or oncoproteins such as Ras, which may cause cancer when their signaling interactions are defective.

When analyzing mutant proteins it is usually not easy to tell an impaired protein interaction apart from some unrelated effect, such as a folding problem. Hence, it is difficult to say if a certain phenotype arises from a defective protein interaction or some indirect cause such as

an instability that prevents a protein from interacting. However, this question can be decided by a detailed structural characterization of the mutated protein.

Interestingly, Giot et al. (Giot et al. 2003) present a human-disease protein view in their *Drosophila* protein interaction map (PIM), in which proteins with sequence similarity to human disease genes are highlighted (Fig. 7 A). 74% of human disease genes in OMIM have strong matches (BLAST e-value < 10^{-10}) to one or more sequences in the *Drosophila* database (Chien et al. 2002). This clearly shows the utility of PIMs in model organisms for medical research.

Using protein interaction networks for drug discovery?

The goal of drug discovery is to design or identify small molecular compounds that help to cure or at least ameliorate diseases. Protein interaction mapping can be useful at several levels of the drug discovery process. The first step should be the **drug target** identification. Protein interaction mapping can help to identify proteins of relevant molecular pathways or complexes that are involved in a specific disease. Dependent on the disease mechanism either a central protein (hub) for blocking a complete process (e.g. for an antibiotic) or a protein with a regulatory function for modulation of a process can be selected.

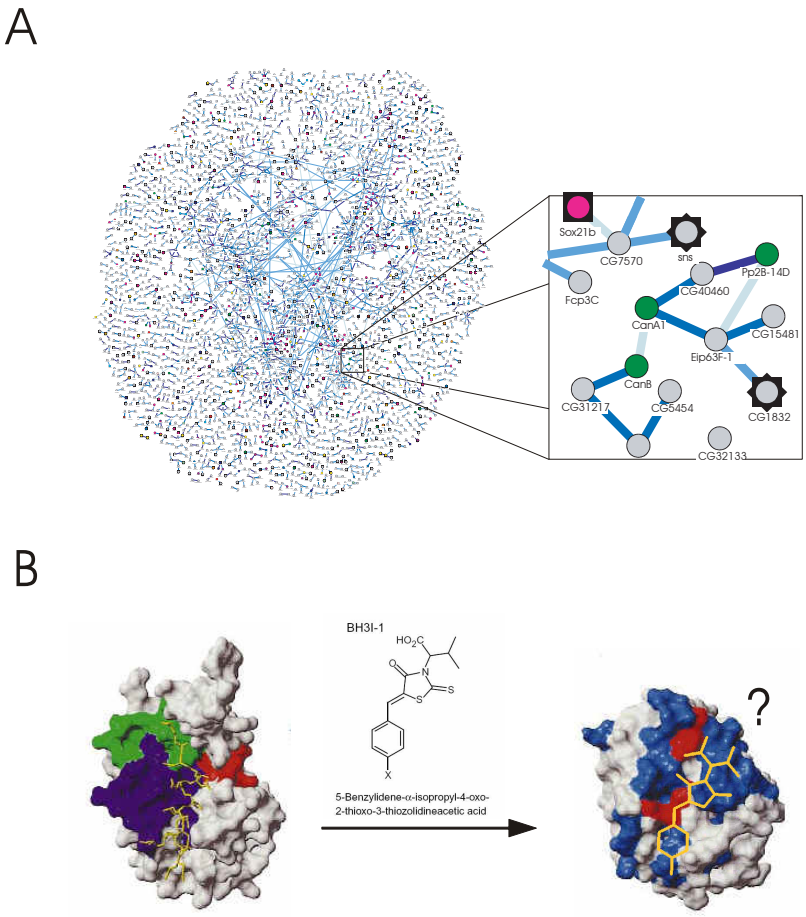


Fig. 7 Protein interaction networks can be used for drug discovery. (A) Drosophila interaction map with proteins that have a human ortholog and which have been reported to be involved in human disease (shown as stars). Such homologous interactions can help to identify potential drug targets. The insert shows the association of CG1832 with two calcium-dependent phosphatases CanA1 and Pp2B-14D, which is mediated by the calcium binding protein Eip63F-1. The homolog of CG1832 (BCL6) is a transcription factor involved in the pathogenesis of human B-cell non-Hodgkin lymphoma. Its association with phosphatases might point to a regulation of this factor akin to NFAT, which translocates into the nucleus after dephosphorylation. These phosphatases are potential new targets for the treatment of B-cell lymphomas (Giot et al. 2003). Figure

adapted from (Giot et al. 2003). Copyright 2003 AAAS. (B) Protein interaction surfaces have been proven to be potential drug targets. Degterev et al. (Degterev et al. 2001) designed a compound (BH3I-1) which inhibits the interaction of Bak to Bcl-xl (left: Structure of Bcl-xl in complex with the Bak BH3 peptide). It is hypothesized that BH3I-1 binds to residues of Bcl-xl (colored red and blue on the Bcl-xl structure on the right-hand panel) and thereby blocks binding of Bak. Note that the structure of Bcl-xl differs depending on bound compounds (left with Bak peptide, right without bound interactor). Inhibition of Bcl-2 interactions leads to apoptosis. Inhibitors such as BH3I-1 can offer new options for anti-tumor therapy by sensitizing transformed cells to chemotherapy. Figure adapted from (Degterev et al. 2001). This figure was published in (Titz et al. 2004).

These proteins or their protein-protein interaction surfaces are promising targets for specific drugs, although only few published examples of interaction inhibitors are available. One example are agents which inhibit the interaction between the BH3 domain and Bcl-XL (Degterev et al. 2001) (Fig. 7 B).

Another recently published example is the hepatitis C virus protease that cleaves the virus-encoded polyprotein. Lamarre et al. (Lamarre et al. 2003) used interactions of the protease with a substrate to identify short peptides that are recognized by the protease. Starting from a 6-amino-acid peptide that acted as a weak enzyme inhibitor, 3-amino-acid inhibitors were selected. These short peptides could then be used to design a specific chemical inhibitor of similar structure. The inhibitor had to be designed to enter the cell and indeed appears to be active in preliminary clinical trials. Theoretically, this approach can be applied to other interactions as well. The limiting problem is to find compounds that mimic peptides and that are able to enter epithelia or cells (Golemis et al. 2002).

The diversity of interactions of a targeted protein might also help to estimate or explain **side effects** of a drug. Protein interaction maps indicate immediately which other proteins or processes may be affected by inhibiting a certain interaction. PIM therefore can help to design selective agents, which target specific interactions of a protein but do not affect others.

Conclusions

High-throughput protein-protein interaction data provides a starting point for the analysis of complexity, signaling and the structural and dynamic organization of cells. In addition, it illuminates an important aspect of the evolution of molecular systems.

If combined with results from other high-throughput methods like microarray analysis, a systematic, global view of the molecular functioning of organisms can be gained which for the first time gives us a glimpse of an organism as a whole. By contrast, "conventional" biological methods are hardly comprehensive; no matter how detailed they are, because they always have to focus on certain selected aspects.

Knowledge about biological networks will help us to understand the complexity of biological systems not only as an intellectual achievement. Eventually systems biology will facilitate the simulation and even manipulation of living systems, for example in order to cure diseases or for the generation of safe and healthy food.

1.4. Objectives of this Thesis

- Generation of a proteome-wide Y2H-based **protein-interaction map (PIM) for *Treponema pallidum*** – one of the **first comprehensive binary interaction maps for prokaryotes**
- Establishing of a supporting informatics platform (**laboratory information management system**) and **high-throughput procedures**, e.g. high-throughput cloning and protein-interaction verification.
- In depth **bioinformatical analysis** of the PIM including:
    - **Topological properties** of the network including scale-free characteristics
    - **Modules/clusters** in the network
    - **Biological links** mediated by protein-interactions, e.g. between compartments, functional categories or genomic locations
    - **Functional predictions** for previously uncharacterized proteins
    - **Comparison** with other datasets
    - Properties of **pathogenicity-related genes**
- **Large-scale phenotyping assays** for complementing the Y2H results – including genome-wide motility phenotyping of *Escherichia coli*
- **Detailed functional characterization** of proteins selected from the high-throughput datasets
- Characterization of the properties of **eukaryotic transcriptional activation domains** to extend knowledge of the Y2H system and transcriptional activation in general

2. Materials & Methods

Chemicals and Enzymes

1kb DNA-Ladder	Invitrogen, Karlsruhe
3AT	Sigma-Aldrich, Taufkirchen
5-azacytidine	Sigma-Aldrich, Taufkirchen
5-bromo-2'-deoxyuridine	Sigma-Aldrich, Taufkirchen
5-fluoro-2'-deoxyuridine	Sigma-Aldrich, Taufkirchen
5-fluorouridine	Sigma-Aldrich, Taufkirchen
5-fluoroorotate	Sigma-Aldrich, Taufkirchen
5-fluorouracil	Sigma-Aldrich, Taufkirchen
5-iodo-2'-deoxyuridine	Sigma-Aldrich, Taufkirchen
acrylamide/N,N`-Methylenbisacrylamide	Roth, Karlsruhe
adenine	Sigma.Aldrich, Taufkirchen
agarose	Peqlab, Erlangen
amino acids	Merck, Darmstadt
ampicillin	Roth, Karlsruhe
anti-BrdU-POD	Roche, Grenzbach
anti-HA.11 IgG	Invitrogen, Karlsruhe
anti-rabbit 680nm IgG	Invitrogen, Karlsruhe
APS	Sigma-Aldrich, Taufkirchen
Bacto-agar	Otto-Nordwald KG, Hamburg
$CaCl_2 \bullet 2H_2O$	Merck, Darmstadt
$CdCl_2$	Merck, Darmstadt
chloramphenicol	Sigma-Aldrich, Taufkirchen
chloroform	Roth, Karlsruhe
$CoCl_2$	Merck, Darmstadt
Cre-Recombinase enzyme	BioLabs, New England
$CuSO_4$	Merck, Darmstadt
D(+)-galactose	Roth, Karlsruhe
D(+)-glucose	Roth, Karlsruhe
DMSO	Fluka, Neu-Ulm
dNTPs for PCR	Metabion, Martinsried
ECL-substrate	Amersham, Freiburg
ethanol	Roth, Karlsruhe
ethidiumbromid	Roth, Karlsruhe
glycerol	Roth, Karlsruhe
Yeast extract	Roth, Karlsruhe
isopropanol	Roth, Karlsruhe
K_2SO_4	Merck, Darmstadt
kanamycine	Roth, Karlsruhe
KOH	Merck, Darmstadt
L(+)-arabinose	Sigma-Aldrich, Taufkirchen
Salmon-sperm-DNA	Sigma-Aldrich, Taufkirchen
lysozyme	Sigma-Aldrich, Taufkirchen
$MgCl_2$	Merck, Darmstadt
milk powder	Saliter, Obergünzburg
$MnCl_2$	Merck, Darmstadt
NaCl	Roth, Karlsruhe
NaOH	Roth, Karlsruhe
NH_4Cl	Merck, Darmstadt

PBS	Gibco, Karlsruhe
PEG 4000	Peqlab, Erlangen
Pfu DNA polymerase	Promega, Mannheim
phenol	Roth, Karlsruhe
Prestained protein marker 6-175 kDa	BioLabs, New England
restriction enzymes	Promega, Mannheim
rifampicin	Boehringer, Mannheim
succhrose	Roth, Karlsruhe
SDS	Roth, Karlsruhe
ß-mercaptoethanol	Roth, Karlsruhe
T4-DNA-ligase	Promega, Mannheim
Taq-DNA-polymerase	Promega, Mannheim
TEMED	Roth, Karlsruhe
tricine	Roth, Karlsruhe
tris base and tris-HCl	Roth, Karlsruhe
trypton	Roth, Karlsruhe
yeast nitrogen base	Roth, Karlsruhe
$ZnSO_4$	Merck, Darmstadt

Materials & Devices

96-well plates	Sarstedt, Nümbrecht
96-deep-well plates	Nalge Nunc, Wiesbaden
Biomek 2000 laboratory robot	Beckman Coulter, Krefeld
BioRad photometer	Biorad, München
Bioruptor (ultrasonic bath)	Diagenode, Liège
Elisa-Reader ELx808	Biotek Instruments, Friedrichshall
Hybond-N+-membrane	Amersham, Freiburg
Miniprep-KitSV A1640	Qiagen, Hilden
Odyssey IR-scanner	LI-COR Biosciences, Lincoln
Omni tray-plates	Nalge Nunc, Wiesbaden
PCR high pure clean up system SV Wizard	Promega, Mannheim
PVDF-membrane	Millipore, Billerica
UV Stratalinker 2400	Stratagene, Heidelberg
Whatman-Paper	Bender und Hobein, Karlsruhe

Used Primers

Primer	**Sequence 5'-3'**
981frag@202for	AATT CT CGA GCA CAG CTT GCT GCT ATT GCC
981frag@222rev	AATT GAG CTC CTA CAT GTC AGT GGT AGC TTG CTC
981frag@50for	AATT CT CGA GCA CGA ATC TAT GAC CTC AAG CAG
GSTyjjGfor	AATTCACC ATG GCC AAGTGGG ACTGGATTTTC
GSTyjjGrev	AATT AAGCTT TCA GTG TTT ACA CAG GAG CTG C
GWY_PCR_B1for	GGGGACAAGTTTGTACAAAAAAGCAGGCT
GWY_PCR_B2rev	GGGGACCACTTTGTACAAGAAAGCTGGGT
hag_forward	AATTCTCGAGGAATGAGAATTAACCACAATAT
hag_reverse	AATTGAGCTCTTAACGTAATAATTGAAGTA
hagHAforward	TACGACGTCCCAGACTACGC TGTTGACA TGGCTAAAGAGATGAG
hagHAreverse	AGCGTAGTCTGGGACGTCGT

	ATGGGTAAATTGTGTGCTCTAGACGATTTTGTAC
hagN255Aforward	AGCGCTTCTGGTGAAGCTTTGACAGCTGCTGAG
hagN255Areverse	CTCAGCAGCTGTCAAAGCTTCACCAGAAGCGCT
I200forward	TTGGCTCGAGGAATCGGCACCATCGATGCTGC
L231forward	TTGGCTCGAGGACTTGACATCGCTGCGGAGAA
L59reverse	GGTTGAGCTCAGAGGCCGCGGATTTGGCTGC
M13forward_pDONR221	CGTTGTAAAACGACGGCCAG
M13reverse_PDONR221	GCCAGGAAACAGCTATGACC
N60forward	TTGGCTCGAGGAAACCAGGCATCCACCAATGC
pAS1forward	TGGCTTACCCATACGATGTTCC
pBad33HA3-loxSacFor	AATT GAGCTC AGGAGG AATTCACC ATG GCA GGT TAC CCA TAC GAC
pBadHDHD4for	AATTCACC ATG GGG CTG AGC CGC GTG C
pBadHDHD4rev	AATT AAGCTT AGT GGA CAT ACT GAC TTT GC
pBadYjjGfor	AATT GAATTC ACC ATGAAGTGGGACTGGATTTTC
pBadYjjGrev	AATT AAGCTT GTG TTT ACA CAG GAG CTG C
pBD@50_rev	GCTTGGCTGCAGTAATACGACTC
pBD@6450_for	GACTGTATCGCCGGAATTCG
pDONR207forward	TCGCGTTAACGCT AGCATGGATCTC
pDONR207reverse	GTAACATCAGAGATTTTGAGACAC
pETM30For	TATTGCTCAGCGGTGGCAGC
pETM30Rev	ATAGCATGGCCTTTGCAGGGC
pGADfor	TTT AAT ACG ACT CAC TAT AGG GCG
pGADrevat2080	AGATGGTGCACGATGCACAG
pGBKfor	GTA ATA CGA CTC ACT ATA GGG CG
pGBKT7reverse	TTTTCGTTTTAAAACCTAAGAGTC
pHB-HA3_pDGforward	AAGGAGGAAGCAGGTATGGCAGGTTACCCATACGAC
pHB-HA3_pDGreverse	GACACGCACGAGGTCAGTCGAGGCTGATAGCGAGCT
pTagLoxRev	GAG CTC CAC CGC GGC CCG
pUniD_forward	CTATCAACAGGTTGAACTG
pUniD_reverse	CAGTCGAGGCTGATAGCGAGCT
pUniDfor	CTA TCA ACA GGT TGA ACT G
pUniDrev	CAG TCG AGG CTG ATA GCG AGC T
S141reverse	GGTTGAGCTCAGGAGAAGCGGCCCGTGAGCA
S199reverse	GGTTGAGCTCAGCTCTTGTTGGCCGAGTCTG
TP0658_pEGSTforward	AATTGGATCCATGGAGATTCAGACGAAGACGC
TP0658_pEGSTreverse	AATTCTCGAGTCAACATTGTTCCTGCGCCCTTC
TP0868_pAC28forward	AATTGGATCCATGATTATCAATCACAACATGAG
TP0868_pAC28reverse	AATTGAGCTCCGGAGAATTGAGAGAATCGAC
V118forward	TTGGCTCGAGGAGTGGCAGAGGTAGACCGCAT
yviF_forward	AATTCTCGAGGAATGATCATTCATACGAAGTA
yviF_p1	CATGGGTGTTGGAGGAAGG
yviF_p2	AGTCGACCTGCAGGCATGCAAGCT
	GTTCTTCTTTTATGTTCATTTGGCC
yviF_p3	CGAGCTCGAATTCACTGGCCGTCG
	TACCATGGCCAAATGAACATAAAAGA
	AGAAACAAAGCATCCGATTGGAGG
yviF_p4	ATCGTTTATATCGACTAAGTCG
yviF_reverse	AATTGAGCTCCTAGCATGATTCTCCTCCAA
yvzB_forward	AATTCTCGAGGAATGGATGCGCTTATTGAGGA
yvzB_reverse	AATTGAGCTCTTAACGTAACAATTGAAGCA

Table 4 Primers used in this study.

Bacterial Strains

strain	description	source
B. subtilis ΔflgM	flgMΔ80 pheA1 trpC2	BGSC
B. subtilis Δhag	argF4 flaC51 hag-1 hisA1 ura	BGSC
B. subtilis Δmot	(SPbc2) motA::Tn917 trpC2	BGSC
B. subtilis Δupp	strain used for yviF deletion	Fabret et al. (Fabret et al. 2002)
B. subtilis ΔyviF	yviF deletion by phleomycin-upp cassette integration (Fabret et al. 2002)	this thesis
B. subtilis 168	trpC2	Bacillus Genetic Stock Center (BGSC)
E. coli BD3.1	Competent cells suitable for propagation of plasmids containing the ccdB gene	Invitrogen
E. coli BL21 (DE3)	T7 RNA polymerase gene under the control of IPTG	Stratagene
E. coli DH5α	Chemically/heat Competent Cells	Invitrogen
E. coli gene deletion strains	based on BW25113	Baba et al. 2006
E. coli K12 BW25113	$lacI^q$, $rrnB_{T14}$, $\Delta lacZ_{WJ16}$, hsdR514, $\Delta araBAD_{AH33}$, Δrha,BAD_{LD78}	Datsenko und Wanner 2000
E. coli knock out library	BW25113 *E. coli* strains	http://ecoli.aist-nara.ac.jp
E. coli PIR	*E. coli* R6K gamma ori	NEB
MC4100	*E. coli* strains	(Wexler et al., 2000)
RP437	*E. coli* strains	Victor Sourijik

Table 5 Bacterial strains used in this study.

Construct	Primer forward	Primer reverse	Vector	Restriction sites	Comment
GST-TPA (~50)	Cre recombination		pMM110		GST-Tag expression
GST-yjjG	GSTyjjGfor	GSTyjjGrev	pETM30	NcoI/HindIII	expression
hag-HA	pUniDfor hagHAforward	hagHAreverse pUniDrev	pUniD/V5-His-TOPO	XhoI/SacI	Mutation
hag-N255A	pUniDfor hagN255Aforward	hagN255Areverse pUniDrev	pUniD/V5-His-TOPO	XhoI/SacI	Mutation
pAC-TP0868	TP0868_pAC28forward	TP0868_pAC28reverse	pAC28	BamHI/SacI	co-expression
pAS1-TPA (~800)	Cre recombination		pAS1-loxP		baits
pBad24HA-HDHD4	pBadHDHD4for	pBadHDHD4rev	pBad24HA	NcoI/HindIII	rescue
pBad24HA-*yjjG*	pBadYjjGfor	pBadYjjGrev	pBad24HA	EcoRI/HindIII	rescue
pBad24Myc-TPA (~10)	Cre recombination		pBad24MycloxP		coEXcoIP
pBad33HA-	Cre recombination		pBad33HAloxP		coEXcoIP

TPA (~10)					
pDG-yviF	pHB-HA3_pDGforward	pHB-HA3_pDGreverse	pDG148-Stu	ligation independent	
pDONR-TPA	see Gateway cloning		pDONR207		TM fragments
pEGST-TP0658	TP0658_pEGSTforward	TP0658_pEGSTreverse	pEGST	BamHI/XhoI	co-expression
pGADT7-DEST-TPA (~100)	LR recombination		pGADT7-DEST		preys
pGAD-TPA (~1000)	Cre recombination		pLP-GADT7		preys
pGBKT7-DEST-TPA (~100)	LR recombination		pGBKT7-DEST		baits
pGBK-TPA (~200)	Cre recombination		pLP-GBKT7-Amp		baits
pHBHA3-TPA (~50)	Cre recombination		pHB-HA3		HA-Tag Expression
pUni-hag	hag_forward	hag_reverse	pUniD/V5-His-TOPO	XhoI/SacI	flagellin
pUni-TPA (~1000)	-	-	pUniD/V5-His-TOPO	-	*T. pallidum* ORFeome (McKevitt et al. 2003)
pUni-yviF	yviF_forward	yviF_reverse	pUniD/V5-His-TOPO	XhoI/SacI	TP0658 ortholog
pUni-yvzB	yvzB_forward	yvzB_reverse	pUniD/V5-His-TOPO	XhoI/SacI	flagellin
TP0868-T1	pUniDforward	L_{59}reverse	pUniD/V5-His-TOPO	XhoI/SacI	Fragment
TP0868-T2	N_{60}forward	pUniDreverse	pUniD/V5-His-TOPO	XhoI/SacI	Fragment
TP0868-T3	N_{60}forward	S_{141}reverse	pUniD/V5-His-TOPO	XhoI/SacI	Fragment
TP0868-T4	V_{118}forward	S_{141}reverse	pUniD/V5-His-TOPO	XhoI/SacI	Fragment
TP0868-T5	V_{118}forward	pUniDreverse	pUniD/V5-His-TOPO	XhoI/SacI	Fragment
TP0868-T6	I_{200}forward	pUniDreverse	pUniD/V5-His-TOPO	XhoI/SacI	Fragment
TP0868-T7	L_{231}forward	pUniDreverse	pUniD/V5-His-TOPO	XhoI/SacI	Fragment
TP0868-T8	N_{60}forward	S_{199}reverse	pUniD/V5-His-TOPO	XhoI/SacI	Fragment
TP0981-T1	pUniDfor	981frag@222rev	pUniD/V5-His-TOPO	XhoI/SacI	TP0981 fragments
TP0981-T2	981frag@50for	981frag@222rev	pUniD/V5-His-TOPO	XhoI/SacI	TP0981 fragments
TP0981-T3	981frag@50for	pUniDrev	pUniD/V5-His-TOPO	XhoI/SacI	TP0981 fragments
TP0981-T4	981frag@202for	pUniDrev	pUniD/V5-His-TOPO	XhoI/SacI	TP0981 fragments

Table 6 Gene constructs. TPA is placeholder for several *T. pallidum* genes (approximate number in parenthesis). See Supplementary Table 34 for vector information.

General procedures

Bacteria culture media

LB liquid medium	<u>for 1l culture medium:</u> 5g yeast extract 10g peptone 10g NaCl add H_2O to 1l and autoclave
2xTY Broth	<u>for 1l culture medium:</u> 10g yeast extract 16g peptone 10g NaCl add H_2O to 1l and autoclave
SOB Medium	<u>for 1l culture medium:</u> 5g yeast extract 20g peptone 0.58g NaCl 0.18g KCl (or 10ml of 250mM stock) add H_2O to 1l and autoclave 2g $MgCl_2$ (or 10ml of 1M stock) 2.5g $MgSO_4$ (or 10ml of 1M stock)
SOC Medium	SOB Medium with 20ml 1M glucose
Solid medium	1l liquid medium with 16g agar
Antibiotics concentrations for bacterial media	100µg/ml ampicillin 50µg/ml kanamycine 50µg/ml gentamycin 34µg/ml chloramphenicol 10µg/ml phleomycine

General DNA related procedures

Competent bacteria for DNA transformation I (TSS-method) (Chung und Miller 1988)

TSS buffer	5ml DMSO 10g PEG 6000 (Sigma) 1M MgCl2 90ml LB medium sterile filter for sterilization

Inoculate bacteria in LB medium (individual colony or from o/n culture) and incubate to OD600 = 0.3-0.4. Centrifuge culture (8,000rpm for 10min) and resuspend in 1/10Vol of ice-cold TSS buffer. Proceed according to chemo-competent transformation protocol.

Competent bacteria for DNA transformation ($CaCl_2$ method)

Inoculate 150ml LB medium with 1ml bacterial pre-culture. Incubate at 37°C to OD600 = 0.35 and cool bacterial culture on ice for 10min. Centrifuge for 10min at 6000rpm (Beckmann J2-HS) and 4°C; discard supernatant. Wash cells with 30ml 100mM $CaCl_2$, centrifuge, resuspend in 30ml 100mM $CaCl_2$, and incubate for 1h on ice. Centrifuge again and resuspend in 3ml 100mM $CaCl_2$ solution. Freeze 100µl aliquots in liquid nitrogen and store at -80°C.

Competent bacteria for DNA transformation ("ultra competent", Inoue method*)*

Protocol is based on protocol published on www.molecularcloning.com.

0.5M PIPES (pH6.7)	15.1 g of PIPES in 80 ml sterile H_2O adjust the pH to 6.7 with 5 M KOH add H_2O to 100 ml sterile filter the solution store at -20°C
Inoue transformation buffer (chilled to 0°C before use)	dissolve in 800ml sterile H_2O: 10.88g $MnCl_2.4H_2O$ 2.20g $CaCl_2.2H_2O$ 18.65g KCl add 20ml PIPES (0.5M, pH 6.7) adjust to 1l and sterilize by sterile filtering

- Pick a single bacterial colony from a plate that has been incubated for 16-20 hrs. at 37°C and transfer it to 25 ml of LB media
- Incubate the culture for 6-8 hrs at 37°C with vigorous shaking (250-300 rpm)
- Inoculate the starter bacterial culture to three 1-liter flasks, each containing 250 ml of SOB. The first flask receives 10 ml of starter culture, the second 4 ml and the third 2 ml
- Incubate all 3 flasks overnight at 18-22°C with moderate shaking
- The following morning, read the OD600 of all 3 cultures. Continue to monitor every 45 minutes
- When the OD600 of one of the cultures reaches 0.55, transfer the culture vessel to an ice-water bath for 10 min. Discard the other 2 cultures
- Harvest the cells by centrifugation at 2500 g (3900 rpm in a Sorvall GSA rotor) for 10 min at 4°C
- Pour off the medium and store the open centrifuge tube on a stack of paper towels for 2 min. Use a vacuum aspirator to remove any drops of remaining medium adhering to the walls of the centrifuge tube
- Resuspend the cells gently in 20ml of ice-cold Inoue buffer
- Add 1,5 ml of DMSO
- Mix the bacterial suspension by swirling and store it on ice for 10 minutes

- Working quickly, dispense the aliquots (50µl) of the suspensions into chilled, sterile microfuge tubes or 96 deep well plates. Immediately snap-freeze the competent cells by immersing the tubes in a bath of liquid nitrogen
- Store tubes at -80 °C until needed

Transformation of chemical competent bacteria

- Remove a tube or 96-deep well plate of competent cells form the -80 °C freezer
- Thaw the cells by keeping the tube or 96 well plate on ice
- Add the transforming DNA, swirl to mix and incubate on ice for 20-30 minutes
- Transfer the tubes into a 42°C water both or heat block for 60s
- Rapidly transfer the tubes to ice for 1-2 minutes
- Add 600µl of SOC or LB medium (without antibiotic) and shake the cultures at 37°C for 1h
- Centrifuge the cells at 13000 rpm for 1 min and resuspend in 200µl sterile H_2O
- Transfer the suspension onto a LB plate with appropriate antibiotic
    - For individual transformations: streak with spatula
    - For large plate numbers: use glass bead method
- Incubate at 37°C

Glass bead streaking method for high-throughput plating

Add 3-4 glass beads to each plate. Swirl a whole stack of plates to spread bacteria. Recycle beads by washing in EtOH and water and autoclaving. Glass beads can be conveniently distributed from 50ml Falcon tube with small hole in lid.

Plasmid preparation (small scale, individual tubes)

buffer P1	50mM Tris-HCl; pH=8.0
	10mM EDTA
	100µg/ml RNase A (DNase-free)
buffer P2	200mM NaOH
	1% (w/v) SDS
buffer N	3M KOAc; pH=5.5

- Pick individual bacterial colony from culture plate and inoculate in 2-5 ml LB liquid medium (with antibiotic for plasmid selection)
- Incubate overnight with shaking at 37°C
- Pellet 1.5ml of bacterial culture (centrifuge 1-2min at max. speed)
- Resuspend pellet in 100 µl buffer P1
- Add 200 µl buffer P2, mix gently by inverting the Eppendorf tube 5 times and incubate on ice for 5 minutes
- Add 150 µl buffer N, mix by inverting 5 times centrifuge at max. speed for 10 minutes. Transfer the supernatant to fresh Eppendorf tube
- Add 1/10 Vol. of 3M NaOAc solution (pH = 5.5)
- Add 0.7 Vol. isopropanol
- Centrifuge at max. speed for 15 minutes at 4°C
- Wash the pellet with 70% ethanol, air dry the pellet and dissolved in 100 µl H_2O

- **alternative:** commercial available silica columns for DNA purification (e.g., Qiagen, Hilden)

Plasmid preparation (96-well plasmid preparation kit)

For plasmid DNA isolation from 96-well cultures different isolation kits were used. These included the "Montage Plasmid Miniprep 96-well kit" (Millipore, Schwalbach) and the "96-well miniprep kit" (Qiagen, Hilden).

Determination of nucleic acid concentration

The concentration of DNA was determined by the spectroscopic measurement of their optical density (OD) at 260 nm and 280 nm. The OD260 value of one is equivalent to 50 μg/ml of double stranded DNA. Pure DNA in aqueous solution should have an OD260/OD280 ratio of 1.6-1.8.

Restriction digestion of DNA

Usually 2-3 units of a restriction enzyme for each μg of DNA were used. 1 to 10 μg of DNA was digested in buffer recommended by the supplier. The reaction was carried out between 2 to 4 hours at enzyme supplier recommended temperature. The quality of the digestion was checked by DNA agarose gel electrophoresis.

Nucleic acid analysis by agarose gel electrophoresis

50x TAE buffer	2M Tris-base 1M acetic acid 0.1M EDTA adjust to pH=8.3 with acetic acid
5x Sample buffer	50% (v/v) glycerol 0.2% (w/v) SDS 0.05% (w/v) bromophenolblue in 1xTAE buffer

Agarose was (final concentration between 0.8 to 1.5 %) was dissolved in 1x TAE buffer and boiled in microwave until the agarose dissolved. Ethidium bromide was added at a concentration of 0.3 μg/ml. The molten gel was poured into a horizontal gel chamber. Load DNA sample with sample buffer. After separation of the samples DNA was visualized by transillumination with 302 nm ultraviolet radiation.

Gel purification of DNA

The DNA band of interest was isolated electrophoretically by running the gel until DNA band of interest is separated from adjacent contaminating fragments. Roche or Promega kit were used for the purification of DNA fragments from agarose gel to isolate the DNA of interest from the agarose gel. The purification was carried out according to supplier recommended protocol (Roche, Mannheim; Promega, Germany).

Ligation of DNA

In all cases, the insert and vector were loaded on an agarose gel to check the DNA content before ligation. Ligation was performed in a total volume of 20 µl with insert-vector ratio 4:1 in 1x ligation buffer with one unit of T4 DNA ligase and incubated for 2h at RT or at 16°C overnight (blunt end ligation).

Polymerase chain reaction (PCR)

A default PCR program is given. This program was modified according to specific PCR requirements. The PCR setup was as follows:

1µl template DNA (20-200ng)
1µl dNTP mix (each 10mM)
Polymerase buffer (with $MgCl_2$, diluted according to instructions)
2µl forward primer (10 pmol/µl)
2µl reverse primer (10 pmol/µl)
0.5-1.0 µl polymerase (Taq polymerase for analytical, Pfu polymerase for preparative PCR)
In a total of 50µl

A commonly used PCR program is given below.
5min at 95°C
(30s at 95°C, 30s at annealing temperature, 2min at 72°C) for 30 cycles
10min at 72°C
Store at 4°C.

The annealing temperature was commonly set to T_m – 5°C.

Colony PCR (from yeast or bacterial cells)

Resuspend small amount of colony in 20µl H_2O. Incubate for 10min at 95°C. Add PCR mix and proceed with PCR.

General protein related procedures

SDS-PAGE (for 2 gels 10 cm x 8 cm with 1mm spacers)

Required material	1M Tris-HCl pH 8.8 (Roth 3029.1) 1M Tris-HCl pH 6.8 0.5M EDTA 20% SDS 30% acrylamid solution (Roth) 10% ammonium peroxodisulfate (APS) TEMED (Sigma) Gel chambers (2 gels 10 cm x 8 cm with 1mm spacers) Protein molecular weight marker
Separating gel buffer (4x)	18.17g tris base 4ml 10% (w/v) SDS adjust pH to 8.8 with HCl

	add DDW (double distilled water) to 100 ml autoclave
Stacking gel buffer (4x)	6.06g tris base 4ml 10% (w/v) SDS adjust pH to 6.8 with HCl add DDW to 100 ml autoclave
APS solution	10% (w/v) APS in DDW store at -20°C
SDS-PAGE running buffer	30g tris base 144 g glycine 100ml 10% (w/v) SDS add DDW to 1 l
SDS sample buffer	12.5% (w/v) SDS 40% (v/v) glycerol 20% (v/v) mercaptoethanol few cristalls bromophenolblue 250mM Tris/HCl pH 6.8

	stacking gel (5%)	**separating gel (10%)**
Acrylamid-bisacrylamid-solution (37,5:1) (Roth, Karlsruhe)	1.5ml	4ml
Separation gel buffer (4x)	-	3ml
Stacking gel buffer (4x)	2ml	-
DDW	4.6ml	5ml
APS solution	15µl	20µl
TEMED	40µl	60µl

Pour separating gel (add reagents as indicated above) into gel chamber (so that it fills up 2/3 of the chamber) and cover with isopropanol and let solidify.
Remove isopropanol and pour stacking gel. Immediately insert the combs and let solidify

Coomassie Blue Staining of Acrylamide Gels

Staining Solution	50% methanol 10% acetic acid 0.2% Coomassie Brilliant blue R250
Destaining Solution	30% methanol 10% acetic acid

- After separation of protein samples, incubate the gel in Coomassie blue stain for 30 minutes
- Recover Coomassie stain (can be used several times)
- Incubate the coomassie stained gel in destain solution (change several times the solution) until the background is sufficiently reduced

- Rinse in the gel in water and dry the gel for longer storage

2.2.6 Western Blot (semi-dry)

Required material	Transfer buffer (see buffers of protocol) Ponceau S (commercial) Blot chamber Whatman paper Nitrocellulose membrane (Immobilon-P, Millipore)
Transfer buffer (Towbin buffer)	3.03 g tris base 14.27 g glycerol 200ml methanol add DDW to 1 l
Ponceau S solution	dissolve 0.1% (w/v) Ponceau S in 5% acetic acid and filter
X%-PBSM	PBS with x% milkpowder
PBST	PBS with 0.05% Tween-20

- Cut blot paper (8 sheets of Whatman paper per gel) and to the size of your gel and equilibrate in transfer buffer
- Cut blotting membrane to the size of your gel, and activate in methanol for 2 minutes (in case of PVDF membrane), then equilibrate in transfer buffer
- Disassemble electrophoresis chamber, lift short plate form saucer plate and carefully transfer gel (cut off stacking gel) into a tray with transfer buffer, shortly equilibrate
- Build up blot: To bottom platinum anode of Trans-Blot-Semi-Dry-place:
- Pre-wet filter paper (4 sheets of Whatman paper)
- Pre-wet membrane
- Gel
- Pre-wet filter paper (4 sheets of Whatman paper)
- Roll out air bubbles
- Secure safety cover and connect to power supply
- Run for 60min at 110mA per gel
- Stop transfer, discard filter paper and briefly wash blot in H_2O
- Check transfer by staining blot in Ponceau S solution and destain in H_2O. Omit Ponceau S staining for infra-red detection
- For blocking: incubate membrane for 30min with 3-5%-PBSM
- Incubate with 1st antibody (e.g., 1:2000) in 1%-PBSTM for 1h at room temperature
- Wash three times with 1%-PBSTM; 5min each washing step
- Incubate with 2nd antibody (e.g., 1:10000; with POD label or IR-label) in 1%-PBSTM for 1h at room temperature
- Wash three times with 1%-PBSTM and conduct chemoluminescence detection or IR detection of bound antibodies.

Expression of 96-constructs in parallel

Lysis buffer	50 mM Tris-HCl, pH 8.0 0.3 M NaCl 1 mM EDTA

Lysis buffer + Brij-Lysozyme (50ml)	45 ml Lysis buffer 5 ml 1% Brij58 (Sigma) 100µg/ml Lysozyme
Proteinase inhibitors	PMSF (200mM stock in isopropanol) → dilute 1:200 Aprotinin + Antipain (5µg/ml in DMSO) → dilute 1:5000
Elution buffer (for GST purification)	120mM NaCl 100mM Tris/HCl pH 8.0 1mM PMSF 20mM glutathione (reduced) 5mM DTT

SB

	1 l/0.95 l	5 l/4.75 l
Bactotryptone	12 g	60 g
Yeast extract	24 g	120 g
Glycerol 100%	4 ml	20 ml

make up to 950 ml (4750 ml)
autoclave 950 ml
cool
add 50 ml of 20x KPB

1L 20x KPB:
46 g KH_2PO_4 + 243 g K_2HPO_4 (Mw=174)

4x SB concentrate

	1 l	5 l
Bactotryptone	48 g	240 g
Yeast extract	96 g	480 g
Glycerol 100%	16 ml	80 ml

Procedure

- start with expression plasmid (e.g. pET) in expression strains (e.g. DE3)
- o/n culture in LB + Kan at 37°C
- next morning: dilute preculture in SB medium containing KPB + Kan
- incubate at 37°C till OD600 = 0.6
- induce with 1mM IPTG
- shake 4-5h at selected temperature (e.g. 23°C)
- spin 10min at 6000rpm
- discard supernatant (storing at-80°C possible) and resuspend cells in 10ml lysis buffer + Brij-Lysozyme + proteinase inhibitors
- incubate for ~30min on ice
- lyse cells by ultrasonic impuls (3* ~15s (in pulses), keep on ice)
- remove 15µl aliquot for SDS-PAGE (whole cellular lysate)
- aliquot into 2ml Eppendorf tubes
- spin 15min atmax and at4°C
- remove 15µl aliquot for SDS-PAGE (soluble protein extract)
- transfer supernatants to new tube

- For GST purification
  - add 30µl glutathione-beads (3x washed with PBS)
  - rotate 45min at4°C

- wash 4-5 times with PBS (rotate for 15min at4°C)
- wash with elution buffer (w/o glutathione!)
- add elution buffer (GST-658: 30µl) and rotate 30min at4°C
- collect eluted fraction and elute for two more times

2.1. Analysis of Transcriptional Activators in Yeast

Selection of transcriptional activators

Transcriptional activators were identified in two genome-wide Y2H studies of yeast proteins (Uetz et al. 2000; Ito et al. 2001). The "Ito screen" resulted in 392 auto-activators which were identified by testing essentially all yeast proteins for transcription activation when fused to the DNA binding domain of Gal4 as full-length open reading frames (Ito et al. 2001). The "Uetz set" contains 68 auto-activators and were identified in two-hybrid screens of ~600 yeast proteins (Uetz et al. 2000).
For analysis of transcription activator properties activators identified by Ito et al. were selected from the Uetz bait library (Uetz et al. 2000) and combined with the Uetz activators to form a set of 451 proteins. These two independent selection steps ensured correct identification of activators. For further quality control, we sequenced 48 samples from the Ito collection and checked another 29 from the Uetz lab by colony PCR for correct insert size. Among these 77 clones only one (out of the 29 mentioned) did not match the expected identity and was thus excluded from further analysis. The activators of the "Ito set" were then divided into activation strength groups (see below). However, 79 strains did not grow well enough to be quantitated, although they were reported to be activators. Their activation strength has been annotated as "not available" (NA) in Supplementary Table 1.

Yeast strains

The activators were selected from the bait proteins described by Uetz et al. (2000) (Uetz et al. 2000) and Hazbun et al. (2003) (Hazbun et al. 2003), and consisted of full length ORFs fused to the Gal4-DBD in the CEN4 plasmid pOBD2 (Cagney et al. 2000). These DBD-activator gene constructs were expressed in the strain YULH (MATa, ura3-52, trp1, lys2, his3, leu2, gal4Δ, gal80Δ, GAL1-URA3, GAL1-lacZ). This "activator strain" was re-arrayed onto 96-well plates and mated with yeast cells of the opposite mating type (namely PJ69-4α: MAT α, trp1-901, leu2–3, ura3–52, his3–200, gal4Δ, gal80Δ, GAL2-ADE2, LYS::GAL1-HIS3, met2::GAL7-lacZ (James et al. 1996), (Uetz et al. 2000)) carrying an empty prey vector pLP-GADT7 (Clontech). This mating was necessary in order to introduce the HIS3 reporter gene of the PJ69-4 α strain.
The handling of yeast colonies was done by automated robotic procedures employing a Biomek 2000 robotic workstation (Beckman Coulter).

Measurements of transcriptional activation strength

The activation strength was measured by two different assays which measure the expression of two reporter genes: His3, which encodes imidazoleglycerol-phosphate dehydratase and catalyzes the sixth step in histidine biosynthesis (LTH assay) and beta-Galactosidase (bGal assay).
His3 gene expression was measured (LTH assay) by growing yeast cells on selective media lacking leucine (L), tryptophane (T), and histidine (H) with the former two corresponding to markers on the two vectors pOBD2 and pLP-GADT7. Activity of the HIS3 reporter was quantitated by increasing amounts of 3-Aminotriazole (3-AT), a competitive inhibitor of His3. The lowest concentration of 3-AT that inhibited growth was considered as the activation strength of the gene construct (Cagney et al. 2000). This assay was done in

quadruplicate in order to ensure reproducibility (see Supplementary Table 1 for detailed results).
The bGal assay was performed in 96-well plates using ONPG as a substrate (Serebriiskii and Golemis 2000). Briefly, diploid yeast cells were grown overnight at 30°C in 100µl selective media (leucine and tryptophane deficient), the media was replaced by 50µl Z-buffer (1.6% (w/v) Na_2HPO_4, 0.55% (w/v) NaH_2PO_4, 0.075% (w/v) KCl, 0.025% (w/v) $MgSO_4$, pH=7) and the cells lyzed by two freeze-thaw cycles. For normalization of the cell density OD_{600} was measured using a microplate reader (Elx808, Bio-Tek Instruments, Vermont, USA). The assay was started by adding 50µl of 1.5 mg/ml ONPG in Z-buffer and the initial OD_{405i} was measured immediately. The reaction was incubated at 37°C and OD_{405} measured at different time points. Time points still in the linear range were considered for calculation of the activation strength:

$$bGal\ activity = \frac{OD_{405(t)} - OD_{405i}}{OD_{600} \cdot t(\min)}.$$

Finally, the mean bGal activity of a randomly chosen set of genes not found to possess auto-activation properties was subtracted. This assay was done in triplicates and mean and SEM (standard error mean) was calculated for each activator (Supplementary Table 1).

Data sources and analysis

General yeast protein properties, e.g. molecular mass and pI, protein annotations and gene ontology (GO) classification were downloaded from SGD (Balakrishnan et al.) (June 2005). Protein localization data was from Huh *et al.* (Huh et al. 2003), which was assumed to be less biased compared to curated data (e.g. GO component data). The abundance of proteins was compared using the genome-wide measurements by Ghaemmaghami *et al.* (Ghaemmaghami et al. 2003). Protein interaction data was downloaded from the MIPS database (Mewes et al. 2004).
Over-representation of certain GO terms was assessed using the program FuncAssociate (Berriz et al. 2003). For in detail analysis of known transcriptional regulator function and definition of the set of known transcriptional regulators (TR) the GO slim term "transcription regulator activity (F-GO 30528)" was used. Proteins annotated with the F-GO term "Transcriptional activator activity" (TermID 16563) from the YPD database (Biobase, Germany) served as an additional reference set.

Physicochemical properties

General physicochemical properties, e.g. molecular mass and isoelectric point, were taken directly from the datasets of the SGD (Balakrishnan et al.). Calculation of amino-acid groups and segments/clusters with specific physicochemical properties, e.g. charge, were done employing the SAPS program (Brendel et al. 1992). Frequencies of amino acids (aa) were directly calculated from SGD sequence data. The minimal and maximal pI of a protein was calculated as the lowest and highest pI of a 20 aa window, respectively. Amino-acid clusters in a protein were defined as the maximal count of a specific amino acid in a 20 aa window of the protein. GRAVY (Grand Average of Hydropathicity) values were calculated as the sum of hydropathy values for all of the amino acids, divided by the number of residues in the sequence (Lobry and Gautier 1994). Aromaticity is the relative frequency of aromatic amino-acids (Lobry and Gautier 1994) and the codon adaptation index (CAI) is an empirical measure of synonymous codon usage bias, which is positively correlated with the expression level of genes (Sharp and Li 1987) (see also "http://www.yeastgenome.org/help /protein_page.html").

Protein domains

The occurrence of protein domains in the set of Y2H activators was assessed using the SMART domain database (Letunic et al. 2004). The number of proteins with each domain in

the Y2H activator set and the whole genome was counted and the enrichment in the former set was calculated. Significance was tested using Fisher's exact test and Holm's procedure for multiple testing correction (Holm 1979).

Protein interactions

A protein-protein interaction map of transcription activators was generated using Cytoscape (Shannon et al. 2003). In the Cytoscape map only physical binary protein-interactions from the MIPS database were considered. Only activators and their direct interaction partners, bridging at least two activators, were selected.
The percentage of activators that interacted with other transcription factors (i.e. proteins with the GO slim term "transcription {P-GO 6350})" was calculated using the set of physical binary protein-interactions from the MIPS database. Similarly, we counted with how many transcription complexes our activators interacted. A "transcription complex" was defined as a protein complex with at least 50% of the proteins annotated as being involved in transcription. The protein interactions with these complexes were assessed by using the MIPS data of protein complexes filtered to contain only high-throughput data (for reduction of bias of well characterized proteins).
Ranking of interaction partners was done by counting with how many proteins of a specific protein set a given yeast protein interacted (using high-throughput protein complex data from the MIPS database).

Statistical analysis

Data-processing was done with PERL (www.perl.org) and statistical calculations with R (R-Development-Core-Team 2004). Correction for multiple testing was done with Holm's procedure using the multtest package of R (Pollard et al.; Holm 1979).

2.2. Generation and Analysis of the Protein-Interaction Network of *T. pallidum*

> The yeast-two-hybrid method described in this section will be published in the Methods of Microbiology series (Rajagopala et al. in press (2007)).

ORF cloning into Y2H bait and prey vectors and Y2H array construction

T. pallidum ORFs were kindly provided as pUni clones by T. Palzkill (McKevitt et al. 2003). ORFs were recombined into bait and prey vectors employing the univector-plasmid-fusion system (UPS) (Liu et al. 1998; Liu et al. 2000). Additional gene constructs were cloned by Gateway system mediated cloning (Invitrogen).

The univector-plasmid-fusion system (UPS)

The UPS is a site-specific recombination based vector system, which uses the Cre–lox site-specific recombination to catalyze a plasmid fusion between an entry vector and a pHost/pAcceptor vector (Liu et al. 1998; Liu et al. 2000). The entry vector (pUniD vector) contains the gene of interest; the pHost vector is designed for the special expression needs, e.g. fusion-gene expression in yeast. The Cre-enzyme is a site-specific recombinase, which catalyzes the recombination between two 34 bp loxP sequences (Fig. 8).

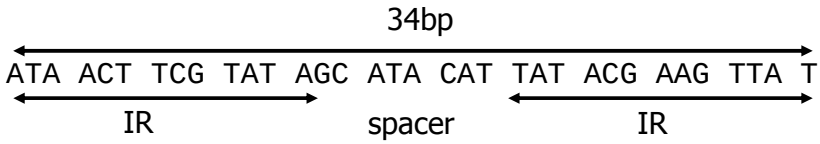


Fig. 8 loxP-site

The product of this recombination is a dimeric fusion plasmid. A crucial feature of the pUNI plasmid is its conditional origin of replication derived from the plasmid R6Kγ that allows its propagation only in bacterial hosts expressing the *pir* gene (encoding the essential replication protein p), and thereby the selection for and propagation of dimeric pUNI-pHOST vectors (Fig. 9).

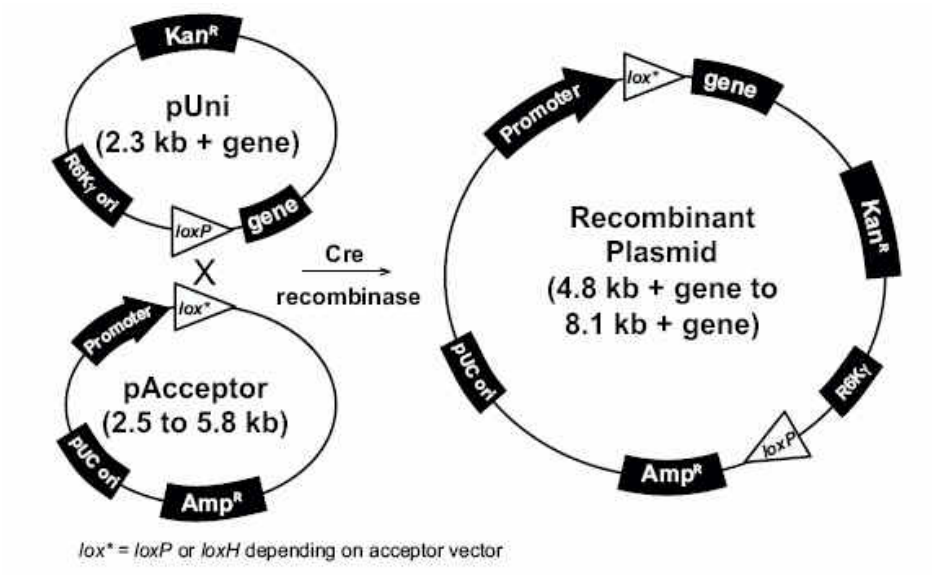


Fig. 9 Schematic representation of the UPS cloning system. A pUni vector is fused with a pAcceptor /pHost vector by the Cre-recombinase via their loxP sites. Source: Invitrogen

Cre Recombination

Cre-recombinase mediated recombination was used for creation of different host vector combinations. The reaction setup was as follows.

2µl 10x Cre-recombinase buffer (NEB)
1µl (1U/µl) Cre recombinase (NEB)
100ng pUniD clones (entry vector constructs)
100 ng UPS host vector (Y2H vectors, bacterial expression vectors)
H_2O --
In 20µl total volume

Incubate the reaction at 37° C for 1 hour. Terminate the reaction by incubation at 70° for 10 minutes. Use 10 µl of the reaction for bacterial transformation.

The Gateway® system

The Gateway® system (Invitrogen) provides an universal technology to clone DNA sequences for functional analysis and expression in multiple systems. It is based on site-specific recombination of bacteriophage lambda (Landy 1989). Similar to the UPS system, the lambda recombinase is employed to recombine attachment (att) sites from different vectors, which leads to the transfer of an ORF from one to the other vector. The advantages compared to the UPS system are the support of PCR product cloning, the feasibility of C-terminal fusions, parallel transfer into several destination vectors, and the availability of a large number of vectors and clones for this system. However, the main disadvantage compared to the UPS system is its high cost.

Cloning of ORFs with the Gateway system – the BP reaction

The first step of ORF cloning is the primer design. The amplification of the ORFs will be done in two steps: in the 1st PCR the ORF is amplified with ORF-specific primers, in the 2nd PCR BP-sites for cloning are added to the resulting PCR product.

For convenient design of primers, the "Express Primer Tool" from the Argonne National Lab is recommended: http://tools.bio.anl.gov/bioJAVA/jsp/ExpressPrimerTool/. The following parameters can serve as guidelines: optimal Tm is 55 °C, the Tm range is 10 °C above and below the optimal Tm, and the maximum Tm difference between forward and reverse primers is 5 °C.

The primers for the 1st PCR are designed as follows:

Forward Primer:

5' AA AAA GCA GGC TCC GCC ***atg*** –18-20nt (specific ORF sequence) 3'

Reverse Primer:

5' A GAA AGC TGG GTA ***cta*** – 18-20nt (specific ORF sequence) 3'

atg: start codon

cta: stop codon (example for TAG); can be omitted for C-terminal fusions

The 1st PCR is done with a standard PCR protocol employing a proof-reading polymerase (e.g., Pfu polymerase) (see PCR protocol). However, the number of cycles in the 1st and 2nd PCR can be reduced if errors are expected.

The PCR products are checked by agarose gel electrophoresis and 1-5µl product is used for the 2nd PCR reaction with the primer pair:

Forward Primer (attB1):

5' G GGG ACA AGT TTG TAC A**AA AAA GCA GGC T** 3'

Reverse Primer (attB2):

5' GGG GAC CAC TTT GTA CA**A GAA AGC TGG GT** 3'

If unspecific bands are detected, the PCR product is gel purified. Otherwise, a column purification of the product is done.

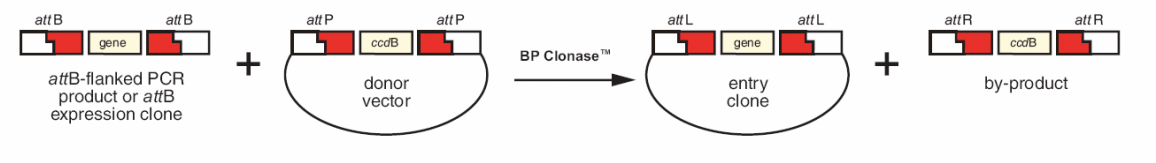


Fig. 10 Gateway® system BP reaction. For generation of entry clones an *attB* substrate (PCR product) is recombined with an *attP* substrate (DONR vector) mediated by BP clonase® mix. Figure taken from Gateway manual (Invitrogen).

The purified PCR product is used in a ***BP recombination*** to create the entry clone (Fig. 10):

1µl BP Clonase (Invitrogen)
1µl BP buffer
1µl vector (pDONR207 / 150ng/µl)
2µl PCR fragment (column purified)
incubate o/n at 25°C
add 1µl Proteinase K
incubate for 10min at 37 °C
transform into TOP10 cells
select on Gentamicin plates

Picking of a single colony is usually sufficient; the construct can be checked by PCR with the primer pair: pDONR207forward and pDONR207reverse.

Destination vector creation with the Gateway system – the LR reaction

The entry clones in pDONR207 can be transferred into different destination vectors with an LR reaction.

Fig. 11 Gateway® system LR reaction. For generation of destination clones an *attL* substrate (entry clone) is recombined with an *attP* substrate (destination vector) mediated by LR clonase® mix. Figure taken from Gateway manual (Invitrogen).

For the Y2H system the pGBKT7-DEST (bait) and pGADT7-DEST (prey) vectors are used (Uetz et al. 2006). The setup of the reaction is as follows:

1µl LR Clonase (Invitrogen)
1µl LR buffer
1µl Entry vector (pENTR207)
1µl Destination vector (150ng/µl)
2µl H_20
incubate o/n at 25°C
add 1µl Proteinase K
incubate for 10min at 37°C

transform into TOP10 cells and select on Kanamycin plates

Y2H vectors & Y2H fusion-protein creation

For the prey constructs (Gal4-activation domain fusions) the vector pLP-GADT7 (Clontech) was used (Fig. 12). Two different bait vectors (Gal4-DNA-binding domain fusions) were selected. The pAS1-loxP vector (created by M. McKevitt) was generally used for the screening. We did not have any experience with this vector in our laboratory. Thus, a second bait vector, pLP-GBKT7-Amp, was adapted for the UPS system (Fig. 12) (Table 7). This bait vector was created from the pLP-GBKT7 vector (Clontech) by exchanging the KanR-gene with the AmpR-gene from the pAS1-loxP vector. For this, pLP-GBKT7 (Clontech) was digested with PvuII&XbaI and the 3.2kb fragment was gel purified. The vector pAS1-loxP was digested with BstXI & PstI and the 4.5kb fragment was gel purified. Both purified fragments were co-transformed into yeast cells and the recombined vector was selected on Trp-deficient plates. The use of these bait vectors and a comparison is presented in the results section.

T. pallidum genes as pUni-clones (McKevitt et al. 2003) were recombined with these vectors, the constructs were checked by PCR or restriction digestion, and transformed into yeast cells.

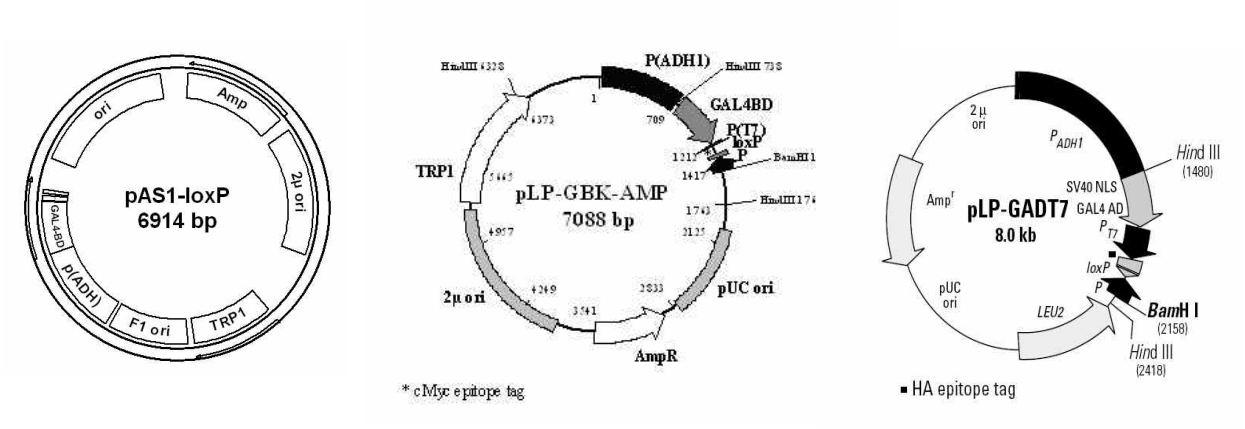


Fig. 12 Y2H vectors used for the interaction map of T. pallidum. The vectors pAS1-loxP and pLP-GBK-AMP are bait vectors, the vector pLP-GADT7 is a prey vector.

feature	position
TRP1	5343-5704
Gal4BD	762-1202
ADHp (trunc.)	30-736
cMyc tag	1248-1280
loxP	1305-1338
bac. Promoter	1339-1465
T7-term	1492-1538
ADH term.	1571-1767
pUC ori	1995-2793
2µ ori	3931-5278
F1 ori	6540-6556
AmpR	2942-3578

Table 7 Features of pLP-GBK-Amp

Verification experiments for gene construct

The gene constructs for the Y2H system were checked by PCR, restriction digest, or DNA sequencing (GATC Biotech AG, München).

Control PCRs were done with the following primer pairs: pUniDfor-pUniDrev (for pUniD constructs), pGADfor-pUniDrev (for preys in pLP-GADT7), pGBKfor-pUniDrev (for baits in pLP-GBKT7-Amp), and pAS1for-pUniDrev (for baits in pAS1).

Restriction digests were done with the following enzyme pairs: XhoI-SacI (for pUniD constructs) and SmaI-NcoI (for pAS1 and pLP-GBKT7-Amp constructs).

Y2H strains

The Y187 strain was selected for transformation of the prey constructs and the AH109 strain was selected for bait construct transformation.

Y187 (MATα, ura3- 52, his3- 200, ade2- 101, trp1- 901, leu2- 3, 112, gal4Δ, met–, gal80Δ,URA3 : : GAL1UAS -GAL1TATA -lacZ) (Harper et al., 1993)

AH109 (MATa, trp1-901, leu2-3, 112, ura3-52, his3-200, gal4Δ, gal80Δ LYS2::GAL1UAS-GAL1TATA-HIS3, GAL2UAS-GAL2TATA-ADE2, URA3::MEL1UAS-MEL1 TATA-lacZ)) (James et al., 1996)

Yeast media and selective plates

YEPD liquid medium	10g Yeast extract 20g Peptone 20g Glucose add H_2O to 1 liter autoclave
YEPD solid medium	YEPD liquid medium with 16g agar/l add 4ml 1% adenine solution (1% in 0.1M NaOH) after autoclaving
Medium concentrate	8.5 g yeast nitrogen base 25 g ammonium sulfate 100g glucose 7 g dropout mix (see below) add H_2O to 1 liter sterile filter
Selective plates	autoclave 16g agar in 800ml water cool medium to 60°-70°C add 200ml medium concentrate add depending on plate type: -T plates (w/o Trp) 8.3ml Leu and 8.3ml His solution - L plates (w/o Leu) 8.3ml Trp and 8.3ml His solution - LT plates (w/o Trp and Leu) 8.3ml His solution - LTH plates (w/o Trp and Leu and His) nothing -LTH + 3mM 3AT plates

	6 ml of 3AT (3-amino-1,2,4-triazole, 0.5 M) to a final concentration of 3mM.
Dropout mix (-His, -Leu, -Trp)	1 g Methionine 1 g Arginine 2.5 g Phenylalanine 3 g Lysine 3 g Tyrosine 4 g Isoleucine 5 g Glutamic acid 5 g Aspartic acid 7.5 g Valine 10 g Threonine 20 g Serine 1g Adenine 1 g Uracil Mix all components and store under dry, sterile conditions.
Amino acid solutions	Histidine (His): dissolve 4 g of Histidine in 1 liter sterile water and sterile filter Leucine (Leu): dissolve 7.2 g of Leucine in 1 liter sterile water and sterile filter Tryptophane (Trp): dissolve 4.8 g of Tryptophane in 1 liter sterile water and sterile filter

Yeast Transformation

Materials required	salmon sperm DNA DMSO competent host yeast strains (AH109, Y187) Lithium Acetate (0.1M) selective plates (depending on the selective markers) 96PEG solution competent yeast cell
Carrier DNA (salmon sperm DNA)	Dissolve 7.75mg/ml salmon sperm DNA Sigma (cat.No. D1626) in water and store at –20°C following a 15min 121°C autoclave cycle
96 PEG solution (100ml)	45.6g PEG (Sigma P3640) 6.1ml 2M LiOAc 1.14 ml 1M Tris pH 7.5 232 μl 0.5M EDTA add H_2O to 100 ml autoclave

- Inoculate yeast strain (e.g. AH0109, Y187 or any other appropriate yeast strain; Y187 strain is used for preys and AH109 is used for baits) into 50 ml YEPD liquid medium in a 250 ml flask (inoculation from fresh YEPD plate is beneficial)
- Grow overnight with shaking at 30 ºC (minimum 15 h, max. 24 h)
- Centrifuge in 50 ml conical tube (3,500 rpm, 5 min at RT), pour off supernatant, dissolve the pellet in 2 ml 0.1M LiOAc, and transfer resuspended yeast into two 1.5

ml microfuge tubes. Spin out yeast and resuspend in a total volume of 1.8 ml 0.1M LiOAc.

- Prepare "CT110" for yeast transformation by mixing:
  - 20.73 ml 96PEG
  - 0.58 ml boiled salmon sperm DNA
  - 2.62 ml DMSO
- Mix the above listed solutions in a 50 falcon tube; add DMSO last and mix quickly by shaking hard for 1min.
- Add the total amount of competent yeast cells prepared above and mix hard by hand or by vortexing for 1 min. Pipet 200 µl into each well of a 96-well dish (e.g. Costar 3596).
- Add min. 100ng of plasmid and positive control (empty vector) and negative control (only CT110). Seal the 96 well plate with plastic or Aluminum tape and vortex for 4 minutes.
- Incubate at 42°C for 30 min.
- Spin the 96 well plate for 10 min at 2,000 rpm; discard the supernatant by tapping on cotton napkin for couple of times. Add 100 µl of sterile water to all 96 wells, resuspend and plate them on selective plates 35 mm -Leu (or -Trp). Incubate the plates at 30ºC for 2-3 days.

Setup of the prey array

Preys rather than baits are arranged on an array, because the former do not generally result in self-activation of transcription. For creation of the prey array, the layout of the array is defined first. Each prey construct of the proteome is given a specific position of a particular 96-well-plate, e.g. position A03 of prey plate #3. The wells of these 96-well-plates are filled with 100µl YEPD medium. Several colonies from a specific prey transformation are combined and manually transferred into the well at the previously defined position. These 96-well plates carrying the prey strains are incubated o/n at 30°C and replicated to Omnitray plates with solid media – at least one selective Omnitray plate (-Leu) and one YEPD plate. 50µl 50% (v/v) glycerol is added to the liquid culture plate; the plate is sealed and transferred to -80°C for long term storage. The solid prey plates with prey strains in the 96-format were quadruplicated to the 384-format using a robotic procedure (Biomek 2000 laboratory robot). For increased throughput, duplicates rather than quadruplicates from two 96-formatted plates can be combined on one 384-formatted plate. This prey array was generally stored on selective plates (-Leu). "Working" copies for Y2H screens on solid YEPD medium were created.

Bait construction

Baits are also constructed by Cre-mediated recombination of the respective pUni-constructs with the bait vectors described above. Baits were transformed into the AH109 yeast strain and stored on –Trp plates and as glycerol stocks.

Self activation test

Prior to the two-hybrid analyses, the bait yeast strains (DB-X) should be examined for self-activation. Self-activation is defined as a detectable DB-X-dependent two-hybrid reporter gene activation in the absence of any prey (AD-Y) interaction partner. Weak to intermediate-strength self-activator baits can be used in two-hybrid array screens because the corresponding DB-X/AD-Y interactions confer stronger readouts that are scoreable over the

self-activation background. In case of the HIS3 reporter gene the self-activation background can be titrated by adding different concentration of 3-AT, a competitive inhibitor of His3.

Self-activation of all the baits is examined on plates containing different concentration of 3-AT. The lowest concentration of 3-AT that suppresses growth in this test is, finally, used for the interaction screen (see below): background growth is suppressed, whereas true interactions are still detected.

Materials required
full medium and selective medium agar in single-well microtiter plates (Omnitray plates, Nunc):
YEPD plates
- LT plates
Selective plates without Trp, Leu, and His, but with different concentrations of 3-AT, e.g., 0mM, 1mM, 3mM, 10mM, 50mM and 100mM (-LTH/3-AT plates)
Prey strain carrying the empty prey plasmid, e.g., Y187 strain with pLP-GADT7 plasmid (Clontech)

- Bait strains are arrayed onto a single-well Omnitray agar plate; either the standard 96-well format or the 384-well format is used. *Baits are first inoculated at the different positions of a 96-well plate as liquid culture, and then cells are transferred (manually or with robot) to solid agar single-well plates (Omnitray plates). In this step the 96-well format can also be converted into the 384-well format, this will position each bait in quadruplicates on the 384-well formatted plate. Full medium agar (YEPD agar) can be used, however, for long term storage of the array selective agar (-Trp) is suggested to prevent loss of plasmids.*
- The arrayed bait strains are mated with a prey strain carrying the empty prey plasmid, e.g., Y187 strain with pLP-GADT7 plasmid (Clontech). Mating is conducted according to the standard screening protocol. *Note: Compared to protocol 2 bait and prey strains are exchanged during mating.*
- After selecting for diploid yeast cells (on –LT agar) the cells are transferred to medium selecting for the His3p reporter gene activity (see below). The -LTH transfer is done to several selective plates with increasing concentrations of the competitive inhibitor of His3p, 3-Aminotriazole (3-AT). *Suggested are 3-AT concentrations of 0mM, 1mM, 3mM, 10mM, 25mM, and 50mM.*
- These –LTH/3-AT plates are incubated for 1 week at 30°C. The self-activation level of each bait is assessed: the lowest 3-AT concentration that completely prevents colony growth is noted. As this concentration of 3-AT suppresses reporter activation in absence of an interacting prey this 3-AT concentration is added to –LTH plates in the actual interaction screening.

Screening for protein interactions using a yeast protein array

The Y2H prey array is screened for protein interactions by a mating procedure that is carried out using robotic procedures. A strain expressing a single candidate protein as a DBD fusion (bait strain) is mated to all the colonies in the prey array. After mating, the colonies are transferred to diploid-selective medium (-Leu and –Trp), and then to two-hybrid selective medium (-Leu, -Trp, and –His). A robotic workstation (Biomek 2000, Beckman Coulter) was used for the screening procedure. A 384 pin stainless steel replicating tool (High-Density Replication Tool; Beckman Coulter) was used to transfer the colonies from one plate to another. Between the transfer steps, the pinning tool must be sterilized by sequential immersion into a 20% (v/v) bleach solution (20 seconds), sterile water (1 second), 95% (v/v)

ethanol (20 seconds), and sterile water (1 second). The level of these liquids should be 2 to 4 mm from the base of the pin and care must be taken that the ethanol does not evaporate.

It is important to ensure that plasticware is compatible with the movement of the robot. Here, the prey array was gridded on 86 x 128-mm single-well microtiter plate (OmniTray, Nalge Nunc International) in 384-colony format.

Materials required
20% (v/v) bleach (1 % sodium hypochlorite)
95% (v/v) ethanol
Single-well microtiter plate (OmniTray; Nalge Nunc international) containing solid YEPD + Adenine medium (see protocol), -Leu –Trp, –His –Leu –Trp and –His –Leu –Trp + different concentration of 3AT
Bait liquid culture (DBD fusion-expressing yeast strain)
yeast protein array on solid YEPD plates („working copy" of prey array)

- Sterilization: Sterilize the 384-pin replicator by dipping the pins into 20% bleach for 20s, sterile water for 1s, 95% ethanol for 20s, and sterile water again for 1s. Repeat this sterilization before each transfer.
- Preparing bait liquid culture (DBD fusion-expressing yeast strain): inoculate 20-30ml of liquid YEPD medium in a 250 ml conical flask with a bait strain and grow overnight in 30ºC shaker. *If the Bait strains are frozen, it is streaked or pinned on a selective plate (-Trp) solid medium and grown 1-2 days at 30ºC. Bait colonies from this plate are then used to inoculate the liquid YEPD medium.*
- Mating procedure: Pour the dense bait strain culture into sterile Omnitray plate. Dip the sterilized pins of the pin-replicator (thick pins should be used to pin baits) into the bait liquid culture and place directly onto a fresh single-well microtiter plate containing solid YEPD medium. Repeat with the number of plates needed for the whole prey array and allow the yeast to dry onto the plates for 10-20 minutes.
- Pick up the prey array (i.e., AD) yeast colonies with sterilized pins (thin pins should be used to pin the preys) and transfer them directly onto the baits pinned onto the YEPD plate, so that each of the 384 bait spots per plate receives different prey yeast cells (i.e., a different AD fusion protein). Incubate 1-2 days at 30ºC to allow mating. *Mating will take place in <15 hr, but longer period is recommended, because some baits strains show poor mating efficiency.*
- Selection of Diploids: For the selection of diploids, transfer the colonies from YEPD mating plates to single-well microtiter plates containing –Leu-Trp medium using the sterilized pinning tool (thin pins should be used in this step). Grow for 2-3 days at 30ºC until the colonies are >1 mm in diameter. *This step is essential because only diploid cell containing Leu and Trp markers on prey and bait vector, respectively, will grow on this medium. This step also helps recovery of the colonies and increase the efficiency of the next selection step.*
- Interaction selection: Transfer the colonies from –Leu-Trp plates to a single-well microtiter plate containing solid –His –Leu –Trp agar, using the sterilized pinning tool. If the baits are self-activating, they have to be transferred on –His –Leu –Trp with a specific concentration of 3AT and incubated at 30ºC for 6-10 days.
- Score the interactions by looking for growing colonies that are significantly above the background by size and that are present for both duplicate colonies. *The plates should be examined every day. Most two-hybrid positive colonies appear within 3 to 5 days, but occasionally positive interactions can be observed later. Very small colonies are usually designated as background; however, there is no absolute measure to distinguish between the background and real positives. When there are many (i.e., > 30) large colonies per array of 6000 positions, these baits are considered as random activators. In this case the screen should be repeated.*

Evaluation of raw results

Filtering of the obtained raw results significantly improves the data quality of the protein interaction set. For filtering at least three parameters should be considered. Detected protein interactions that can not be reproduced should be discarded. The reproducibility can either be assessed directly from the initial screen, e.g., by screening in quadruplicates, or by conducting an independent retest of initially detected protein interactions. For each prey the number of different interacting baits is calculated. Preys interacting with a significant high number of baits – judged by evaluating the distribution of these numbers – are assumed to interact unspecifically and are neglected ("sticky preys"). The last parameter is the background activation activity of the tested bait. The activation strength of interaction pairs must be significantly higher than with remaining pairs. In principle, at least with the His3p reporter, no activation (no colony growth) should be observed in non-interacting pairs.

Protocol– Retest of protein interactions

Testing for reproducibility of interactions greatly increases the reliability of the interaction data. This protocol is used for specifically retesting interaction pairs detected in an array screen.

Materials required

- 96-well microtiter plates (U- or V- shaped)
- YEPD medium and YEPD agar in Omnitrays (Nunc)
- selective agar plates (-LT, -LTH with 3-AT)
- prey yeast strain carrying empty prey plasmid, e.g. pLP-GADT7 in Y187 strain
- bait and prey strains to be retested

- Bait and prey strains of each interaction pair to be tested are re-arrayed into 96-well microtiter plates. An individual 96-well plate is used for the baits, as well as for the preys. For each retested interaction one well of the bait plate and one corresponding well of the prey plate is filled with 150µl YEPD.
- For each retested interaction the bait strain is inoculated into a well of the 96-well bait plate and the prey strain is inoculated at the corresponding position of the 96-well prey plate. *For example, bait at position B2 of bait plate and prey at position B2 of prey plate.*
- The plates are incubated o/n at 30°C. In addition, the prey strain with the empty prey vector, e.g. strain Y187 with plasmid pLP-GADT7, is inoculated into 50ml YEPD; this strain is incubated o/n in a shaker at 30°C.
- The prepared baits grown in the bait plate are mated with their corresponding preys in the prey plate. In addition, each bait is mated with the prey strain carrying an empty prey vector as a background activation control. The mating is done as described above using the bait and prey 96-well plates directly as the source plates. *First the baits are transferred from their 96-well plate to two YEPD plates (interaction test and control plate) using a 96-well replication tool. After drying the preys are transferred from their 96-well plate onto the first YEPD plate and the empty prey vector control strain is transferred onto the second YEPD plate.*
- The transfers to selective plates and incubations are done as described above. *As usually different baits with different activation strength are tested on a single plate, the diploid cells*

are pinned to LTH plates with different concentrations of 3-AT. For choosing the 3-AT range the measured activation strengths (Protocol "Self activation test") serve as a guideline.

- After incubating for ~1 week at 30°C on –LTH/3-AT plates the interactions are scored. *Positive interactions show a clear colony growth at a certain level of 3-AT, whereas no growth should be seen in the control (bait mated with empty vector strain).*

Co-immunoprecipitation of co-expressed proteins in E. coli (coEXcoIP)

Proteins of *T. pallidum* expressed in *E. coli* often only showed a limited solubility, which reduces the throughput of protein interaction verification experiments. A commonly used strategy for the independent large-scale verification of protein interactions in the eukaryotic environment is the co-immunoprecipitation of proteins co-expressed in tissue culture cells (Uetz et al. 2006). Thus, a similar system for prokaryotic proteins relying on the co-expression in *E. coli* cells was established. The vector selection is crucial for such a system as too high expression levels were found to be detrimental for protein solubility. Vectors of the pBad-series were selected and adapted for the UPS system (Guzman et al. 1995; Liu et al. 1998). These vectors carry promoters regulated by L-arabinose and show a lower well regulated expression level.

Vectors for the coEXcoIP system

pBad33HAloxP – Chloramphenicol resistance, HA-tag, loxP-site, pBad promoter

This vector was created by inserting a HA-tag fused to a loxP site from pTagloxPHA3 (PCR product employing the primers pBad33HA3-loxSacFor and pTagLoxRev) (kindly provided by Prof. Elledge) between the SacI and HindIII sites of pBad33 (Guzman et al. 1995).

pBad24MycloxP – Ampicillin resistance, Myc-tag, loxP-site, pBad promoter

This vector was created by inserting the NcoI/HindIII fragment containing a Myc-tag fused to a loxP-site from pTagloxPMyc3 (kindly provided by Prof. Elledge) between the NcoI and HindIII sites of pBad24.

Material & Buffers

NP-40 lysis buffer	140mM NaCl 5mM $MgCl_2$ 20mM Tris/HCl, pH 7.6 1mM PMSF 1% NP-40
Protein-G-beads (washed)	- prepare 2*30µl / coIP (~15µl resin) - collect beads by centrifugation at 800g for 2min - aspirate with 25-gauge needle - wash 3x with NP-40 buffer (don't vortex) - adjust to n*40µl and store on ice - use 2*40µl for each pulldown

Fusion-protein construction

- Select respective pUni
- Cre recombination :

  - 2µl Miniprep DNA of pUni
  - 100ng destination vector
  - 1µl Cre buffer
  - 0.5µl Cre
  - add 10µl with water

→ 1h at 37°C and 10min at70°C
→ Transformation (TOP10) and Kan^R (pUni) selection

- Check DNA miniprep by RD (buffer : **Promega E)**:
  - pBad33HaloxP : HindIII+SacI (additional band at 2.2kb and 300bp)
  - pBad24MycloxP:
- Sequential co-transformation:
  - In TSS competent DE3 cells (freshly prepared)
  - Select on Kanamycine LB plates
  - Prepare TSS competent cells and do co-transformation (use empty vector as negative control for coIP!)
  - Select on LB plates with Ampicillin&Chloramphenicol

CoIP procedure

- Grow co-transformed DE3 cells o/n in Ampicillin&Chloramphenicol medium (always include co-transformation with empty vector, e.g. Myc vector, as a control)
- Dilute 1:10 in fresh LB Ampicillin&Chloramphenicol
- Incubate to OD=0.6 (~2h) at 37°C
- Induce with 0.2% L-Arabinose
- Incubate for 3h at 30°C
- Collect 1.5ml by centrifugation in Eppendorf tube
- Add 200µl of NP-40 buffer + 0.25mg/ml lysozyme
- Incubate 20min at RT
- Sonicate using bioruptor (7min total, 30s on, 30s off, max power) → **collect 5µl total lysate**
- Centrifugate 20min at max at 4°C
- Collect supernatant → **collect 10µl soluble lysate (2x3µl for SDS-PAGE)**
- Mix 40µl washed beads with soluble supernatant
- Incubate for 20min at 4°C (rotating) → **preclearing**
- Centrifuge and use supernatant
- Add co-IP antibody: 4µl anti-Myc (co-IP and control!) or 3µl anti-HA
- Adjust to 500µl with NP-40 buffer
- Incubate 2h at 4°C
- Add 40µl washed Protein-G beads
- Incubate 2h at 4°C
- Wash 4 times with 1ml NP-40 buffer
- Add 50µl of 2xSDS sample buffer and boil
- Run on SDS-PAGE gel

Fragmentation of TP0981

Fragments of TP0981 were prepared (Fig. 40). The fragments were PCR amplified from the pUni clone of TP0981. For this the following primer pair combination were used: T1 (pUniDfor/981frag@222rev), T2 (981frag@50for/981frag@222rev), T3 (981frag@50for/ pUniDrev), and T4 (981frag@202for/pUniDrev). The PCR products were cloned into the

pUniD vector mediated by XhoI and SacI. Preparation of bait and prey constructs were done according to procedures described for whole library.

Bioinformatical Analysis

General

Protein interaction networks were visualized with the Cytoscape software package (Shannon et al. 2003). Data analysis was done with perl (www.perl.org) and R (R-Development-Core-Team 2004). Statistical analysis was done with R and MS-Excel. Tightly connected clusters in networks were identified with the MCODE algorithm as implemented into the Cytoscape software package (Bader and Hogue 2003). Topological parameters of networks were computed with the NetworkAnalyzer plug-in for Cytoscape (MPI for Informatics, Germany, med.bioinf.mpi-inf.mpg.de/netanalyzer). Network centralities (node degree, centroid value) were calculated with CentiBiN (Junker et al. 2006). Paralogous gene families for *T. pallidum* were downloaded from the TIGR-CMR database (Peterson et al. 2001). Orthologous relationships between genes were taken from the String (von Mering et al. 2005) and MBGD databases (Uchiyama 2003).

Randomization and evaluation

For statistical filtering and significance estimations, the actual protein interaction network was compared to 1,000 randomized versions of this network. For randomization a rewiring algorithm as proposed by Maslov and Sneppen was employed (Maslov and Sneppen 2002). In these "null model" networks, all proteins have the same connectivity (in- and out-degrees of nodes) as in the actual protein network, whereas the identity of the interacting partners of all proteins is entirely randomized. Enrichment compared to the randomized networks was commonly expressed as a Z-score: $Z = \frac{n - < n_{rand} >}{\sigma_{rand}}$ with a particular parameter of the actual network n (e.g., the number of interactions between two functional classes), the average $<n_{rand}>$, and the standard deviation σ_{rand} of this parameter in 1,000 randomized networks.

The interaction dataset filtered for a certain prey count (in-degree) threshold was evaluated by calculating the percentage of interactions supported by bioinformatical association methods as provided by the String database (combined confidence score > 0.4) (von Mering et al. 2005).

Motility dataset randomization

For the motility subset a special randomization procedure was developed. The reason was that at the time of analysis of the motility set, the whole interaction network was not finished. Usually, networks are randomized under conditions where all in and out degrees are conserved. For a limited subset of protein interactions, the rewiring algorithm does not yield reliable results. For example, in the analysis of over-represented GO terms the same number of proteins for each functional class would be retained and the expected over-representation of motility proteins in the motility subset would be the same in the "random" set.

The randomization algorithm developed for limited interaction networks tries to solve this problem, although rewiring of a complete network might still be the better choice.

The following strategy was selected for randomization:

- Retain all proteins of selected functional class, but don't add more proteins of same class
- Retain the in and out degrees of selected class

- Select interacting proteins randomly until all in and out degrees of functional class are saturated

The procedure was as follows:

- Focus on proteins of specific functional class, e.g. KEGG motility proteins.
- Define their in and out degrees
- Remove all edges
- Add random edges until all original in and out degrees are used
- Select protein of selected class and an in or out degree randomly
- Random sample interacting protein from whole genome

Other datasets and orthology

The following interaction studies were considered for comparison: two *E. coli* complex purification studies which were conducted by Arifuzzaman *et al.* and Butland *et al.* (Butland et al. 2005; Arifuzzaman et al. 2006), a partial yeast-two-hybrid interaction map for *Helicobacter pylori* generated by Rain *et al.* (Rain et al. 2001), and a comprehensive yeast-two-hybrid interaction map for *C. jejuni* produced by Parish *et al.* (kindley provided by the Finley group). For complex purification studies both the spoke model and a socio-affinity-index (SAI) model as described by Gavin *et al.* (Gavin et al. 2006) were considered.

Dataset comparisons were based on orthology relationships between genes. Two sources for orthology relationships were chosen: clusters of orthologous groups (Tatusov et al. 2003) from the String database (von Mering et al. 2005) and orthology clusters from the MBGD database (with average alignment coverage > 50%) (Uchiyama 2003).

Connections of functional classes

Functional assignments for proteins were taken from the TIGR/CMR database (TIGR main roles & TIGR subroles) (Peterson et al. 2001) and from the GOA project (automatically generated GO terms) (Camon et al. 2003). GO terms were mapped onto GO slim terms (GO slim terms present in prokaryotic GO subset). Interactions between functional categories were counted. Overrepresentation of a functional link compared to 1000 randomized networks was assessed by calculating a Z-score (see above). Functional links based on at least two Y2H interactions with $Z > 2$ for TIGR roles and $Z > 3$ for GO terms were selected. Note that the filtering procedure is meant to reduce the influence of unspecifically interacting protein categories. However, in a biological network a single interaction can form a significant link between two categories. Thus, no more stringent statistical filtering, e.g. correction for multiple testing or ranking statistics, was applied.

For the motility subset, the analysis was done slightly different. Associations of the class of known motility proteins ("motility") (defined by the KEGG database, www.genome.jp/kegg/) to a certain functional class (TIGR sub role) defined by their protein interactions were evaluated by counting the number of links between these two classes. Known motility proteins were only counted for the class "motility" not for additional classes to prevent artificial links introduced by intra-motility interactions between proteins annotated with more than one functional class. Comparing the percentage of a link in the interaction set to the percentage of the respective functional class in the genome gives a first idea of its over-representation. For a further assessment of the significance of a specific link the number of interactions was compared to a random distribution of 1,000 randomized network (see motility dataset randomization).

Generation of domain centered network

Domain/protein family information for *T. pallidum* proteins was taken from the Pfam database (Bateman et al. 2004). The number of interactions between pairs of domains was counted. Overrepresentation of a domain link compared to 1,000 randomized networks was assessed by calculating a Z-score (see above). Links based on at least two Y2H interactions, which were enriched compared to the randomized networks ($Z > 2$) were selected for visualization. Peptide chain links were defined when two domains were present in the same protein. Predictions of domain links from the InterDom database were integrated (Ng et al. 2003).

Links between genomic locations

Y2H interaction-mediated links between genomic locations covering 20 neighboring genes were analyzed. The number of interactions between two genomic locations was counted (neighboring locations were overlapping and shifted by 5 genes). Overrepresentation of a link compared to 1000 randomized networks was assessed by calculating a Z-score (see above). Links based on at least three Y2H interactions, which were enriched compared to the randomized networks ($Z > 2$) were selected and the number of linking interactions was visualized in a matrix. The underlying interaction pattern for each genomic location link was inspected and a number of links were selected for detailed visualization.

Essential and pathogenicity related genes

Essential genes were predicted for *T. pallidum* based on essential gene datasets for three different species: *E. coli* (Baba et al. 2006), *B. subtilis* (Kobayashi et al. 2003), and *M. genitalium* (Glass et al. 2006). Orthologs as defined by the MBGD database (Uchiyama 2003) of these experimentally defined essential genes were assumed to be essential for *T. pallidum*.

Possible virulence factors (pathogenicity related genes) were defined by Weinstock *et al.* (Weinstock et al. 1998) and divided into six groups: Tpr proteins, hemolysins, regulators, polysaccharide biosynthesis, potential membrane or surface-exposed proteins, and proteins with miscellaneous functions.

Gene expression levels during experimental rabbit infection with *T. pallidum* were measured by Smajs *et al.* (Smajs et al. 2005). Genes with the highest expression levels (TOP 50) were selected.

These datasets were analyzed with respect to graph centrality measures (e.g., node degree and centroid value) and connections to functional protein classes (as described above).

Taxonomy tree & phylogenetic interaction profile

The taxonomy tree was taken from the String database (von Mering et al. 2005) and pruned for the selected species. For species with more than one sequenced strain, only one representive genome was selected. The tree was drawn using Phylodendron (http://iubio.bio.indiana.edu/treeapp/). A subset of filtered Y2H interactions either supported by an association by the String database or overlapping with any interaction dataset (see network comparisons) was selected. Based on COG orthology, for each selected interaction and each selected species the presence of the interacting proteins in the genome was checked. A matrix (species vs. interactions) of these conservation values was defined. The interaction vectors were clustered by complete linkage clustering based on euclidean distance measures (treating interactions with one protein absent and one present as equal) as implemented in the R package (R-Development-Core-Team 2004). In addition, the ratio of the number of interactions that can be predicted for each species to the maximal possible

number of interactions in each species was calculated. For these predictions, the filtered *T. pallidum* dataset was taken as a basis. From this set, a protein interaction was predicted for a species, when orthologs for both interacting proteins were present in this species. Cluster of orthologous groups for these predictions were obtained from the String database (von Mering et al. 2005). The number of predicted interactions was provided by J. Goll.

Annotation of proteins by Guilt-by-association approach

Hypothetical and conserved hypothetical proteins of *T. pallidum* were selected and the connections of each protein to functional categories (GO slim mapping and TIGR sub roles) were analyzed. The fraction of interactions connecting a protein to a specific functional category was calculated. To remove unspecific links -- due to highly abundant or unspecifically interacting categories --, the number of links was compared to a random distribution from 1000 randomized networks. Only links with $Z > 2$ and involving at least 50% (GO slim mapping) or 33% (TIGR sub roles) of the total number of interactions were considered.

2.3. Whole Genome Phenotypic Motility Assay for *Escherichia coli*

A systematic single-gene knockout collection of *Escherichia coli*, the Keio collection (Baba et al. 2006), which contains 3985 individual mutant strains, was tested for reduced motility by a swarming assay. Each gene mutation was tested in two independent strains as provided by the Keio collection. Strains were grown till saturation in LB medium at 37°C and transferred to Omnitrays (Nunc) with swarming agar (LB medium with 0.25% Agar) in a 24 colonies per plate format by pin replication with a Biomek 2000 lab robot (Beckman-Coulter). The swarming diameters of the mutant strains were compared after ~8h incubation at 37°C. The swarming behavior of each mutant was classified as normal, reduced (reduction by at least 50%) or none motile (reduction by at least 90%). Gene mutations with reproducible reduction in both strains were selected for a retest and mutants with reproduced swarming phenotype were selected for the "*E. coli* motility" dataset.

2.4. Individual Gene I: TP0658 – a novel conserved assembly factor for the bacterial flagellum

Expression and purification of GST-658 and GST-yviF

For construction of GST fusions of TP0658 and yviF the UPS recombination system was used (Liu et al. 1998; Liu et al. 2000). The pUni entry clone of TP0658 was selected from the *T. pallidum* ORFeome collection (McKevitt et al. 2003). The yviF gene was PCR-amplified from *B. subtilis* genomic DNA using the primer pair yviF_forward/yviF_reverse and cloned into pUniD/V5-His-TOPO (Invitrogen, Carlsbad, USA) using XhoI and SacI. GST fusions for expression in *E. coli* were created by Cre mediated recombination of the pUni vectors with a GST host vector pMM110 (Liu et al. 1998; Liu et al. 2000; McKevitt et al. 2003). The GST fusions were termed GST-658 and GST-yviF, respectively. These constructs were transformed into *E. coli* BL21/DE3 cells (Novagen, EMD Biosciences, CA, and USA). Overnight cultures of these *E. coli* cells were used to inoculate SB medium containing kanamycine. After incubating to an $OD_{600} = 0.6$ at 37°C, protein expression was induced for 3h at 37°C with 1mM isopropyl p-D-thiogalactopyranoside (IPTG). The cells were collected, lyzed, and the GST fusion proteins were purified with glutathione-sepharose FF matrix (Amersham Biosciences, Freiburg, Germany) using standard procedures.

Overlay assay and peptide competition

Entry clones of *T. pallidum* proteins (in pUniD/V5-His-TOPO vector) were taken from the *T. pallidum* ORFeome collection (McKevitt et al. 2003). The hag and yvzB genes of *Bacillus subtilis* were PCR-amplified from genomic DNA with primer pairs hag_forward/hag_reverse for the hag gene and yvzB_forward/yvzB_reverse for the yvzB gene. Site-directed mutagenesis of hag was done by a PCR based approach. For hag-HA two overlapping PCR products incorporating the mutation were amplified with primer pairs pUniDfor/hagHAreverse and hagHAforward/pUniDrev using pUniD-hag as a template. These products were joined in a second PCR reaction using the primer pair pUniDforward/pUniDreverse. The construct hag-N255A was produced accordingly using primer pairs pUniDforward/hagN255Areverse and hagN255Aforward/pUniDreverse in the first PCR reaction. These PCR products were cloned into pUniD/V5-His-TOPO (Invitrogen, Carlsbad, USA) using XhoI and SacI. HA-tag fusions for expression in *E. coli* were created by Cre-mediated recombination of the pUni vectors with a HA-tag host vector, pHB-HA3.

HA-tagged fusion proteins were expressed in *E. coli* BL21/DE3 cells and the total lysate was electrophoretically separated on a SDS-polyacrylamide gel and transferred onto a PVDF membrane. The membrane was blocked overnight at 4 °C in blocking buffer (5% milk powder in PBS) and then incubated with 25nM purified GST fusion protein or 25nM GST control protein in overlay buffer (1% milk powder and 0.5% Tween in PBS) for 2h at RT. After washing three times with overlay buffer, the membranes were probed with an anti-GST antibody (G1160; Sigma-Aldrich, Germany), and additionally, with an anti-HA antibody (HA.11, Covance Research Products, CA, USA).

The *in vivo* overlay assay using different *B. subtilis* mutants was done alike. Lysates of *B. subtilis* 168 wild type and the given mutant strains were prepared, separated by SDS-PAGE, transferred onto a PVDF membrane and probed with GST-yviF or GST control protein as described above.

For peptide competition HA-tagged flagellin proteins were transferred onto the PVDF membrane. Olaf Zwernemann (Forschungszentrum Karlsruhe) using standard peptide chemistry protocols synthesized the peptides for competition experiments. GST-658 was pre-incubated with the respective concentration of inhibitory peptide (VGLDIAAENLQAAESRIRD) or a control peptide (DRRLADHFCGKIHCG) in overlay buffer for 2h at 4°C. The overlay assay was done as described incubating the membrane with the GST-658/peptide mixtures.

Cloning of flagellin fragments

A pUni vector containing the TP0868 (flagellin) gene was used as PCR template (McKevitt et al. 2003). Specific fragments were PCR-amplified using the following primer pairs: pUniDforward/L_{59}reverse for fragment T1, N_{60}forward/pUniDreverse for fragment T2, N_{60}forward/S_{141}reverse for fragment T3, V_{118}forward/S_{141}reverse for fragment T4, V_{118}forward/pUniDreverse for fragment T5, I_{200}forward/ pUniDreverse for fragment T6, L_{231}forward/pUniDreverse for fragment T7, and N_{60}forward/S_{199}reverse for fragment T8. The PCR products were cloned into pUniD/V5-His-TOPO (Invitrogen, Carlsbad, USA) using XhoI and SacI. HA fusions for expression in *E. coli* were created by Cre-mediated recombination of the pUni vectors with a HA-tag host vector, pHB-HA3. HA-tagged fusion proteins were produced in *E. coli* BL21/DE3 cells. An overlay assay with GST-TP0658 was done as described above.

Epitope mapping by SPOT synthesis

Cellulose membrane-bound peptides were prepared according to standard SPOT synthesis protocols (Rual et al. 2005) using an automated Spot synthesizer (MultiPep, Intavis,

Germany); Fmoc derivatives of amino-acids and further reagents for peptide synthesis were obtained from Novabiochem, Fluka, and Merck. The generated peptide arrays were synthesized on amino-PEG membranes (Intavis, Germany). After activation of the membrane with methanol the membrane-bound peptide arrays were blocked overnight at 4 °C in blocking buffer (5% milk powder in PBS and 0.5% Tween) and then incubated with 25nM purified GST fusion protein or 25nM GST control protein in overlay buffer (1% milk powder and 0.5% Tween in PBS) for 2h at RT. After washing three times with overlay buffer, the membranes were probed with an anti-GST antibody (G1160; Sigma-Aldrich, München, Germany). The membrane was washed three times with overlay buffer and the membrane was incubated for 1 h at RT with POD-labeled anti-mouse mAb (Sigma-Aldrich, München, Germany) in overlay buffer, followed by washing three times with washing buffer (0.5% Tween in PBS). Analysis and quantification of peptide-bound GST proteins were carried out using a chemoluminescence substrate (ECL, Amersham Biosciences, Freiburg, Germany).

For mapping of the C-terminal interaction epitope of TP0658 on TP0868 (FlaB1) the C-terminal amino-acid sequence of TP0868 starting from L_{231} was selected; this sequence was spotted as overlapping 15mer peptides with one amino-acid shifts from the beginning; the membrane was probed with GST-658 and GST as a control.

An alanine scan was done for the TP0658-binding peptide (V_{229}GLDIAAE NLQAAESRIRD$_{247}$) of TP0868 (*Treponema* FliC). Each amino-acid position was systematically replaced by alanine. The peptides were probed with GST-658 and GST as a control.

Deletion of yviF and cloning of rescue plasmid

Deletion of yviF in *B. subtilis* was achieved by phleomycin-cassette integration as described by Fabret *et al.* (Fabret et al. 2002). Briefly, primer pairs yviF_p1/yviF_p2 and yviF_p3/yviF_p4 were used to PCR-amplify the flanking regions of the yviF gene. Phleomycin-cassette DNA was mixed with both PCR products and subjected to a joining PCR reaction using primer pair yviF_p1/yviF_p4. *B. subtilis* 168 Δupp competent cells were transformed and selected for phleomycin resistance. The presence of the phleomycin-cassette at the correct locus in the chromosome was checked by PCR.

The vector pDG-yviF was created by ligation-independent cloning as described in Joseph *et al.* (Joseph et al. 2001). The pUni entry clone of yviF (pUniD-yviF) was recombined with Host vector pHB-HA3. The resulting HA-tagged yviF construct served as template for a PCR reaction with the primer pair pHB-HA3_pDGforward/ pHB-HA3_pDGreverse. The PCR product was, finally, cloned into the vector pDG148-Stu. This plasmid was used for rescue experiments of the ΔyviF strain described above.

Swarming assay

Swarming plates were prepared as LB plates with 0.25% agar. Bacteria were incubated overnight at 37°C in liquid culture and spotted onto the agar. Swarming plates were evaluated after incubating for 10h at 37°C.

Test of yviF mutant for flagellin expression

B.subtilis Δupp (wild type for yviF cassette integration) cells and ΔyviF cells were transformed with empty expression vector, pDG148-Stu, or yviF rescue plasmid, pDG-yviF, and compared. For induction of yviF expression the bacterial cultures were incubated for 3h at 37°C with 1mM IPTG. Cells were harvested and lyzed using standard procedures. Equal amounts of protein as judged by Coomassie staining of a SDS-PAGE gel were loaded. In a Western Blot the cell lysates were probed for the HA-tag (anti-HA antibody HA.11, Covance Research Products, CA, USA) and flagellin (using a GST-yviF overlay, see above).

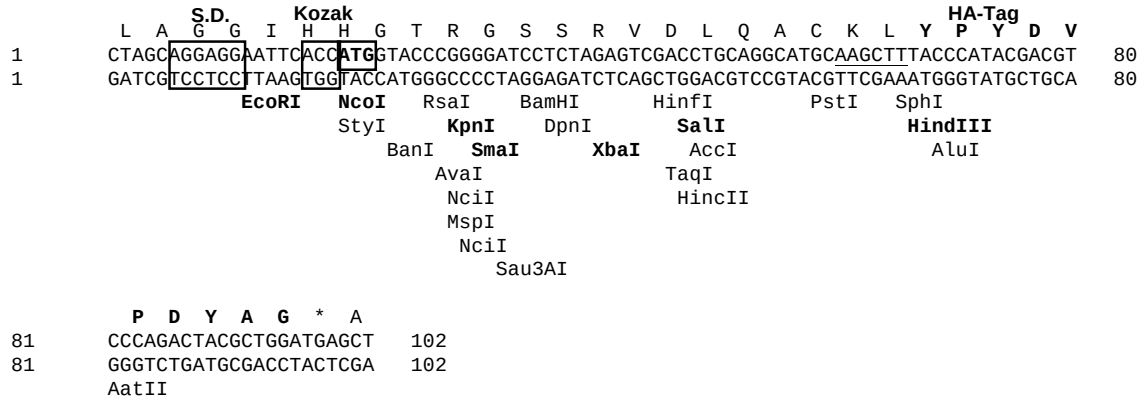
Co-expression of TP0658 and TP0868

TP0658 was PCR-amplified from its pUni clone (McKevitt et al. 2003), pUniD-TP0658, using the primer pair TP0658_pEGSTforward/TP0658_pEGSTreverse. The PCR product was cloned into pEGST (Kholod and Mustelin 2001) using BamHI and XhoI generating a GST fusion of TP0658. TP0868 was PCR-amplified from its pUni clone (McKevitt et al. 2003) using the primer pair TP0868_pAC28forward/ TP0868_pAC28reverse. The PCR product was cloned into pAC28 (Kholod and Mustelin 2001) using BamHI and SacI generating a His-tag fusion of TP0868. *E. coli* BL21/DE3 cells (Novagen) were co-transformed with both plasmids. After overnight incubation at 37°C –relying on the basal level expression of the promoters- the cells were lyzed, proteins separated by SDS-PAGE, blotted, and the blot probed for GST (antibody G1160, Sigma-Aldrich, München, Germany) or His (His probe H-15, Santa Cruz Biotechnology, CA, USA).

2.5. Individual Gene II: YjjG – an *in vivo* house-cleaning nucleotidase

Construction of pBad18HA &pBad24HA vectors

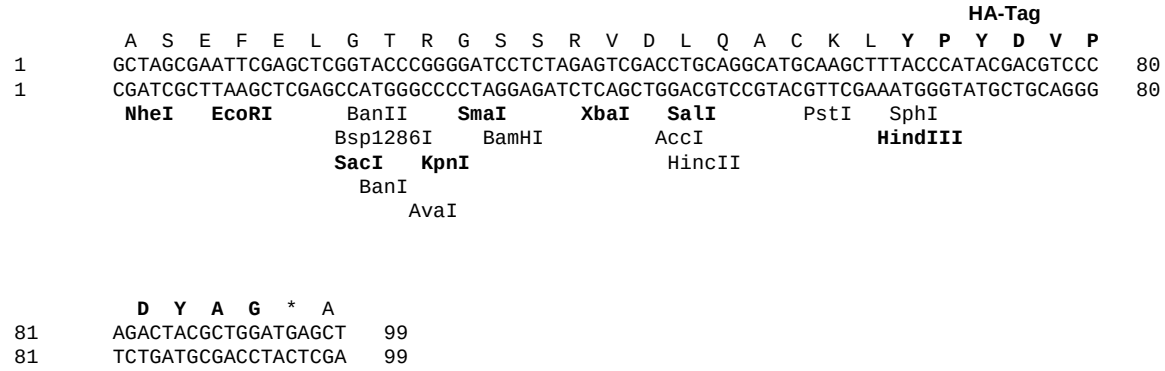
For expression of HA-tagged proteins under the control of an L-arabinose promoter, the pBad24HA vector was constructed. By a DNA cassette mediated approach, a HA-tag (YPYDVPDY) was added to the HindIII site of pBad18 and pBad24 (Guzman et al. 1995). The HA-tag cassette was produced by annealing of oligo 1 (AG CT T TAC CCA TAC GAC GTC CCA GAC TAC GCT GGA TG) and oligo 2 (AGCTCATCCAGCGT AGTCTGGGACGTCGTA TGGGTAA). This strategy retains the HindIII site of both vectors (Fig. 13&Fig. 14).



FEATURES:

- based on pBAD24 (addition of HA tag @ HindIII site)
- pBad promoter
- Amp^r
- pBR322 ori

Fig. 13 Multiple cloning site and features of pBad24HA



FEATURES:

- based on pBAD18 (addition of HA tag @ HindIII site)
- pBad promoter
- Amp^r
- pBR322 ori

Fig. 14 Multiple cloning site and features of pBad18HA

Strains, Gene Cloning, and Protein Purification

Single-gene knockout mutants of *E. coli* were taken from the KEIO Collection (Baba et al. 2006) and tested for 5-fluoro-2'-deoxyuridine sensitivity. For further experiments, the gene inactivation cassette of the *yjjG* mutant was removed by Flp-recombinase-mediated recombination (Datsenko and Wanner 2000).

For complementation of the phenotype, *yjjG* was amplified by PCR from genomic DNA (*E. coli* K-12 BW25113) and cloned into pBad24HA (pBad24 (Guzman et al. 1995) with an HA-tag added at its C-terminus) using EcoRI and HindIII (forward primer: AATT GAATTC ACC ATGAAGTGGGACTGGATTTTC; reverse primer: AATT AAGCTT GTG TTT ACA CAG GAG CTG C). The resulting construct was named pBad24HA-yjjG.

HDHD4, the closest human homolog of YjjG (see below), was PCR amplified from plasmid DNA (kindly provided by E. Van Schaftingen) (Maliekal et al. 2006) and cloned into pBad24HA using NcoI and HindIII (forward primer: AATTCACC ATG GGG CTG AGC CGC GTG C, reverse primer: AATT AAGCTT AGT GGA CAT ACT GAC TTT GC). The resulting construct was named pBad24HA-HDHD4.

For protein expression and purification, *yjjG* was amplified by PCR from genomic DNA and cloned into pETM30 (EMBL-Heidelberg, Protein Expression Facility) using NcoI and HindIII (forward primer: AATTCACC ATG GCC AAGTGGG ACTGGATTTTC; reverse primer: AATT AAGCTT TCA GTG TTT ACA CAG GAG CTG C). The recombinant GST fusion protein was expressed employing *E. coli* (BL21/DE3) and affinity-purified using glutathione-beads (Amersham Biosciences).

Agar-plate based sensitivity screen

The sensitivity of *Escherichia coli* single-gene deletion mutants (Baba et al. 2006) towards 5-fluoro-2'-deoxyuridine was tested using an agar-plate based phenotyping assay. Selected gene mutants (Supplementary Table 21) were arrayed onto a 384-well plate. Saturated cultures of these mutants were inoculated in fresh LB growth medium and incubated for 1h. Cells were transferred to Omnitray plates (Nunc) with LB agar containing 0, 0.1, 0.5, and 1 μM 5-fluoro-2'-deoxyuridine. Growth of mutant colonies was scored after overnight incubation. Liquid

handling and transfer of mutant cultures was done using a Biomek 2000 laboratory robot (Beckman-Coulter).

Nucleotide Metabolism Sensitivity Tests

For confirmation of the 5-fluoro-2'-deoxyuridine phenotype, Δ*yjjG* and the wild type (BW25113) were transformed with pBad24HA and pBad24HA-yjjG. As over-expression of YjjG was found to have a toxic effect, the following experiments relied on basal expression levels. Precultures were diluted to an OD_{600} of 0.01 with and without added 5-fluoro-2'-deoxyuridine and the cell density was measured at OD_{600} in 1h-intervals (ELx808Biotek Instruments, Friedrichshall). The measurement was done in triplicates with 5-fluoro-2'-deoxyuridine concentrations ranging from 0-1,000 μM.

The sensitivity of *ΔyjjG* towards different types of nucleobase and nucleotide derivates was tested using untransformed strains.

In vivo BrdU Incorporation

The *yjjG* mutant strain and the wild type (*E. coli* K-12 BW25113) strain were tested directly as well as transformed with pBad24HA (vector control) and pBad24HA-yjjG (YjjG expression plasmid). The strains were inoculated in LB medium at an OD_{600} of 0.05; for transformed strains 0.2% L-arabinose was added to the medium. After 2h of incubation at 37°C, the cultures were checked for an equal OD_{600}, and bromodeoxyuridine (BrdU) was added to the medium (10μM for untransformed strains and varying concentrations for the transformed strains). The cells were incubated for 2.5h at 37°C and total DNA was isolated using standard procedures. The DNA concentrations were adjusted to equal levels. The DNA was denatured by incubation with 0.5M NaOH for 20min at 42°C and 2μl were spotted onto a Hybond-N+ membrane (Amersham Biosciences). After drying the DNA was UV crosslinked (Stratalinker, Stratagene). BrdU incorporation was measured by usual Western Blot procedures with anti-BrdU-peroxidase (POD) (1:1000, Roche). Blocking, incubation and washing was done with 1% (w/v) BSA and 1% (w/v) milk powder in PBS. A chemiluminescence-based detection with ECL substrate (Amersham Biosciences) was used.

In vitro *Enzymatic Assay*

Nucleotidase activity towards thymidine monophosphate (dTMP) and 5-fluoro-2'-deoxyuridine monophosphate (5-FdUMP) was measured in 400μl reaction buffer (50mM Tris/HCl, pH=7.5; 5mM $MgCl_2$; 0.5mM $MnCl_2$) with 0.25μg purified GST-YjjG and substrates at concentrations of 0-1,500 μM. After 20-30 min at 37°C the reaction was terminated and the free P_i concentration measured using 100μl Malachite reagent (Baykov et al. 1988). One unit of activity is defined as 1 μmol P_i/min.

3. Results

3.1. Overview

The following part is split into two major subdivisions: "Transcriptional Activators of Yeast" and the "Protein-Interaction Map of *T. pallidum*". The first section deals with a more extended characterization of the properties of the Y2H-system used in this study, and exemplifies, how biological knowledge can be gained by an in detail analysis of Y2H high-throughput datasets. The second section, the "Interaction Map of *T. pallidum*" presents the main topic of this thesis: the complete protein-interaction map of *T. pallidum* is generated, analyzed, and an in detail functional characterization based on these protein interactions is shown.

3.2. Transcriptional Activators of Yeast

> Results of this section were published in the paper "Transcriptional activators in yeast" in Nucleic Acids Research (Titz et al. 2006b).

Transcriptional activators are composed of at least two domains, a DNA-binding domain and an activation domain. Whereas the properties of several DNA-binding domains are well understood and patterns for these domains can easily be identified on the primary structure level, only rough ideas about the requirements of transcriptional activation domains exist (see introduction).

In Y2H studies a subset of bait fusion proteins, Gal4-DBD fusion proteins, activate transcription of a reporter gene without requirement of a prey protein. These proteins are called "auto-activators" (or activators for short) and thereby possess properties of an activation domain.

These activators are commonly identified in the course of large-scale Y2H studies, because high self-activation levels of proteins prevent their screening in the Y2H assay. Thus, genome-wide two-hybrid screens provide data about activation properties of nearly all proteins of a genome. Of special interest in this respect are Y2H screens of yeast proteins as the proteins are tested in their natural species context. Still, by design such screens do not necessarily identify physiological activators as the fusion partners are artificially targeted to the promoter of a single, arbitrarily selected reporter gene.

Here, Y2H auto-activators from two large-scale screens are selected, their activation strength is measured, and their properties are analyzed in detail.

Y2H Activators and their Activation Strength

Datasets on self-activation properties of bait constructs from two large-scale Y2H studies of yeast proteins were taken as the basis. These consisted of about 450 Y2H activators which were not listed in the original publications and provided by P. Uetz and T. Ito (Supplementary Table 1) (Uetz et al. 2000; Ito et al. 2001). The activation strength of the activators was measured using two different reporter genes, whose expression depends on their level of transcription: His3 and beta-galactosidase (bGal assay) (Fig. 15, Supplementary Table 1). According to the activation strength in the LTH assay the activators were grouped into weak (3-25 mM 3-AT), medium (50-200 mM 3-AT) and strong (>200 mM 3-AT) activators. These groups were termed LTHw, LTHm and LTHs, respectively. The bGal assay distribution was divided into strong activators (bGalS) which activate above the median and weak activators that activate below the median (bGalW).

protein set	description
all yeast	all yeast proteins
non acts	all yeast proteins not in the activator list
TR	known transcriptional activators (GO slim term "transcription activator activity")
all acts	all Y2H activators
nucleus	nuclear proteins (Huh et al.)
acts nucleus	Y2H activators localized to the nucleus
LTHw, LTHm, LTHs	Weak (LTHw), medium (LTHm), and strong (LTHs) activators in LTH assay
TR+1, nucleus+1, acts nucleus+1	Protein sets as indicated above but including bridging proteins in the analysis of binary protein interactions.

Table 8 Definition of datasets for analysis of activators.

A comparison of activation strength in both assays revealed an intermediate (Pearson's correlation coefficient of 0.58) but highly significant correlation ($p<2.2e^{-16}$) of activation values (Fig. 15 B). Although the Gal1 promoter drives both reporters, the lacZ reporter is actually present in two copies with two different promoters (a GAL7 promoter in PJ69-4a and a GAL1 promoter in YULH). It was not tried to determine the contribution of each of the two lacZ genes and the following analysis is restricted to the His3 data.

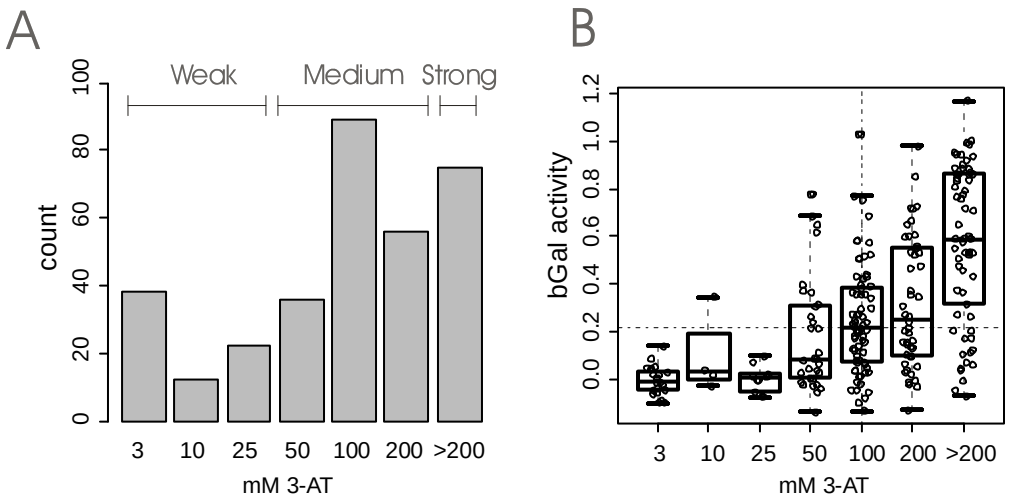


Fig. 15 Activation strength in Y2H activators. (a) Number of activators showing the indicated activation strength in the LTH assay. They were divided into weak (LTHw), medium (LTHm) and strong (LTHs) activators as indicated. (b) Correlation of activation strength in LTH and bGal assays. The actually measured values are shown as dots, the median and two quartiles by an overlayed boxplot. Dotted lines indicate the median of bGal activity and LTH activity, respectively. See Table 8 for an explanation of data sets. Figures published in the paper "Transcriptional activators in yeast" in Nucleic Acids Research (Titz et al. 2006b).

In summary, 72 weak, 179 medium, and 75 strong transcriptional activators were identified in these experiments (Supplementary Table 1).

Function, Localization, and Abundance of Activators

Previous studies have identified several unspecific properties of proteins that lead to transcriptional activation, e.g. acidic stretches or glutamine-rich regions (Sadowski et al. 1988; Courey et al. 1989; Kunzler et al. 1994). On the other hand, known transcriptional regulators seem to be transcription activators also under Y2H settings. Therefore, the annotated function, localization and abundance of Y2H activators were analyzed.

First, over-represented GO terms in the set of Y2H activators were assessed with the FuncAssociate program (Berriz et al. 2003). This indicated a clear over-representation of GO terms associated with a role in transcription and localization in the nucleus. Interestingly, the highest-ranking GO attribute was "transcription regulator activity" (GO 0030528) with 92 occurrences among the 451 activators (Table 9).

Rank	N	X	LOD	P	P-adj	GO Attribute
1	92	319	0.816	5.7e-35	<0.001	0030528: transcription regulator activity
2	105	461	0.684	3.4e-30	<0.001	0006350: transcription
3	95	429	0.657	3.5e-26	<0.001	0006351: transcription, DNA-dependent
4	72	265	0.759	1.9e-25	<0.001	0006366: transcription from Pol II promoter
5	47	123	0.959	8.9e-24	<0.001	0003702: RNA polymerase II transcription factor activity
6	233	1940	0.430	1.9e-23	<0.001	0005634: nucleus
7	83	426	0.573	5.4e-19	<0.001	0050789: regulation of biological process/regulation
8	29	62	1.095	6e-18	<0.001	0016251: general RNA polymerase II transcription factor activity
9	87	516	0.494	9.3e-16	<0.001	0007049: cell cycle/cell-division cycle
10	60	283	0.602	1.4e-15	<0.001	0005654: nucleoplasm

Table 9 Functional groups among Y2H activators. GO terms in the set of Y2H activators were compared to the whole yeast genome using the program FuncAssociate (Berriz et al. 2003). GO terms are ranked according to the significance of their overrepresentation in this dataset. See http://llama.med.harvard.edu/cgi/func/funcassociate for technical details. Rank = position in the attribute list ranked by significance of association, N= number of genes in your query with this attribute, X = number of genes overall with this attribute, LOD = the natural log of the odds ratio; positive and negative values indicate over- and under representation, respectively, P = single hypothesis one-sided P-value of the association between attribute and query (based on Fisher's Exact Test), P-adj = adjusted P-value: fraction (as a %) of 1000 null-hypothesis simulations having attributes with this single-hypothesis P value or smaller.

Transcription activity was significantly correlated with activation strength: 27% of all strong activators are annotated to have "transcription regulatory activity" (Fig. 16 A) whereas this annotation drops to 21% and 7% of the medium and weak activators, respectively. These numbers are significantly higher than for the Y2H non-activators (~ 3%). As an additional reference set, we selected 138 proteins annotated to possess "transcriptional activator activity" in the YPD database. Only 55 (or 12%) of the Y2H activators were annotated as transcriptional activators in YPD. This annotation correlated with the activational strength: 19% of strong, 16% of medium, and 4% of weak activators were annotated with this term. This suggests that many more proteins may act as transcriptional activators than currently known.

The intracellular localization of activators was analyzed using the large-scale localization study by Huh et al. (Huh et al. 2003). Compared to 22% of nuclear localized non-activators, nuclear proteins were highly over-represented in the activator set (41%) (Fig. 16 B). The activation strength correlated with nuclear localization, for example, the percentage of nuclear localization increased by 12% when the weak LTH activators were compared with the strong ones. The percentage of strong activators in the nucleus was lower than the value of 67% found for known transcriptional activators (GO annotation "transcription regulator activity"). However, even when the known transcription regulators were excluded from the analysis, nuclear proteins were still over-represented in the activator set (33% vs. 20%) (not shown in figure). As certain properties of proteins, e.g. the isoelectric point depend on the localization, the protein sets of nuclear localized activators and the nuclear non-activators was commonly included as references in further analyses.

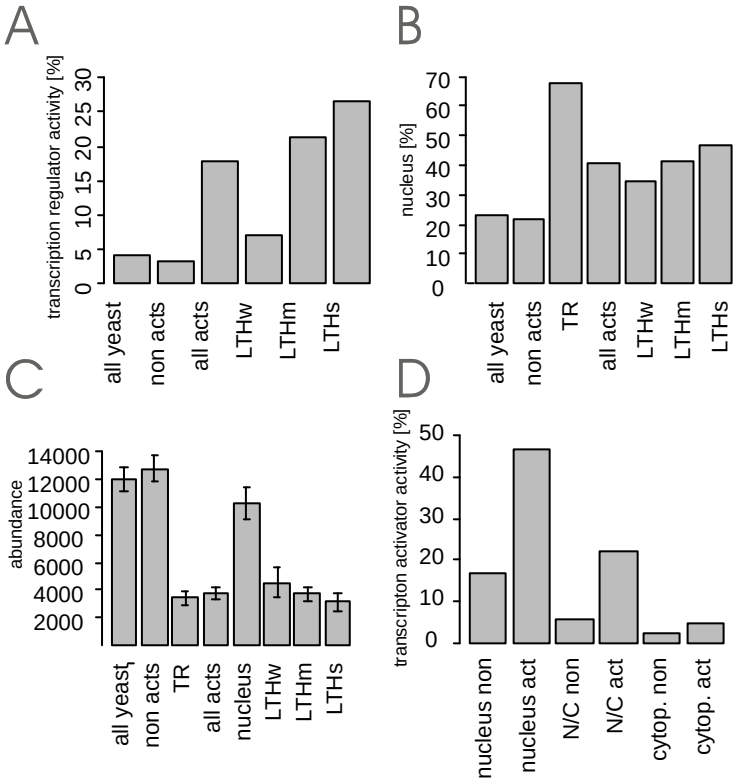


Fig. 16 Function, localization and abundance of yeast activators. (a) Percentage of proteins annotated to have „transcriptional regulator activity" (GO term, see also Supplementary Table 1). (b) Percentage of protein localized to the nucleus as analyzed by Huh et al. 2003. (c) Abundance of proteins as analyzed by Ghaemmaghami et al. 2003. (d) The percentage of proteins annotated as transcriptional regulators (F-GO term „transcription regulator activity) in different cellular compartments is compared. These sets are: non activators (non) and activators (act) localized only to the nucleus (nucleus), only to the cytoplasm (cytop.) or to both the nucleus and the cytoplasm (N/C). Figures published as "Transcriptional activators in yeast" in Nucleic Acids Research (Titz et al. 2006b).

Combining GO function and localization revealed a significant overrepresentation of known transcriptional regulators in the sets of activators in the nucleus as well as in the set of nuclear and cytoplasmatic localized proteins, but not in the set of only cytoplasmaticaly-localized proteins (Fig. 16 D). Strikingly, 47% of nuclear Y2H activators were known transcriptional regulators. This number points to the fact that an overwhelming fraction of these activators carries the biological function of transcriptional regulation. As a large fraction of activator

proteins have no assigned function (~35%) this finding can be used for functional annotation of these proteins (see below).

Ghaemmaghami et al. (Ghaemmaghami et al. 2003) measured the protein abundance in yeast at a genome-wide scale. A comparison of protein copy numbers revealed a significant lower concentration of activators (Fig. 16 C). Interestingly, known transcription regulators were also expressed at lower levels, once more, indicating similar properties of known transcriptional regulators and Y2H activators.

Taken together, yeast-two-hybrid activators tend to be proteins with a described function in transcription, a nuclear localization, and less abundance. Interestingly, similar trends are observed for known transcription regulators.

Physicochemical Properties of Y2H Activators

Although characteristics such as abundance and localization allow us to classify activators, they do not explain their behavior. In fact, it has been unclear which properties turn a protein into a transcriptional activator even though certain physicochemical properties such as acidic stretches have been identified (Sadowski et al. 1988). We therefore revisited the influence of physicochemical properties on the propensity of a protein to activate transcription.

Well defined general properties were analyzed first (Fig. 17). These were the isoelectric point (Fig. 17 A), molecular mass (Fig. 17 B), overall hydrophobicity (GRAVY score) (Fig. 17 C), and aromaticity (Fig. 17 D). The most pronounced effect was found for the isoelectic point: the mean pI for activators was ~1.5 pH units below the value for non activators. This effect was also observed for activators in the nucleus, although with ~0.5 pH units the difference between nuclear localized activators and nuclear proteins in general was lower. Interestingly, known transcriptional regulators had only a slightly reduced mean pI, which was even higher than for nuclear proteins in general. The influence of activation strength onto the mean pI was not significant (judged by Student's t-test).

The mean molecular weight of activators was ~9 kDa higher than for non-activators. This tendency is also reflected by the higher mean molecular weight of known transcriptional regulators. Activators in the nucleus showed a slightly higher mean molecular weight compared to nuclear localized proteins and the mean molecular weight increased with activation strength.

The overall hydrophobicity (GRAVY score) and the aromaticity showed the same pattern. Both properties were reduced in activators as well as in known transcriptional regulators. The effect was much smaller but at least for the GRAVY score highly significant (Student's t-test $p=2.4e-5$) for nuclear localized proteins and activators.

In addition, the codon adaptation index (CAI) was analyzed. As lower codon scores are associated with lower protein expression levels (Ghaemmaghami et al. 2003), the lower CAI for activators as well as for known transcriptional regulators underlines the previous finding of lower protein levels for these two protein sets (Fig. 17 E).

Interestingly, known transcriptional regulators showed the same tendency for all properties except for the isoelectric point.

For a further refinement, we analyzed more specific physicochemical properties. These included the overrepresentation of certain amino-acids or amino-acid classes, the occurrence of stretches of charged, acidic and basic residues and clusters of certain amino-acids. As many of these properties are highly influenced by the localization, we only took activators in the nucleus into account and compared them to the remaining nuclear proteins. After correction for multiple testing using Holm's procedure (Holm 1979), 15 parameters remained highly significant. These included the minimum pI in a 20 aa window, the overall percentage of several amino-acids (Ala, Gly, Ser, Val, Lys, Asn, Gln) and amino-acid clusters (Ser, Asp,

Pro, Asn, Gln). An in detail analysis of the amino-acid clusters and the minimum pI is shown in Fig. 17.

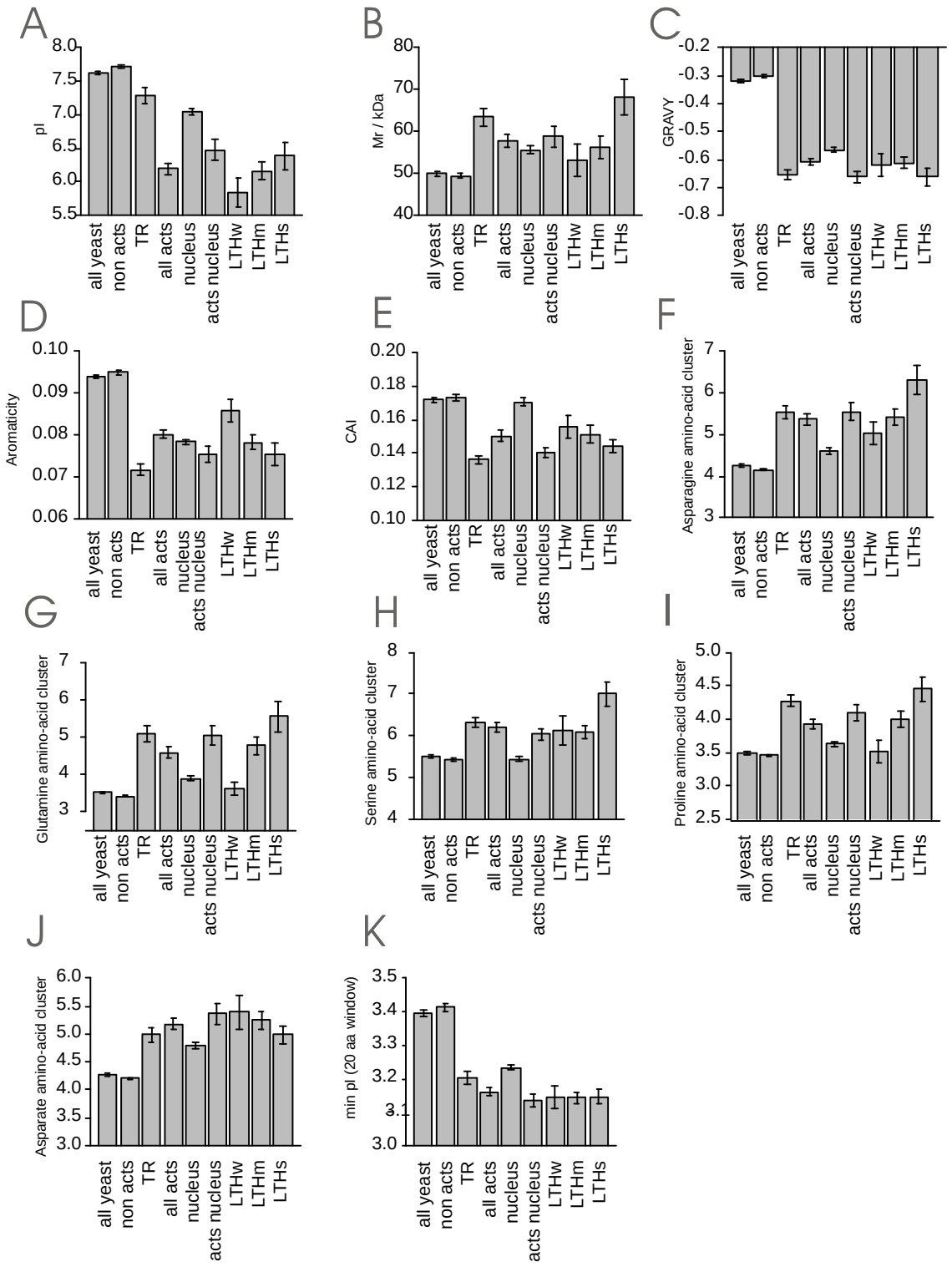


Fig. 17 Physicochemical properties of activators. Mean and SEM of physicochemical properties is shown for several protein sets. (a) isoelectric point (pI), (b) molecular mass (Mr), (c) GRAVY score (overall hydrophobicity), (d) aromaticity and (e) codon adaptation index (CAI). (f,g,h,i,j) amino-acid clusters indicating the maximum number of the respective amino-acid in a window of 20 amino-acids of the protein. (k) Minimum isoelectric point (pI) of a protein in 20 amino-acids window. Figures published in the paper "Transcriptional activators in yeast" in Nucleic Acids Research (Titz et al. 2006b).

Taken together, the analysis of physicochemical properties showed that activators tend to possess a lower isoelectric point, have a lower hydrophobicity, higher molecular weight, lower codon adaptation index and show specific properties like enrichment of asparagine clusters.

Protein Domains

Transcriptional activation domains are still not well defined structurally. This is also reflected in specialized domain databases such as SMART (Letunic et al. 2004) or Interpro (Mulder et al. 2005) which have hardly any defined entries for transcriptional activation domains. Therefore, we have analyzed the Y2H activators for enrichment of known domains. As expected, certain DNA-binding domains such as helix-loop-helix motifs or zinc fingers are indeed significantly overrepresented among the activators (Table 10).

Certain domains are also significantly underrepresented such as the AAA domain. However, these domains are not considered here.

Domain	Description	#	enrich-ment	significance level
HLH	helix loop helix domain	6	6,64	**
ZnF_C2C2	C2C2 Zinc finger	4	8,85	**
GAL4	GAL4-like Zn(II)2Cys6 (or C6 zinc) binuclear cluster DNA-binding domain	16	2,53	*
RPOL9	RNA polymerase subunit 9	3	8,85	*
ZnF_C2H2	zinc finger	13	2,30	*
ZnF_C2HC	zinc finger	5	4,02	*
IBR	In Between Ring fingers	2	8,85	*
BRLZ	basic region leucine zipper	5	2,95	*
ArfGap	Putative GTP-ase activating proteins for the small GTPase, ARF	3	4,43	*
PP2C_SIG	Sigma factor PP2C-like phosphatases	3	4,43	*
STYKc	Protein kinase; unclassified specificity.	10	2,06	*
CNH	Domain found in NIK1-like kinases, mouse citron and yeast ROM1, ROM2	2	5,90	*
Cu_FIST	Copper-Fist	2	5,90	*
S_TK_X	Extension to Ser/Thr-type protein kinases	4	2,95	*
PP2Ac	Protein phosphatase 2A homologues, catalytic domain.	4	2,95	*

Table 10 Domains of Y2H activators. Domains over-represented in the Y2H activator set ranked by their significance are shown. The number of Y2H activators containing the domain (#) and enrichment of this domain in the set of Y2H activators compared to the whole genome are shown. The significance level indicates significant over-representation using Fisher's exact test only ($P<0.05$, *) or also after correction for multiple testing using Holm's procedure ($P<0.05$, **).

Specific Transcriptional Activation by Interaction with the Transcription Machinery

Specific transcription activation is mediated by physical contact with the transcriptional machinery or other factors necessary for transcription, like chromatin remodeling proteins (Stringer et al. 1990; Ingles et al. 1991; Goodrich et al. 1993; Ptashne and Gann 1997; Koh et al. 1998; Neely et al. 1999).

Activators form a tightly connected protein interaction network (Fig. 18 A). Therefore, we identified proteins with direct physical contact to the transcription machinery employing the MIPS (Mewes et al. 2004) physical protein-protein interaction dataset (Fig. 18 B).

ORF	%	% ratio	Definition	Description	P	P_{adj}
YDL140C	17,7	3,8	RNA polymerase II core subunit	RNA polymerase II large subunit	4,95E-09	1,02E-05
YOL086C	17,7	2,9	alcohol dehydrogenase	Adh protein catalyzes activities for the production of certain carboxylate esters.	1,29E-06	2,63E-03
YGL112C	16,0	4,5	TATA-binding protein-associated-factor	Subunit (60 kDa) of TFIID and SAGA complexes, involved in transcription initiation of RNA polymerase II and in chromatin modification, similar to histone H4	1,53E-09	3,17E-06
YBR081C	15,5	4,7	histone acetyltransferase SAGA complex member|transcription factor	Subunit of the SAGA transcriptional regulatory complex, involved in proper assembly of the complex; also present as a C-terminally truncated form in the SLIK/SALSA transcriptional regulatory complex	1,75E-09	3,61E-06
YML007W	14,4	8,0	jun-like transcription factor	bZip transcription factor required for oxidative stress tolerance and localized to the nucleus in response to the presence of oxidants.	2,52E-12	5,22E-09
YGR252W	14,4	6,5	histone acetyltransferase	functions in the Ada and SAGA (Spt/Ada) complexes to acetylate nucleosomal histones	4,63E-11	9,60E-08
YDR448W	13,8	6,1	transcription factor	transcription factor, member of ADA and SAGA, two transcriptional adaptor/HAT (histone acetyltransferase)complexes	3,36E-10	6,95E-07
YNL236W	13,8	5,7	RNA polymerase II holoenzyme/mediator subunit	involved in positive and negative regulation of transcription, possibly via changes in chromatin structure; regulation of YGP1 expression	8,88E-10	1,84E-06
YOR174W	13,8	3,4	RNA polymerase II holoenzyme/mediator subunit	Member of RNA Polymerase II transcriptional regulation mediator	1,72E-06	3,51E-03
YHR174W	10,5	3,9	enolase	Enolase II, catalyzes the first common step of glycolysis and gluconeogenesis; expression is induced in response to glucose	6,61E-06	1,35E-02
YHR147C	9,4	8,0		Mitochondrial ribosomal protein of the large subunit	2,11E-08	4,36E-05
YNL025C	9,4	4,0	C-type cyclin|associates with the Ssn3p cyclin-dependent kinase	Component of RNA polymerase II holoenzyme, involved in RNA pol II carboxy-terminal domain phosphorylation. Activity of the kinase (SSN3)/cyclin (SSN8) pair required, along with SSN6 & TUP1, for transcriptional repression of a-specific genes	1,84E-05	3,73E-02
YBR198C	8,8	4,3		Subunit (90 kDa) of TFIID and SAGA complexes, involved in RNA polymerase II transcription initiation and in chromatin modification	1,53E-05	3,12E-02
YKL060C	8,8	4,3	aldolase	Fructose 1,6-bisphosphate adolase, required for glycolysis and gluconeogenesis	1,53E-05	3,12E-02
YGL025C	8,3	9,6		Probable transcription factor, polyglutamine domain protein	3,43E-08	7,09E-05

YBR253W	8,3	9,6	part of Srb/Mediator complex|transcription factor	involved in transcription as part of Srb/Mediator complex	3,43E-08	7,09E-05
YHR058C	8,3	9,6		RNA polymerase II transcriptional regulation mediator	3,43E-08	7,09E-05
YER022W	8,3	9,6	RNA polymerase II holoenzyme/mediator subunit	subunit of RNA polymerase II holoenzyme/mediator complex	3,43E-08	7,09E-05
YPL042C	8,3	8,8	cyclin (SSN8)-dependent serine/threonine protein kinase	Component of RNA polymerase II holoenzyme, involved in RNA pol II carboxy-terminal domain phosphorylation. Activity of the kinase (SSN3)/cyclin (SSN8) pair required, along with SSN6 & TUP1, for transcriptional repression of a-specific genes	6,89E-08	1,42E-04
YCR081W	8,3	8,8		activation mediator subcomplex of RNA polymerase I holoenzyme	6,89E-08	1,42E-04

Table 11 Proteins co-occurring in protein complexes with nuclear activators. Proteins significantly overrepresented in protein complexes with nuclear Y2H activators (N=181) are shown. The list is sorted by the percentage of nuclear Y2H activators found to be in at least one protein complex with the respective ORF. For example, the large subunit of RNA polymerase II, YDL140C, was found in a complex with 17.7% of all nuclear Y2H activators. The percent % ratio is the previous percentage divided by the percentage of nuclear non-activators (in other words: the % ratio is the enrichment compared to nuclear non-activators). A significant co-occurrence was assessed using Fisher's exact test comparing the set of nuclear Y2H activators with nuclear non-activators (P). The P value was adjusted (Padj) for multiple testing using Holm's procedure (Holm 1979). Only the top 20 significance list ranked by percentage is shown.

Significantly more nuclear Y2H activators (~36%) interacted with components of the transcription machinery compared to other nuclear proteins (~23%). The same is true for known transcription activators, which show an even higher fraction of proteins interacting with the transcription machinery (~46%). Considering bridging proteins (looking for transcription proteins that can be reached over two protein-interaction edges), even increases the number of interacting transcription proteins to ~57% (nuclear activators) and ~64% (transcription regulators), respectively. The activation strength showed no effect on the number of proteins interacting with the transcription machinery. However, one needs to point out that the overall false negative rate of protein-protein interactions is still quite high. Therefore, it cannot be excluded that many explanatory protein links are still missing. In addition, one needs to take into account that the MIPS dataset is biased towards well characterized proteins probably leading to an overrepresentation of known links between described transcriptional regulators and the transcription machinery.

To analyze a less biased dataset, we considered the interactions found in large scale MS studies (Gavin et al. 2002; Ho et al. 2002; Mewes et al. 2004). For each protein set, we checked how many proteins interacted with a protein complex involved in transcription (at least 50% proteins annotated as transcription) (Fig. 18 C). 19% of nuclear activators interacted with transcription complexes compared to 8% of nuclear proteins. An even higher fraction (27%) if known transcriptional regulators interacted with complexes involved in transcription. Strikingly, activators in the nucleus that were not annotated as transcriptional regulators showed a significant higher number of interactions with the transcription machinery compared to other nuclear non transcriptional regulator proteins. This might indicate that many of these proteins are also biological relevant transcriptional regulators (see below). Once more, the high false negative rate of interaction studies is, most probably, the reason for the overall low percentages. Assuming that all known transcriptional regulators should interact with the transcription machinery gives a false negative rate of 73%. Applying

this rate to the interactions of nuclear activators, we would expect that ~70% of them could interact with the transcription machinery.

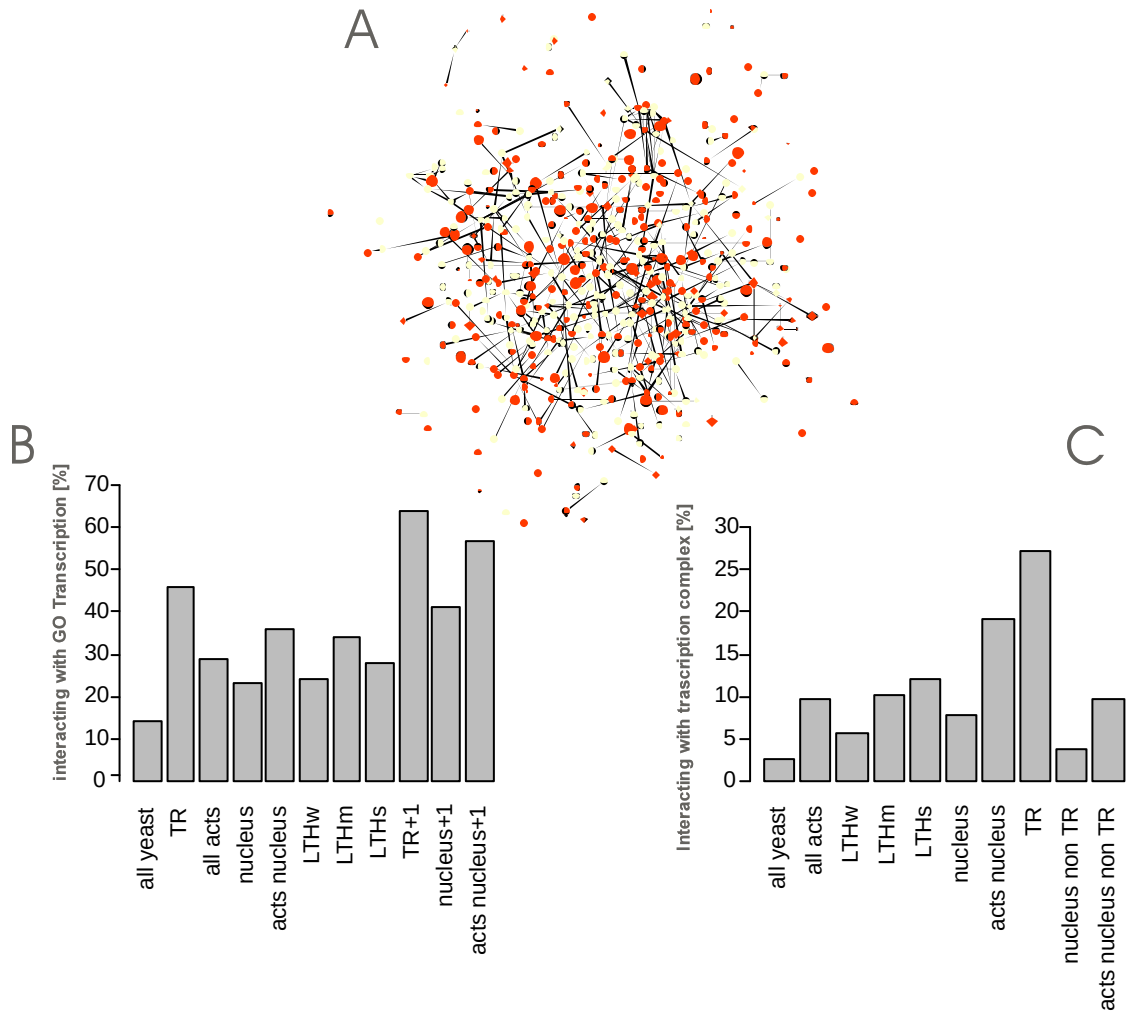


Fig. 18 Interactions of transcription activators. (a) This protein interaction network shows the activators (red) and the proteins interacting with at least two activators. Proteins involved in transcription are indicated by a diamond shape and the activation strength (bGal and LTH combined) is reflected by the node size. (b) For indicated protein sets (table 1) the percentage of proteins interacting with a protein involved in transcription (P-GO term „transcription“) is shown. Physical, binary protein interaction data from the MIPS database (Mewes et al. 2004) was used. Direct interactions or interactions involving a bridging protein (indicated by „+1“ interaction) were taken into account. (c) Percentage of proteins from a given protein set (table 1) interacting with a protein complex involved in transcription is shown. Only high-throughput derived protein complex data from the MIPS database (Mewes et al. 2004) was considered. Figures published in the paper “Transcriptional activators in yeast” in Nucleic Acids Research (Titz et al. 2006b).

To reveal the nature of proteins interacting with transcriptional activators we ranked each interacting protein according to the number of interacting proteins in the query set. Proteins showing the highest number of interactions with nuclear transcription activators are shown in Table 11. This analysis reveals that a high percentage of activators, as well as known transcriptional regulators interact with components required for transcription. These were components of the RNA-Polymerase II holoenzyme and proteins involved in chromosome remodeling, like the SAGA complex. In contrast, nuclear proteins in general do not show this clear tendency whereas even 19% of the nuclear activators not known to be

transcriptional regulators interacted with RNA polymerase II. Interestingly, both nuclear activators and transcription regulators interacted with the metabolic enzyme alcohol dehydrogenase. With 17.7% and 19%, respectively, the fractions were much higher than in the set of nuclear proteins (~10%, not shown). However, the relevance of the interactions needs to be further evaluated.
All in all, activators and known transcriptional regulators tend to specifically interact with components of the transcription machinery.

Y2H Activators as Genuine Transcriptional Regulators

Many of the Y2H activators described here may be bona fide transcriptional regulators even if they have not been annotated as such. We therefore may have identified Y2H activators of yet unknown function given their ability to activate transcription efficiently, their nuclear localization, and their protein-interaction pattern with other components of the transcription machinery. The following Y2H activators of yet unknown function are predicted to be physiological activators.
YFL049W, a protein with no assigned function, was co–purified with Rtt102p, Snf2p, and Snf5p indicating that it is a real Swi/Snf component (Defeu Soufo and Graumann 2005). The yeast SWI/SNF complex is required for transcription of several yeast genes and has been shown to alter nucleosome structure in an ATP-dependent reaction. Transcription stimulation by SWI/SNF requires an activation domain with which it directly interacts. Strikingly, the acidic activation domains of VP16, Gcn4, Swi5, and Hap4 interacted directly with the purified SWI/SNF complex and with the SWI/SNF complex in whole-cell extracts (Neely et al. 1999). A physical interaction of YFL049W with the SWI/SNF complex together with the strong transcription activation properties (strong Y2H activator) strongly supports the possible transcription stimulation function involving the SWI/SNF complex.
YJR070C is both localized to the nucleus and the cytoplasm. Nucleic acid binding proteins are overrepresented in its set of genetic and physical interaction partners. As it is known to bind eIF5 (Krogan et al. 2006) it might have regulatory functions involving translation in the cytoplasm and transcription in the nucleus.
YDR520C, also localized to the cytoplasm and the nucleus, was shown to bind a zinc finger-containing transcriptional repressor, Dal80 (Ito et al. 2001), suggesting the interesting hypothesis that Dal80 is repressing the activator properties of YDR520C.
YGL066W/SGF73, a protein with unknown molecular function, was identified as a novel subunit of the SAGA (Spt/Ada/Gcn5 acetylase) multisubunit complex (Sanders et al. 2002). Ataxin-7 is the human ortholog of the yeast SAGA SGF73 subunit and is a bona fide subunit of the human TFTC-like transcriptional complexes (TATA-binding protein-free TAF-containing complex) (Helmlinger et al. 2004)**.** The physical association of YGL0066W with the TFTC transcription complex and its activation properties supports a role in transcriptional regulation function.
A profiles/patterns analysis of **YKR064W** revealed the presence of a Zn[2]-Cys[6] fungal-type binuclear cluster domain in the N-terminal region. This domain binds to DNA and is also found in ArgR2p, a component of the ARGR transcription regulatory complex (ArgR1p, ArgR2p, ArgR3p, Mcm1p) (This domain already leads to the annotation as transcription factor in the YPD database) (Amar et al. 2000). A search in the eMOTIF database (Huang and Brutlag 2001) reveals a "fungal transcriptional regulatory protein" motif (the eMotif search tool is also available in SGD). Together with the strong transcriptional activation properties of YKR064W, this finding indicates a true transcriptional regulation and activator function of YKR064W relying on its DNA-binding as well as its activation domain, probably involving the ARGR transcription regulatory complex.

YCR082w (= Ahc2) is a protein localized in the nucleus as well as in the cytoplasm without known function. It was identified as a strong activator in this study and is known to interact with chromatin reorganization components like a histone acetyltransferase complex (Ahc1) (Uetz et al. 2000) and Abf1, a DNA binding protein involved in chromatin-reorganisation (Venditti et al. 1994). In addition, YCR082w interacts with a transcription factor, Srb4, a subunit of the RNA polymerase II mediator complex (Ito et al. 2001).

ORF	Name	LTH Class	Biological Process (GO)	Localization	Interaction with transcription machinery	Additional evidence
YFL049W	YFL049W	Medium	unknown	Nucleus	Yes	Yes
YJR070C	YJR070C	Medium	unknown	Cytoplasm, Nucleus	No	Yes
YDR520C	YDR520C	Strong	unknown	Cytoplasm, Nucleus	Yes	Yes
YGL066W	SGF73	Medium	Protein modification	Nucleus	Yes	No
YKR064W	YKR064W	Medium	unknown	Cytoplasm, Nucleus	No	Yes
YCR082W	YCR082W	Medium	unknown	Cytoplasm, Nucleus	Yes	No

Table 12 Potential physiological transcription activators.

3.3. The Protein-Interaction Map of *Treponema pallidum*

This section contains the main topic of this thesis, the analysis of the whole *T. pallidum* protein-interaction network. For this, almost all possible pair-wise combinations of proteins of the proteome of *T. pallidum* are tested for a protein interaction. This map reveals biological insights on different levels ranging from topological properties, over functional classes/complexes, to individual proteins. Finally, detailed studies shed light on the molecular function of two proteins.

Protein Interactions of Bacteria

Several large-scale protein-interaction studies have been conducted mainly for eukaryotes (see introduction), but bacteria only recently became a focus for the comprehensive analysis of protein-protein interactions. To assess the number and characteristics of known bacterial protein-protein interactions, the BIND database (Bader et al. 2001) was employed. BIND is a comprehensive source for known protein-protein interactions: curators of BIND enter data from low throughput studies, all major high throughput studies are incorporated, and data from other interaction databases such as DIP (Salwinski et al. 2004) is imported.
In August 2006, the BIND database contained ~11,000 records for bacterial proteins representing 8066 non-redundant interactions (Table 13).
An overview of the used methods, the analyzed proteins, and the species in the BIND database is shown in Table 14. Most of the interactions stored in the BIND database are based on the determination of the three-dimensional structure of a co-crystal. The method ranking second is the yeast-two-hybrid system, but this number is mainly based on a single large-scale study conducted by Rain *et al* (Rain et al. 2001). The top ranking protein is VirB10, a component of the type-IV-secretion system, which was focus of recent protein-interaction studies. *Escherichia coli*, the bacterial model organism, is still on the top rank, but due to one large-scale study *H. pylori* is already found on the second position. Please note that co-affinity-purification/mass spectrometry (coAP/MS) studies are not considered.

		Bacteria	*E. coli*	*B. subtilis*	*H. pylori*
# non redundant interactions		8066	1637	226	1479
Homodimers		1262	392	55	68
# distinct proteins		8014	1991	299	761
methods[1]	**LTP**	178	121	2	-
	Y2H	1747	52	-	1456
	3D prediction	5625	1477	209	21

Table 13 BIND Database - known protein-interactions for bacteria. LTP identifies interactions found by classical small-scale (low-throughput, less than 40 interaction per paper) experiments, Y2H the number of yeast-two-hybrid interactions, and „3D prediction" denotes interactions derived from three-dimensional structures of proteins. The dataset was downloaded in August 2006. [1]Note: The sum over all methods and the total number of non redundant interactions is not comparable due to redundancy and missing values in used methods.

To identify tightly connected clusters in the set of known bacterial interactions, the MCODE algorithm was employed (Bader and Hogue 2003): 127 protein complexes were identified. These complexes include the well-characterized DNA polymerase and the ribosome, the RNA polymerase, and metabolic enzyme complexes like histidine decarboxylase.
However, the most striking point is the low number of protein-interactions derived from small-scale studies in the BIND database (178 interactions). Only a small fraction of the

original literature on protein-interactions in bacteria is included. Thus, a comparison of the interactions presented in this study with published protein-interactions needs to wait for a more comprehensive protein-interaction dataset. However, manual curation of bacterial protein interactions is in process now.

Proteins		Methods		Species	
#	name (gi)	#		#	
65	VirB10 28262059	5625	three-dimensional-structure	1637	*Escherichia coli*
55	HP1409 15645054	1747	two-hybrid-test	1479	*Helicobacter pylori*
51	HP0336 15644964	56	other	436	*Thermus thermophilus*
46	flgB 15646166	47	affinity-chromatography	227	*Thermotoga maritima*
43	HP0849 15645468	16	gel-retardation-assays	226	*Bacillus subtilis*
33	HP0879 15645498	12	gel-filtration-chromatography	207	*Mycobacterium tuberculosis*
32	rpoB 15645812	11	immunoprecipitation	154	*Haemophilus influenzae*
30	Photosynthetic Reaction Center Protein H Chain 46447	11	cross-linking	144	*Pseudomonas aeruginosa*
28	HP1259 15645873	8	far-western	125	*Salmonella typhimurium*
27	VirD4 28262057	5	elisa	116	*Rickettsia sibirica*

Table 14 Top 10 lists for known bacterial interactions from the BIND database

Setup of the Y2H Procedure

The analysis of the *T. pallidum* protein-interaction network relied on an array-based Y2H system. All ORFs of the genome need to be cloned, preferentially, into a versatile vector system. The set of cloned ORFs is the so-called ORFeome. Baits (DNA-binding domain fusions) and preys (activation domain fusions) of these ORFs are prepared, transformed into yeast cells, and all bait/prey combinations are systematically tested for a protein interaction.

Bait Strain Construction

The baits were cloned by Cre-recombinase mediated recombination of the *Treponema pallidum* ORFeome into the selected bait vector.
Bait vector selection is a crucial issue in Y2H studies as slight modifications of the vector can lead to differences in the obtained results. For example, for construction of the pAS2.1 vector, Clontech (USA) removed the HA-tag of pAS2 and exchanged a single glutamine to valine. These slight modifications eliminated the autonomous activation activity of pAS2 (assayed in Y187 strain using the lacZ reporter).
As no experience with bait vectors for the employed Cre-mediated cloning system (UPS) was at hand in our lab, two possible bait vectors were compared before starting large-scale cloning: the pAS1-loxP vector, which is based on pAS2.1 (Clontech) (vector "pAS1") and the pLP-GBK-Amp vector (vector "pGBK").
The pLP-GBK-Amp vector was created by exchanging Kan^R by Amp^R in pLP-GBKT7 (Clontech) (see Material & Methods). The reason for selection of a 2nd bait vector was a) that this type of vector was established to work with the employed prey vector, pLP-GADT7 (Clontech), and b) that this bait/prey vector combination has proven to work well in a screen of Gateway-system cloned ORFs (Uetz et al. 2006).

To test and compare these bait vectors, a set of 57 genes mainly belonging to the flagellum subset (see below) were cloned into both vectors and compared. With the "pAS1" vector, 191 interactions were recovered after specificity filtering (see below or Materials & Methods); the "pGBK" vector recovered only 99 filtered interactions (Fig. 19). For both sets the percentage of interactions supported by the String database (von Mering et al. 2005)– a database storing predicted associations between genes – was calculated. With 10% and 8% for the pAS1 and pGBK vector, respectively, the support was similar indicating a similar interaction quality for both vectors.
For baits with interactions for both vectors (filtered set), ~50% (15 out of 31) had overlapping interactions with both vectors. The number of overlapping interactions ranged from one to five and covered a percentage range from 5-100%. For baits without overlapping interactions in nearly all cases (15 out of 16) at least one of the bait vectors recovered only a single interaction. This clearly implies, that the high false-negative rate in the Y2H system (see introduction) is the main reason for the observed limited overlap. Table 15 shows interactions recovered with both bait vectors.

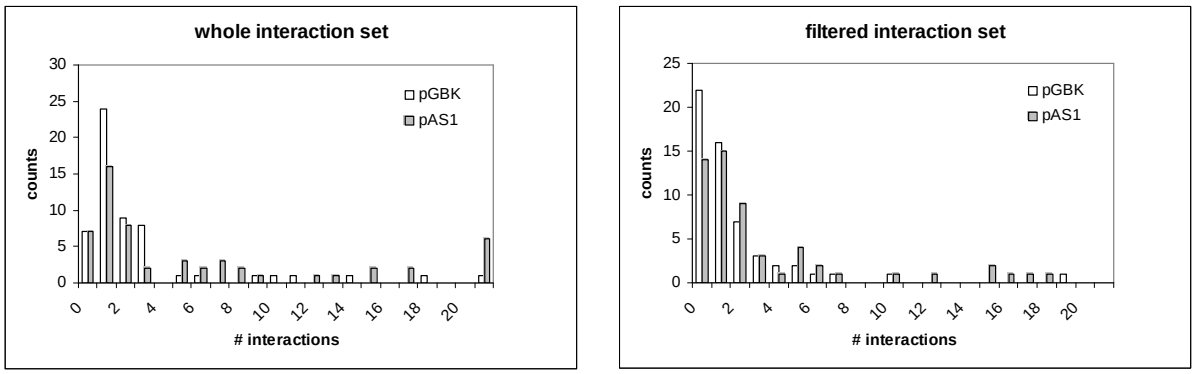


Fig. 19 Comparison of pAS1 and pGBK. Number of interactions identified with each bait vector. The number of bait constructs yielding a certain number of interactions is given (counts).

bait	description	prey	description
TP0058	replicative DNA helicase (dnaB)	TP0001	chromosomal replication initiator protein (dnaA)
TP0058	replicative DNA helicase (dnaB)	TP0005	DNA gyrase, subunit A (gyrA)
TP0058	replicative DNA helicase (dnaB)	TP0046	hypothetical protein
TP0058	replicative DNA helicase (dnaB)	TP0066	hypothetical protein
TP0058	replicative DNA helicase (dnaB)	TP0896	hypothetical protein
TP0100	thioredoxin, putative	TP0832	hypothetical protein
TP0271	chromosome partitioning protein (parB)	TP0586	leucyl-tRNA synthetase (leuS)
TP0387	cell division protein (ftsW)	TP0561	conserved hypothetical protein
TP0387	cell division protein (ftsW)	TP0917	Mg2+ transport protein (mgtE)
TP0400	flagellar motor switch protein (fliG)	TP0014	hypothetical protein
TP0400	flagellar motor switch protein (fliG)	TP0066	hypothetical protein

TP0400	flagellar motor switch protein (fliG)	TP0209	ribosomal protein L36 (rpmJ)
TP0492	DNA primase (dnaE)	TP0197	ribosomal protein L29 (rpmC)
TP0567	conserved hypothetical protein	TP0421	conserved hypothetical protein
TP0567	conserved hypothetical protein	TP0917	Mg2+ transport protein (mgtE)
TP0631	protein-glutamate methylesterase (cheB)	TP0832	hypothetical protein
TP0716	flagellar biosynthetic protein (fliR)	TP0917	Mg2+ transport protein (mgtE)
TP0717	flagellar biosynthetic protein (fliQ)	TP0561	conserved hypothetical protein
TP0717	flagellar biosynthetic protein (fliQ)	TP0917	Mg2+ transport protein (mgtE)
TP0725	flagellar motor rotation protein (motA)	TP0917	Mg2+ transport protein (mgtE)
TP0763	hypothetical protein	TP0917	Mg2+ transport protein (mgtE)
TP0870	flagellar filament 31 kDa core protein (flaB3)	TP0396	flagellar basal-body rod protein (flgB)
TP0870	flagellar filament 31 kDa core protein (flaB3)	TP0658	transmembrane protein, putative
TP0870	flagellar filament 31 kDa core protein (flaB3)	TP0832	hypothetical protein
TP0870	flagellar filament 31 kDa core protein (flaB3)	TP0873	hypothetical protein
TP0870	flagellar filament 31 kDa core protein (flaB3)	TP0943	flagellar protein (fliS)
TP0959	hypothetical protein	TP0260	hypothetical protein
TP0959	hypothetical protein	TP0832	hypothetical protein
TP0981	sensory transduction histidine kinase, putative	TP0396	flagellar basal-body rod protein (flgB)
TP0981	sensory transduction histidine kinase, putative	TP0832	hypothetical protein
TP0981	sensory transduction histidine kinase, putative	TP1005	DNA polymerase III, subunits gamma and tau (dnaH)

Table 15 Interactions from filtered *T. pallidum* set identified with pAS1-loxP and pLP-GBK-Amp bait constructs.

Judged by the support by the String database, both vectors showed a similar interaction quality, but the pAS1 vector recovered a larger number of interactions. Since the false-negative rate is a major concern in Y2H studies, the pAS1 vector was selected for bait constructs of the remaining ORFs.

Prey Library Construction

The prey library was created by Cre-mediated recombination of the *T. pallidum* ORFeome (McKevitt et al. 2003) with the Y2H prey vector, pLP-GADT7 (Clontech). The prey strains (prey constructs transformed into Y187 yeast cells) were arranged onto eleven 96-well plates. Either these plates were quadruplicated onto 384-well plates, or two of these 96-well plates were duplicated and combined on one 384-well plate (6 plates for whole prey array). About 20% of the screenings were done with the quadruplicated prey array (11 plates); the remaining baits were screened against the duplicated array (6 plates) with the purpose to increase throughput.

LIMS

High-throughput studies heavily rely on the informatics infrastructure. Several thousand cloning events need to be tracked, verification experiments linked to gene constructs, storage positions remembered, yeast-two-hybrid experiments scheduled, and finally raw results entered and evaluated.

Software systems handling these diverse data types and supporting experimental procedures in the lab are so-called laboratory-information-management-systems (LIMS). Several commercial LIMS exist including Starlims (Starlims Corporation, USA) and SQL*LIMS (Applied Biosystems, USA). These powerful systems support workflows on the industrial scale.

On the other hand, more and more freely available LIMS for specific scientific procedures become available. These include systems for genotyping, structure determination, and microarray analysis (Maurer et al. 2005; Monnier et al. 2005; Amin et al. 2006; Baran et al. 2006; Jayashree et al. 2006).

No particular system for the Y2H workflow is freely available. Thus, a LIMS was set up, which supports all steps of the Y2H-procedure including the cloning process and the storage of Y2H results (Fig. 20). This system was based on a database management system (DBMS), the FileMaker software (FileMaker, USA), which provides a relational database framework and tools to set up specific database schemes and programmable user-interfaces. The programming language perl (www.perl.org) extended the functionality of this system.

A relational database scheme for this LIMS was developed following standard guidelines (Kandzia and Klein 1993). Fig. 20 A shows the database scheme. The database can be divided into a section storing information about ORFs (general gene properties, sequences, structural features), a section storing information for gene constructs (vectors data, verification experiments, storage information), and a section storing the Y2H results. Each of these sections consists of several tables, which are connected to each other. The table "gene construct" is the central element of the database and can exemplify the connectivity of this relational database scheme. Each record of this table represents an individual gene construct, e.g. protein TP0658 cloned into bait vector pLP-GBKT7-Amp. It stores the name of the construct, information about the cloning procedure, and information about the author and the creation date. Each record is linked to one vector and one ORF, which unambiguously defines the cloned construct (for fragments, start and end positions can be defined or ORF fragments can be added to the database). In addition, a gene construct has been verified using one or more verification experiments such as restriction digests, PCR reactions and sequencing runs ("verification" table). A gene construct is stored at a specific position, e.g. in "bait plate 1" at position A1, which is stored in the linked "storage position" table. Finally, bait and prey constructs are transformed into yeast and tested for interactions, which is captured by the link to the interaction section of the scheme.

The graphical user interface supports data look-up and data entry (Fig. 20 B) and perl scripts have been developed to support more extended data handling, e.g. prediction of restriction patterns, cloning a whole plate to a new vector, and extracting the overall status for a list of genes.

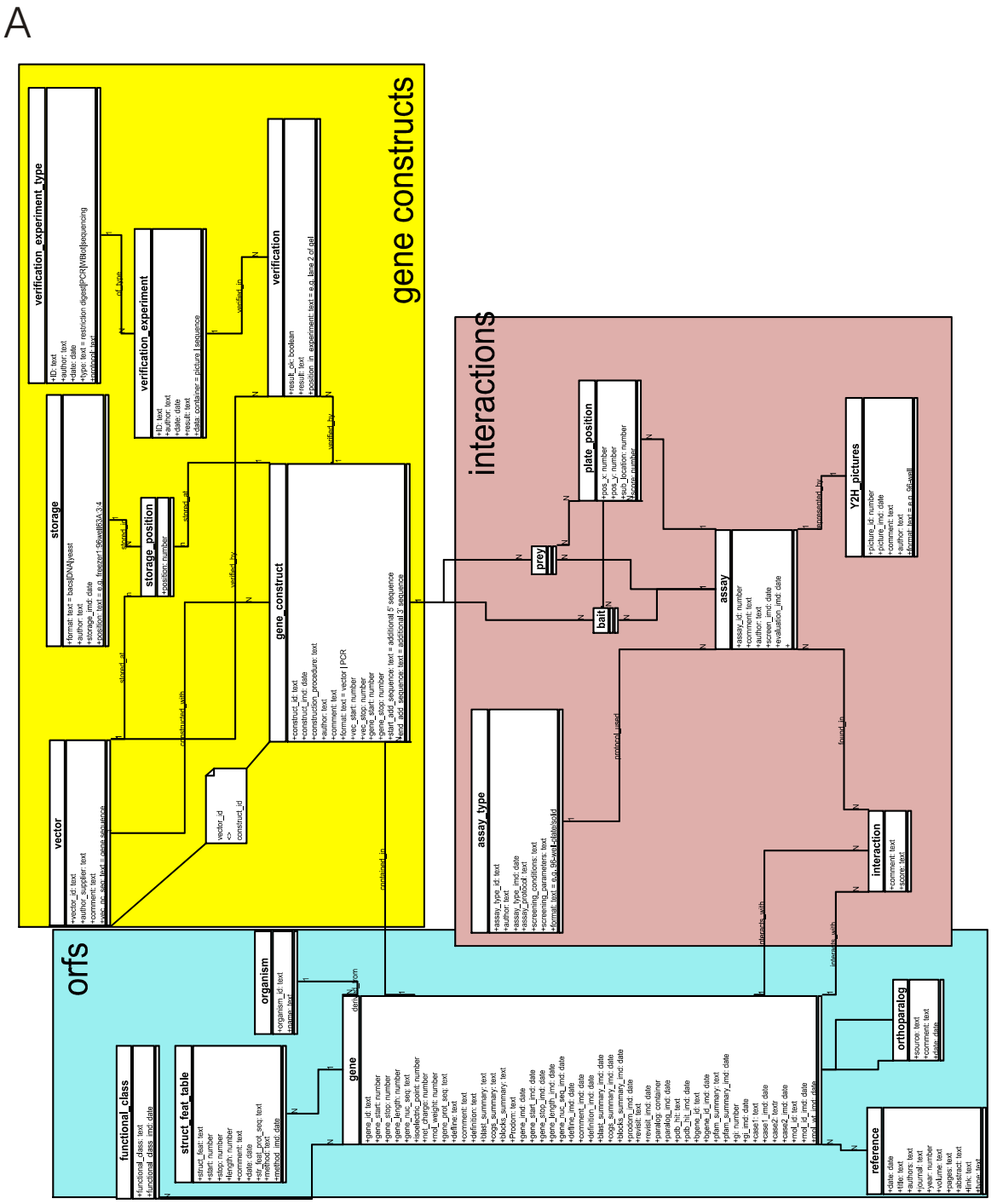
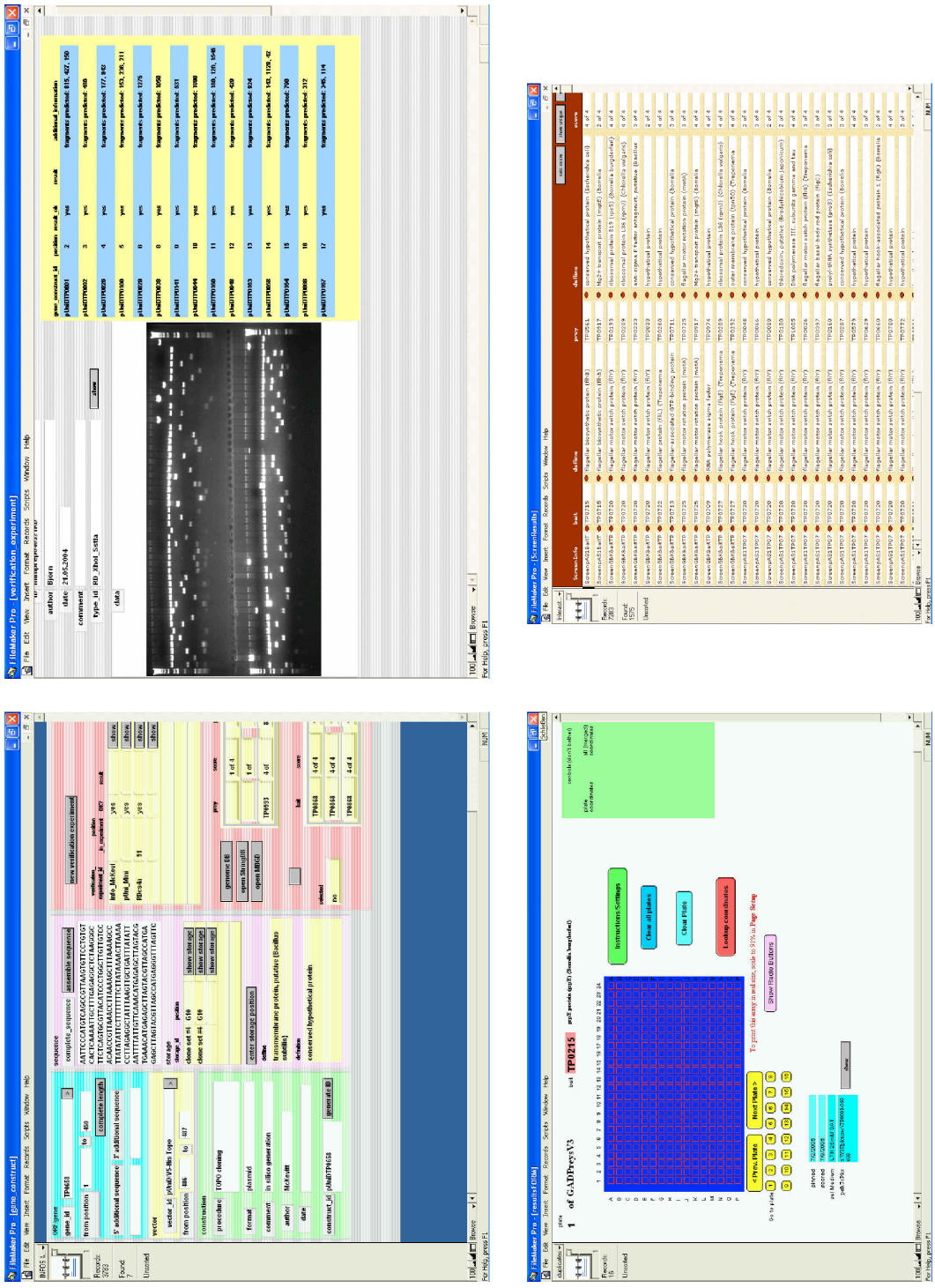


Fig. 20 LIMS for the *T. pallidum* interaction project. (A) Database scheme with tables dedicated to ORFs (blue), gene constructs (yellow), and interactions (purple). (**continued…**)

B



(…continued) (B) Examples for the graphical user interface (GUI). Several information for an individual gene construct are stored (left upper panel), verification experiments are linked to the gene constructs (right upper panel), interactions are entered via a special entry form (left lower panel), and a list of all interactions is stored (right lower panel). Refer to PDF version for details.

During the course of this project, the established LIMS proved to be well suited to store all relevant information including the links between different types of data. The graphical user interface, however, has room for improvements. The main disadvantage in this respect is the heterologous setup integrating external perl scripts for large-scale data manipulation. For

future projects, we plan to migrate the LIMS to the most recent version of the FileMaker DBMS.

Establishment of a Pooling Strategy

The array-based Y2H system has a quadratic dependency of hand-on time and the amount of resources – plates, media and incubator space- on the number of tested proteins; the screening of a small bacterial genome like *T. pallidum* with ~1,000 ORFs requires 100 times more time and resources than a viral genome, e.g. KSHV with ~100 ORFs (Uetz et al. 2006). The actual time heavily depends on the robotic equipment, e.g., in our laboratory a single Biomek 2000 (Beckman Coulter) robot is sufficient for testing about 50 baits per week against a bacterial genome of 1000 ORFs or all 100 proteins of a viral genome against each other. The screening effort can be reduced by lowering the number of repetitions: testing of each interaction pair in quadruplicates is preferred, however, for larger projects (>200 proteins) testing in duplicates is advisable. Alternatively, an increase of the array's colony density, e.g., from 384 to 768 colonies per plate, is an option, although, this approach requires a higher precision of the robot and can reduce the number of detected interactions, e.g. due to a smaller number of transferred cells.

A completely different screening strategy, the pooling strategy, has the potential to accelerate screening significantly, but might also have the disadvantage to increase the number of false negatives. In the first step, sets of proteins (pools, rather than single proteins) are tested for interactions against each other. In the second step, these interacting protein sets are selected and the proteins in this set are individually tested for their binary interactions (as in the classical array based Y2H strategy). Depending on the pool size, the first level of screening is very fast and, as only a few interactions are expected for each protein, only a few pools need to be tested for binary interactions in the second step. Such a pooling strategy was established by Zhong *et al.* (Zhong et al. 2003). Pools of prey proteins were tested against single bait proteins and it was shown that the pools can contain 96 or even more proteins. The authors calculate that the Y2H array screening of the whole yeast genome (~6,000 proteins) requires only 1/24 of time and effort when using the proposed pooling strategy.

In this thesis, initial results and the crucial steps for adapting a pooling strategy for the specific Y2H procedure used in our lab are presented.

For establishing of the pooling strategy, baits with a known interaction pattern were tested and the mating and transfer of cells were controlled by colony counting. Pools of several prey strains rather than bait strains were created. Bait strains commonly show different levels of autonomous activation of the reporter constructs, which hampers the combination of different baits in one screen. A small subset of preys is commonly found to undergo unspecific interactions with many bait strains ("sticky-preys"); these were removed from the prey array before pooling.

The following procedure was established. Prey strains were grown in individual wells of 96-well plates until saturation. Preys from corresponding positions, e.g. A03, of all *T. pallidum* prey plates (11 plates) were mixed and 100µl aliquots were transferred to fresh 96-well plates ("prey pooling plates"); glycerol was added to these plates with 96 pools of 11 prey strains (whole *T. pallidum* prey array) and the plates were stored at -80°C. Freezing did not affect the number of living prey cells at the day of mating. A day before mating, one prey-pooling plate was thawed, 100µl YEPD added and incubated overnight. For mating, the saturated prey-pooling plate was quadruplicated onto a solid-agar YEPD plate with thick replication pins. The number of transferred prey cells was found to be crucial for mating efficiency. A single bait strain from a saturated culture was pinned on top of the preys employing a thick-pin 384-well replication tool. For mating the plates were incubated for one day at 30°C; increasing the incubation time to two days did not increase the number of diploid cells. Transfer of a sufficient number of diploids to –LT plates was found to be crucial: only ~150 diploids were transferred with the standard replication procedure with thick pins; a higher

number of transferred cells (~500, ~3x more) could be obtained by changing the pinning procedure: a swirling step on the source and the destination plate was included. This procedure was also employed for the transfer to –LTH plates.
Based on the tested baits, this procedure proved to work in principle. Strong interactions such as the interaction between TP0974 and TP0709 (see below) were reproduced in every attempt. However, in total only about 20-50% of the interactions found in the individual tests were reproduced with the pooling scheme. This seems to be in agreement with observations from another project: Parish *et al.* (*pers. comm.*) retested interactions found in the *T. pallidum* screen and found that ~50 out of ~170 interactions were reproduced that were not detected by their pooling protocol.
Due to the high number of undetected interactions in the pooling strategy, the *T. pallidum* network was generated without pooling. However, for larger genomes the use of a pooling strategy will be essential. In this thesis, the crucial steps for such a pooling scheme have been identified. Note that one reason for the low number of reproduced interactions might be the overall low activation level seen with the UPS yeast-two-hybrid vectors (or the *T. pallidum* ORFs compared with results from viral screens (Uetz et al. 2006)). Thus, for a project based on Gateway-based Y2H vectors, pGBKT7-DEST and pGADT7-DEST, the presented pooling scheme can yield a sufficient number of detected interactions.

Screening Results – General

For analyzing the protein-protein interaction network of *T. pallidum*, individual bait fusions were tested in an array-based Y2H test against the whole *T. pallidum* prey array. 920 out of 1039 proteins were tested as baits (~90%). The remaining baits could not be tested, mainly due to lack of correct entry clones; a summary of tested baits is given in Table 16.

category	number of baits
possible baits	1039
correct bait constructs	~920
screened baits	920
baits with interactions	606
baits with reliable interactions[1]	423

Table 16 Bait Summary. [1]Interactions retained in a filtered interaction set.

category	number of preys
possible preys	1039
correct prey constructs	~1000
prey with interactions	357
preys with reliable interactions[1]	338

Table 17 Prey Summary. [1]Interactions retained in a filtered interaction set.

For most of the baits the screening was done in duplicates; each prey was arrayed twice on the prey array to check for reproducibility of the interactions. Interactions only detected in a single test were retested (the corresponding bait and prey were selected and individually tested for an interaction). Interactions reproduced either directly on the prey array or by the retest were considered.

A common source for false positive interactions are "sticky" preys, which unspecifically interact with a large number of bait fusions. The array-based Y2H-system allows for removing these potential false positive interactions by selecting a certain "prey count" cut-off – the "prey count" is defined as the number of distinct baits a given prey is interacting with. The distribution of "prey counts" is shown in Fig. 27. To define the prey count cut-off, the percentage of interactions supported by the String database – a database of bioinformatical associations between genes – and the percentage of interactions with identical functional classes were calculated for each cut-off value (Fig. 21). For further analysis, a "prey count" cut-off of 50 was selected. This cut-off is far beyond the maximum of 285 and corresponds to a reasonable percentage of 5% of the proteome (and tested baits). In addition, the selected subset of interactions incorporates the major fraction of interactions supported by the comparisons in Fig. 21. However, several interactions with high support are excluded by this cut-off, e.g. 14 interactions with TP0961 as a prey, which are supported by a high String database score (peak at interaction 2263 in Fig. 21). Thus, the interested reader is free to choose an own cut-off when analyzing the reported data.

In total, 3,649 reproducible protein interactions were detected (Table 18). The selected cut-off yielded 1,633 reliable interactions linking 601 (~60% of genome) proteins in the whole proteome *T. pallidum* screen (Table 18).

category	number of interactions	number of linked proteins
total	3649	726
with prey count <51	1633	601
with prey count <41	1451	570
with prey count <21	970	515

Table 18 Summary Y2H interactions

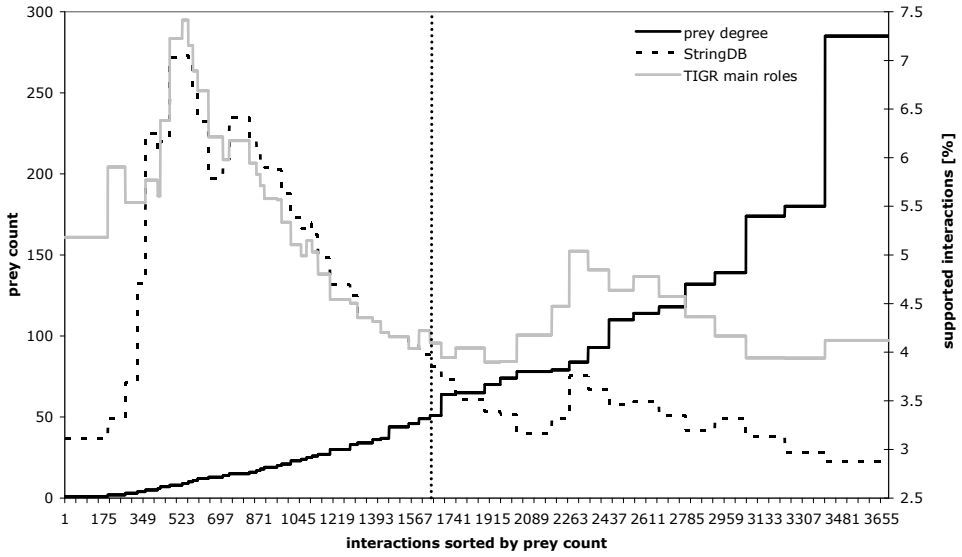


Fig. 21 Selection of prey count cut-off. All interactions below a given prey count (prey degree) were selected and the percentage of interactions supported by the String database (von Mering et al. 2005) (with medium confidence, String score >=0.4) or for which both interacting proteins showed the same main role (TIGR classification) was calculated.

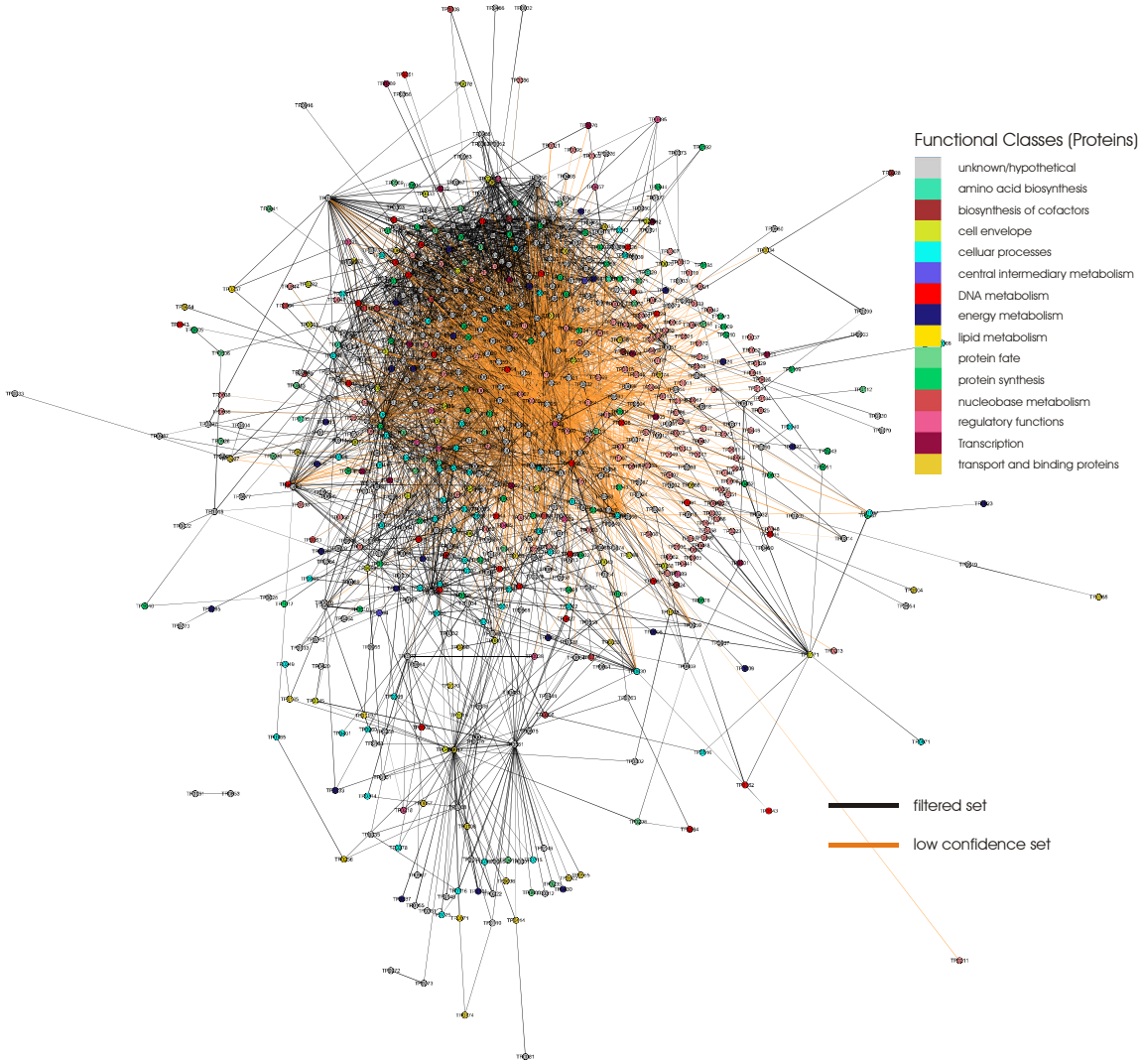


Fig. 22 Whole interaction network of *T. pallidum*. Proteins are represented as nodes and their interactions as edges of a graph. The nodes/proteins are colored according to their functional role (TIGR main role), the color of the edges designates the interaction subset (filtered or whole set).

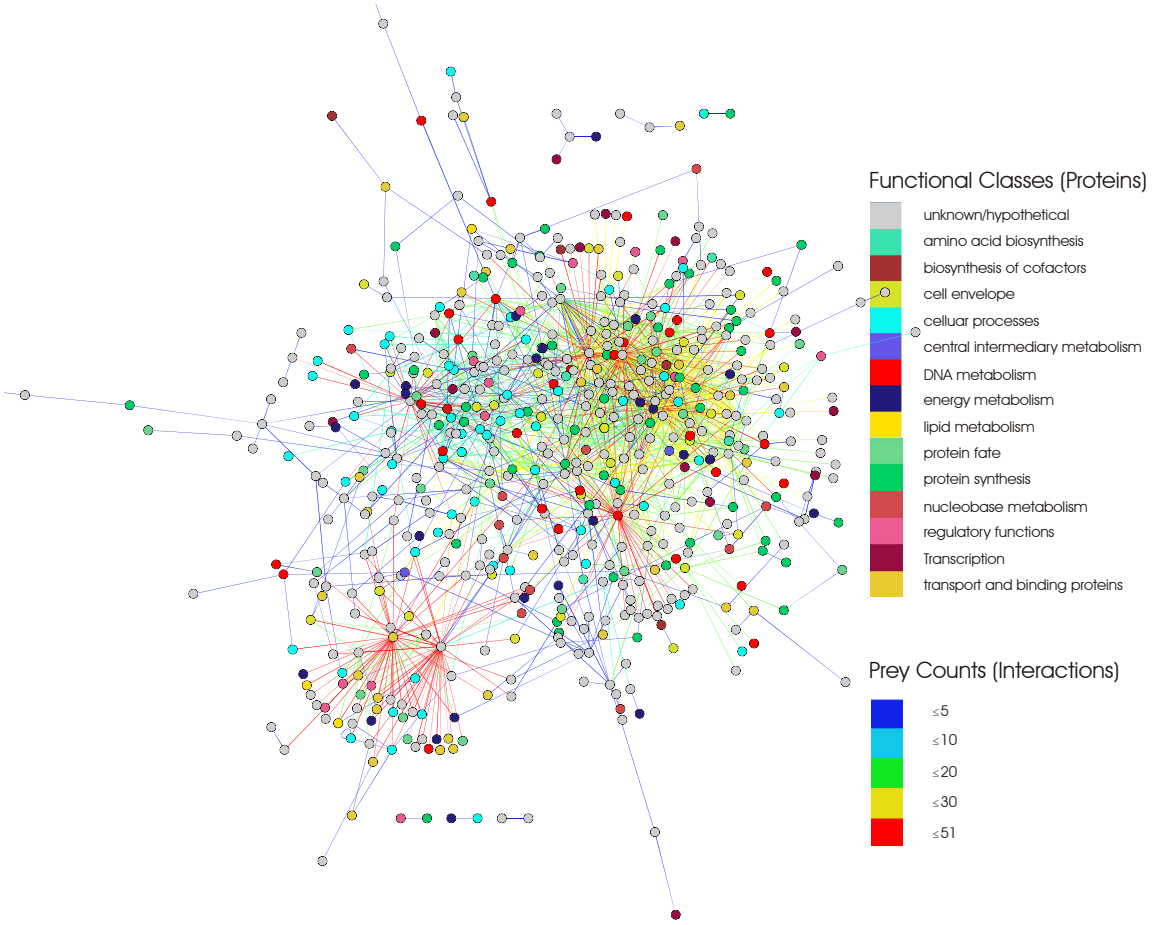


Fig. 23 Filtered protein-interaction network for *T. pallidum*. Proteins are represented as nodes and their interactions as edges of a graph. The nodes/proteins are colored according to their functional role, the color of the edges designates the prey count (specificity) of the interactions.

Features of "sticky" Preys

"Sticky" preys, i.e. preys unspecifically interacting with a large number of bait fusions, are a common annoyance in Y2H tests. The features that lead to this property, however, have not been analyzed in detail. One hypothesis is that these proteins expose hydrophobic patches that have the propensity to stick to many protein surfaces.

The prey with the highest number of interactions is TP0993 ("rare lipoprotein A, putative") with 285 distinct interacting baits. A Top 10 list of "sticky" preys is shown in Table 19. In addition to the lipoprotein, another putative surface protein (P26), several hypothetical proteins, and two flagellar proteins are in this list.

Interestingly, each of these sticky preys shows a different interaction profile (Fig. 24). Thus, a certain level of specificity is retained even in the subset of "unspecifically" interacting preys.

prey	# interactions	description
TP0993	285	rare lipoprotein A, putative
TP0989	180	P26
TP0258	173	conserved hypothetical protein
TP0764	139	conserved hypothetical protein
TP0788	132	hypothetical protein
TP0661	117	hypothetical protein
TP0398	114	fliE
TP0907	110	conserved hypothetical
TP0563	93	hypothetical protein
TP0961	84	flgG

Table 19 Top 10 list. Preys with the highest number of interacting baits.

Only TP0989 has a predicted membrane localization. Thus, the propensity to undergo unspecific interactions is not generally due to exposed membrane regions of transmembrane proteins.
The flagellar proteins, the only proteins with well-characterized functions in this list, are known to form polymeric complexes in the bacterial cell. In the non-natural environment of the yeast's nucleus, interaction partners might be lacking, which might lead to the exposure of unbound hydrophobic interaction epitops.

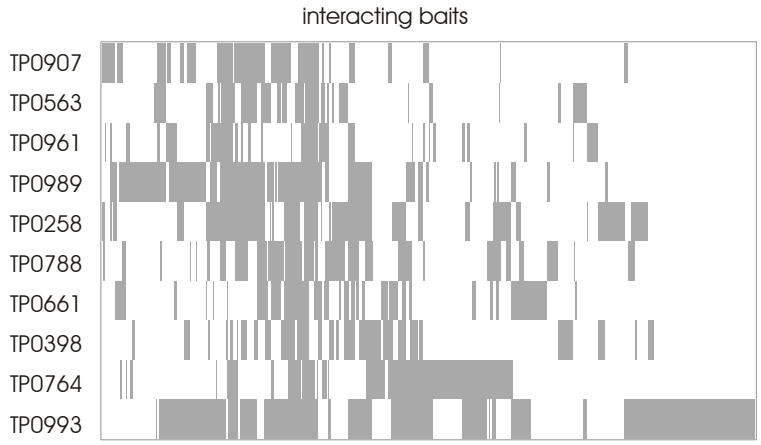


Fig. 24 Interaction profiles of "sticky" preys. Each row reflects one prey and each column one bait. Interactions are marked in grey. The arrangement of the columns (baits) results from clustering.

The protein TP0563 is a specific case. It carries a DnaJ domain, a chaperone domain. Thus, its unspecific interaction pattern might be explained by unspecific interactions formed by this chaperone, e.g. with exposed hydrophobic patches.
The "stickiness" of a protein has various reasons. These include specific protein features such as chaperone domains, exposed transmembrane regions, and presumably exposed binding epitopes of protein complexes. This diversity is nicely reflected by the variability of the interaction profiles of these proteins. It will be interesting to learn more about the nature of these distinct interaction patterns by performing comparative analyses of several datasets.

Comparison with bioinformatical predictions

The large number of sequenced prokaryotic genomes forms the basis for a number of bioinformatical methods, which predict associations between pairs of genes or pairs of orthologous gene groups. The String database (von Mering et al. 2005) was designed to compute and store associations derived from several bioinformatical prediction methods

including gene-neighborhood, gene-fusion, phylogenetic profiling, and simple text- and database-mining.
In this paragraph, the Y2H dataset is compared with these bioinformatical predictions. Protein interactions supported by bioinformatical predictions were found to be enriched (compared to randomized networks) on all levels of significance (Fig. 25). Enrichment was found for both the genomic context and the combined score of the String database. The genomic context score integrates the genomic neighborhood, gene-fusion, and phylogenetic profiling, whereas the combined score additionally includes predictions based on text- and database-mining. In general, a higher enrichment for interactions in the filtered interaction set was observed.

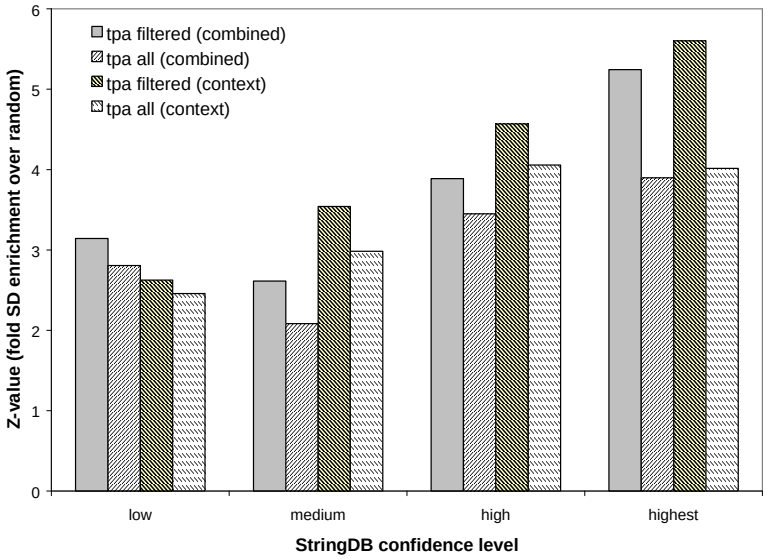


Fig. 25 String database comparison (enrichment over random). The number of Y2H interactions supported by the String database (overall score and genomic context score) for different significance levels compared to numbers from random networks is shown. The Z-value indicates times standard deviation enrichment compared to the average of 1000 randomized networks. The "combined score" encorporates all bioinformatical prediction methods, whereas the "context score" includes genomic neighbourhood, gene fusion, and co-occurrence. The confidence levels are as defined by the String database: low (score ≥ 0.15), medium (score ≥ 0.40), high (score ≥ 0.70), and highest (score ≥ 0.90).

A more detailed analysis of different significance levels and bioinformatical prediction methods is presented in Fig. 26. An overall enrichment compared to randomized networks is generally observed. At different significance levels, different bioinformatical methods have the major contribution to the enrichment score. In a low significance bin (combined string score 0.2-0.3), for example, interactions supported by the "experiment score" are highly enriched compared to randomized networks. This analysis can only give an impression on the contribution of different methods, however, the small sample sizes in each bin leads to an unstable statistics. Thus, for the evaluation the data from Fig. 25 should be preferred.
This analysis can also be employed for filtering of the interaction set. Supplementary Table 7 lists Y2H interactions supported by the StringDB at a medium confidence level (combined score > 0.4). This list of overlapping interactions represents a higher confidence set, which could be the basis of selections for initial follow-up studies.
In summary, the *T. pallidum* interaction set is well supported by bioinformatical predictions.

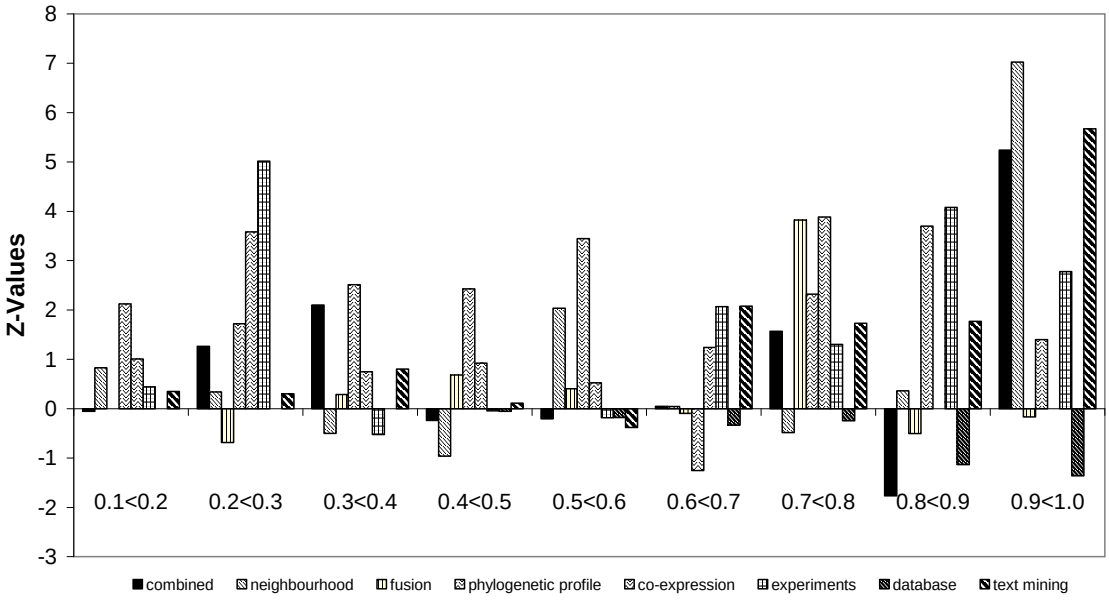


Fig. 26 The set of filtered Y2H interactions is supported by bioinformatical predictions. The number of interactions supported by the bioinformatical predictions by the String database was computed for bins of the significance score. This number of found associations was compared to a distribution of 1000 random networks. The z-scores (see Materials & Methods) for different bioinformatical methods are shown: combined (overall score), gene neighbourhood, gene fusion, phylogenetic profile, co-expression, experiments, database, and text mining.

General Topological Properties

Biological networks are commonly characterized by a certain set of topological network properties (Uetz et al. 2006). In this section, topological properties of the *T. pallidum* network and networks of other species are compared (Table 20).

	T. pallidum		***H. pylori***	***C. jejuni***		**KSHV**	**Yeast**
	filtered	*all*		HCF	all		
Number of Proteins (% genome)	601 (58%)	726 (70%)	732 (47%)	1108 (69%)	1332 (83%)	50 (56%)	1004 (17%)
Number of Interactions	1634	3684	1465	3209	12012	123	948
Number of Edges (w/o reciprocal int.)	1633	3649	1465	3152	11871	115	948
avg. node degree	5.4	10.0	3.8	5.3	17.5	4.6	1.8
avg cluster coefficient	0.064	0.232	0.015	0.039	0.095	0.146	0.021
Diameter	10	7	9	9	6	7	20
Avg. shortest path length	3.88	3.0	4.15	3.80	2.91	2.84	7.49
Power coefficient	1.47	1.15	1.68	1.51	1.27	0.95	2.43

R^2	0.91	0.85	0.91	0.89	0.90	-	0.95
largest connected component nodes (edges)	586 (1609)	724 (3648)	710 (1450)	1081 (2961)	1329 (11869)	-	474 (559)
distinct baits	423	606	244	604	650	-	505
distinct preys	338	357	615	971	1259	-	630

Table 20 General topological properties. Network properties were calculated with NetworkAnalyzer 2.0 (Max Planck Institut für Informatik, Mario Albrecht). The H. pylori dataset was generated by Rain et al.. (Rain et al. 2001), the *C. jejuni* dataset was shared prior to publication by the Finley laboratory (Parish *et al.*), features of the KSHV network work taken from Uetz et al. (Uetz et al. 2006), the yeast dataset (Uetz et al. 2000) was downloaded from the homepage of the Fields lab (http://depts. washington.edu /sfields).

In agreement with previous observations, the majority of protein-protein interactions were only found in one direction (with specific bait/prey direction). Table 21 contains interactions identified in both directions (with bait and prey reversed) in the complete *T. pallidum* dataset. The observation of an interaction in both directions can increase their reliability, but note that several interacting proteins in this list show a high prey count (node degree as prey).

protein A	description	prey count	protein B	description	prey count
TP0046	hypothetical protein	18	TP0398	flagellar hook-basal body complex protein (fliE)	114
TP0050	conserved hypothetical protein	10	TP0398	flagellar hook-basal body complex protein (fliE)	114
TP0050	conserved hypothetical protein	10	TP0870	flagellar filament 31 kDa core protein (flaB3)	79
TP0059	hypothetical protein	21	TP0258	conserved hypothetical protein	173
TP0059	hypothetical protein	21	TP0661	hypothetical protein	117
TP0121	conserved hypothetical protein	7	TP0661	hypothetical protein	117
TP0188	ribosomal protein S10 (rpsJ)	2	TP0661	hypothetical protein	117
TP0258	conserved hypothetical protein	173	TP0398	flagellar hook-basal body co mplex protein (fliE)	114
TP0258	conserved hypothetical protein	173	TP0563	hypothetical protein	93
TP0258	conserved hypothetical protein	173	TP0661	hypothetical protein	117
TP0258	conserved hypothetical protein	173	TP0664	flagellar filament outer layer protein (flaA)	34
TP0258	conserved hypothetical protein	173	TP0673	glutamyl-tRNA synthetase (gltX)	1
TP0258	conserved hypothetical protein	173	TP0870	flagellar filament 31 kDa core protein (flaB3)	79
TP0359	hypothetical protein	2	TP0661	hypothetical protein	117
TP0398	flagellar hook-basal body complex protein (fliE)	114	TP0530	V-type ATPase, subunit E, putative	19
TP0398	flagellar hook-basal body complex protein (fliE)	114	TP0661	hypothetical protein	117
TP0398	flagellar hook-basal body complex protein (fliE)	114	TP0870	flagellar filament 31 kDa core protein (flaB3)	79
TP0398	flagellar hook-basal body complex protein (fliE)	114	TP0989	P26	180
TP0530	V-type ATPase, subunit E, putative	19	TP0661	hypothetical protein	117
TP0561	conserved hypothetical protein	44	TP0985	aspartyl-tRNA synthetase (aspS)	2

TP0563	hypothetical protein	93	TP0870	flagellar filament 31 kDa core protein (flaB3)	79
TP0563	hypothetical protein	93	TP0981	sensory transduction histidine kinase, putative	5
TP0563	hypothetical protein	93	TP1023	recX protein (recX)	13
TP0587	hypothetical protein	23	TP0661	hypothetical protein	117
TP0626	exonuclease, putative	12	TP0661	hypothetical protein	117
TP0630	chemotaxis protein methyltransferase (cheR)	1	TP0870	flagellar filament 31 kDa core protein (flaB3)	79
TP0660	flagellar hook-associated protein 1 (flgK)	4	TP0661	hypothetical protein	117
TP0661	hypothetical protein	117	TP0803	hypothetical protein	2
TP0661	hypothetical protein	117	TP0870	flagellar filament 31 kDa core protein (flaB3)	79
TP0661	hypothetical protein	117	TP0946	glucose-inhibited division protein B (gidB)	19
TP0664	flagellar filament outer layer protein (flaA)	34	TP0961	flagellar basal-body rod protein (flgG)	84
TP0870	flagellar filament 31 kDa core protein (flaB3)	79	TP0873	hypothetical protein	1
TP0870	flagellar filament 31 kDa core protein (flaB3)	79	TP0943	flagellar protein (fliS)	15
TP0870	flagellar filament 31 kDa core protein (flaB3)	79	TP0961	flagellar basal-body rod protein (flgG)	84
TP0870	flagellar filament 31 kDa core protein (flaB3)	79	TP0981	sensory transduction histidine kinase, putative	5

Table 21 Y2H interactions found in both (bait - prey) directions.

One advantage of the Y2H system compared to coAP/MS studies is that homodimers can be identified. Homodimers found in the *T. pallidum* dataset are shown in Table 22. 22 homodimers were observed in total. In 1000 randomized networks only 6.7 +/- 1.9 homodimers were found. Thus, the observation of 22 homodimers is highly significant and is only expected with $p = 2.22\ 10^{-16}$ by chance.

Protein	Description	Prey Count
TP0330	cell division protein (ftsH)	2
TP0725	flagellar motor rotation protein (motA)	2
TP0121	conserved hypothetical protein	7
TP0088	conserved hypothetical protein	8
TP0641	histidyl-tRNA synthetase (hisS)	9
TP0708	hypothetical protein	13
TP0943	flagellar protein (fliS)	15
TP0530	V-type ATPase, subunit E, putative	19
TP0059	hypothetical protein	21
TP0587	hypothetical protein	23
TP0559	conserved hypothetical protein	26
TP0519	response regulatory protein (atoC)	30
TP0833	hypothetical protein	34
TP0561	conserved hypothetical protein	44
TP1005	DNA polymerase III, subunits gamma and tau (dnaH)	44
TP0383	conserved hypothetical protein	65
TP0870	flagellar filament 31 kDa core protein (flaB3)	79
TP0961	flagellar basal-body rod protein (flgG)	84

TP0563	hypothetical protein	93
TP0398	flagellar hook-basal body co mplex protein (fliE)	114
TP0661	hypothetical protein	117
TP0258	conserved hypothetical protein	173

Table 22 Homodimers in the *T. pallidum* PIM.

Biological networks were described to exhibit scale-free properties such as scale-free degree distributions. For these networks their degree distribution can be described by a power-law – $P(k) \sim k^{-\gamma}$ with node degree k, frequency of a certain node degree P(k), and power coefficient γ. As shown in Fig. 27 the degree distribution of the PIM of *T. pallidum* can be approximated by a power law.

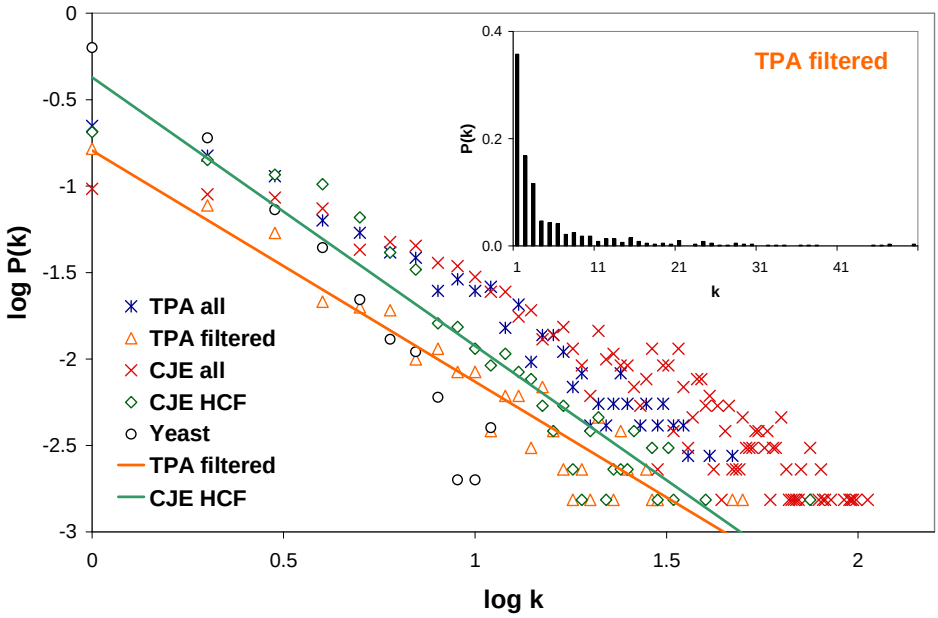


Fig. 27 Frequency-degree plot showing node degree distributions of *T. pallidum* networks (TPA), *C. jejuni* networks (CJE), and a yeast network. The insert shows a plain histogram of the node-degree distribution for the filtered *T. pallidum* network.

However, Tanaka *et al.* (Tanaka et al. 2005) found that some experimental networks were wrongly labeled as scale-free, although their node degree distribution is better described by an exponential function. The problem with these analyses was the use of frequency-degree plots rather than rank-degree plots, which are standard in statistics.
For *T. pallidum* these rank-degree plot show, that the whole network can be approximated by a power-law, whereas the distribution of the filtered network is better described by an exponential law.
To gain biological insight into the "sticky" preys, I investigated whether the prey count of a protein was dependent on its functional class Fig. 29. However, no specific trend was observed.

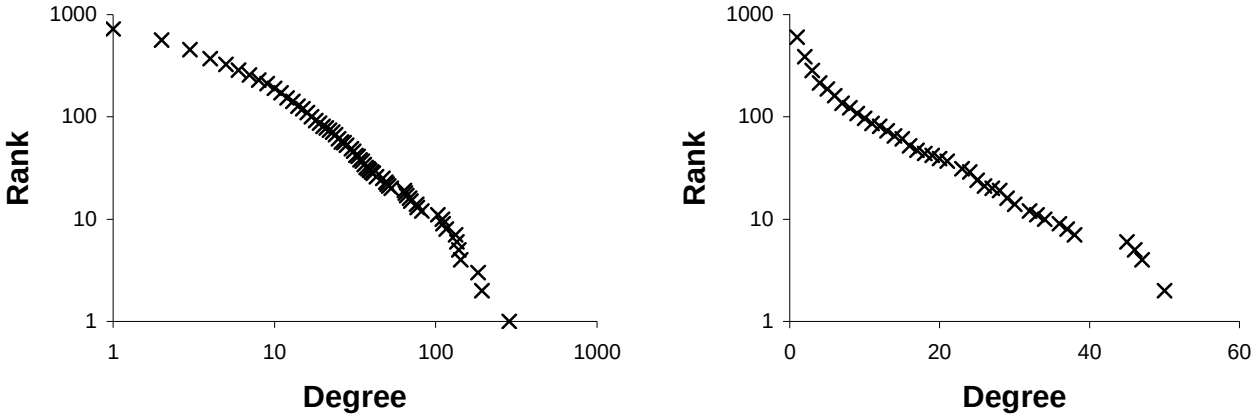


Fig. 28 Rank-degree plots. The plot for the whole *T. pallidum* network is shown left; the filtered network is shown right. Note that the whole network is drawn on logarithmic scales (power-law); the filtered network is drawn on semi-logarithmic scales (for exponentials).

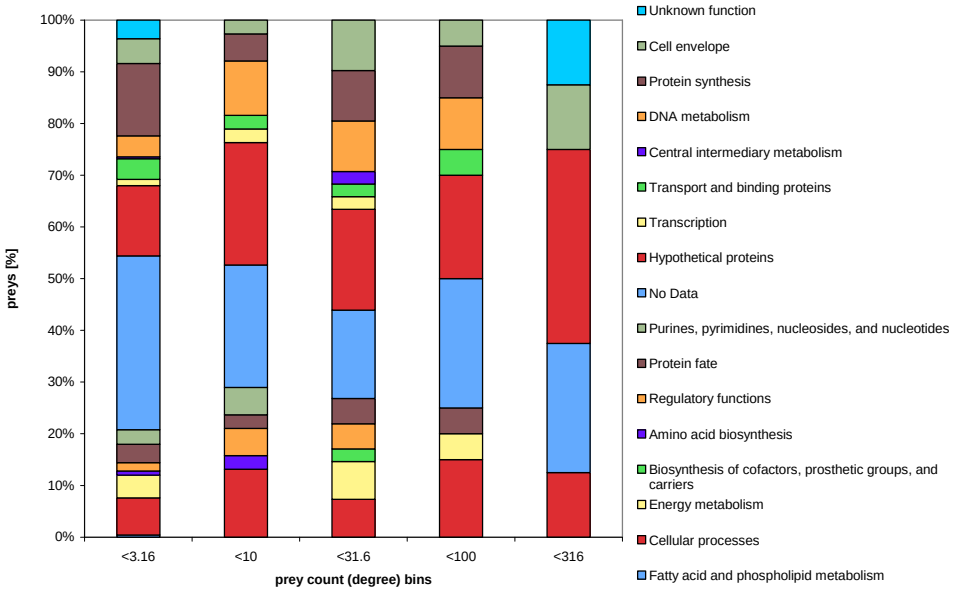


Fig. 29 Prey counts vs. functional classes. Preys were logarithmical binned (two bins per decade) according to their prey count and the percentage of preys with a certain TIGR main role was calculated.

Identification of Tightly Connected Clusters

Protein clusters form functional modules in protein-interaction networks. Examples for protein clusters found in bacterial networks are the DNA polymerase, the ribosome, and the RNA polymerase. Several algorithms for the identification of clusters in protein-interaction networks have been devised among them a set of algorithms by Spirin and Mirny (Spirin and Mirny 2003) and MCODE by Bader and Hogue (Bader and Hogue 2003). MCODE is used for cluster identification in this study due to its availability as a Cytoscape plug-in (Shannon et al. 2003). Using the default parameters (node score cutoff = 0.2; haircut on; fluff off; max. depth = 100) six clusters were identified (Table 23, Fig. 30).

Complex	Score (Density* #Proteins)	# Proteins	# Interactions	Proteins
1	1,56	25	44	TP0751, TP0344, TP0345, TP0492, TP0389, TP0559, TP0237, TP0773, TP0409, TP0197, TP0873, TP0870, TP0630, TP0497, TP0209, TP0530, TP0455, TP0554, TP0833, TP0720, TP0832, TP0567, TP0708, TP0561, TP0668
2	1,2	5	7	TP0084, TP0587, TP0333, TP0268, TP0664
3	1,167	6	8	TP0514, TP0648, TP0965, TP0341, TP0519, TP0634
4	1	3	4	TP0711, TP0059, TP0661
5	1	3	3	TP0716, TP0042, TP0917
6	1	3	4	TP0945, TP0943, TP0048

Table 23 MCODE clusters. Tightly connected clusters in the filtered *T. pallidum* PIM identified by MCODE (Bader and Hogue 2003).

Since all these clusters contain proteins with diverse functions, a classification into functional categories was not possible. Cluster 3, for example, contains two interacting DNA repair enzymes (DNA ligase (TP0634) and an exonuclease (TP0514)), but also two proteins belonging to the cell envelope category, MurC (TP0341) and a membrane fusion protein (TP0965).

These clusters were also tested for support by genomic context methods as provided by the String database (von Mering et al. 2005). In cluster 1, genomic neighbourhood and co-occurrence at a medium confidence level (score > 0.4) support the association between TP0389, TP0345, and TP0344. In cluster 3, the COGs of TP0648, TP0965, and TP0516 are associated at medium confidence level; the remaining COGs except for TP0514's COG are associated at the low confidence level (Fig. 30 B) Thus, cluster 3 is well supported not only by Y2H interactions, but also by genomic context methods.

Cluster 6 represents a special case. This cluster is formed by homodimerisation of TP0943 (FliS) and its interaction with a neighboring gene, TP0945, a pentose-phosphate pathway enzyme. In addition, both proteins are interacting with the conserved hypothetical protein TP0048. These interactions are only two out of six interactions constituting a genomic link between the regions surrounding TP0943/TP0945 and TP0048, respectively (see below).

These clusters indicate previously unidentified tight functional associations between protein sets. The functional implication of cluster 6 (motility involvement) is discussed below. Cluster 3 is strongly supported by genomic context methods and might represent a link between DNA metabolism and the cell envelope.

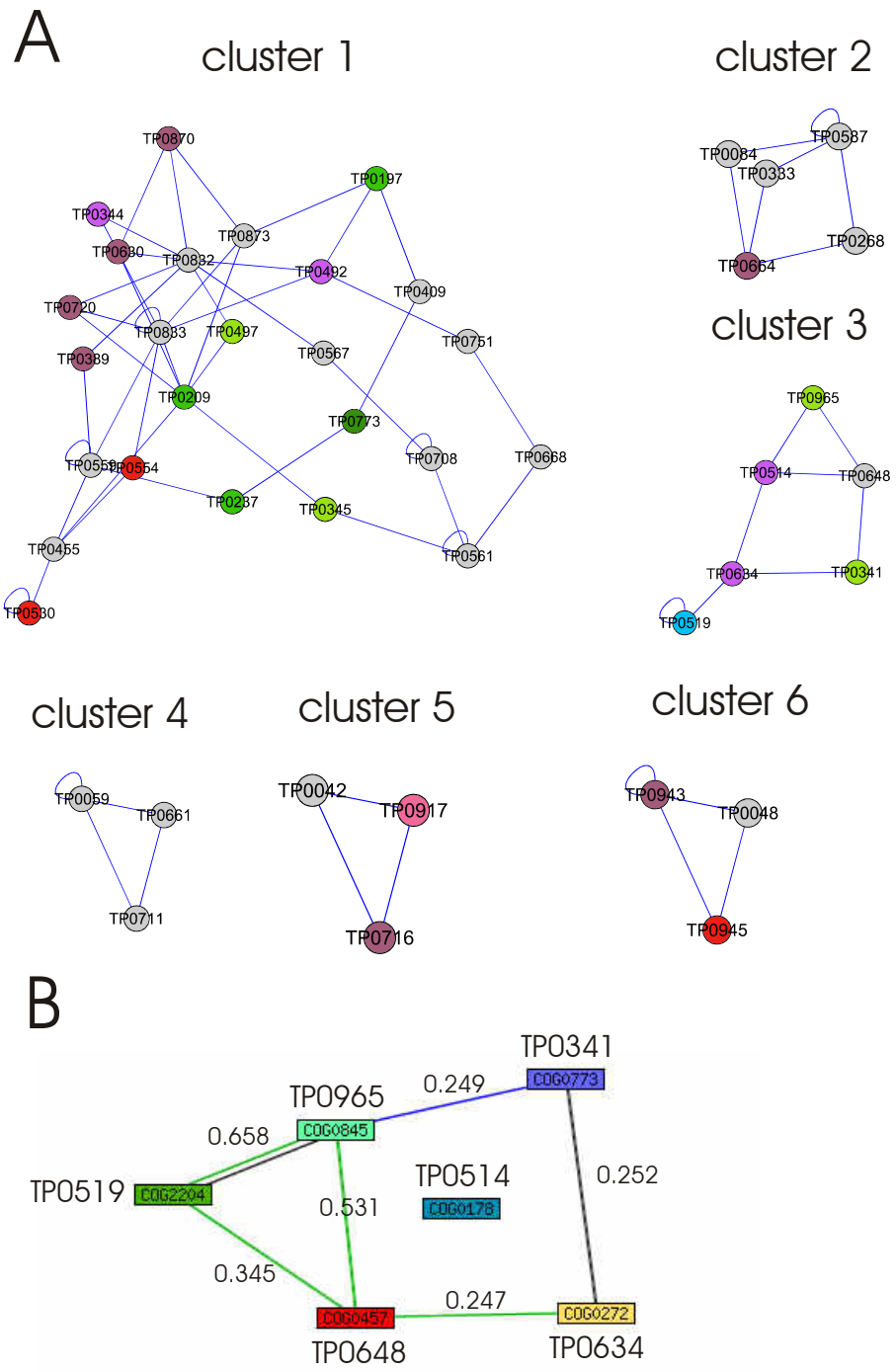


Fig. 30 Tightly connected protein complexes in the filtered *T. pallidum* network identified by MCODE algorithm. (A) Protein complexes colored according to TIGR main roles; see main network for color key. (B) Bioinformatical associations between proteins of complex 3 obtained from the String database (von Mering et al. 2005). The edge labels represent associations scores, the edge color indicates the underlying genomic context methods: neighborhood (green), co-occurrence (blue), and co-expression (black).

Interactions of Paralogs

Paralogous proteins are homologous proteins, which are present in one species and developed by gene duplication events. Since they originated from one ancestral gene, a related, but distinct function can be hypothesized. Therefore, paralogous proteins can be assumed to have overlapping, but different interaction profiles. To test this hypothesis, paralogous proteins of *T. pallidum* were collected and their interaction patterns compared.

Paralogs of *T. pallidum* were downloaded from the TIGR-CMR database (August 2006) (Peterson et al. 2001); their assignments are based on sequence comparisons combined with manual inspection of the alignments. Please note that a new release of the CMR database appeared in October 2006, which contains a differently defined set of paralogous genes for *T. pallidum* (discussed below).

42 paralogous gene families containing 127 genes (more than 10% of the genome) are present in the genome of *T. pallidum*. These include conserved hypothetical protein families, transporter families, and families of special interest for *T. pallidum* such as the flagellin family (paralogous family 39) and the tpr protein family (paralogous family 2).

Each of these paralogous families was checked for overlapping interactions (Table 24). For summary of the number of interactions and the number of overlapping interactions for each paralogous gene family, refer to Supplementary Table 13.

paralogous family (gtp family #) (annotation)	interacting ORF	annotation	#	interactions
02 (tpr proteins)	TP0209	ribosomal protein L36	2	TP0117-**TP0209** TP0610-**TP0209**
04 (fliG)	TP0399	fliF	2	TP0400-**TP0399** **TP0399**-TP0026
23 (ftsW, rodA)	TP0561	conserved hypothetical	2	TP0501-**TP0561** TP0387-**TP0561**
23 (ftsW, rodA)	TP0917	Mg2+ transport protein	2	TP0501-**TP0917** TP0387-**TP0917**
39 (flagellin)	TP0050	conserved hypothetical	2	TP0868-**TP0050** TP0870-**TP0050**
39 (flagellin)	TP0658	conserved hypothetical	3	TP0792-**TP0658** TP0868-**TP0658** TP0870-**TP0658**
39 (flagellin)	TP0832	hypothetical	3	TP0792-**TP0832** TP0868-**TP0832** TP0870-**TP0832**
40 (flgG)	TP0832	hypothetical	2	TP0960-**TP0832** TP0961-**TP0832**

Table 24 Overlapping interactions of paralogs (status August 2006). Paralogous gene families (paralog family), for which different members interacted with the same protein (interacting ORF), are shown. The number of distinct interactions with this ORF is given (#) and the individual interactions are shown (paralog in normal case, interacting ORF in bold case).

As mentioned a new release of the TIGR-CMR database contained a different list of paralogous gene families. Presumably, the computation of these families was based on an algorithm developed for the reannotation of the *Arabidopsis* genome (Tanja Davidsen, *pers. comm.*) (Haas et al. 2005). In this algorithm, Pfam and TIGRfam profiles are assigned using HMMER2; the unassigned sequence space is clustered based on sequence identity (BlastP) and protein domains are defined on basis of these clusters. Thus, the current "paralogous gene family" set from the TIGR-CMR database contains domains rather than real paralogous gene families. However, a corresponding analysis of these families is presented in Supplementary Table 14.

The protein TP0658 interacts with all flagellin proteins indicating a close functional association of TP0658 with this gene family; flagellin proteins form the propeller-like structure of the bacterial filament. This served as one criterion to select TP0658 for a more detailed analysis, which revealed that TP0658 functions as an conserved assembly factor of the bacterial filament (see section 3.5) (Titz et al. 2006a).

Unlike other bacteria, *T. pallidum* has a flagellum with two copies of the basal body protein fliG, fliG-1 and fliG-2 (Charon and Goldstein 2002). It was hypothesized that this redundancy is the basis for the polarized rotation of the flagellum. Since both paralogs still show the previously described interaction with FliF (MS ring complex) (Oosawa et al. 1994), their general function in the basal body seems to be retained. However, their distinct interaction pattern with other proteins indicates a modulation of this function (Rajagopala 2006).

Because of its association to both members of the "gtp family_23", whose members are involved in cell division, TP0561 can be hypothesized to have a function in cell division as well. Orthologs of TP0561 are widely distributed among bacteria including ygcG (B2778) in *E. coli* and ydjH (BSU06200) in *B. subtilis*.

Two interacting paralogous protein families could also have co-evolved in a way that different paralogs of one family interact with different paralogs in another family. However, in the *T. pallidum* interaction set such cases could not be identified, although 19 interactions between members of paralogous protein families were identified.

Most paralogs show a different set of interactions. Nevertheless, the cases with overlapping and distinct interactions can serve as the basis for further investigations. Detailed epitope mappings of these can provide insights into the evolution of different interaction specificities.

Functional Classes present in Interaction Networks

Functional classes present in the whole and the filtered *T. pallidum* network were analyzed and compared to the whole genome (Supplementary Table 8, Supplementary Table 9). Based on an exact Fisher's test with Bonferroni's and Holm's correction for multiple testing, none of the functional classes tested was significant enriched or depleted in the protein interaction networks. The main functional classes in the filtered network were conserved hypothetical proteins (27%), chemotaxis and motility (7%), DNA metabolism (6%), and ribosomal proteins (4%). This corresponds to the distribution of functional classes in the genome.

Connections between Functional Classes

To assess a higher organization level of the bacterial cell, proteins can be functionally classified. Several classification schemes are applied to bacterial proteins. The TIGR role categories (main role and sub role, www.tigr.org/CMR) capture the general function of a protein, e.g. an involvement in DNA replication (Peterson et al. 2001). The TIGR categories are forming a rather flat classification scheme (with two levels). In contrast, the gene ontology (GO) classification scheme is based on three "directed acyclic graphs (DAG)" (Lewis 2005). Each protein can be associated to a number of functional terms from each of these ontologies: biological process, molecular function, and cellular component.

Here, the connections of TIGR roles and GO terms based on the identified Y2H links are analyzed. For this, the number of Y2H interactions between proteins of all pair-wise functional term combinations was counted and compared to the distribution from 1000 randomized networks. The GO terms were taken from a GO slim mapping (GO slim and prokaryotic subset) from the GOA@EBI project, which employs automated algorithms for GO term classifications (Camon et al. 2003). The results are shown in Fig. 31 and Supplementary Table 10-Supplementary Table 12.

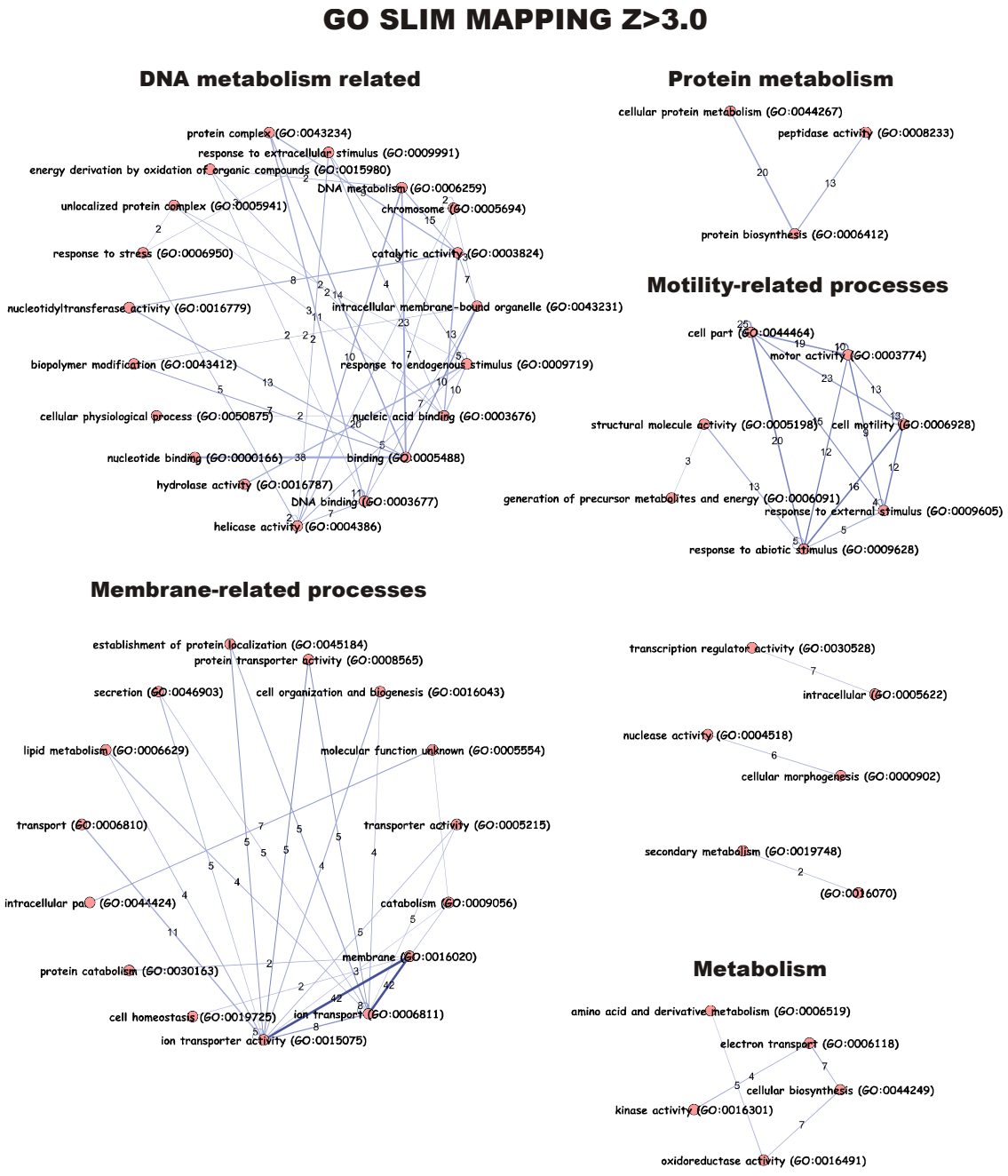


Fig. 31 Functional associations. The connections between functional categories in the filtered *T. pallidum* dataset are shown. The width of edges between functional categories are scaled according to the number of Y2H interactions connecting them, the number of interactions is given as edge label, and the darkness of the edge indicates the statistical significance (Z-value, see supplementary tables). Only connections with Z>2.0 for TIGR roles and Z>3.0 for GO terms are shown. **(continued…)**

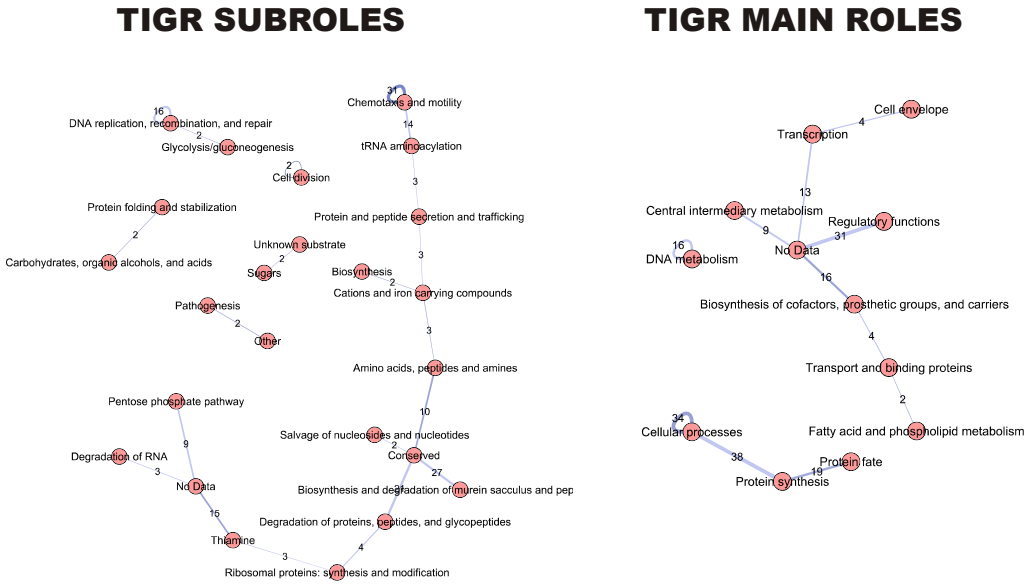


Fig. 31 **(…continued)**

Considering TIGR roles, a significant self-association is observed for "chemotaxis and motility" (31 interactions), "DNA replication, recombination, and repair" (16 interactions), and "cell division" (2 interactions).

Interactions of motility proteins are discussed below. Interactions between proteins involved in "DNA metabolism" constitute an interesting subset (Table 25).

bait	description	prey	description
TP0058	replicative DNA helicase (dnaB)	TP0001	chromosomal replication initiator protein (dnaA)
TP0058	replicative DNA helicase (dnaB)	TP0005	DNA gyrase, subunit A (gyrA)
TP0058	replicative DNA helicase (dnaB)	TP0102	rep helicase, single-stranded DNA-dependent ATPase (rep)
TP0058	replicative DNA helicase (dnaB)	TP1005	DNA polymerase III, subunits gamma and tau (dnaH)
TP0162	Holliday junction DNA helicase (ruvB)	TP0543	Holliday junction DNA helicase (ruvA)
TP0328	DNA mismatch repair protein (mutS)	TP0946	glucose-inhibited division protein B (gidB)
TP0344	transcription-repair coupling factor (trcF)	TP0514	excinuclease ABC, subunit A (uvrA)
TP0380	DNA repair helicase, putative	TP0704	single-stranded-DNA-specific exonuclease (recJ)
TP0380	DNA repair helicase, putative	TP1005	DNA polymerase III, subunits gamma and tau (dnaH)
TP0492	DNA primase (dnaE)	TP0380	DNA repair helicase, putative
TP0492	DNA primase (dnaE)	TP1006	DNA gyrase, subunit B (gyrB)
TP0517	Holliday junction nuclease (ruvC)	TP0704	single-stranded-DNA-specific exonuclease (recJ)
TP0526	ATP-dependent helicase (hrpA)	TP1023	recX protein (recX)
TP0634	DNA ligase (lig)	TP0514	excinuclease ABC, subunit A (uvrA)
TP0946	glucose-inhibited division protein B (gidB)	TP0514	excinuclease ABC, subunit A (uvrA)
TP1005	DNA polymerase III, subunits gamma and tau (dnaH)	TP1005	DNA polymerase III, subunits gamma and tau (dnaH)

Table 25 Y2H interactions linking two proteins involved in DNA metabolism

"Protein synthesis" and "protein fate" (TIGR main roles) are linked by 19 interactions. These include interactions between ribosomal proteins and proteases, between the trigger factor (TP0506) and translation elongation factor TS (TP0605), and between methionyl-tRNA formyltransferase (fmt, TP0756) and polypeptide deformylase (def, TP0757) (Table 26).

bait	description	role	prey	description	role
TP0030	heat shock protein (groEL)	F	TP0160	prolyl-tRNA synthetase (proS)	S
TP0063	ribosomal protein S6 (rpsF)	S	TP0757	polypeptide deformylase (def)	F
TP0063	ribosomal protein S6 (rpsF)	S	TP0997	protease IV (sppA)	F
TP0097	translation initiation factor 1 (infA)	S	TP0757	polypeptide deformylase (def)	F
TP0097	translation initiation factor 1 (infA)	S	TP0773	periplasmic serine protease DO (htrA)	F
TP0097	translation initiation factor 1 (infA)	S	TP0997	protease IV (sppA)	F
TP0185	signal peptidase I (sip)	F	TP0644	lysyl-tRNA synthetase	S
TP0237	ribosomal protein L11 (rplK)	S	TP0773	periplasmic serine protease DO (htrA)	F
TP0255	ribosomal protein L31 (rpmE)	S	TP0757	polypeptide deformylase (def)	F
TP0452	isoleucyl-tRNA synthetase (ileS)	S	TP0185	signal peptidase I (sip)	F
TP0506	trigger factor (tig)	F	TP0605	translation elongation factor TS (tsf)	S
TP0507	ATP-dependent Clp protease proteolytic component (clpP)	F	TP0362	ribosomal protein L28 (rpmB)	S
TP0578	cell division protein (ftsY)	F	TP0160	prolyl-tRNA synthetase (proS)	S
TP0756	methionyl-tRNA formyltransferase (fmt)	S	TP0757	polypeptide deformylase (def)	F
TP0756	methionyl-tRNA formyltransferase (fmt)	S	TP1013	chaperonin (groES)	F
TP0807	ribosomal protein L32 (rpmF)	S	TP0773	periplasmic serine protease DO (htrA)	F
TP0926	signal peptidase I, putative	F	TP0209	ribosomal protein L36 (rpmJ)	S
TP0985	aspartyl-tRNA synthetase (aspS)	S	TP0757	polypeptide deformylase (def)	F
TP0985	aspartyl-tRNA synthetase (aspS)	S	TP0773	periplasmic serine protease DO (htrA)	F

Table 26 Interactions between protein synthesis (S) and protein fate (F).

"Chemotaxis and motility" and "tRNA aminoacylation" are linked by 14 interactions. This might indicate a regulatory link between motility and the tRNA/aminoacid status of the cell. Interestingly, the network of interconnected GO terms is subdivided into several functional clusters: DNA metabolism, membrane-process related, intracellular, protein metabolism, and motility-related processes. An example for an internal connection is the link between ion transporters ("ion transport" and "ion transporter activity") and other membrane proteins.
An analysis of connections between KEGG pathways (www.genome.jp/kegg) did not reveal further insights (not shown).
A significant number of interactions within the same functional category allow further insights into its molecular details. On the other hand, interesting functional links between categories are discovered, e.g. between motility and tRNA metabolism.

A Domain Centered View

Proteins are composed of individual domains, which form the "building blocks" in evolution (Bornberg-Bauer et al. 2005). The Pfam database (Bateman et al. 2004) identifies and stores information about the domain content of each protein. Table 27 shows the 15 most abundant protein domains in the genome of *T. pallidum* (Pfam families). The TPR_1 domain is found in 17 proteins with as many as 50 copies in total. TPR domains are described as versatile protein-protein interaction domains (D'Andrea and Regan 2003).

Pfam family	Description	Number of proteins	Number of regions
TPR_1 (PF00515)	Tetratricopeptide repeat	17	50
Ank (PF00023)	Ankyrin repeat	2	27
TPR_2 (PF07719)	Tetratricopeptide repeat	12	21
ABC_tran (PF00005)	ABC transporter	17	20
LysM (PF01476)	LysM domain	7	11
MOSP_N (PF02707)	Major Outer Sheath Protein N-terminal region	9	9
MOSP_C (PF02722)	Major Outer Sheath Protein C-terminal region	9	9
Helicase_C (PF00271)	Helicase conserved C-terminal domain	8	8
AAA (PF00004)	ATPase family associated with various cellular activities (AAA)	8	8
S1 (PF00575)	S1 RNA binding domain	3	7
MMR_HSR1 (PF01926)	GTPase of unknown function	5	6
DNA_gyraseA_C (PF03989)	DNA gyrase C-terminal domain, beta-propeller	1	6

Table 27 Top 15 Pfam families in the *T. pallidum* genome. Data was taken from the Pfam database.

The filtered *T. pallidum* PIM was taken as a basis to construct a network of interacting domains (Fig. 32, Supplementary Table 15).

Several significant links between protein domains are present in the *T. pallidum* protein network. Striking examples such as the wide range of TPR domain links and the interaction of flagella protein domains with peptidoglycan enzyme domains are discussed below.

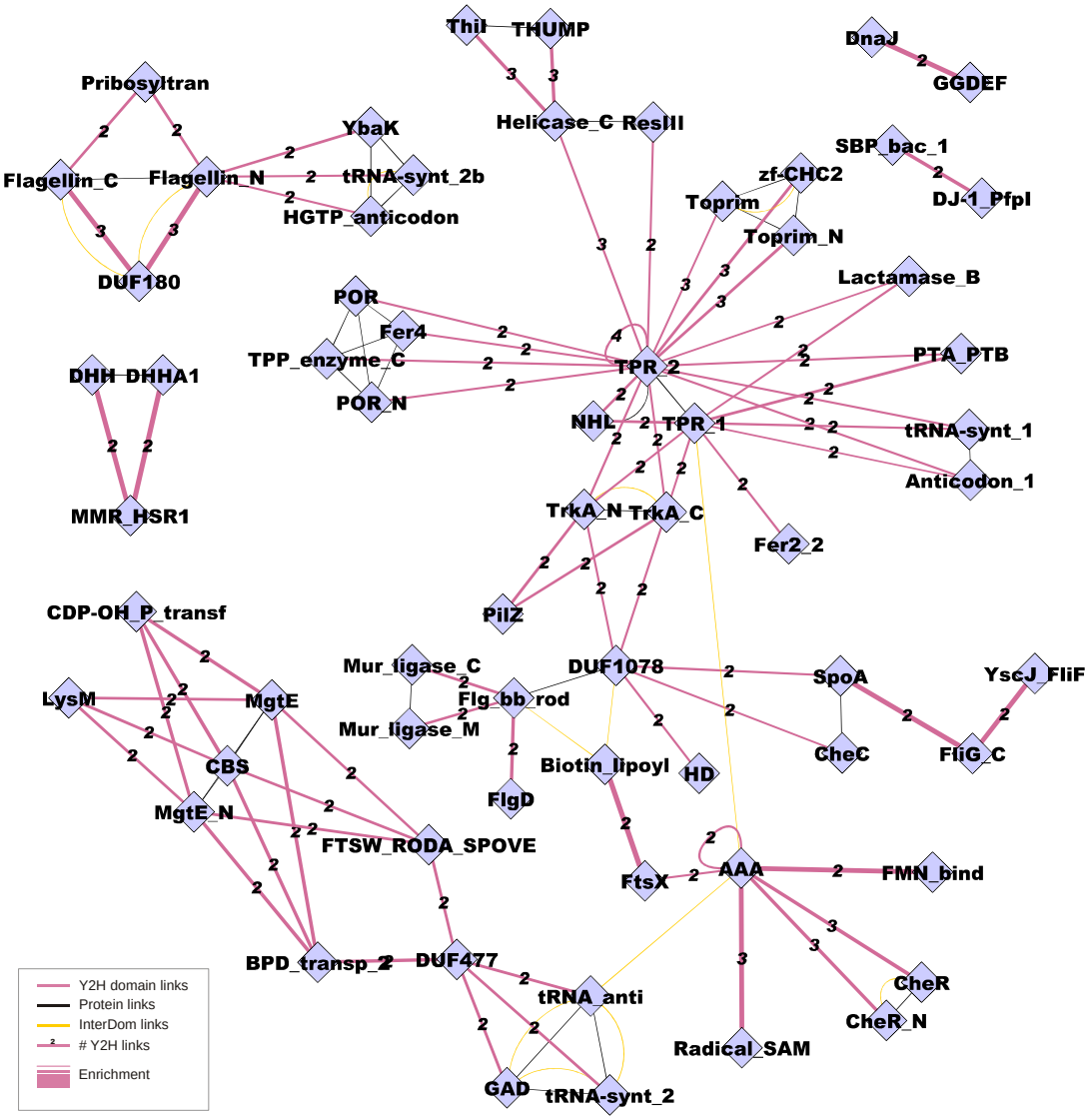


Fig. 32 A Domain-centered PIM for *T. pallidum*. Domains for proteins embedded in the filtered PIM of *T. pallidum* were extracted from the Pfam database. The number of Y2H links between two domains (N_i) was calculated (shown as edge labels) and compared to a distribution of randomized networks. A Z-value for each domain interaction was calculated (enrichment), only links with Z>2 are shown, and the edge line width is scaled proportional to the Z-value. In addition to links based on Y2H interactions (red lines), the fusion of domains in a single *T. pallidum* protein is indicated (black lines; e.g., the fusion of Flagellin_N and Flagellin_C domains compose the flagellin proteins), and putative domain-interactions from the InterDom database (Ng et al. 2003) are shown (yellow lines).

Links between Genomic Locations

Neighboring genes in the genome, e.g. genes in one operon, tend to have a related function (Overbeek et al. 1999).

In this paragraph, links between two genomic locations, which can be far apart in the genome, are analyzed. For this, the number of Y2H links between genomic locations is counted and compared to a distribution obtained from 1000 randomizations of the Y2H

network. Links formed by more Y2H interactions than expected by chance are displayed in Fig. 33.
Indeed, significant links between genomic locations are identified. Examples for different underlying interaction patterns are given in the following.
First, at the diagonal of the matrix homodimerisations and interactions with neighboring genes are observed: the conserved hypothetical protein TP0561 forms a homodimer and interacts with neighboring genes (Fig. 33, lower left zoom-out); TP0559 (ThiI) also forms a homodimer and interacts with a neighboring gene of unknown function, TP0552.

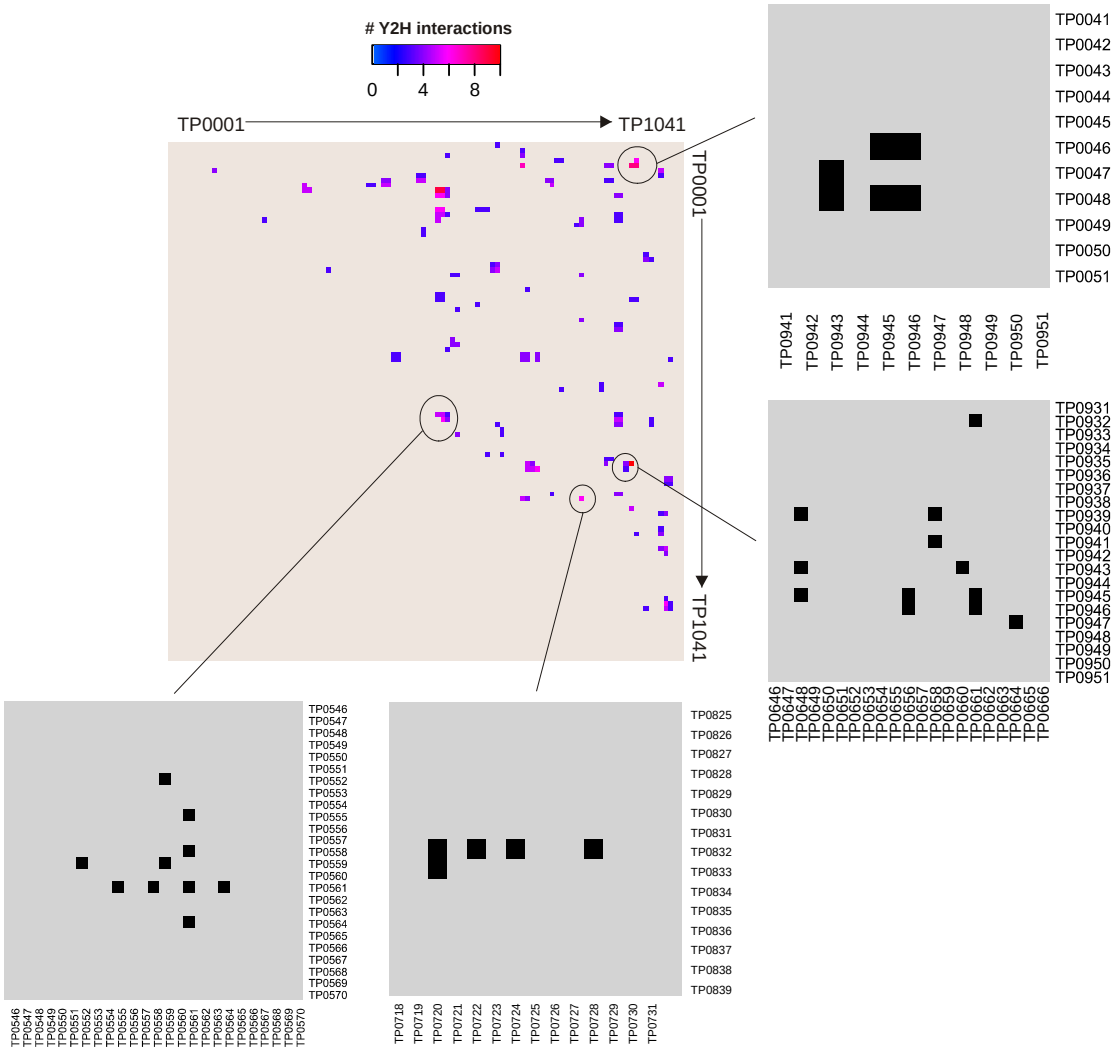


Fig. 33 Links between genomic locations. A matrix showing the number of Y2H links between genomic locations is shown. Genomic locations with 20 neighboring genes were selected (neighboring locations are shifted by 5 amino acids) and the number of Y2H interactions between all pair-wise combinations of these locations was counted. For estimation of statistical significance, only genomic links between two locations with Z-value > 2 (based on comparison with 1000 randomized networks) and at least three Y2H interactions were selected. Zoom-outs show examples for individual interactions forming a link between two genomic locations.

Second, a genomic link can be also based on one protein interacting with several neighboring genes: TP0832, a hypothetical protein, (Fig. 33, lower right zoom-out) interacts with several flagellar proteins. Interestingly, TP0833 the neighbor of TP0832 and annotated as hypothetical protein, as well, shows an overlapping interaction with TP0720 (FliY). This might indicate that both hypothetical proteins, TP0832 and TP0833, have a function related

to bacterial motility. TP0832 is located in a COG with the *B. subtilis* protein gerM, a germination protein. GerM was speculated to be involved in peptidoglycan synthesis (Slynn et al. 1994). Taken together, TP0832 (and TP0833) might be implicated in reorganization of peptidoglycan to accommodate the flagellum.
Third and most interesting, a link between two loci potentially implicated in bacterial motility was identified (Fig. 33, upper right zoom-out). A region flanking TP0943 (FliS), the FliC chaperone, is linked to a gene cluster including TP0046-TP0048. TP0046 and TP0048 were found to have reduced motility in *B. subtilis* (see below). TP0945 (R5P3E) and TP0946 (gidB), two proteins related to sugar metabolism, are linked to this cluster. Interestingly, this genomic location link is additionally supported by the identification of a network cluster (Fig. 30).
Protein interaction links between genomic locations are present in the interactome of *T. pallidum*. This finding reveals another level of organization of the genome/interactome space.

Links between Subcellular Locations

Compared to eukaryotic cells, only a small number of separated compartments exist in prokaryotic cells: the cytoplasm, the periplasmic space, and the membranes. In addition, bacteria secrete proteins into their environment. The PSORT2.0 algorithm (Gardy et al. 2005) was used to predict subcellular locations for all *T. pallidum* proteins (Table 28). This algorithm employs a multiple classification approach and evaluates features such as signal peptides, transmembrane helices, homologies, and motifs.

predicted location	count	percent
Cytoplasmic	408	39
Unknown	395	38
CytoplasmicMembrane	177	17
Unknown (This protein may have multiple localization sites.)	20	2
OuterMembrane	18	2
Periplasmic	15	1
Extracellular	3	<1

Table 28 Subcellular locations of *T. pallidum* proteins predicted by PSORT 2.0

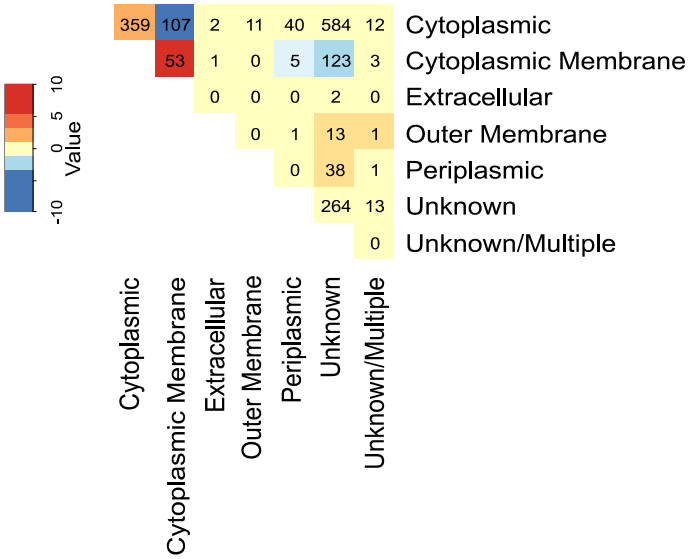


Fig. 34 Location links. Enrichment of protein-interaction based links between bacterial compartments (based on predicted localizations). Number of linking interactions is given in the matrix. The color code indicates the statistical significance of an observed link compared to randomized protein networks: the color encodes a Z-score.

As expected, most of the proteins (~39%) were predicted to be localized in the cytoplasm. For a large fraction, a prediction was impossible ("unknown", 38%) and only a minority of proteins was predicted to be localized to other compartments.
The analysis of protein-interaction links between these compartments revealed only two significant (Z-value > 2.0) links: between pairs of cytoplasmic proteins and between pairs of cytoplasmic membrane proteins (Fig. 34, Supplementary Table 3). A significant association of two different subcellular locations could not be identified. However, a highly significant under-representation of interactions between cytoplasmic and cytoplasmic-membrane proteins was observed. In addition, a slight overrepresentation of links between proteins of unknown localization and proteins with periplasmic (38 interactions) and outer membrane localization (13 interactions) was observed.

Functional Predictions – Guilt by Association

One main objective in the analysis of protein-protein interactions is the annotation of protein functions, especially for hypothetical and conserved hypothetical proteins, which completely lack a functional annotation. The basis for these annotations is that proteins rarely function alone but in nearly all cases work in the context of other proteins. Thus, the molecular environment can provide clues about the respective protein's function. This approach is commonly called "guilt-by-association" (Oliver 2000) approach and will be applied to hypothetical proteins and conserved hypothetical proteins in this thesis.

The strength of this approach for functional annotation can be exemplified with the conserved hypothetical protein **TP0658**. TP0658 was found to specifically interact with all three flagellin proteins (FlaB1-3), the proteins forming the filament of the bacterial flagellum. These interactions clearly point to a role of TP0658 related to flagellin protein metabolism. Indeed, an in detail characterization (see below) (Titz et al. 2006a) definitely showed a function of TP0658 as a conserved assembly factor of the bacterial flagellum.

However, in a functional genomics study not all interesting candidate genes can be followed up in detail. This section will provide a statistically filtered list of proteins without known function and their associations with functional categories based on their protein interactions. Nevertheless, one should keep in mind that these links not necessarily reveal a direct protein function, but, for example, can be based on regulatory links between functional categories in the cell (see paragraph on functional associations on page 107).

The procedure was as follows. The number of interactions linking a protein of interest to a functional category (GO slim terms or TIGR sub roles) was counted. To remove unspecific associations, e.g. associations to highly abundant categories, a comparison with 1000 randomized networks was done. Only functional links enriched compared to the randomized networks (Z-value > 2.0) and present in at least 50% (30% for TIGR sub role) of the interactions were selected (Table 29, Table 30).

TPA	defline	GO term	Z-Value	# ints to GO	# ints total	ratio
TP0004	H	nucleotide binding (GO:0000166)	4.10	2	2	1.00
TP0087	CH	hydrolase activity (GO:0016787)	2.80	3	5	0.60
TP0110	H	membrane (GO:0016020)	2.38	2	3	0.67
TP0150	H	hydrolase activity (GO:0016787)	2.62	3	5	0.60
TP0296	CH	nucleotide binding (GO:0000166)	2.52	2	3	0.67
TP0338	H	membrane (GO:0016020)	3.17	2	3	0.67
TP0432	H	nucleotide binding (GO:0000166)	3.29	2	3	0.67
TP0467	H	membrane (GO:0016020)	2.38	2	4	0.50
TP0496	CH	nucleotide binding (GO:0000166)	2.56	3	6	0.50
TP0496	CH	protein biosynthesis (GO:0006412)	2.54	3	6	0.50
TP0496	CH	RNA metabolism (GO:0016070)	5.17	3	6	0.50
TP0561	CH	membrane (GO:0016020)	11.00	33	47	0.70
TP0582	CH	nucleotide binding (GO:0000166)	3.10	5	10	0.50

TP0629	H	cell motility (GO:0006928)	3.72	3	6	0.50
TP0650	CH	protein biosynthesis (GO:0006412)	3.14	2	3	0.67
TP0702	CH	catalytic activity (GO:0003824)	7.53	2	3	0.67
TP0702	CH	molecular function unknown (GO:0005554)	4.85	2	3	0.67
TP0708	H	membrane (GO:0016020)	4.97	9	16	0.56
TP0744	CH	hydrolase activity (GO:0016787)	2.30	2	3	0.67
TP0771	CH	protein biosynthesis (GO:0006412)	4.71	2	3	0.67
TP0802	H	hydrolase activity (GO:0016787)	2.65	5	10	0.50
TP0813	H	RNA binding (GO:0003723)	5.53	2	3	0.67
TP0826	CH	hydrolase activity (GO:0016787)	2.76	2	3	0.67
TP0873	H	structural molecule activity (GO:0005198)	4.92	3	6	0.50
TP0937	CH	binding (GO:0005488)	6.30	2	2	1.00
TP1002	CH	metal ion binding (GO:0046872)	7.04	2	2	1.00
TP1002	CH	cation binding (GO:0043169)	7.53	2	2	1.00
TP1002	CH	hydrolase activity (GO:0016787)	3.95	2	2	1.00

Table 29 Guilt-by-association via GO slim mapping. Each row represents the association of an uncharacterized protein (H for "hypothetical", CH for "conserved hypothetical") with a functional category via its protein interactions. The number of interactions to this category (# ints to GO) and the number of total interactions (#ints total) are given. The ratio defines the fraction of its interactions linking a protein to a function category. The Z-value indicates an enrichment of this link compared to 1000 randomized networks (see Materials & Methods section)

TPA	defline	TIGR sub role	Z-Value	# ints to role	# ints total	ratio
TP0302	CH	Cations and iron carrying compounds	11.49	2	2	1.00
TP0629	CH	Chemotaxis and motility	4.88	4	6	0.67
TP0050	CH	Chemotaxis and motility	4.17	5	10	0.50
TP0579	CH	Chemotaxis and motility	2.71	3	6	0.50
TP0066	CH	Chemotaxis and motility	3.68	5	11	0.45
TP0064	H	Chemotaxis and motility	3.16	4	9	0.44
TP0877	CH	Chemotaxis and motility	2.42	2	5	0.40
TP0832	CH	Chemotaxis and motility	6.12	14	37	0.38
TP0183	CH	DNA replication, recombination, and repair	4.56	6	16	0.38
TP0873	CH	Ribosomal proteins: synthesis and modification	4.54	2	6	0.33
TP0496	CH	tRNA aminoacylation	3.30	2	6	0.33
TP0772	CH	Chemotaxis and motility	2.75	3	9	0.33
TP0583	CH	Chemotaxis and motility	2.70	3	9	0.33
TP0658	CH	Chemotaxis and motility	2.38	3	10	0.30
TP0782	H	Chemotaxis and motility	2.17	2	6	0.33

Table 30 Guilt-by-association via TIGR sub roles. See previous table for details.

Here, the focus will be on proteins not associated to bacterial motility; proteins presumably involved in bacterial motility are discussed in the thesis of Rajagopala SV (Rajagopala 2006).

TP0302 is a conserved hypothetical integral membrane protein associated to proteins "carrying cations". TP0302 interacts with TP0917, a Mg^{2+} transport protein, and TP1038, bacterioferrin – an iron binding protein with unclear function. TP0302 has a "Branched-chain amino acid transport system / permease component" domain (PF02653) which implies that TP0302 is involved in transport of either amino acids or sugars. A genomic neighbourhood (and homology) link to TP0301 in the String database indicates that these two integral membrane proteins might form a transporter complex in the membrane. The found interactions imply a functional link to cation transport.

TP0183, a hypothetical protein only conserved in *Treponema* species, is linked to the process of "DNA replication, recombination, and repair" via six interactions. The interaction partners include DnaA, a DNA repair helicase (TP0380), UvrA, an exonuclease (TP0626),

ParB, and RecX. Strikingly, TP0183 is associated to the SsrA-binding protein (TP0184) by the genomic neighbourhood method in the String database (combined score 0.418). SsrA-binding protein (SmpB) binds and regulates ssrA's (tmRNA) function, a small RNA that interacts with selected ribosomes to target the nascent polypeptides for degradation. SsrA is required for correct timing of DNA replication (Keiler and Shapiro 2003) and the SmpB-SsrA complex was, for example, found to be required for *Yersinia pseudotubercolosis* pathogenicity (Okan et al. 2006). In this context, TP0183 might be a specific factor present in *T. pallidum* and *T. denticola*, which functions as a regulatory protein in DNA replication and other processes via an unknown mechanism, potentially involving the SsrA-SmpB pair.
The hypothetical protein **TP0873** associates with several ribosomal proteins. On the contrary, it was also found to interact with TP0870 in a reciprocal manner and an association with flagellar genes is supported by the gene neighbourhood method as provided by the String database (combined String score of 0.383 to FliD). Thus, TP0873 might link flagellum related processes to the translational machinery.
The interactions of **TP0496**, a protein conserved in *Treponema* and *Borrelia* species, include several proteins involved in protein biosynthesis/tRNA metabolism. A link to DNA replication is formed by the interaction with DNA primase (DnaE). TP0496 is located in an operon with ROD shape-determining proteins MreB/C (von Mering et al. 2005). The interaction with the DNA replication protein DnaE is in concordance with the known link between MreB and DNA replication (Defeu Soufo and Graumann 2005). Therefore, TP0496 might function as a link between tRNA metabolism (amino acid or translational status) and DNA replication.

Comparison with protein networks of other species

Binary comparison with datasets from other species

The *T. pallidum* network was compared with protein interaction networks of other species. This comparative interactomics analysis is based on orthologous relationships between genes from different species. The common assumption is that orthologous proteins share a similar function, and thus show a similar interaction pattern. However, this hypothesis does not need to hold for all orthologs considered.

Interaction datasets from three different bacterial species were considered. Rain *et al.* generated a partial Y2H-based protein-interaction map for *H. pylori* (HPY); Parish *et al.* analyzed the whole proteome of *C. jejuni* for binary protein-interaction with the Y2H system (unpublished data, kindly provided by R. Finley's group) (CJE); Butland *et al.* and Ariffuzaman conducted two large-scale complex purification for *E. coli* (ECO I&II) (Rain et al. 2001; Butland et al. 2005; Arifuzzaman et al. 2006; Baba et al. 2006).

The comparison were based on two different definitions of orthologous gene relationships: by the COG algorithm as provided by the String database (von Mering et al. 2005) and by the MBGD database (Uchiyama 2003). MBGD provides a more stringent definition of orthology; for this thesis, the alignment was demanded to cover at least 50% of the smaller protein's sequence.

The results of this comparison with the number of interactions identified in another species' set are shown in Table 31.

		HPY	CJE all	CJE HCF	ECO SPK I	ECO SAI I	ECO SPK II	ECO SAI II
TPA all	**MBGD**	6/132 =4.5%	10/1016 =1.0%	6/318= =1.9%	9/2037 =0.4%	4/455 =0.9%	6/1268 =0.5%	8/546 =1.5%
	COG	10/196 =5.1%	25/1314 =1.9%	15/428 =3.5%	12/2381 =0.5%	7/588 =1.2%	10/1549 =0.6%	12/685 =1.8%
TPA filtered	**MBGD**	5/132 =3.8%	8/1016 =0.9%	6/318 =1.9%	8/2037 =0.4%	4/455 =0.9%	5/1268 =0.4%	7/546 =1.3%
	COG	9/196 =4.6%	18/1314 =1.4%	11/428 =2.6%	10/2381 =0.4%	7/588 =1.2%	9/1549 =0.6%	11/685 =1.6%

Table 31 Overlap between interaction datasets. *T. pallidum* interactions were compared with other datasets: HPY (H. pylori, (Rain et al. 2001)), ECO SPK I (*E. coli* spoke, (Butland et al. 2005)), ECO SAI I (E.coli SAI, socio-affinity-index (Gavin et al. 2006), (Butland et al. 2005)), ECO SPK II (*E. coli* spoke, (Arifuzzaman et al. 2006)), ECO SAI II (*E. coli* SAI, (Arifuzzaman et al. 2006)). Interolog predictions were based on orthologous relationships as defined by the MBGD database or the COG database (taken from StringDB). Interologs were predicted for *T. pallidum* and the number of *T. pallidum* interactions overlapping with these predicted interactions was counted. Overlap is given as: X/Y=Z%, with X being the number of interactions in *T. pallidum* overlapping with predicted interologs from reference set; Y being the total number of predicted interologs only counting a maximum of one interolog per identified interaction; z percentage of overlap. Please note: Butland et al. include homodimers in their interaction set.

In addition, the data was compared to an intermediate-scale Y2H study focusing on bacterial DNA replication in *B. subtilis* (Noirot-Gros et al. 2002). The dataset obtained from the SpiD database (genome.jouy.inra.fr/spid) contains interactions identified in the library screens, by additional matrix screens (directly testing for known interactions), and a few literature derived interactions. In total, 110 entries with mapped systematic *B. subtilis* genes were present. Only 27 interologs could be predicted for *T. pallidum* based on MBGD orthology, and of these only two were reproduced in our Y2H screen: TP0058 (DnaB)-TP1005 (DnaH) and TP1005-TP1005 (7.4%).
The identity of overlapping *T. pallidum* interactions with predicted interologs is shown in Supplementary Table 4.

Overlap with (predicted) Protein Complexes

In the previous section, the direct, binary overlap of interactions was calculated. Here, the interactions will be compared with predicted complexes from complex purification studies. The raw results of complex purification studies show co-purified proteins, not distinct protein complexes. To identify defined protein complexes the specific affinity between protein pairs in an *E. coli* complex purification study was defined (Arifuzzaman et al. 2006) – the limited coAP/MS study (Butland et al. 2005) was not considered. For this, the socio-affinity model (SAI) as defined by Gavin *et al.* (Gavin et al. 2006) was used (the SAI calculation was done by J. Goll). SAI combines the spoke and matrix model of co-purifications into one statistical framework. The SAI score indicates the propensity of two proteins to co-purify specifically in the whole dataset. A SAI score cutoff of 5 (as judged from the SAI score distribution and similar to the cutoff defined by Gavin *et al.* (Gavin et al. 2006)) was chosen and the clustering algorithm MCODE (Bader and Hogue 2003) was applied to this network to identify protein complexes (Supplementary Table 6). Table 32 shows a summary of these complexes with more than 5 orthologous components in *T. pallidum* (as defined by the MBGD database) and *T. pallidum* interologs connecting the homologous components of these complexes. Complex 8 is the complex with the highest

number of internal Y2H connections. However, these internal interactions were only found for a huge complex covering ~5% of the genome of *E. coli*.

# components	# Hom. components	interactions in complex	# internal interactions
344	74	TP0757-TP0947 TP0757-TP0459 TP0757-TP0255 TP0519-TP0519 TP0519-TP0234 TP0519-TP0094 TP0519-TP0237 TP0519-TP0067 TP0124-TP0067 TP0498-TP0397 TP0586-TP0397 TP0586-TP0648 TP0586-TP0067 TP0643-TP0397 TP0459-TP0067 TP0773-TP0237 TP0660-TP0067 TP0094-TP0067 TP0162-TP0959 TP0034-TP0469	20
118	32	TP0554-TP0985 TP0554-TP0097 TP0097-TP0684	3
113	25		0
71	23	TP0519-TP0519	1
83	19	TP0071-TP0519 TP0632-TP0339 TP0188-TP0519 TP0094-TP0519 TP0519-TP0519	5
32	12	TP0870-TP0760 TP0870-TP0640	2
36	12		0
22	9		0
37	6	TP0121-TP0121	1
35	6		0
17	6		0

Table 32 *E. coli* protein complexes (Mori SAI defined by MCODE) and *T. pallidum* interologs. Only complexes with more than five orthologous components (as defined by MBGD) are shown.

Experimental Overlap

The overlap with the *C. jejuni* data from Parish et al. is small (~3%). Interestingly, Parish et al. retested 173 interactions from the *T. pallidum* dataset with their system and classified ~28% as positive (*pers. comm.*). Thus, the actual number of reproducible interactions between two species and two different Y2H systems seems to be bigger than one would conclude from the direct comparison of large-scale datasets.

However, only a limited reproducibility rate was observed when testing *T. pallidum* derived interologs in an Y2H system of *H. pylori* proteins. 71 *H. pylori* interologs were selected (Supplementary Table 5) and the corresponding Gateway-based entry clones (pDONR221 vector) were obtained from the "Pathogen Functional Genomics Resource Center" (TIGR, Rockville, U.S.A.). The ORFs were transferred into a bait (pBD-ccdB, Satoko Yoshida, LMU München) and prey vector (pGADT7-DEST), transformed into yeast, and re-tested for Y2H interactions; as a control, the activation level on –LTH (without 3-AT) of the bait-prey combination was compared with the combination of bait and empty prey vector (pGADT7-DEST).

The results are presented in Table 33 and Supplementary Table 5. In total, only 5 out of 71 tested interologs were reproduced (~7%). This percentage is in the same range as the overlap between the whole networks. However, it demonstrates that additional interologs can be still identified, especially for *H. pylori*, for which only 261 baits were tested in the large-scale screen (Rain et al. 2001).

bait	HP0238 (TP0160)	HP0238 (TP0160)	HP0238 (TP0160)	HP0238 (TP0160)	HP0717 (TP1005)	HP1111 (TP0939)	HP0772 (TP0247)	HP1547 (TP0586)
prey	HP0787 (TP0582)	HP0763 (TP0578)	HP1063 (TP0946)	HP1030 (TP0720)	HP0269 (TP0754)	HP1154 (TP0658)	HP1139 (TP0272)	HP1138 (TP0271)
Y2H								
control								
result	+	+	(+)	+	+	(+)	+	(+)

Table 33 Y2H test of *H. pylori* interologs. Only tested interologs which showed higher activation (Y2H) compared to the background (control, empty prey vector) are shown. 5 interactions were marked as positive "+"; three showed too much background activation and were not considered (in parenthesis).

In addition, it should be mentioned that the high false negative rate of the Y2H system prevents conclusions on the absence or non conservation of an interaction. For a large-scale Y2H study on herpesviral interactions only ~10% of a set of predicted interologs could be verified by Y2H using orthologs of another herpes virus, whereas up to 90% could be verified by co-immunoprecipitations (groups of P. Uetz and J. Haas, *manuscript in preparation*).

Essential and Pathogenicity-related Genes

Pathogenicity related genes are of special interest as insights on these proteins could be the basis for further understanding of the Syphilis disease and potentially be used as targets for antibiotic interference. Essential genes are required for survival, and thus for pathogenicity. In addition, specific pathogenicity associated genes can be identified.

Prediction of Essential Genes for T. pallidum

The literature about gene essentiality and their protein interaction properties is ambiguous. Essential genes were suggested to show a higher number of interactions than other gene classes (Jeong et al. 2001), but this finding has been questioned (Coulomb et al. 2005) (see introduction).

	method	**essential genes (% of genome)**	**predicted for *T. pallidum* (MBGD) (% of genome)**
***B. subtilis* (Kobayashi *et al.*)**	systematic gene inactivation & integration of previous studies	271 (6.6%)	181 (17.4%)
***E. coli* (Baba *et al.*)**	systematic gene inactivation & integration of previous studies	303 (6.8%)	179 (17.2%)
***M. genitalium* (Glass *et al.*)**	Saturated transposon screen	382 (79.2%)	204 (19.6%)

Table 34 Overview of datasets and results for the prediction of essential genes in *T. pallidum*.

Gene essentiality is always dependent on the selected growth conditions and there are large variations between datasets. Since *T. pallidum* cannot be cultured continuously *in vitro* and

genetic manipulation methods are not established, no dataset on gene essentially for *T. pallidum* itself is available. However, essential genes can be predicted based on orthologous gene relationships. Still, many essential genes seem to be essential only in a specific species, for example, due to the differential presence of paralogous proteins.
In this thesis, three species with corresponding essential gene datasets were selected for the prediction of essential genes in *T. pallidum*: *E. coli* (Baba et al. 2006), *B. subtilis* (Kobayashi et al. 2003), and *M. genitalium* (Glass et al. 2006). The union of these sets can be assumed to cover most of the bacterial essential genes, which are conserved in several species. Orthology relationships were obtained from the MBGD database (Uchiyama 2003).
An overview of the predictions is given in Table 34, a list of these predictions can be found in Supplementary Table 17.
In total, 282 genes of *T. pallidum* were predicted to be essential. Only 99 of these genes were found to be essential in all three species, on which the prediction was based (Fig. 35).

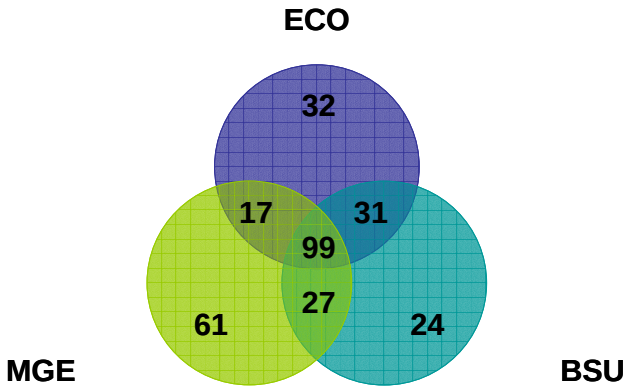


Fig. 35 Overlap of predicted essential genes for *T. pallidum*. Venn diagram shows the overlap between the essential gene predictions from three different datasets (ECO=*E. coli*, BSU=*B. subtilis*, MGE=*M. genitalium*)

Pathogenicity Associated Genes

Possible virulence factors (pathogenicity associated genes) were defined by Weinstock *et al.* (Weinstock et al. 1998) and divided into six groups: Tpr proteins, hemolysins, regulators, polysaccharide biosynthesis, potential membrane or surface-exposed proteins, and proteins with miscellaneous functions. Several protein interactions were identified for these proteins (Supplementary Table 18). Examples of these interactions are discussed next.
The capsular polysaccharide biosynthesis protein (Cap5D, TP0077) interacts with TP0297, a conserved hypothetical protein without known function. TP0297 contains a "SPOR" domain (Interpro: IPR007730). This 35 residue repeat is found in bacterial proteins involved in sporulation and cell division and might be involved in binding peptidoglycan (Mulder et al. 2005). The interaction supports a function for TP0297 in cell wall metabolism and puts this gene into a pathogenicity context.
TP0038, the regulatory protein PfoS/R, interacts with the hypothetical protein TP0708. TP0708 is the gene neighbor of TP0709, a RNA polymerase sigma factor. This might indicate a role of TP0708 in transcriptional regulation in association with TP0038.
Two binary pathogenicity-related complexes were identified. The virulence factor (MviN), TP0516, interacts with TP0171 (Tpp15), another virulence factor. The membrane antigen tpd, TP0971, interacts with another virulence gene, TP0171 indicating a functional link of these proteins.
Due to the presence of the "HD_hydro" (Interpro: IPR006674) domain, the conserved hypothetical protein TP0877 can be predicted to function as a metal-dependent HD-GYP

hydrolase involved in signal transduction. Its interactions points to a signal integration function. It interacts with TP0492 (DNA primase), TP0630 (CheR, chemotaxis methyltransferase), TP0461 (hypothetical protein with DNA binding domain), and TP0981 (signal transduction histidine kinase).
In addition to TP0877, the interactors of the signal transduction protein TP0981 include TP0089 (cyclic nucleotide binding protein) and TP0092 (RNA polymerase sigma factor).
The conserved hypothetical protein TP0819 has a "Blactmase-like" domain (Interpro: IPR001279) and shows three interactions with cell wall enzymes: TP0247 (AmiA), TP0341 (MurC), and TP0670 (D-ala-D-ala-ligase). Thus, this enzyme is most probably involved in cell wall metabolism. However, a certain sequence similarity to ribonucleases needs to be functionally tested.
These individual examples provide starting points for a detailed investigation of the mechanisms of virulence.
A second set of putative pathogenicity associated genes is provided by a microarray study. Gene expression levels during experimental rabbit infection with *T. pallidum* were measured by Smajs *et al.* (Smajs et al. 2005). In this microarray study, the cDNA/DNA signal ratio was calculated giving relative expression levels of all *T. pallidum* proteins. Several flagellar, but also ribosomal proteins were found among the genes with highest expression levels. This study gives an impression on the genes that are highly expressed during infection, but does not report specific virulence factors (due to lack of differential expression profiles).

Topological Properties

Different protein classes can be assessed in respect to several topological properties. Here, only the node degree and the centroid values are analyzed.
The centroid value indicates the localization of a protein towards the center of the network and is defined as

$$\mathcal{C}_{cen}(v) := \min\{\mathrm{f}(v,w) \colon w \in V \setminus \{v\}\}$$

Where f (v,w) := $\gamma_v(w)$- $\gamma_w(v)$ and $\gamma_v(w)$ denotes the number of vertices that are closer to v than to w (Junker et al. 2006). The centralities were computed with CentriBin (Junker et al. 2006).
However, no significant difference of the analyzed distributions was observed except for the distribution of centroid values for the pathogenicity related gene classes (Fig. 36). Regulatory proteins, which are classified as pathogenicity related proteins, had significantly higher centroid values compared to other proteins. Since the centroid value of a protein indicates its location in the center of the PIM, regulatory proteins can be thought to be well embedded in the network, and thus capable to measure the status of the network.

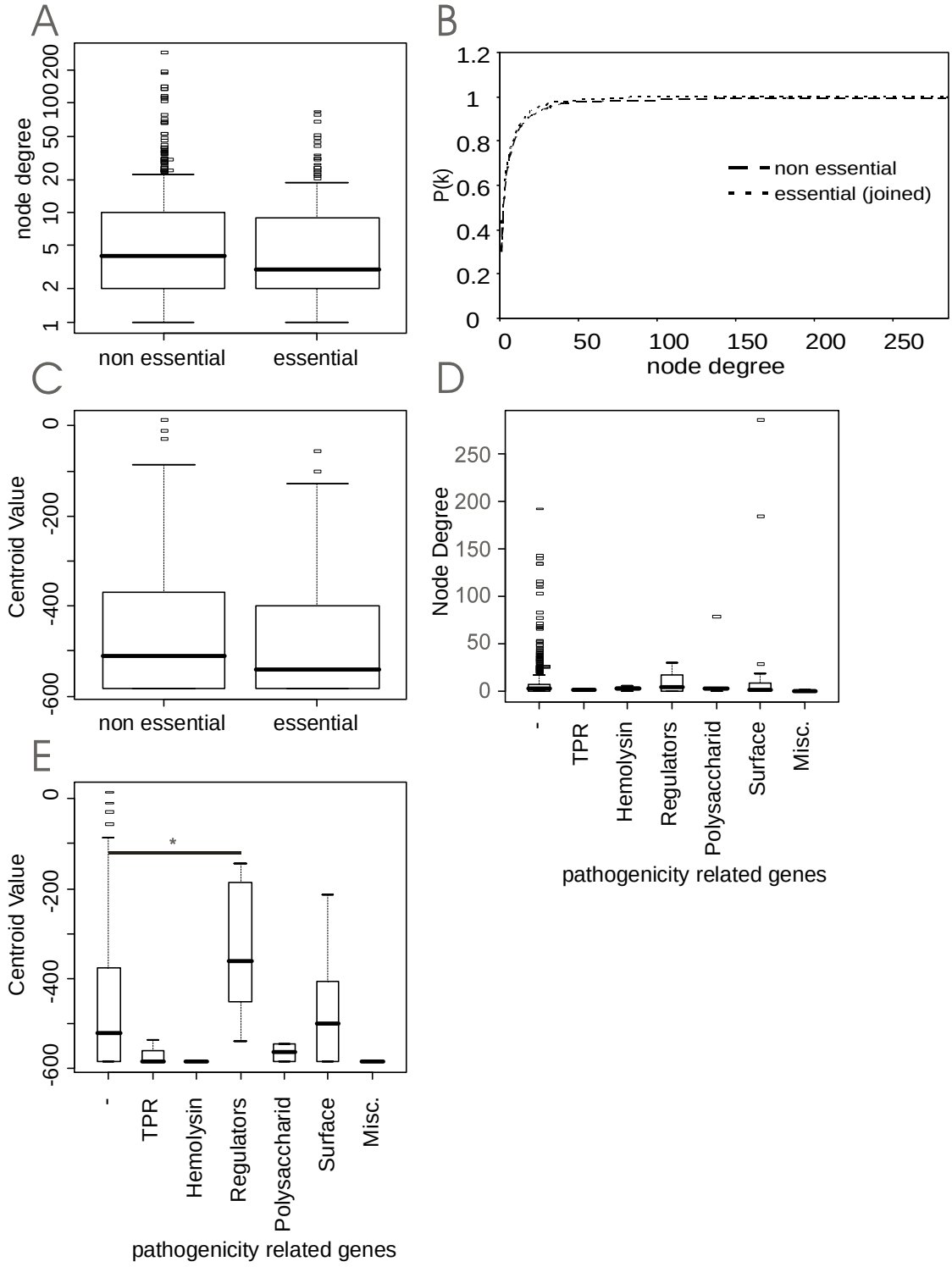


Fig. 36 Centralities. (A) Boxplot of node degrees comparing predicted essential vs. remaining proteins. Proteins with node degree of zero were not considered. The whole *T. pallidum* network was used. (B) Cumulative probability for node degrees comparing predicted essential vs. remaining proteins. Proteins with node degree of zero were considered and the computation was based on the filtered *T. pallidum* network. (C) Boxplot of centroid values comparing predicted essential vs. remaining proteins. The filtered *T. pallidum* network was used. (D) Boxplot of node degrees comparing different classes of pathogenicity related genes and remaining proteins (-). The filtered *T. pallidum* network was used. (E) Boxplot of centroid values comparing different classes of pathogenicity related genes and remaining proteins. The filtered *T. pallidum* network was used. (*) Statistically significant difference ($p<0.05$) based on Kruskal-Wallis rank sum test.

Functional Associations

Functional associations of pathogenicity related genes and predicted essential genes were analyzed analogously to the functional class connections in the whole network (see above). Only connections between gene classes with at least two interactions and a Z-value > 2 (statistical significance) were considered (Fig. 37, Supplementary Table 19, Supplementary Table 20).

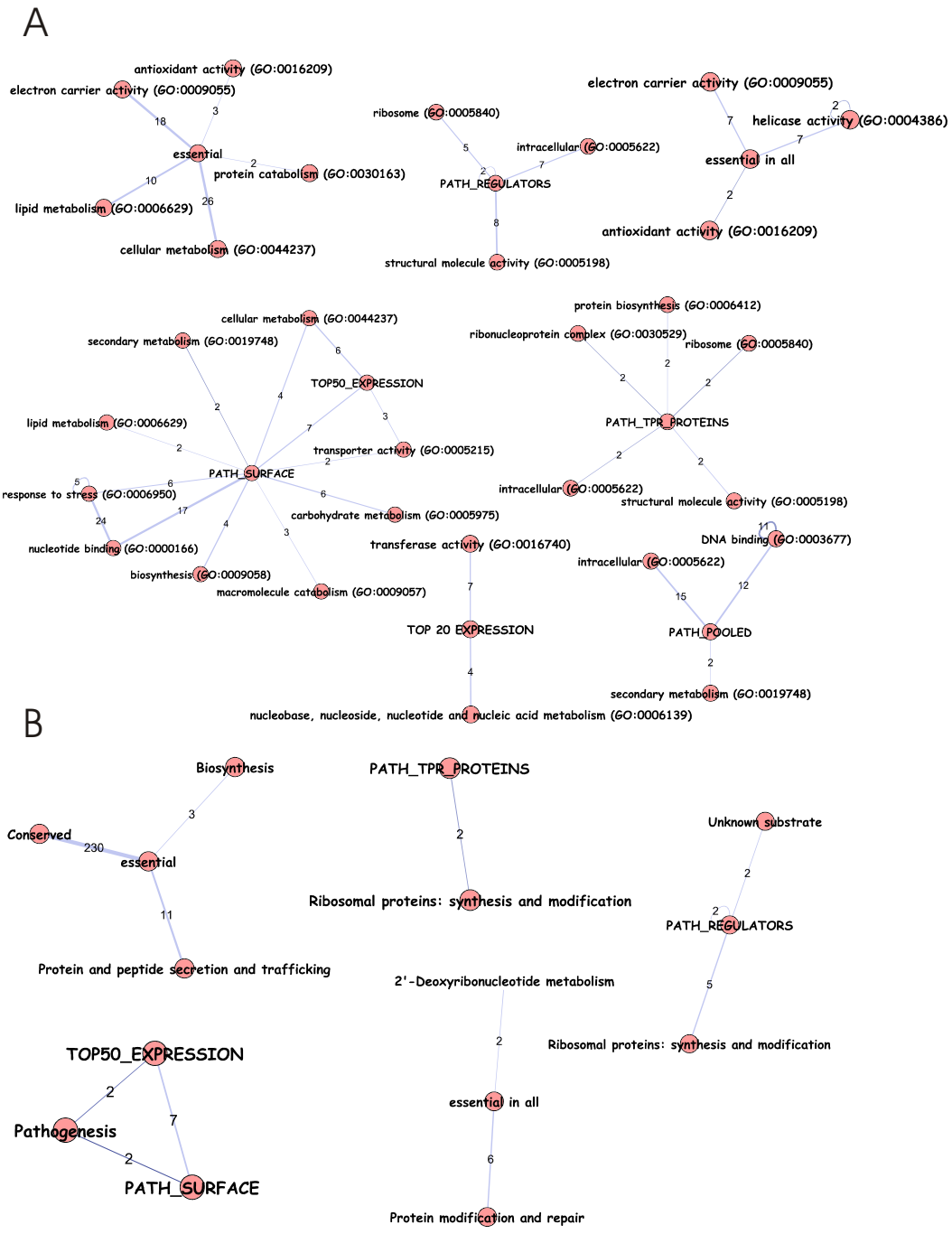


Fig. 37 Functional associations of pathogenicity related and essential genes. The connections between pathogenicity related and predicted essential genes and functional categories in the filtered *T. pallidum* dataset are shown. Connections to GO terms are shown in (A) and connections to TIGR main roles are shown in (B). The width of edges between functional categories are scaled according to the number of Y2H interactions connecting them, the number of interactions is given as edge label, and the darkness of the edge indicates the statistical significance (Z-value, see supplementary tables). Only connections with Z>2.0 are shown.

Surface localized pathogenicity proteins ("PATH_SURFACE") were linked to proteins with the highest expression during experimental rabbit infection ("TOP50_EXPRESSION") (Table 35). The linking interactions include, for example, the heterodimer of pathogen-specific membrane antigen (Tpd, TP0971) and 15kDa lipoprotein (Tpp15, TP0171). Both proteins are highly expressed and classified as pathogenicity-related genes indicating the formation of a pathogenicity-related binary complex. The hypothetical protein TP0869 interacts with the leucine-rich repeat protein TpLRR (TP0225) indicating a pathogenicity-related function for TP0869, as well.

Bait	Description	Class	Prey	Description	Class
TP0006	Tp75 protein	S	TP1013	chaperonin (groES)	E
TP0163	ABC transporter, periplasmic binding protein (troA)	S	TP1013	chaperonin (groES)	E
TP0228	biotin synthase, putative (bioY)	E	TP0034	ABC transporter, periplasmic binding protein	S
TP0869	hypothetical protein	E	TP0225	leucine-rich repeat protein TpLRR	S
TP0870	flagellar filament 31 kDa core protein (flaB3)	E	TP0702	conserved hypothetical protein	S
TP0971	membrane antigen, pathogen-specific (tpd)	E, S	TP0171	lipoprotein, 15 kDa (tpp15)	E, S
TP1038	bacterioferrin (TpF1)	S	TP0171	lipoprotein, 15 kDa (tpp15)	E

Table 35 Interactions linking PATH_SURFACE (S) and TOP50_EXPRESSION (E)

Genes essential in *E. coli*, *B. subtilis*, and *M. genitalium* were, for example, linked to genes possessing helicase activity (Table 36).

Bait	Description	Class	Prey	Description	Class
TP0058	replicative DNA helicase (dnaB)	H	TP0001	chromosomal replication initiator protein (dnaA)	E
TP0058	replicative DNA helicase (dnaB)	H	TP0005	DNA gyrase, subunit A (gyrA)	E
TP0058	replicative DNA helicase (dnaB)	E	TP0102	rep helicase, single-stranded DNA-dependent ATPase (rep)	H
TP0526	ATP-dependent helicase (hrpA)	H	TP0192	ribosomal protein L2 (rplB)	E
TP0526	ATP-dependent helicase (hrpA)	H	TP0892	N utilization substance protein A (nusA)	E
TP0578	cell division protein (ftsY)	E	TP0380	DNA repair helicase, putative	H
TP0687	DNA recombinase (recG)	H	TP1013	chaperonin (groES)	E

Table 36 Interactions linking "essential in all" (E) and "helicase activity GO:0004386" (H)

Another interesting interaction class, although not over-represented, links genes essential in all three considered bacteria to other essential genes (Table 37). These interactions are attractive targets for antibiotics directed against protein interaction epitopes.

Bait	Description	Prey	Description
TP0058	replicative DNA helicase (dnaB)	TP0001	chromosomal replication initiator protein (dnaA)
TP0058	replicative DNA helicase (dnaB)	TP0005	DNA gyrase, subunit A (gyrA)
TP0192	ribosomal protein L2 (rplB)	TP0756	methionyl-tRNA formyltransferase (fmt)
TP0354	thymidylate kinase (tmk)	TP0097	translation initiation factor 1 (infA)
TP0394	DNA topoisomerase I (topA)	TP0208	preprotein translocase subunit (secY)

TP0641	histidyl-tRNA synthetase (hisS)	TP0641	histidyl-tRNA synthetase (hisS)
TP0756	methionyl-tRNA formyltransferase (fmt)	TP1013	chaperonin (groES)
TP0794	S-adenosylmethionine synthetase (metK)	TP0002	DNA polymerase III, subunit beta (dnaN)
TP0842	methionine aminopeptidase (map)	TP0294	phosphoribosyl pyrophosphate synthetase (prs)
TP0842	methionine aminopeptidase (map)	TP0354	thymidylate kinase (tmk)
TP1024	ribosomal protein S9 (rpsI)	TP0743	ribosomal protein L27 (rpl27)

Table 37 Interactions between genes essential in all considered bacteria (*E. coli*, *B. subtilis*, and *M. genitalium*).

Protein interactions of essential and pathogenicity related proteins provide interesting clues on the function and functional links of these proteins. However, these clues need to be taken as a basis for functional and pathogenicity related tests.

Set of Interactions Supported by Additional Evidences & Evolutionary Conservation

In this paragraph, a subset of protein interactions identified by Y2H and supported by additional evidences is defined and analyzed with respect to evolutionary conservation.
Interactions supported by the String database at a medium confidence level (score > 0.4) or reproduced by any other dataset considered in this study were selected. In total, 155 interactions were compiled in this subset with the majority (106) supported by the String database.
The network of these selected interactions is shown in Fig. 38 A. Conservation of these protein interactions through evolution is visualized in Fig. 38 B and individual interactions can be found in Supplementary Table 16.
Conserved interactions fall into different conservation classes: the protein-interaction partners might be overall conserved (class II, IV), always present and absent together (class I), or one interacting protein might be abundantly expressed whereas the other is optional (class III).
These conservation classes are based on different distributions of functional categories. Class I consists mainly of "chemotaxis and motility proteins" (~65% of the interacting proteins). These motility-related interaction pairs are present in motile bacteria and absent in non-motile bacteria. Class II contains several DNA metabolism-related (27%) and protein translation (24%) proteins. These interaction pairs are highly conserved in prokaryotes. Class III contains conserved hypothetical proteins (20%), DNA metabolism (17%), and "chemotaxis and motility" (13%) proteins. These interactions are formed between one constitutive and on optional interaction partner. For example, the constitutive protein ribonucleoside-diphosphate reductase (NrdB) interacts with a flagellar filament protein (FlaB3) in motile bacteria. This link is probably involved in regulation and is supported by the discovery of a regulationary link between NrdB and motility by Nishimura & Hirota (Nishimura and Hirota 1989). Another example is the constitutive excinuclease uvrC, which is co-conserved with the interacting conserved hypothetical protein TP0894 in a subset of bacterial species. TP0894 carries a DNA binding domain (OB-fold nucleic acid-binding domain), which is also present in DNA repair proteins such as RecG and BRCA2. Thus, the orthologous group of TP0894 appears to contain novel DNA repair proteins, whose function involves the binding to uvrC. Class IV contains an even higher number of conserved proteins (45%) and DNA metabolism proteins (18%).
In addition, note that the protein interaction network of *T. pallidum* serve as a reliable basis to predict protein interactions for other sequenced species (Fig. 38).

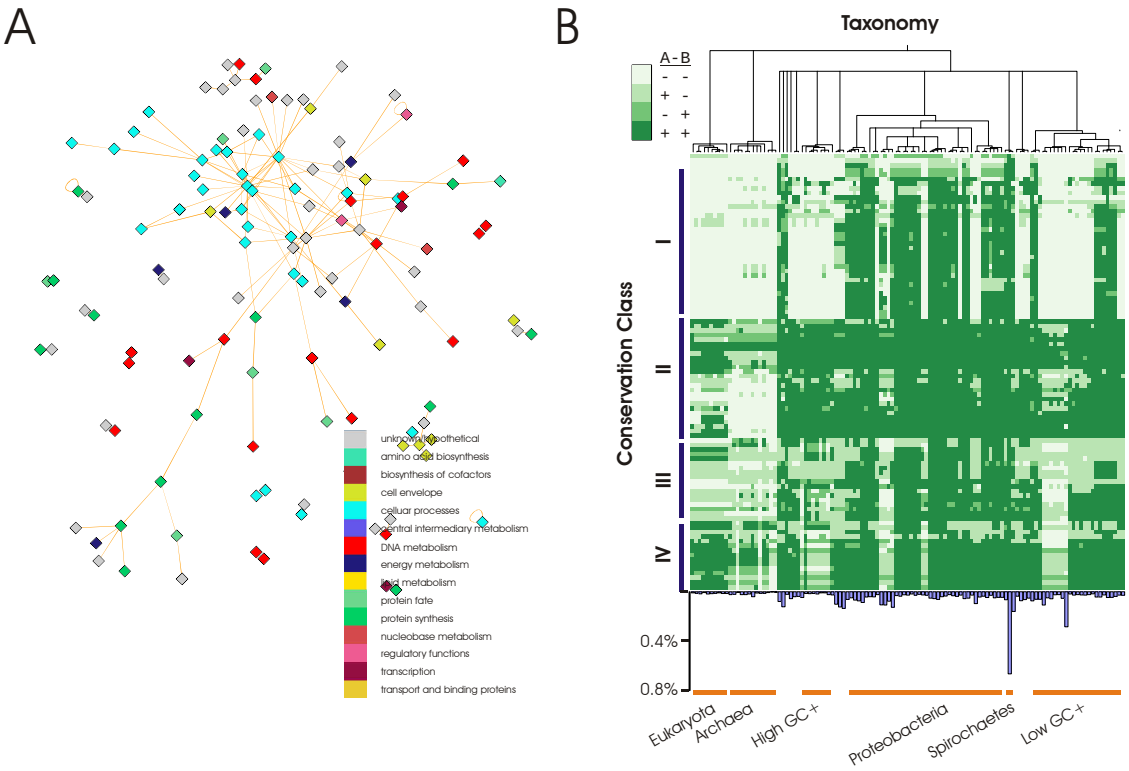


Fig. 38 Subset of interactions supported by additional evidences. Y2H interactions from the whole *T. pallidum* dataset, which are supported either by the String database (medium confidence level) or by an overlap with any other protein-interaction study, are selected. (A) Network of these interactions colored according to TIGR main roles. (B) Conservation of protein interactions through evolution. Phylogenetic profiles of selected protein interactions (only from filtered dataset) are shown: each column reflects one species, each row one protein interaction. The color indicates the conservation of each protein interaction (on proteins' level) in each species ranging from white (both interacting proteins are absent) to dark green (both proteins are present) (see color key). The species are arranged according to their taxonomic relationships (String database). The phylogenetic profiles are based on predicted orthology relationships taken from the String database (von Mering et al. 2005). Orthology can be used for predicting protein interactions in other species. Predictions were based on the filtered interaction set of *T. pallidum*. The maximal number of protein interactions depends on the number of proteins of the organism. The bar diagram below the conservation diagram shows the percentage of predicted interactions for each species taking the maximal number of interactions as the basis.

Establishing of Co-Immunoprecipitation Strategy and Initial Results (coEXcoIP method)

The yeast-two-hybrid system employed in this study is designed to reduce the number of false positive interactions. Nevertheless, verification of the identified protein-interactions is usually the first step before focusing on functional details of a protein-interaction.
In this paragraph, a method that allows for intermediate-throughput verification of protein-interactions is presented. This method relies on the co-immunoprecipitation (coIP) of proteins co-expressed in *E. coli* cells.

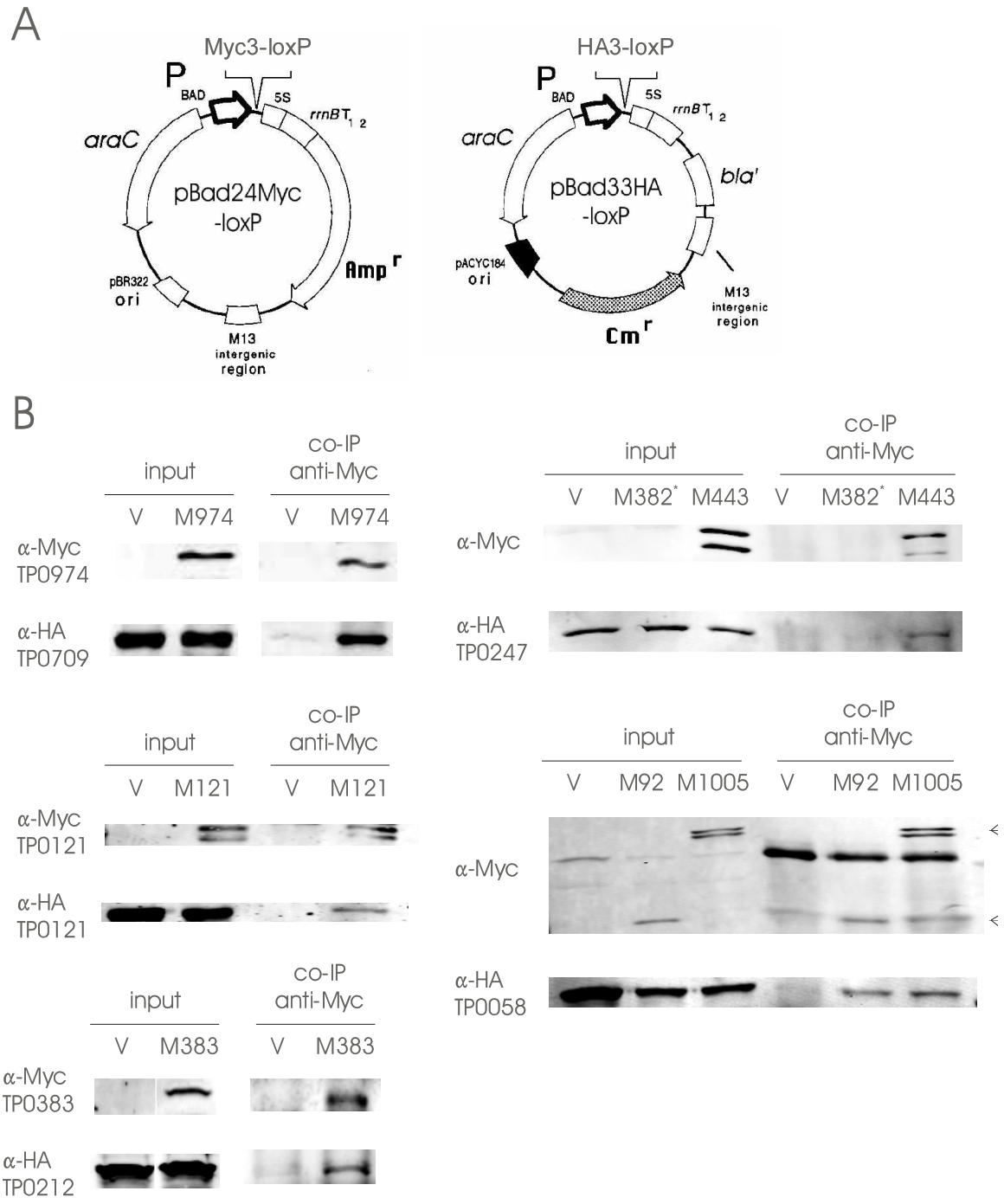


Fig. 39 coExCoIP method. Verification of protein-interactions by co-immunoprecipitation of co-expressed proteins. (A) Vectors designed for co-expression in *E. coli*. (B) Co-immunoprecipitation done for *T. pallidum* interactome. (*) Myc-fusion not expressed in soluble form.

The selection of the expression systems is most crucial; a non-physiological high expression level can, for example, lead to aggregation and precipitation of the proteins. The co-expression vectors were designed on basis of the pBad-vector series (Fig. 39 A) (Guzman et al. 1995). A Myc-tag fused to a loxP-site was inserted into the multiple cloning site (MCS) of pBad24 and a HA-tag fused to a loxP-site was inserted into the MCS of pBad33. Co-transformation of a single *E. coli* cell with these vectors is feasible due to compatible origins, pBR322 origin and pACYC184 origin, and complementary resistance genes, Amp^R

(ampicillin) and Cm^r (chloramphenicol). Entry clones from the UPS-cloning system can easily be recombined with these vectors, co-transformed into *E. coli* DE3 cells, and used for co-immunoprecipitation. Because the anti-Myc antibody (Santa Cruz) proved to work well for co-immunoprecipitation, coIPs were done with this antibody.
A small subset of protein-interactions from the Y2H screen was tested with this method (Fig. 39 B). The following interactions could be confirmed: TP0974 (newly identified FlgM protein)-TP0709 (sigma factor), TP0247 (AmiA)-TP0443 (hypothetical protein), TP0121 (hypothetical, lysine aminomutase) -TP0121, TP0212 (RNA polymerase alpha chain) -TP0383 (conserved hypothetical protein), TP0058 (DNA helicase)-TP0092 (sigma factor), and TP0058-TP1005 (DNA polymerase III, subunits gamma and tau).
Thus, the system works as a verification method for protein-interactions detected by the Y2H system. In addition, a higher solubility of proteins is observed in this system compared to expression from a GST-vector, pMM110. However, this system should be adapted for higher throughput in the future. This can be done performing the co-expression in 96-well plates and optimizing the coIP-method for the same plate format.

An Individual Gene Truncation Study – TP0981

TP0981 is a putative sensory transduction enzyme, which carries a GAF and a DUF1/GGDEF domain. The GAF domain probably functions as a signal input domain, whereas the output is mediated through cyclic-di-GMP produced by the GGDEF domain (Jenal and Malone 2006).
Due to its signalling function TP0981 is of special interest. It was found to interact with several proteins including DNA metabolism and tRNA metabolism proteins (Supplementary Table 2).
TP0981 was split into its domains and these fragments were tested for interactions in the Y2H assay (Fig. 40).

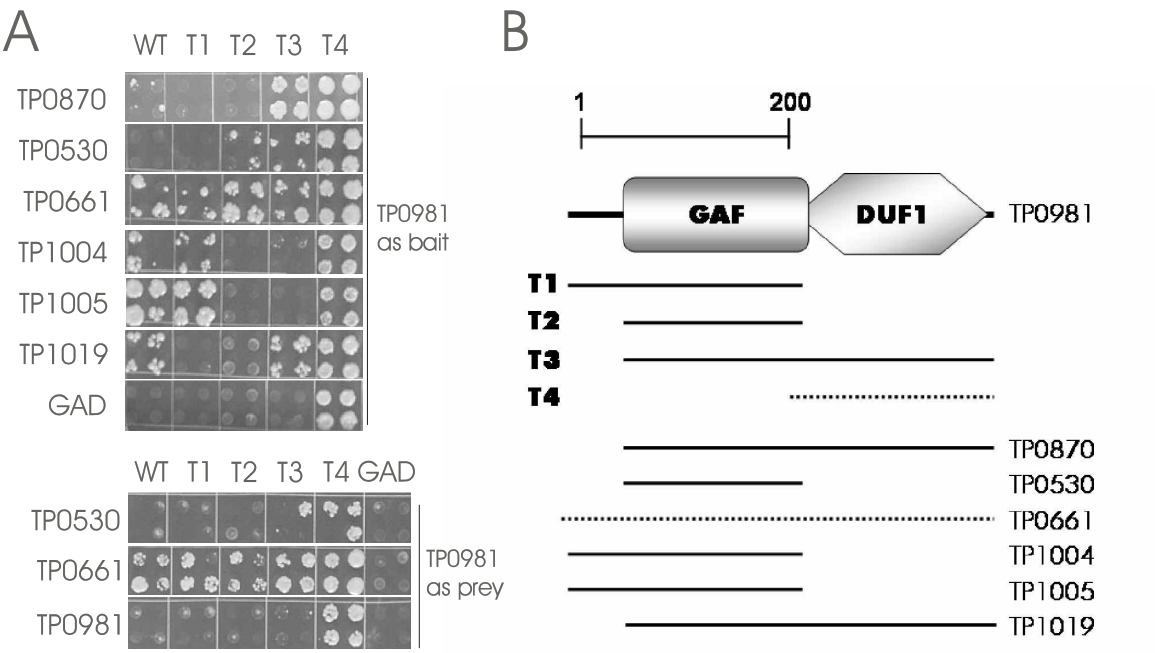


Fig. 40 Interactions of TP0981's fragments. Four fragments of TP0981 (T1-T4, see B) were prepared and tested for interactions in the Y2H assay (A). Only tests which yielded a positive interaction are shown. In the upper panel TP0981 and its fragments are tested as baits, in the lower panel as preys. GAD is the mating with the empty prey vector (pLP-GADT7) and serves as a negative control. (B) Summary of TP0981 fragments and interacting regions. TP0981 consists of a GAF and a DUF1 (GGDEF) domain. The rows T1-T4 show the region of the individual fragments of TP0981. For the interactors of TP0981 (TP0870-TP1019), the interacting regions of TP0981 is shown.

The DUF1/GGDEF domain alone (fragment T4) showed unspecific interactions (self-activator). Even at higher concentrations of 3-AT (competitive inhibitor of His3p) no specific interactions were identified. Thus, results involving interactions with this fragment could not be evaluated.
TP0661 interacts unspecifically with all fragments indicating that its interactions are false positives (interaction is not contained in filtered interaction map).
TP0530, TP1004, and TP1005 appear to bind to the N-terminal part, which also includes the GAF domain. TP1019 interacts only with fragment T3, thus it might interact with the GGDEF domain.
TP1004 (RecR) and TP1005 (DnaA) are both involved in DNA metabolism indicating a link of the input domain to DNA metabolism. TP1019 is involved in tRNA metabolism and might constitute another regulatory link.
Thus, it can be concluded that the interacting domains of TP0981 could be narrowed down for a few interacting proteins. The results indicate a link between the input domain and DNA metabolism. However, the biological significance of this link is still not clear.

3.4. A Functional Complex – Proteins Involved in Bacterial Motility

A special type of motility, e.g. involving periplasmic flagella, characterizes *T. pallidum*. However, understanding of its motility is still at its infancy. What can large-scale studies contribute to the characterization of bacterial motility?

Several interactions involving known motility proteins were discovered by Y2H screening. These include intra motility interactions and interactions with other functional classes (see Fig. 31). Among them, several uncharacterized proteins showed an interaction with known motility proteins (see Table 30). These are candidates for *bona fide* motility proteins. In chapter 3.5 the in detail characterization of a newly identified assembly factor for the bacterial flagellum is presented.

This section is limited to two aspects. First, a genome-wide motility screen for *E. coli* is presented. Secondly, connections of motility proteins to other functional categories in several datasets are compared. These results are part of a broader analysis of bacterial motility, which will be published separately. An in detail analysis of *T. pallidum*'s motility proteins can be found in the PhD thesis of SV Rajagopala (Rajagopala 2006).

Genes Essential for Bacterial Motility

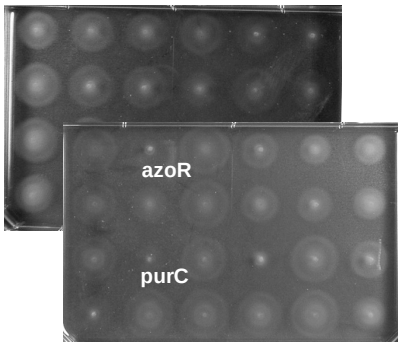


Fig. 41 Example plates of genome-wide motility phenotyping for *E. coli*. Two "swarming plates" with 24 tested mutant strains on each plate are shown.

Although, interaction datasets provide evidence for physical links of proteins with the motility complex, they do not offer insights into the functional relevance of the found interactions. Thus, the interaction sets need to be complemented with functional data.
For *B. subtilis,* a genome-wide analysis of genes affecting motility is available (Schumann et al. 2000). Additional mutants were added to this set (Rajagopala 2006; Titz et al. 2006a).
For *E. coli* such a systematic analysis of motility phenotypes has not been undertaken. Therefore, a systematic knockout library comprising of 3985 individual mutant strains (Baba et al. 2006) was tested for a reduction of motility using an automated robotic procedure (Supplementary Table 22).
Both large-scale motility datasets contain a similar number of affected mutants: 146 for *B. subtilis* and 159 for *E. coli* (Table 38). About 4% of genes in both species show an effect on motility under the conditions tested. Among them are 45

(30%) and 43 (27%) known motility genes, respectively. The others belong to several functional classes (Fig. 42): Both datasets are, for example, significantly enriched for proteins involved in "Energy metabolism" and "Biosynthesis and degradation of surface polysaccharides and lipopolysaccharides".
Both motility datasets show a high fraction (~30%) of known motility proteins supporting the quality of both datasets. The overlap between both datasets, however, is small with 37% and 50% of the orthologs present in the other species showing a motility phenotype.

	E. coli	***B. subtilis***
motility mutants	159	146
(% genome)	(3.7%)	(3.5%)
orthologs (MBGD)	81	68
in other species	(51%)	(47%)
orthologs with reduced motility	30	34
(% overlap of orthologs)	(37%)	(50%)

Table 38 Comparison of E. coli and B. subtilis motility mutant data. The number of mutant strains (genes) with reduced motility in *B. subtilis* and *E. coli* is given. For each motility mutant set, the number of orthologs in the other species is shown, e.g. 81 motility mutant genes of *E. coli* are present in the genome of *B. subtilis* as orthologous proteins. Orthology was defined by the MBGD database (Uchiyama 2003). For these orthologous mutant genes the number showing a motility phenotype in the other species is given.

The overlap between both motility datasets is mainly based on known motility proteins (Table 39). Apart from these, only a single peptidoglycan enzyme, AmiA, was reproducibly found in both species. On can conclude, that most (if not all) *bona fide* core motility proteins, which are conserved throughout evolution, have already been identified. On the other hand, it is clear that a large number of additional genes show an effect on motility. This can be explained by different levels of essentiality of certain metabolic or peptidoglycan enzymes (for general processes required for motility) in these species. Strikingly, only about 50% of genes affecting motility in one species are conserved in the other. A certain subset of these genes might be species-specific genuine motility genes. Examples of species-specific motility proteins are given by Pallen *et al.* (Pallen et al. 2005) and another example is presented in chapter 3.5.

Gene	Description
B1073	flgB (flagellar component of cell-proximal portion of basal-body rod)
B1074	flgC (flagellar component of cell-proximal portion of basal-body rod)
B1078	flgG (flagellar component of cell-distal portion of basal-body rod)
B1081	flgJ (muramidase)
B1082	flgK (flagellar hook-filament junction protein 1)
B1083	flgL (flagellar hook-filament junction protein)
B1879	flhA (predicted flagellar export pore protein)
B1880	flhB (predicted flagellar export pore protein)
B1883	cheB (fused chemotaxis regulator)
B1884	cheR (chemotaxis regulator, protein-glutamate methyltransferase)
B1885*	tap (methyl-accepting protein IV)
B1887	cheW (purine-binding chemotaxis protein)
B1888	cheA (fused chemotactic sensory histidine kinase)
B1889	motB (protein that enables flagellar motor rotation)

B1890	motA (proton conductor component of flagella motor)
B1922	fliA (RNA polymerase, sigma 28 (sigma F) factor)
B1923*	fliC (flagellar filament structural protein (flagellin))
B1924	fliD (flagellar filament capping protein)
B1925	fliS (flagellar protein potentiates polymerization)
B1938	fliF (flagellar basal-body MS-ring and collar protein)
B1939	fliG (flagellar motor switching and energizing component)
B1941	fliI (flagellum-specific ATP synthase)
B1942	fliJ (flagellar protein)
B1945	fliM (flagellar motor switching and energizing component)
B1946	fliN (flagellar motor switching and energizing component)
B1948	fliP (flagellar biosynthesis protein)
B1949	fliQ (flagellar biosynthesis protein)
B1950	fliR (flagellar export pore protein)
B2435	amiA (N-acetylmuramoyl-l-alanine amidase I)
B4355*	tsr (methyl-accepting chemotaxis protein I, serine sensor receptor)

Table 39 Mutated *E. coli* genes with motility phenotype in *E. coli* and *B. subtilis*.
** more than one paralog with reduced motility in B. subtilis.*

TPA protein	…interacts with	description	…has motility Phenotype
TP0738	FlgC, FlaA, FliS	conserved hypothetical protein	B0637
TP0247	FlaA	N-acetylmuramoyl-L-alanine amidase (amiA)	B2435
TP0255	FlaA	ribosomal protein L31 (rpmE)	B3936
TP0339	FlgD	conserved hypothetical protein	B2594
TP0773	FlgG	periplasmic serine protease DO (htrA)	B0161
TP0209	FliG, CheR, FliY, FlgE, FliS	ribosomal protein L36 (rpmJ)	B3299
TP0945	FliS	ribulose-phosphate 3-epimerase (cfxE)	B3386

Table 40 Orthologous proteins interacting with motility proteins and showing motility phenotype in *E. coli*.

TPA protein	…interacts with	description	…has motility Phenotype
TP0247	FlaA	N-acetylmuramoyl-L-alanine amidase (amiA)	BSU35620
TP0046	CheR, FlgD, FlaB3, FliE	hypothetical protein	BSU00320
TP0048*	FliY, FlgC, FlaA, FliS	conserved hypothetical protein	BSU08950 BSU08960
TP0658*	FlaB1, FlaB2, FlaB3	transmembrane protein, putative	BSU35380

Table 41 Orthologous proteins interacting with motility proteins and showing motility phenotype in *B. subtilis*. * mutants from (Rajagopala 2006; Titz et al. 2006a).

A large fraction of the proteome (143 proteins) of *T. pallidum* had at least a single interaction with a known motility protein (TIGR sub role). 65 and 68 of these have orthologs in *E. coli* and *B. subtilis*, respectively. Only seven and four of these orthologs showed a motility

phenotype (Table 40, Table 41). The hypothetical proteins among these are candidates for *bona fide* motility proteins.

Connections of Motility Genes with other Functional Classes

To get a broader overview of the connections of known motility proteins, several motility related datasets were compared. These included interactions from the motility subset of *T. pallidum* (Rajagopala 2006), *C. jejuni* (Parish *et al.* unpublished), *H. pylori* (Rain et al. 2001), and *E. coli* (Arifuzzaman et al. 2006). In addition, both motility phenotyping sets were included (see previous chapter). A set of genes regulated by the master regulator of the flagellum, FlhD, was obtained from Prüß *et al.* (Pruss et al. 2003).
These datasets were analyzed for a significant enrichment of functional categories (TIGR sub roles). For interaction sets, the enrichment in the set of proteins interacting with known motility proteins was analyzed by comparison to randomized networks (see materials and methods). For the individual datasets, an enrichment compared to the distribution in the genome was assessed.
The results are visualized in Fig. 42; details can be found in Supplementary Table 23-Supplementary Table 31.
Strikingly, nearly all sets showed a clear overrepresentation of known motility proteins (top row in Fig. 42) supporting the overall quality of the data. An interesting finding is the high number of interactions with proteins of unknown function in the *T. pallidum* set (44 interactions); many motility-related proteins required in a subset of bacterial species might be still undiscovered.
Although statistical overrepresentation of functional associations can be calculated and is given in Fig. 42, one needs to keep in mind that individual links might be sufficient to mediate a biological function.
The *T. pallidum* motility set is significantly associated to enzymes involved in tRNA aminoacylation (11 interactions). However, only in the *E. coli* motility dataset a somewhat similar association to proteins involved in "tRNA and rRNA base modification" is observed.
Four interactions to the "DNA-dependent RNA polymerase" category are found; these include interactions of a sigma factor with components of the basal-body complex of the flagellum. Albeit not statistically significant, the link is enriched compared to the genome and might constitute a regulatory control system. An especially interesting interaction, which falls into this category (although not classified yet), is formed between a sigma factor, TP0709, and a hypothetical protein, TP0974. This interaction was also verified by co-immunoprecipitation (see page 127). TP0974 was found to have remote homology to FlgM, an anti-sigma factor controlling the timing of flagellar gene expression during assembly (Pons et al. 2006). This exemplifies that in cases with limited sequence similarity only the combination of bioinformatics and experimental verification can prove orthologous relationships between proteins.
A link between motility and energy metabolism is both found in the set of FlhD-regulated genes and the high-confidence *C. jejuni* interaction set; this indicates that these processes are not only linked in the metabolic network (energy requirement), but also on the regulatory and protein-interaction level.
Both motility phenotyping datasets show an enrichment of enzymes involved in the "biosynthesis and degradation of polysaccharides", which demonstrates the dependency of motility on the proper structuring of the cell wall.

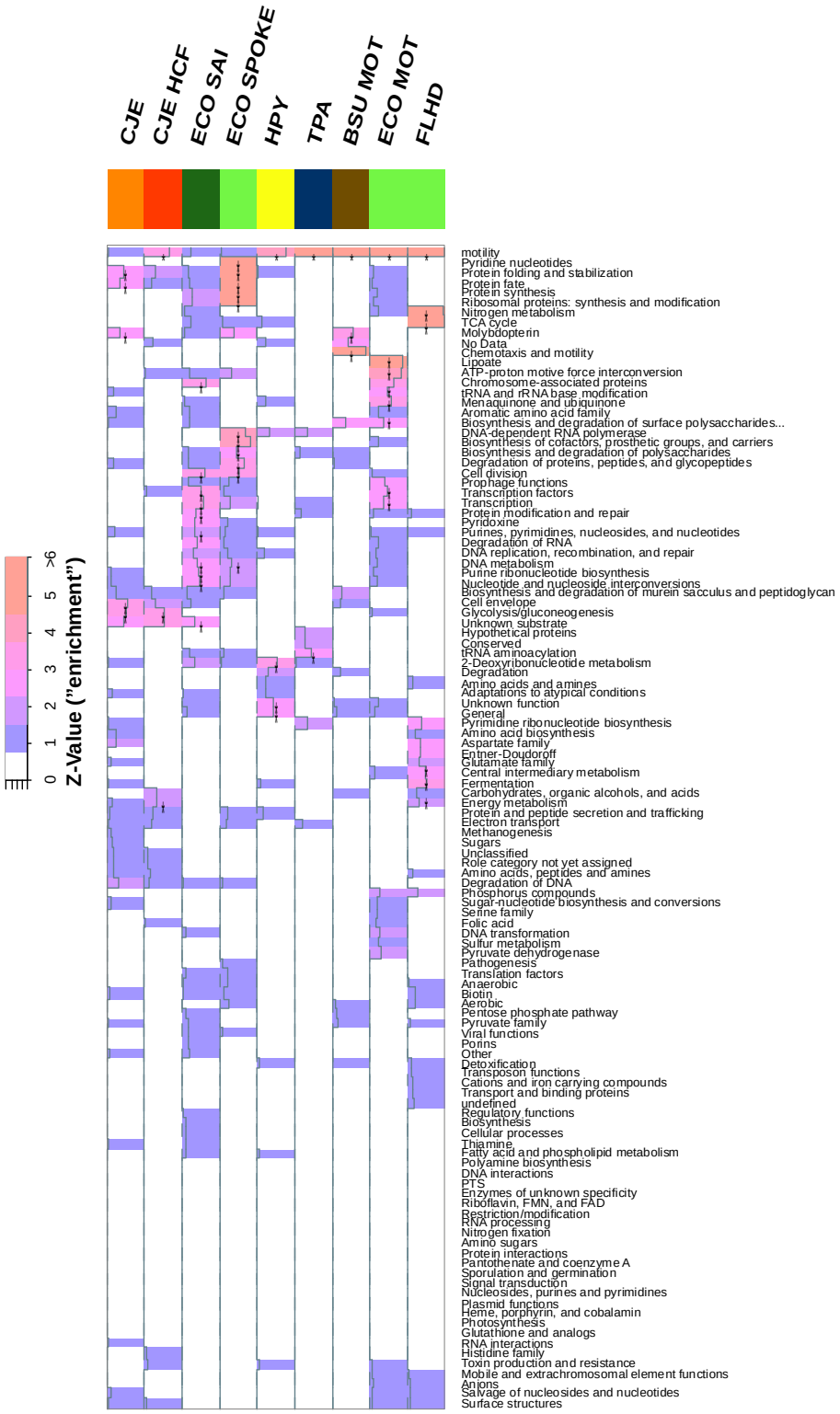


Fig. 42 Enriched TIGR sub roles in several motility related datasets. The associations of known motility proteins with several functional classes are shown for the interaction datasets (TPA=*T. pallidum*, CJE=*C. jejuni*, ECO=*E. coli*), motility phenotyping sets (BSU MOT=*B. subtilis* phenotypes, ECO MOT=*E. coli* phenotypes), and for the set regulated by the master regulator of the flagellum, FlhD, (ECO FlhD). Overrepresentation of a specific category in a certain dataset is color coded according to the shown color key – the color encodes the z-value of the respective association, which corresponds to the times standard deviation distance of the found association to a random set (1000x). Statistical significance of each association is indicated by "*" and is calculated by a ranking statistic for the interaction sets and by a hypergeometric distribution for the others. Please, refer to PDF version or supplementary table to identify the identity of individual functional categories.

3.5. Towards a Membrane Protein Interaction Map

Membrane proteins mediate interesting biological functions like metabolite transport, signalling or cell division regulation. Protein-interactions play a role in many of these functions, e.g. interactions of periplasmatic binding proteins with ABC-transporters, signalling molecule interactions (chemoreceptors), or regulation of transport processes. Unfortunately, protein interactions of membrane proteins are difficult to analyze using the Y2H system as they do not localize to the nucleus or undergo unspecific hydrophobic interactions. Interestingly, in the analysis of membrane protein connections an enriched number of interactions to other membrane proteins, but a lower number of interactions to cytoplasmic proteins was found (Fig. 34). One solution is to fragment these proteins into their intracellular and periplasmic parts and test these fragments individually (against each other and the whole prey array by Y2H).

First, the topology of membrane proteins was predicted. 99 fragments, which are mainly located at the cytoplasmic face of the membrane, were selected. These are cloned and tested for protein interactions against the whole *T. pallidum* prey array.

Prediction of Membrane Protein Topology and Selection

Prediction of transmembrane segments for the whole proteome of *T. pallidum* was conducted with TMHMM v. 2.0 (Krogh et al. 2001). The predictions are based on a Hidden Markov Model and TMHMM has been rated as the best performing transmembrane prediction program (Moller et al. 2001). 243 proteins with at least one transmembrane region were identified; this corresponds to ~24% of the whole proteome and is in concordance with data for other genomes (Krogh et al. 2001). The distribution of predicted membrane segments is shown in Fig. 43: most of the membrane proteins carry only a single predicted transmembrane region (97 proteins); a slight over-representation of an even number of segments is observed (for proteins with at least two segments); note that signal peptides can not unambiguously be separated from membrane segments.

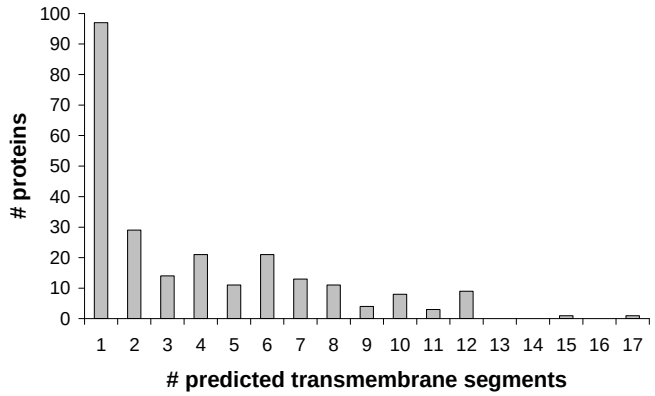


Fig. 43 Predicted membrane proteins in the *T. pallidum* proteome. The number of proteins with a given number of predicted transmembrane segments is shown.

Most of the transmembrane protein fragments (TMPFs) – protein at N- or C-terminus or between predicted transmembrane regions – are shorter than 30 amino-acids (Fig. 44). The C-terminal regions have a length distribution shifted to bigger sizes.

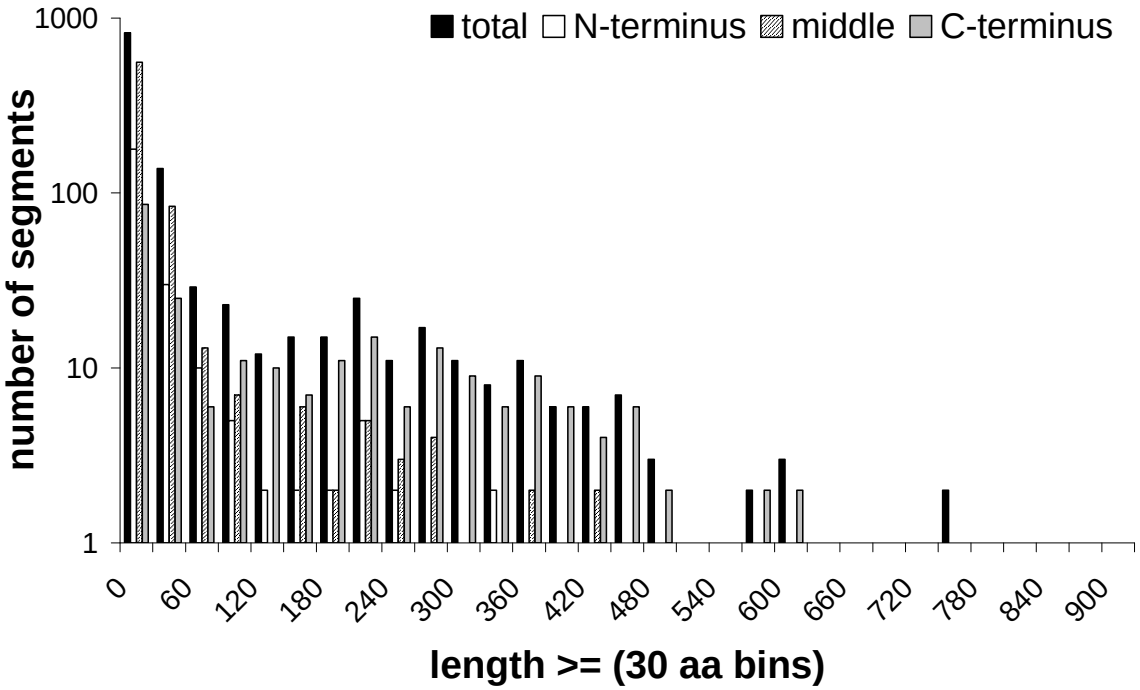


Fig. 44 Length distribution of inter-transmembrane segments. The length of inter-transmembrane segments were binned (30 amino-acid bins). The number of segments with a length falling into these bins is shown. The length distribution for all segments (total), for N-terminal regions (N-terminus), for C-terminal regions (C-terminus), and for regions in between are shown.

A subset of these TMPFs was selected for cloning and, eventually, testing of their protein interactions. Fragments comprising of at least 30 amino acids, which were predicted to be located at the cytoplasmic face of the membrane, were selected. A number of fragments, for which cloning of the full-length construct failed, were omitted. A few fragments with a predicted periplasmic localisation were selected in addition. The full list of selected TMPFs can be found in Supplementary Table 32 and the length distribution of this set is shown in Fig. 45.

Primers for cloning of these fragments were designed with high-throughput primer design software (Express Primer Tool, F. Collart, Argonne National Laboratory). The cloning was done by BP clonase mediated recombinations of PCR products into the pDONR207 vector. For Y2H analysis the cloned segments were transferred to pGBKT7-DEST (bait vector) and pGADT7-DEST (prey vector) and transformed into yeast cells. At present ~80% of the selected fragments have been cloned.

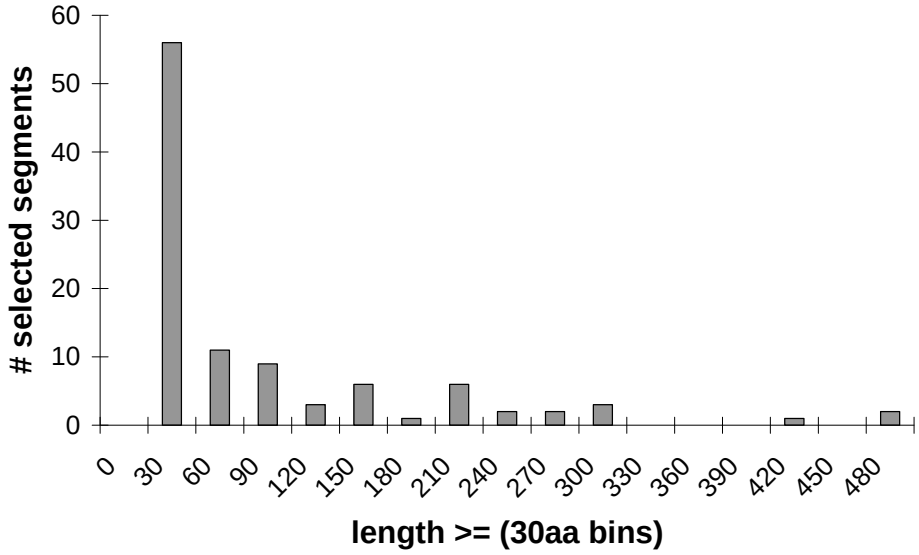


Fig. 45 Length distribution of selected inter-transmembrane segments. Ranges of 30 amino-acids were binned.

Initial Protein Interaction Mapping of Transmembrane Protein Fragments (TMPFs)

In this thesis only an initial protein interaction map of the TMPFs is presented. 59 out of 99 fragments were screened as baits against the whole *T. pallidum* Y2H prey library and against each other. Thus, only a broad overview of the features and expected outcome of this screen is given.

In the screen against the whole prey array, 229 reproducible interactions were detected in total, of these only 107 were retained in a specificity filtered set (prey count < 51, "filtered set"). 84 additional interactions with prey constructs of the TMPFs were detected; a specificity filtered subset contains 45 interactions (prey count less than 6).

Thus, 152 specific interactions were detected for this set of membrane protein fragments (Supplementary Table 33).

Only a small number of these were supported by the String database (Table 42) (von Mering et al. 2005). However, note that a bioinformatical association can only support an interaction, but lack of an association does not exclude it. The interaction with the highest bioinformatical score is formed between FtsH (TP0765) and SecY (TP0208). Interestingly, FtsH is known to degrade SecY (Kihara et al. 1995). Topology mapping of the FtsH ortholog in *E. coli* indicated that the N-terminal part is located in the periplasm (the *E. coli* ortholog was suggested to carry an additional N-terminal transmembrane segment) (Tomoyasu et al. 1993). In contrast, the interacting C-terminal part of SecY is localized to the cytoplasm (Kaufmann et al. 1999) (Fig. 46). This might indicate an involvement of mislocalized protein regions in the recognition of substrates by FtsH.

bait	description	prey	description	combined String score
TP0765_1-83	cell division protein (ftsH)	TP0208-409_450	preprotein translocase subunit (secY)	960
TP0392_94-319	conserved hypothetical protein	TP0995	cyclic nucleotide binding protein	830
TP1036-235_389	cation-transporting	TP0995	cyclic nucleotide binding	591

	ATPase, P-type		protein	
TP1036-1_102	cation-transporting ATPase, P-type	TP0995	cyclic nucleotide binding protein	591
TP0730-1_86	conserved hypothetical protein	TP0392-94_319	conserved hypothetical protein	501
TP1036-1_102	cation-transporting ATPase, P-type	TP0519	response regulatory protein (atoC)	394
TP0471-38_469	hypothetical protein	TP0519	response regulatory protein (atoC)	345
TP0392_94-319	conserved hypothetical protein	TP0445	4-methyl-5(b-hydroxyethyl)-thiazole monophosphate biosynthesis enzyme (thiJ)	274
TP0392_94-319	conserved hypothetical protein	TP0917	Mg2+ transport protein (mgtE)	253
TP0771-1_33	conserved hypothetical integral membrane protein _	TP0995	cyclic nucleotide binding protein	245
TP0765-1_83	cell division protein (ftsH)	TP0995	cyclic nucleotide binding protein	196

Table 42 TMPF interactions with supporting String score.

Another noteworthy interaction is the homodimerisation of the flagellar protein FliL (fragment TP0722_58-182) (Fig. 46).

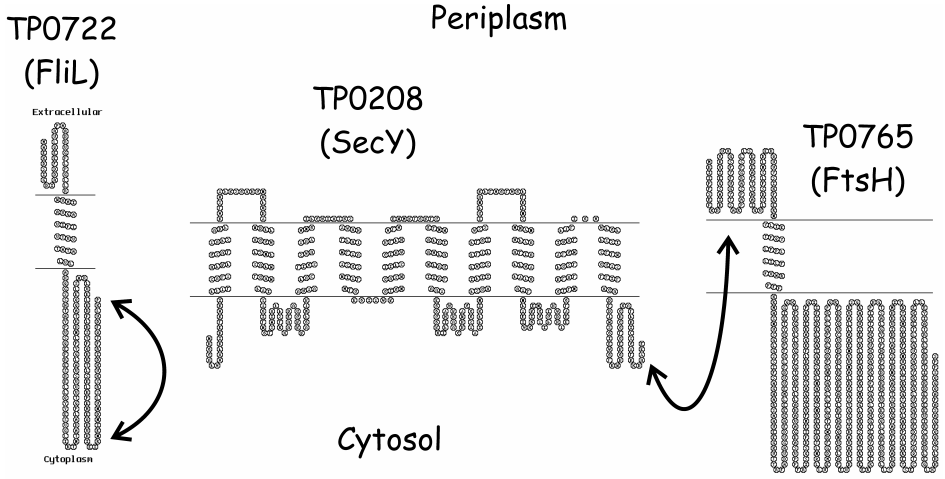


Fig. 46 Examples for TMPF interactions. Proteins drawn with TOPO2 (http://www.sacs.ucsf.edu/TOPO2)

First Comparison and Outlook

The results obtained with the inter-transmembrane segments and with the full-length constructs were compared. When we consider the filtered dataset, we find the following: out of 47 distinct proteins tested, 11 did not show interactions in both approaches, 6 showed interactions only with the full-length proteins, and 14 showed interactions only with a fragment; out of 16 proteins with interaction from both approaches, only 3 showed overlapping interactions (5 interactions in total).

Thus, the datasets obtained from full-length and from fragment screens are rather complementary.

However, the screening yields additional interactions and further investigations are necessary to evaluate their biological relevance.

3.6. Individual Gene I: TP0658 – A Novell Conserved Assembly Factor for the Bacterial Flagellum

Results in this section have been published in the Journal of Bacteriology (Titz et al. 2006a). The text is modified compared to the published manuscript.

Protein interactions networks can support the annotation of previously uncharacterized gene products. The molecular environment of a protein provides clues about the function of a protein ("guilt-by-association approach", see above). This section should exemplify, how results from protein interaction network can be the starting point for an in detail characterization of a previously unknown motility protein.
Motility of most bacterial species depends on the proper function of the flagellar apparatus. Embedded in the membrane its motor transmits torque via parts of the basal body and the hook structure to the filament, a long helical protein assembly rotating as a propeller. In *Salmonella typhimurium*, for example, the filament consists of a homopolymer of ~20,000 flagellin (FliC) proteins (O'Brien and Bennett 1972). In other species, such as *Treponema pallidum*, three flagellin proteins, FlaB1-3, are thought to form a heteropolymeric filament (Charon and Goldstein 2002). The assembly of the flagellum proceeds in a stepwise, well-regulated manner. Only after the assembly of the basal body complex, similar to a type III secretion system, the outer parts of the flagellum are secreted: first the proximal parts, the rod proteins, then the hook proteins, and finally the distal parts including the flagellin proteins. The new components are secreted through a hollow tube and polymerize on the distant tip of the structure (Macnab 2003). Additional assembly factors are required, most prominently chaperones that prevent premature polymerization of flagellum proteins in the cytosol. Several substrate-specific export chaperones have been identified: The chaperone FlgN for the hook-filament junction proteins FlgK and FlgL, FliT for the filament capping protein FliD, and FliS for flagellin proteins (Yokoseki et al. 1995; Fraser et al. 1999; Auvray et al. 2001; Bennett et al. 2001). FliS binds to the C-terminal part of flagellin, most likely preventing premature polymerization in the cytosol (Auvray et al. 2001).
The Y2H network provided evidence that a protein of unknown function, TP0658, is an additional factor required for assembly of the flagellum.

TP0658 Interacts with Flagellin Proteins

Surprisingly, a screen with the *Treponema* FliC homolog, FlaB3 (= TP0870) resulted in an unusually large number of 20 positives while the other FliC homologs yielded only four (FlaB1 = TP0868) and five positives (FlaB2 = TP0792), respectively (Supplementary Table 2). Strikingly, all three flagellin proteins of *T. pallidum* reproducibly interacted with TP0658, an uncharacterized protein of unknown function. This specific interaction with all three paralogs clearly pointed to a role of TP0658 linked to flagellin metabolism (see "guilt-by-association" list, Table 30). Therefore, TP0658 was selected for further investigations starting with a biochemical verification of these interactions.
Indeed, all three flagellin interactions of TP0658 could be verified in vitro using an overlay assay (Fig. 47 A).

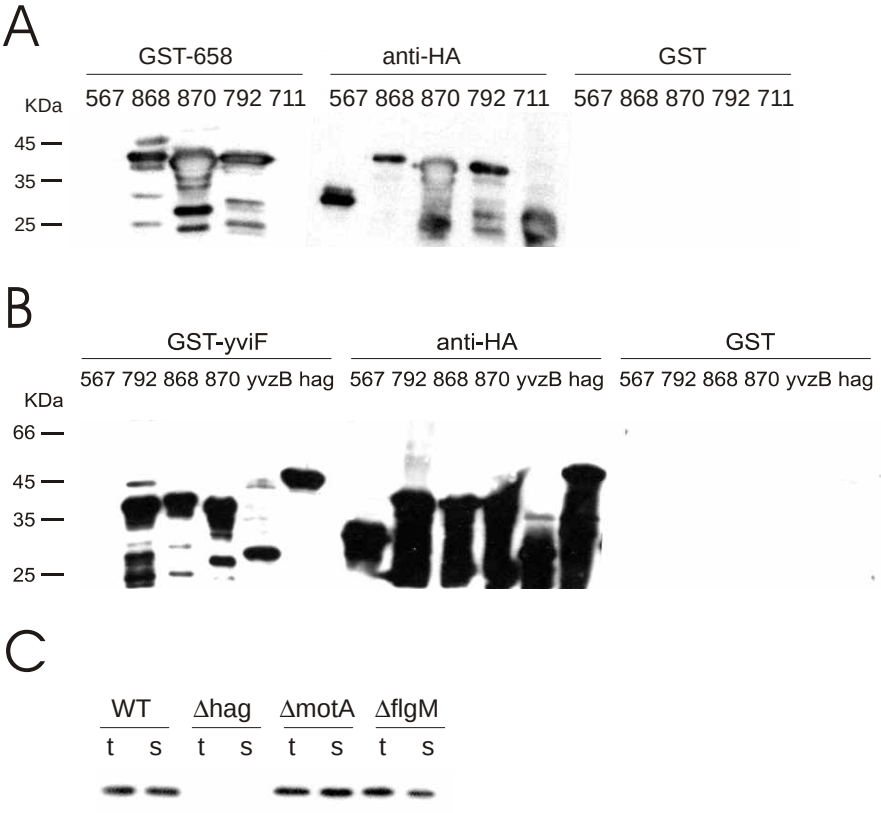


Fig. 47 T. pallidum protein TP0658 and its B. subtilis ortholog yviF interact with flagellin proteins. (A) HA-tagged flagellin proteins of *T. pallidum* - TP0868 (FlaB1), TP0792 (FlaB2), and TP0870 (FlaB3) - were expressed in *E. coli* BL21/DE3 cells and the total lysate was separated by SDS-PAGE and transferred onto a PVDF membrane. The membrane was blocked and then incubated with 25nM purified GST-TP0658 fusion protein (left panel) or 25nM GST control protein (right panel). Detection of bound GST-protein (anti-GST antibody G1160, Sigma-Aldrich, Germany) and HA-tagged proteins (anti-HA antibody HA.11, Covance Research Products, CA, USA) were done using standard Western Blotting procedures. The proteins TP0567 and TP0711 are randomly chosen negative controls to exclude unspecific binding of TP0658. Probing with anti-HA (middle panel) and anti-GST antibodies (right panel) served as controls for expression levels and unspecific binding, respectively. (B) HA-tagged flagellin proteins of *T. pallidum* (TP0792, TP0868, and TP0870) and *B. subtilis* (hag and yvzB) were expressed in *E. coli* and tested for protein interactions with GST-tagged yviF (GST-yviF) in an overlay assay. The protein TP0567 was included as negative control. Probing with anti-HA and GST alone served as controls for expression levels and unspecific binding, respectively. (C) Lysates of a *B. subtilis* wild type strain (168) and of hag, motA and flgM mutants (Table 2) were tested for proteins interacting with GST-yviF in an overlay assay. The molecular mass of the bands shown corresponds to hag (~ 31 kDa); total (t) and soluble (s) extracts are shown. Done in collaboration with Rajagopala SV. Figures as published in (Titz et al. 2006a).

The Interaction is conserved in B. subtilis

Sequence orthologs of TP0658 were identified in the MBGD database (Uchiyama 2003). TP0658 is conserved in a variety of bacteria including *Spirochetes*, *Bacillales*, and *delta/epsilon Proteobacteria*. To test whether the protein interactions of TP0658 are conserved as well, the interaction of its ortholog in *B. subtilis,* YviF, with the two flagellin proteins of *B. subtilis*, Hag and YvzB, was tested: hag is the full-length flagellin protein of *B. subtilis* while yvzB represents an N-terminally truncated form of unknown function. The overlay assay clearly showed that YviF interacts with both *B. subtilis* flagellin proteins (Fig. 47 B). In addition, YviF bound to all three flagellin proteins of *T. pallidum,* suggesting that the interaction epitope is highly conserved even among distantly related species. In addition, the interaction between

YviF and Hag could be confirmed in an overlay assay using different *B. subtilis* deletion strains (Fig. 47 C). The truncated flagellin protein, YvzB, could not be detected in this Western Blot (not shown), probably due to insufficient YvzB expression under the conditions used.

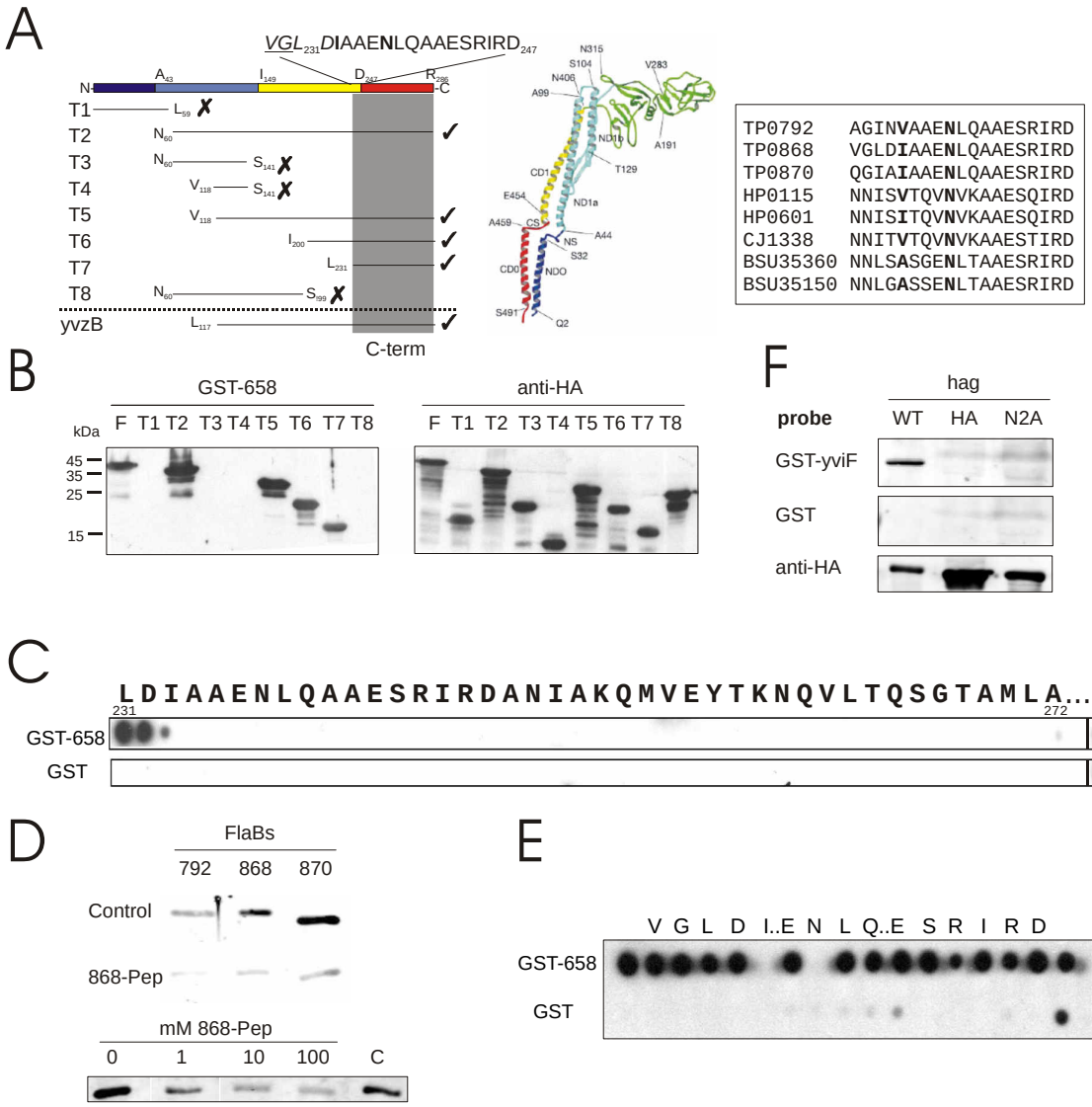


Fig. 48 TP0658/YviF binds to the C-terminal loop region of flagellin. (A) Schematic representation of TP0868 (FlaB1) fragments and results of interaction epitope mapping. The S. typhimurium flagellin structure is shown (19); the primary sequence of TP0868 is color-coded accordingly (not drawn to scale). (B) Eight fragments of TP0868 (T1-T8) were tested for interactions with GST-658 in an overlay assay; positive and negative results for the fragments are indicated by ticks and crosses in (A). The interaction region is indicated by a shaded box in (A). (C) The corresponding sequence (L231-C-terminus) as tested by peptide spotting: the sequence was synthesized as overlapping peptides of 15 amino acids with one amino acid shifts directly onto a cellulose membrane. These peptides were tested for interactions with GST-658 or GST as a control. The first amino acid of each 15-mer peptide is shown above its spot; the last peptide is a positive control recognized by the anti-GST antibody. Only the first three peptides starting from L231 interacted, indicating an interaction epitope between L231 to D247. (D) 100 mM synthetic peptide of this epitope region (868-Pep) but not a control peptide (DRRLADHFCGKIHCG) was able to inhibit the binding of GST-658 to all three flagellin proteins, FlaB1 (TP0868), FlaB2 (TP0792), and FlaB3 (TP0870) in an overlay assay. Lower panel: The inhibitory effect of 868-Pep was concentration-dependent (shown for TP0868, FlaB1). (E) An extended interaction peptide (V229-D247) was tested in an alanine-scan showing that I233 and N237 are crucial for binding. The first and the last spot of the row comprise of the wild type and an antibody control sequence, respectively. The remaining peptide spots have the indicated amino acid

replaced by alanine. Double dots ("...") indicate positions not synthesized, because of naturally occurring alanine residues at these positions (these peptides correspond to the wild type sequence in position 1). (F) Mutants of the *B. subtilis* hag binding epitope (i.e. *B. subtilis* flagellin) were tested for binding to yviF in an overlay assay. The construct hag-HA has the interaction epitope replaced by a HA-tag, hag-N255A (N2A) has the crucial Asn255 residue (Asn237 in FlaB1/TP0868) replaced by alanine. Probing with GST protein and anti-HA antibodies served as controls. The interacting region in different flagellin orthologs is shown in the alignment in (A), right panel: *Treponema pallidum* flagellins TP0792 (FlaB2), TP0868 (FlaB1), and TP0870 (FlaB3); Helicobacter pylori flagellins HP0115 (flagellin B) and HP0601 (flagellin A); *Campylobacter jejuni* flagellin CJ1338 (flagellin B); and *Bacillus subtilis* flagellins BSU35360 (hag) and BSU35150 (yvzB). Peptide spotting was done in collaboration with Claudia Ester. Figures as published in (Titz et al. 2006a).

TP0658 and FliS Bind to Similar Epitopes of Flagellin

As the structure of flagellin is known (Samatey et al. 2001) the interaction epitope of the flagellin protein was mapped to get structural insight into the function of this interaction. A combination of systematic truncations of TP0868 (FlaB1) with an overlay assay showed that TP0658 interacts with an epitope within the C-terminal 55 amino acids of TP0868 (L_{231} – C-terminus) (Fig. 48 A, B). An interaction with the C-terminal half of flagellin is also supported by the interaction of YviF with the N-terminally truncated flagellin, YvzB (Fig. 48 A), which is naturally lacking the region homologous to the first 110 amino acids of TP0868 (Fig. 48 A). Strikingly, the TP0658 interaction epitope of FlaB1 is similar to the FliS-binding site in FliC: FliS binds to the C-terminal 40 amino acids of *S. typhimurium* flagellin (Ozin et al. 2003). For a more detailed characterization of the interaction epitope the SPOT peptide synthesis technology was employed (SPOT synthesis was conducted by Claudia Ester) (Rual et al. 2005). The amino-acid sequence of the binding domain was synthesized as overlapping 15-mer peptides on a cellulose membrane and then probed with a GST-fusion protein to identify interacting peptides. TP0658 interacted with peptides that correspond to the sequence between L_{231} and D_{247} of TP0868 (Fig. 48 A, C). The relevance of the interacting peptide was further demonstrated by a competition experiment. A peptide comprising the interaction epitope sequence ($VGL_{231}DIAAENLQAAESRIRD_{247}$) (synthesized by Olaf Zwernemann) was able to inhibit the binding of TP0658 to all three *T. pallidum* flagellin proteins (Fig. 48 D). Inhibition strength also depended on peptide concentration (Fig. 48 D, lower panel). An alanine scan was then used to identify amino acids crucial for binding: each position of the previously identified peptide (VGLDIAAENLQAAESRIRD) was systematically replaced by alanine and then tested for binding, showing that I_{233} and N_{237} of the previously identified interaction epitope are crucial for binding (Fig. 48 E). For additional verification and testing of evolutionary conservation of this interaction epitope in *B. subtilis* two targeted mutations of Hag (flagellin protein of *B. subtilis*) were created. First, in the construct hag-HA the homologous interaction epitope (Fig. 48 A), N_{247}NLSASGENLTAAESRIRD$_{265}$ in hag, was replaced by a HA-tag sequence. Second, in the construct hag-N255A only the Asparagine residue at position 255 of hag was replaced by Alanine. This residue corresponds to N_{237} found to be crucial for TP0658 binding to TP0868 in the *T. pallidum* SPOT analysis. Strikingly, an overlay with GST-yviF showed complete loss of binding to these mutated forms of Hag (even when probing a large surplus of the mutants) (Fig. 48 F) – verifying the essentiality of Asn_{255} (Asn_{237} in TP0868) and demonstrating the evolutionary conservation of the interaction epitope identified for *T. pallidum* proteins.

These findings are summarized in Fig. 48 A: TP0658/YviF bind to an evolutionary conserved interaction region of flagellin proteins, which is localized to the so-called c_s-loop of flagellin. A conserved Asparagine (position 237 of TP0868) is crucial for binding.

YviF is required for Motility

A functional involvement of YviF in bacterial motility was tested using a *B. subtilis* deletion mutant of yviF. The ΔyviF strain was created by specific integration of a phleomycin-upp cassette into the yviF locus as described by Fabret *et al.* (Fabret et al. 2002). Despite several attempts, the cassette could not be removed from the genome by the suggested counter-selection procedure. As an additional control, the rescue of the phenotype by over-expression of YviF was conducted. The ΔyviF mutant showed a strong reduction of motility in a swarming assay (Fig. 49 A). As expected, only IPTG-induced expression of YviF from a plasmid (P_{spac} promoter) could rescue the motility phenotype, clearly proving that the reduced motility is due to the lack of the yviF gene in the ΔyviF mutant.

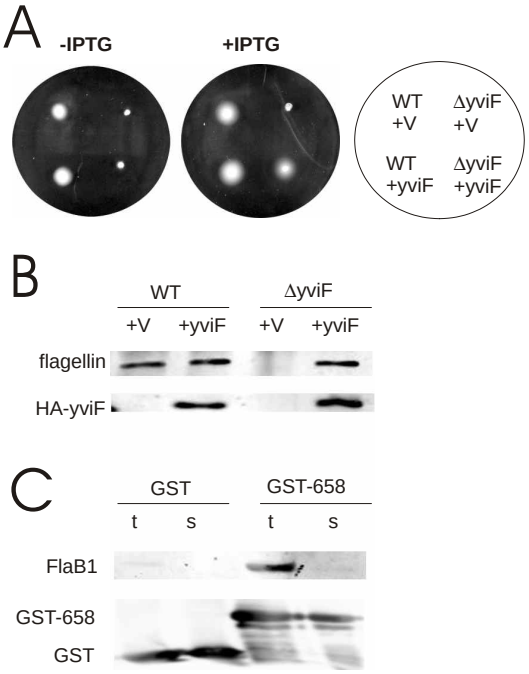


Fig. 49 (a) YviF deletion mutant shows impaired motility. The *B. subtilis* ΔyviF mutant was tested in a swarming assay without (-IPTG) and with (+IPTG) induction of YviF expression from a plasmid (+yviF). *B. subtilis* cells transformed with the empty vector, pDG148-Stu, served as controls (+V). The ΔyviF mutant has a clear swarming defect that can be rescued by yviF expression. (b) TP0658 and yviF stabilize flagellin. *B. subtilis* strains were tested for flagellin (hag) and yviF expression from a plasmid. Hag and HA-yviF were detected by a GST-yviF overlay and anti-HA antibodies, respectively. Wild type (WT) and ΔyviF cells carrying an empty plasmid, pDG148-Stu (+V), or the YviF expression plasmid, pDG-yviF (+yviF), are compared. Flagellin can only be detected when yviF is present. (c) His-tagged TP0868 (FlaB1) and GST-tagged TP0658 (or GST) were co-expressed in *E. coli*. The expression was done overnight relying on the basal expression levels of both constructs to obtain physiological more relevant expression levels. Total (t) and soluble (s) lysates were tested for the presence of protein. TP0868 (FlaB1) can only be detected when TP0658 is present; co-expression of TP0658 thus leads to TP0868 stabilization. Please note that stabilized TP0868 is not found in the soluble fraction, e.g. supporting stabilization at the membrane (see text). Figures as published in (Titz et al. 2006a).

TP0658 and its Orthologs are New Assembly Factors of the Flagellum

Based on the similar interaction pattern of FliS and TP0658/YviF (with flagellin), I hypothesized that TP0658/YviF might be a novel assembly factor or chaperone for flagellin proteins. Deletion of yviF leads to a strong reduction of the amount of flagellin protein detected in *B. subtilis* cells (Fig. 49 B), probably due to an inhibition of flagellin incorporation into the nascent filament. Strikingly, a similar stabilization was found when TP0658 and

TP0868 were co-expressed in *E. coli,* supporting a direct stabilization effect of TP0658 mediated by an interaction between the two proteins (Fig. 49 C).

3.7. Individual Gene II: YjjG – An *in vivo* House-Cleaning Nucleotidase

Results of this section have been submitted for publication.

Despite the power of interaction mapping demonstrated in the previous paragraphs, the thorough understanding of gene function can only be accomplished by the combination of several approaches. A promising strategy is to start with high-throughput methods to collect new ideas and to follow up these ideas employing classical in detail experiments. Here, a screening for gene mutants affected in detoxification of nucleotide compounds is combined with several individual experiments.

Bacteria are constantly exposed to innumerable toxic compounds, both substances from their environment, as well as by-products of their own metabolism (Galperin et al. 2006). Several protection mechanisms evolved to cope with this challenge and range from blocking the uptake (e.g., by the outer membrane of gram-negative bacteria), over export by specific transporters (e.g., ABC transporters), to specific inactivation of these compounds by dedicated enzymes. An especially noteworthy class of toxic compounds are non-canonical nucleobase compounds as these can either inhibit DNA replication directly or lead to an elevated mutation rate (Kamiya 2003). Enzymes recognizing these non-canonical nucleobase derivatives are so-called "house-cleaning nucleotidases" which dephosphorylate non-canonical nucleotides and, in so doing, prevent their incorporation into the classical nucleotide metabolism (Galperin et al. 2006). The most extensively studied of these enzymes is the *Escherichia coli* protein MutT, which specifically dephosphorylates 8-oxo-GTP and thereby reduces the mutation rate ~100 – 3200-fold (Treffers et al. 1954; Bacon and Treffers 1961; Cox and Yanofsky 1969). Several nucleotidases have been identified that show activity against canonical nucleotides with a Km (Michaelis-Menten constant) in the millimolar range. These Km values are higher than expected for an *in vivo* function in canonical nucleotide metabolism. In addition, these nucleotidases do not show an obvious knock-out phenotype under normal laboratory conditions except for elevated mutation rates – these can be as highly elevated as for the *mutT* deletion (~100 to 3200-fold) or only slightly elevated (~ 2-fold) like for the *mazG* mutant (Galperin et al. 2006). Galperin *et al.* (Galperin et al. 2006) hypothesized that many of these nucleotidases function as house-cleaning nucleotidases *in vivo*. However, the identification of their house-cleaning substrates remains a challenge, which can only be solved by extensive screening.

Here, a screen of conserved hypothetical gene deletion mutants with the toxic non-canonical nucleoside 5-fluoro-2‘-deoxyuridine is presented.

YjjG *Mutant Shows High Sensitivity towards 5-fluoro-2'-deoxyuridine*

A screen for mutants ((Baba et al. 2006), Supplementary Table 21) with altered sensitivity towards 5-fluoro-2'-deoxyuridine, a toxic non-canonical nucleotide, yielded one highly sensitive mutant, *ΔyjjG* (B4374, JW4336) (Fig. 50 A). Growth of *ΔyjjG* was already completely blocked at a concentration of 1μM 5-fluoro-2'-deoxyuridine in the agar-plate based assay, whereas the wild type and the remaining mutants were not affected. As the mutant strains of the systematic knockout library used for the screen retain the gene-inactivation cassette, this cassette was removed for the following assays by the procedure suggested by Datsenko and Wanner (Datsenko and Wanner 2000). The observed sensitivity towards 5-fluoro-2'-deoxyuridine was clearly reproduced in a growth assay with a striking effect even at 1μM 5-fluoro-2'-deoxyuridine (Fig. 50 B). Additionally, the phenotype was considerably rescued by expressing *yjjG* from a plasmid.

Recently, YjjG was found in an *in vitro* screen for proteins with phosphatase activity and shown to have activity against thymidine monophosphate (dTMP), uridine monophosphate (UMP), and deoxyuridine monophosphate (dUMP) (Proudfoot et al. 2004). Based on this observation, a function of YjjG in canonical nucleotide metabolism was suggested, probably with involvement in regulatory pyrimidine nucleotide substrate cycles. However, Galperin *et al.* (Galperin et al. 2006) hypothesized in a recent review that many nucleotide phosphatases identified to act on canonical nucleotides are indeed "house-cleaning" phosphatases. These enzymes prevent the incorporation of non-canonical nucleotides into the metabolism and thus protect the cell from toxic side effects and mutations. The most extensively studied of these enzymes is the *Escherichia coli* protein MutT, which specifically dephosphorylates 8-oxo-GTP and thereby reduces the mutation rate by ~100 - 3200-fold (Treffers et al. 1954; Bacon and Treffers 1961; Cox and Yanofsky 1969). The finding clearly implies that YjjG has a "house-cleaning" function *in vivo* rather than a regulatory function in canonical nucleotide metabolism: the assays clearly show a protection against toxic 5-fluoro-2'-deoxyuridine even at a concentration of 1µM; no growth inhibition of the mutant could be observed under standard conditions pointing to a non-essential role of YjjG in canonical nucleotide metabolism.

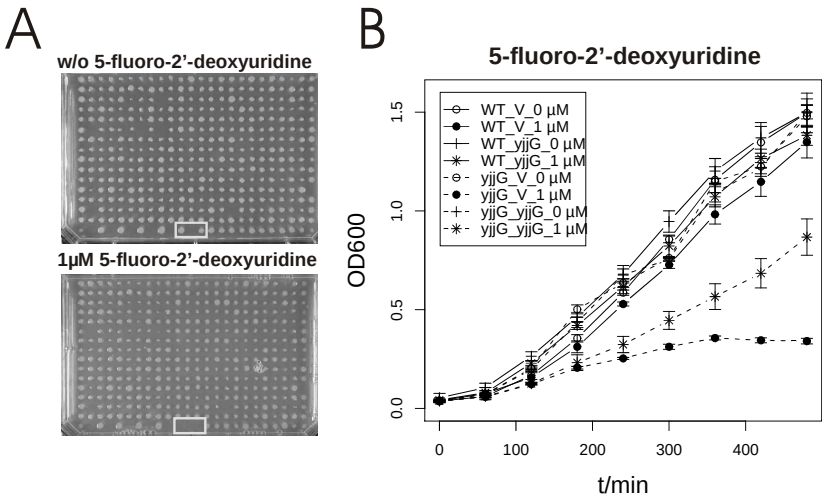


Fig. 50 YjjG mediates resistance against 5-fluoro-2'-deoxyuridine. (a) An array of conserved hypothetical gene mutants of *E. coli* was tested for sensitivity towards 5-fluoro-2'-deoxyuridine; the yjjG mutant (two independent mutant strains: white box) was found to be highly sensitive towards 5-fluoro-2'-deoxyuridine even at a concentration of 1µM 5-fluoro-2'-deoxyuridine. (b) The yjjG mutant phenotype could be verified after flipout of the resistance gene and rescued by YjjG expression in a growth curve assay. Tested conditions are indicated in the diagram legend as follows: wild type (WT, solid line) or yjjG mutant (yjjG, dashed line), transformed with empty vector (V) or YjjG expression vector (yjjG), grown in LB medium without (0 µM) or with 1µM 5-fluoro-2'-deoxyuridine (1 µM). Phenotyping was done in collaboration with Roman Häuser.

YjjG Shows in vivo Activity against Pyrimidine Derivatives

To assess the activity of YjjG to a further extend, several related nucleobase/nucleoside compounds were tested in an *in vivo* assay (Fig. 51). YjjG protects the cell from all 5-fluoropyrimidine derivatives tested: 5-fluorouracil (5-FU) is metabolized by the pyrimidine salvage pathway, 5-fluoroorotate (5-FOA) is an intermediate of the *de novo* synthesis of pyrimidines, and 5-fluorouridine is the ribonucleoside analog of 5-fluoro-2'-deoxyuridine. The protective effect of YjjG towards these fluorinated compounds is found regardless of the way the derivatives are channeled into nucleotide metabolism, indicating a general

function of YjjG that is not focused on either the salvage pathway or *de novo* synthesis. Interestingly, YjjG not only mediated resistance against these uridine derivatives, but also against the cytidine nucleoside analog, 5-aza-2'-deoxycytidine.
Finally, 5-bromo-2'-deoxyuridine (BrdU) and 5-iodo-2'-deoxyuridine at concentrations as high as 1mM were not toxic for the cell, preventing the estimation of an effect of YjjG in this assay. Nevertheless, activity of YjjG towards BrdU was shown in an *in vivo* DNA incorporation experiment (see below).
Taken together, YjjG shows a "house-cleaning" function for non-canonical pyrimidine nucleotides but is not specific for a single nucleotide species.

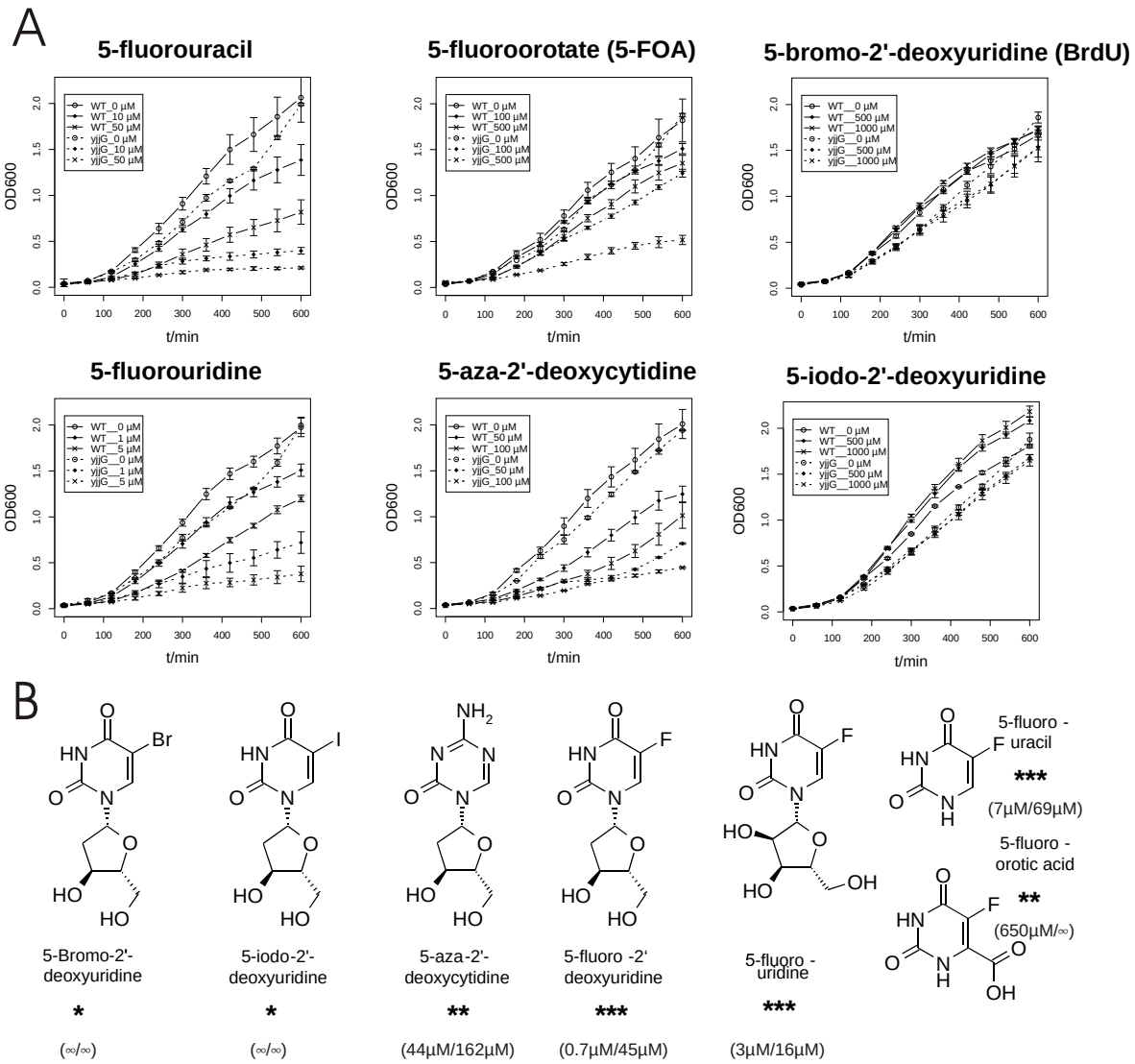


Fig. 51 YjjG shows activity against several non-canonical pyrimidine derivatives. (a) Several non-canonical nucleosides were tested for toxicity in growth curve assays. Tested conditions are indicated in the diagram legend as follows: wild type (WT, solid line) or yjjG mutant (yjjG, dashed line) grown in LB medium with varying concentrations (µM) of a non-canonical nucleoside analog or nucleobase (as given in the title of the diagrams). (b) Summary of structures and effects of tested non-canonical nucleosides. Strong (***), intermediate (**), and no effect (*) on the YjjG mutant. For comparison pyrimidine derivative concentrations inhibiting growth by 50 percent (at 8h time point) are given in parentheses (Δ yjjG/WT). Phenotyping was done in collaboration with Roman Häuser.

YjjG Prevents Incorporation of Non-canonical Nucleotides into DNA

House-cleaning phosphatases are expected to eventually prevent the incorporation of non-canonical nucleotides into DNA, and thus avoid a detrimental increase of the mutation rate. To test a direct effect of YjjG on the incorporation of these nucleotide analogs into DNA, we conducted a BrdU incorporation assay (Fig. 52 A). Whereas BrdU is readily incorporated into DNA of *yjjG* mutants, no incorporation could be seen in the wild type background. Additionally, an overexpression of YjjG in the *yjjG* mutant was able to rescue the phenotype to a large extent.

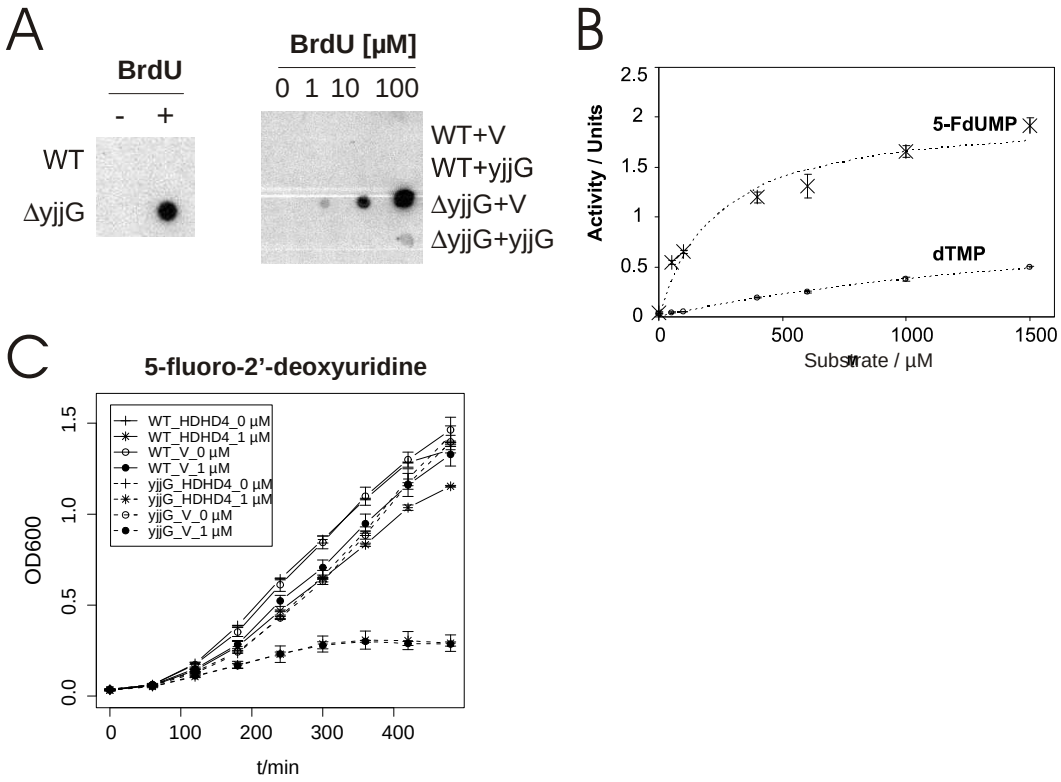


Fig. 52 YjjG is a nucleotide house-cleaning phosphatase. (a) Incorporation of bromo-2'-deoxyuridine (BrdU) is prevented by YjjG. The yjjG mutant and wild type (WT) strain were incubated with BrdU and incorporation into DNA was tested by a genomic DNA dot-blot procedure (probing with anti-BrdU antibody, Roche); with untransformed strains (left panel) or transformed with empty vector (V) and YjjG expression vector (+yjjG) (right panel). (b) Kinetic measurement with purified YjjG shows higher activity (release of Pi in µmol/min) against non-canonical 5-fluoro-2'-deoxyuridine monophosphate (5-FdUMP) compared to canonical thymidine monophosphate (TMP). (c) The closest human homolog of YjjG, HDHD4, was tested for complementation of the yjjG mutant's sensitivity towards 5-fluoro-2'-deoxyuridine; no complementation was observed.

YjjG shows in vitro Selectivity towards Non-canonical 5-FdUMP

Galperin *et al.* (Galperin et al. 2006) proposed that house cleaning phosphatases show at least a ten-fold higher affinity (Km) against their physiological "house-cleaning" substrates in contrast to canonical nucleotides. We compared the *in vitro* activity of YjjG against thymidine monophosphate (dTMP) and 5-fluoro-2'-deoxyuridine monophosphate (5-FdUMP) (Fig. 52 B). YjjG showed a K_m of 2.14 +/-0.49 mM towards dTMP and of 0.237 +/- 0.074 mM towards 5-FdUMP. The apparent difference of the K_m observed for dTMP compared to the value given by Proudfoot *et al.* (Proudfoot et al. 2004) is probably due to the different conditions used. In this assay, YjjG showed an approximately ten-fold higher activity towards

the non-canonical nucleotide, explaining the biochemical basis for the observed *in vivo* phenotypes.

House-cleaning Functions of YjjG's Homologs

Most of the tested substrates are employed as chemotherapeutic drugs in cancer therapy. Therefore, human orthologs of YjjG could in principle interfere with cancer therapy. The closest homolog of YjjG in human is HDHD4, which can be classified as a sequence ortholog due to a best-best blast-hit (30% sequence identity, 42% sequence similarity) and the occurrence in the same phylogenetic branch in the Pfam database (Bateman et al. 2004). HDHD4, although recently identified as a phosphatase involved in neuraminidase metabolism (Maliekal et al. 2006), was hypothesized to possess in addition a moonlighting house-cleaning function. We tested whether HDHD4 has the propensity to replace YjjG in the *yjjG* mutant functionally (Fig. 52 C). However, no phenotypic complementation by HDHD4 was observed. This clearly indicates that YjjG and HDHD4 despite their close sequence similarity have evolved different specificities. This finding makes interference of HDHD4 with non-canonical pyrimidine nucleoside based cancer therapy unlikely.

The closest sequence homolog of YjjG in yeast is SDT1 (24% sequence identity, 44% sequence similarity); however, SDT1 is not classified as a sequence ortholog by the MBGD database (Uchiyama 2003). Interestingly, Nakanishi *et al.* discovered a nucleotidase activity for SDT1 directed against UMP and CMP (Nakanishi and Sekimizu 2002). Additionally, overexpression of SDT1 in yeast cells leads to hyposensitivity towards 6-azauracil, 5-fluorouracil, and 5-fluorocytosine implying a physiological role of SDT1 as a house-cleaning nucleotidase.

These two homologs of YjjG, HDHD4 and SDT1, show different physiological functions despite comparable sequence similarity. Both enzymes are classified by the Pfam database as "haloacid dehalogenase-like hydrolases (PF00702)" (Bateman et al. 2004), a large group of hydrolytic enzyme with more than 6500 members. This group shows diverse hydrolytic specificities (Koonin and Tatusov 1994). Our data suggests that sequence similarity alone is not sufficient to identify specific functions; the identification of true functional orthologs of YjjG in other species should therefore not rely solely on sequence similarity but should also be supported by experimental data.

4. Discussion

The individual parts of this thesis are discussed separately: first, properties of transcriptional activators in yeast, which were unraveled by an detailed analysis of self-activating proteins in the Y2H assay; secondly, the major topic of this thesis, the protein-interaction network of *T. pallidum*; and finally, the detailed analysis of two individual proteins employing low-scale experiments.

4.1. Transcriptional Activators in Yeast

Transcriptional activation is the basis of the yeast two-hybrid system. However, some bait proteins activate transcription without requiring an interacting protein that bears a separate activation domain. In fact, this property prevents the study of many transcriptional regulators by means of the two-hybrid system. Nevertheless, this observation can help to extend our knowledge about the properties of transcriptional activation domains.

In this thesis, previously identified (but mostly unpublished) activators from several Y2H screens (Uetz et al. 2000; Ito et al. 2001) were selected and their activation strength was measured. Properties distinguishing this set from non-activator proteins were analyzed. Although many well-characterized transcriptional regulators and nuclear proteins are highly over-represented in the set of Y2H activators, many proteins that have not been associated with transcription previously were identified. Irrespective of their physiological role, these activators must be able to interact with and recruit the transcriptional machinery.

Similar assays have been used previously by Wiesner *et al.* (Wiesner et al. 2002) and Ma *et al.* (Ma and Ptashne 1987) for screening human and *E. coli* proteins/peptides for their transcriptional activation properties.

Which features or sequences mediate the recruitment of the general transcriptional machinery to the activator? Although there is no single feature, several rather general properties of transcription activators have been defined previously. These included the protein sequence composition as in acidic activators (Ma and Ptashne 1987) or more specific features such as defined interactions between activators and the basal transcription machinery (Neely et al. 1999; Bhaumik et al. 2004).

Acidic activators, i.e. activators with stretches of acidic amino-acids, were the first class to be identified in yeast and the ones studied most extensively (Sadowski et al. 1988; Ptashne and Gann 1990). Their importance was emphasized by screens for random activating fragments of the *E. coli* genome or activating peptides, both of which mainly identified acidic activators (Ruden et al. 1991). The finding was confirmed in this thesis by the lower isoelectric point of activators, more acidic stretches and by the increased clustering of aspartate (Fig. 16 & Fig. 17).

Other previously defined activator classes were also found by this study: glutamine-rich activators (Courey et al. 1989), proline-rich activators (Mermod et al. 1989), and serine-rich activators (van de Wetering et al. 1993). Elevated asparagine levels and cluster values of activators may indicate a role of an additional amino acid in transcription activation, possibly similar to the closely related amino-acid glutamine in glutamine-rich activators.

It is generally accepted that activation domains mediate their function by specific interactions with the basal transcription machinery (Ptashne and Gann 1997) or additional factors involved in transcription, like chromosome remodeling complexes (Utley et al. 1998). Transcription activators analyzed in this study form a highly interconnected protein interaction network involving transcription related proteins (Fig. 18). Protein interactions with transcription-related proteins are highly over-represented, even in the set of activators that have not been described as transcriptional regulators.

A significant fraction of nuclear Y2H activators as well as known transcriptional regulators interact with the basal transcription machinery (like RNA polymerase II) and chromosome

remodeling complexes (like the SAGA complex) (Table 11). These interactions possibly explain their activation properties. Strikingly, the top ranking interaction partner of nuclear activators **not** previously known to regulate transcription was also RNA polymerase II. This indicates that genuine transcription regulators are contained in this set and form the basis for annotating them as transcriptional regulators (see results). However, for a large fraction of the Y2H activators, no interactions are known and thus their mode of action remains unclear. A surprising finding is the frequent interaction of activators with alcohol dehydrogenase. This enzyme is found with ~10% of nuclear proteins (not shown) but with ~20% in both the nuclear activator and known transcription regulator dataset. Thus, alcohol dehydrogenase might be more a specific component of activation complexes than an unspecific contamination. Such moonlighting functions (Jeffery 1999) have been found in other components of various transcription factor complexes but also among other proteins such as actin which acts both as a cytoskeletal protein and a transcription factor (Hofmann et al. 2004).

Screening of protein fragments fused to the DNA binding domain of Gal4 has been used before to identify transcriptional activators. Ruden *et al.* (Ruden et al. 1991) screened fragments of the *E. coli* genome and mainly identified acidic stretches that activate transcription in yeast. Wiesner *et al.* established a screening system based on a GFP reporter gene in a murine cell line and identified human transcription factors using a cDNA library (Wiesner et al. 2002). In contrast to this study I could make use of extensive large-scale studies which not only identified a set of transcription activators (Uetz et al. 2000; Ito et al. 2001), but also localized proteins (Huh et al. 2003), measured protein concentrations (Ghaemmaghami et al. 2003) and protein interactions (Uetz et al. 2000; Ito et al. 2001; Gavin et al. 2002; Ho et al. 2002). The measurement of the activation strength allowed focusing on sets of proteins highly enriched in known transcriptional regulators. Combining several data sources, for six uncharacterized yeast proteins additional evidence for their genuine role in transcriptional regulation could be identified.

Still, a number of activators has been missed by this strategy: of 138 proteins annotated with the GO-term "transcriptional activator activity" in the YPD database, 55 (40%) were detected as activators in this study (Supplementary Table 1), suggesting a false negative rate of about 60%. This discrepancy may be explained by the fact that some transcriptional *regulators* are annotated as *activators* although they do not act as such in our assay. Other proteins may require specific promoters, cofactors, or conditions to exhibit activating activity. For example, several activators are only active when yeast is grown in glucose-free media. Interestingly, Gal4 itself becomes a very weak activator when fused to another Gal4-DBD, i.e. the DBD domain appears to inhibit the activating properties of some proteins. Thus, our studies need to be extended in order to get a more complete picture of all transcriptional activators in yeast, e.g. by using different conditions or fusing the DBD C-terminally.

Although a large number of transcriptional activators in yeast were identified and their activation strength was semi-quantitatively measured, this measurement was not truly quantitative. New reporter strains with luciferase or some other enzyme need to be used in the future for more precise measurements.

In addition, by this study the actual activation domains were not determined. Given the poor definition of activation domains, it remains an important challenge to map these domains by fragmenting the proteins described here. As activation domains do not appear to be well-defined structural domains it appears to be likely that they do not require a defined three-dimensional structure. Instead, short linear peptides may contain the activation activity proper.

Once the activation domains have been mapped, their interactions with the transcriptional machinery have to be identified. Unfortunately, the classical two-hybrid system cannot be used for this purpose. Thus either classical biochemistry or alternative systems have to be used such as the split-Ubiquitin system (Johnsson and Varshavsky 1994).

Finally, activators can differ in their ability to activate transcription dependent on the promoters to which they are bound (Harbury and Struhl 1989). Hence, all activators need to be tested in different promoter contexts and their transcriptional activity quantitated.
Once their interactions have been mapped on a proteome-wide scale and their promoter context evaluated, it may be possible to generalize these findings and predict the transcriptional activity of every protein, including their activation strength. This would be a major step towards quantitative and thus systems biology.

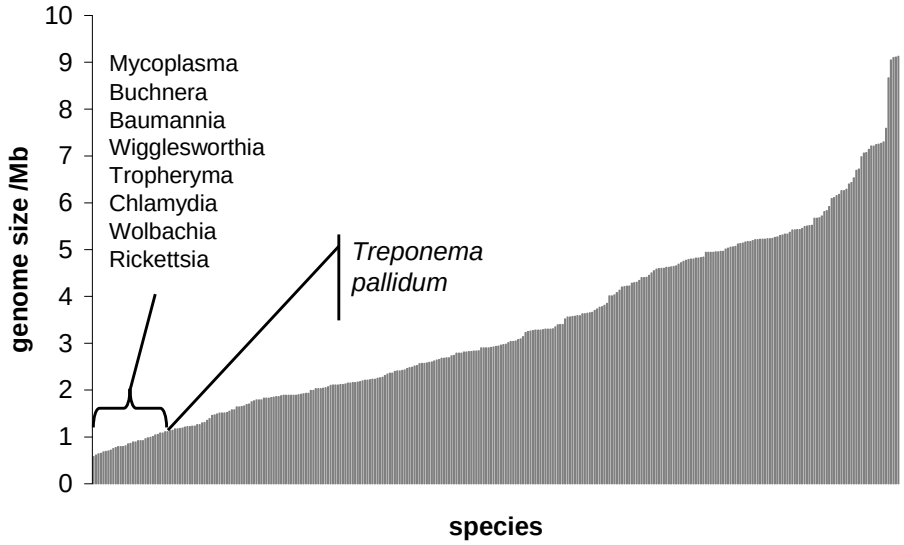
4.2. A Protein Interaction Map of *T. pallidum*

In this thesis the **binary protein-interaction map of *T. pallidum***, the Syphilis spirochete, is presented. The aim was to test all pair-wise protein combinations of *T. pallidum* for a protein interaction in the yeast-two-hybrid assay. These up to 1,000,000 individual tests revealed 3684 interactions, from which a specificity-filtered set of 1634 interactions was selected for the analysis. 726 (70% of the proteome) and 601 (58% of the proteome) distinct proteins were incorporated in the complete and filtered network, respectively. However, only 0.3-0.7% of the total number of possible interactions (540,280) was tested positive, which supports the common notion that protein interaction graphs are sparse (Uetz et al. 2006).
Protein-interaction mapping – both by Y2H and by coAP/MS (co-affinity purification & mass-spectrometry) – is one of the favorite functional genomics approaches to elucidate the functions and connections of the gigantic number of gene-products catalogued by whole genome sequencing. Several large-scale interaction studies have been published – ranging from virus, over yeast, to human (Table 3). Despite their large number, the published interactome studies are far from being complete; still, most of interaction space is *terra incognita*: a) classical individual protein studies can never cope with the number of gene-products, b) most published Y2H studies tested only a fraction of the interactome or did not systematically test all pair-wise interactions, c) interaction mapping approaches suffer from a high percentage (up to 90% in Y2H) of false negatives, d) post-translational modification dependent interactions are not covered by Y2H, and e) interactions only taking place in specific cell states, e.g. activation of a signaling pathway, are not detected by common coAP/MS studies.
In parallel to this study, the Y2H interaction map of *C. jejuni* was analyzed by the group of R. Finley (Parish *et al.*, *pers. comm.*). With respect to interactome coverage, the *T. pallidum* and the *C. jejuni* networks are currently the **most comprehensive available Y2H maps**. They incorporate, for example, 70% and 83% of the proteome, respectively, compared to up to 55% in yeast ((Ito et al. 2001), Table 3, Table 20). Please note that the tested interaction space can be even smaller: for *H. pylori* only 261 out of 1552 (17%) possible baits were tested, although already 47% of the proteome is incorporated. This compares to ~90% tested baits in this study (Table 16).
The majority of large-scale interaction mapping studies targeted eukaryotic proteomes; prokaryotic interactions were only analyzed in three studies. However, only a single study tried to achieve whole proteome coverage for a bacterium: Arifuzzaman *et al.* recently conducted a coAP/MS study and tried to identify co-purified proteins for all *E. coli* proteins (Arifuzzaman et al. 2006). Another coAP/MS study for *E. coli* was published before (Butland et al. 2005). In this study, the expression conditions were closer to physiological levels, but only ~900 proteins (out of ~4,300) were analyzed. Only a single incomplete Y2H interaction map for a bacterium was published: Rain *et al.* tested 261 baits (17% of proteome) against the whole proteome of *H. pylori* (Rain et al. 2001). In addition, a few small-scale Y2H studies (testing only 5-20 baits) for bacteria were published including interactions involved in DNA replication in *B. subtilis* (Noirot-Gros et al. 2002) and several studies analyzing the Type-IV-secretion-system of bacteria (Alegria et al. 2005).
Thus, the interaction maps presented for *T. pallidum* and *C. jejuni* (Parish *et al.*, *pers. comm.*) constitute the **first comprehensive binary interaction maps for bacteria**. They form the

basis for comparative interactomics studies with the ultimate goal to understand the evolution of protein interactions. However, comprehensive interaction maps for several other bacterial species (out of >300 genomes at present) need to be analyzed until this goal can be achieved (discussed below). Moreover, they will constitute the basis for systems biology approaches to understand the biology of bacteria at the system's level.
With 3684 interactions between 726 proteins for *T. pallidum* the key question is: What can we learn (for biology) from this comprehensive dataset? A few answers to this question are given below.

Special Topic: Interaction Map of a Minimal Proteome?

With 1039 genes the genome of *Treponema pallidum* can be considered as small.



The common model bacteria, *Escherichia coli* and *Bacillus subtilis*, carry with ~4500 a considerable larger number of genes. However, recent genome sequencing projects revealed much smaller genome sizes: the bacterial endosymbiont *Carsonella* has only 182 ORFs (Nakabachi et al. 2006) and the endosymbiont *Buchnera aphidicola* BCc carries only 362 ORFs (Perez-Brocal et al. 2006). Both bacteria follow an intracellular life style in uttermost close association to its host, which allowed for a significant genome reduction. *T. pallidum* also strictly depends on its host, but due to its extracellular life style is less closely associated to its host. Thus, a larger number of genes are required, e.g. additional genes involved in transport and metabolism. A reduced proteome was selected for this study to reduce the time required for screening, while focusing on the crucial processes of a bacterial cell. *T. pallidum* represents a good tradeoff, since it carries a reduced genome sufficient for extracellular living. The diagram shows the size distribution of bacterial genomes available, today (TIGR-CMR database). All bacteria with smaller genomes than *T. pallidum* show an intracellular life style.

Generation of the Interaction Map

Before discussing the biological insights gained from the interaction network, a few technical issues should be discussed.
Large-scale functional genomics studies (except for the majority of microarray studies) are enabled by **versatile vector systems**, which allow for convenient transfer of ORFs from one

vector to the other. These systems employ site-specific DNA recombinases to engineer DNA. The most commonly used system is the lambda-phage recombinase based Gateway system (Invitrogen). Another system, the univector plasmid-fusion system (UPS), relies on a Cre-recombinase mediated reaction between loxP-recognition sites (Liu et al. 1998; Liu et al. 2000). The main advantage of the latter system is its cost efficiency; the main disadvantages are that C-terminal fusions are not possible, cloning of PCR products is not directly supported, and most importantly the availability of many more cloned genes and vectors for the Gateway system only. A prerequisite of functional genomics projects is the availability of all cloned genes in such a versatile vector system (called the ORFeome). The reason for selecting the UPS system for the *T. pallidum* interaction map was the availability of an ORFeome in this system (McKevitt et al. 2003). However, no experience with this system was present in our lab and high-throughput cloning strategies had to be established. In addition, a commonly used bait vector (pGBKT7, Clontech) was adapted for this system (Fig. 12).

An observation when working with the Y2H system for *T. pallidum* was that the reporter gene activation level was generally lower than for several viral interactomes tested at the same time in our laboratory ((Uetz et al. 2006) and *unpublished data*). The ORFs of these viruses were cloned into the well tested pGBKT7-DEST (bait vector) and pGADT7-DEST (prey vector) combination employing the Gateway system. This difference may be due to properties of the ORFs or the vectors. Because of its versatility, future projects should be based on the more commonly used Gateway system.

The array-based Y2H system has a quadratic dependency of time and resources on the number of tested proteins, meaning that a genome twice as big as *T. pallidum* would require four times more effort; the interactome of *E. coli* would take 19 times longer than that of *T. pallidum*. One can only escape from this quadratic dependency by changing the strategy: several proteins need to be combined and tested in pools for their interactions; in a second step these pools need to be deconvoluted by individual retests. Such a strategy was proposed by Zhong *et al.* (Zhong et al. 2003). In this thesis a **pooling scheme** for the sytem used in our laboratory is presented and crucial steps were identified (chapter 3.3). However, a certain fraction of interactions get lost with this system. Therefore, it was not used for the study presented in this thesis, but should be reconsidered for the next large-scale project, especially when a higher activation level of the reporter genes is observed.

Probably, the most crucial issue for high-throughput projects is the proper storing of data, both for the setup step (e.g., information on cloned gene constructs) and of the obtained results. For this thesis, a laboratory information management system (**LIMS**) based on the FileMaker system was developed (page 89). This LIMS is especially designed for the needs of a large-scale Y2H study and tracks all steps of this functional genomics study – ranging from the cloning steps to entering of Y2H results. This system proved to be well suited for this purpose. However, for future projects the user interface needs to be optimized to allow for more convenient data entry.

Co-immunoprecipitation of genes co-expressed in tissue culture is used as a second-level protein-interaction test for interactions from the eukaryotic system (Rual et al. 2004; Uetz et al. 2006). No such system was available for bacterial proteins. Thus, the **coEXcoIP**-method was established, which involved co-immunoprecipitation of proteins co-expressed in *E. coli* (page 127). For this, a special vector combination was adapted for the UPS system. The combination allows for better-controlled expression conditions and higher yields of soluble protein pairs. To test this system, a few interaction pairs were tested and verified with this system. This system can still be optimized for higher-throughput and an adaptation for the Gateway system should be possible.

The Quality of the Network

The quality of a protein interaction network is hard to evaluate. One main problem is that all employed reference sets are more or less incomplete and biased (see introduction). In other studies, 50%-80% of the Y2H interaction could be verified by an independent method (Rual et al. 2004; Uetz et al. 2006). However, due to this finding a large-scale verification was not attempted here; only a small subset of interaction was verified with another method (Fig. 39 & Fig. 47).

Evidences for the quality of the dataset can be obtained from **bioinformatical analyses**. Microbial functional genomics studies can make use of the large number of sequenced genomes: evolutionary patterns such as operons and phyologenetic profiles indicate conserved associations between genes (or orthologous gene groups). The String database computes and stores these bioinformatical associations between genes (von Mering et al. 2005); a statistically significant fraction of Y2H interactions was found to be associated by the String database supporting the overall significance of the data (page 97). Interactions supported by the String database can also be used as a pre-filtered set for further investigations (Supplementary Table 7). However, protein interactions are also formed between proteins without leaving significant traces for bioinformatical prediction methods; possible examples are regulatory links between pathways and the noteworthy class of hypothetical proteins, which are only conserved in *Treponemes* or *Spirochetes*.

Another interesting observation is the high enrichment of **homodimeric interactions**, which would not be expected by chance ($p = 2.22\ 10^{-16}$) (Table 22).

Several other properties of the network strongly deviate from observations in randomized networks, e.g. the topology (see below), clearly indicating a biological structuring of the observed network.

However, interactions might be biologically meaningful or just occurring without detrimental effects for the cell. Thus, the biological relevance of the observed interactions can only be found on a case-by-case basis (like TP0658; see chapter 3.5), but the bioinformatical analysis presented here can identify the most interesting candidates, which can then be prioritized.

Topological Features

Biological insights can be obtained at all levels of a protein interaction network (see introduction). At the topmost level topological features of the network are analyzed (Table 20).

On average 5.4 interactions were found for each protein, which is in agreement with other protein interaction studies, e.g. for *C. jejuni* and KSHV. On average each protein can be reached from each other protein through 3.9 protein interactions (**average shortest path length**) which also corresponds to values observed in other interactions networks (Table 20). This exemplifies that all proteins of a cell are closely connected. One might consider this principle, for example, when signalling pathways are analyzed: a relatively close link between every given pair of signalling molecules must be anticipated and only the status of the whole network can eventually explain the observed output (rather than considering linear pathways). This "**small world phenomenon**" was first observed for social networks, for which an average distance of 6 between two people has been found (Milgram 1967). Later this concept was called "**six degrees of separation**" (Guare 1990).

Another topological property that often deviates from random graphs is the clustering coefficient, which is proportional to the number of interactions between direct neighbours of a protein. The **clustering coefficient** of the *T. pallidum* networks is relatively high compared to other protein interaction networks (Table 20). Interestingly, especially the clustering coefficient of the unfiltered network has a high value of 0.23; apparently, proteins interacting with highly connected proteins (hubs) tend to interact with each other. This might be explained by the existence of certain general properties leading to unspecific interactions, e.g.

exposed hydrophobic patches that make a protein to interact with other proteins showing the same property.

Biological networks show a few proteins with many interactions (hubs) and many proteins with few interactions (Jeong et al. 2000). The same is found for the *T. pallidum* network (Fig. 27). Moreover, in many biological network the node-degree distribution follows a power-law ($P(k) \sim k^{-\gamma}$ with node degree k, frequency of a node degree P(k), and power-coefficient γ); these networks are often called "**scale-free**". The node degree distributions of both *T. pallidum* networks approximate a power-law in frequency-degree plots. However, Tanaka *et al.* (Tanaka et al. 2005) insisted to base this analysis on rank-degree plots to circumvent statistical problems posed by the underlying distribution (many data points in the lower degree range, only few data points in the higher degree range). In rank-degree plots only the whole *T. pallidum* network appears to be scale-free, whereas the distribution of the filtered network follows an exponential law ($P(k) \sim e^{-k}$) (Fig. 28). Since the result of this classification heavily depends on the data source, one cannot unambiguously conclude for one or the other model. Probably, a final conclusion on the topological building principle of bacterial networks (and for other organisms) can only be made once much more sophisticated networks also encoding the biological relevance of each interaction become available.

The same is probably true for **biological features of hubs**. Hubs were, for example, found to have a higher probability to be essential proteins for the cell ((Jeong et al. 2001), page 27). However, this finding has been questioned and suggested to rely on the underlying biased data (Coulomb et al. 2005). For *T. pallidum* no difference in the node degree distribution of essential vs. non essential genes was observed (Fig. 36); the same observation was made for *C. jejuni* (Parish *et al.*, *pers. comm.*). Thus, at least from single networks no reliable conclusions on the biological properties of hub proteins can be drawn; large-scale protein interaction networks also encoding the biological meaning of interactions need to be integrated with other important networks such as gene regulatory networks and the metabolic network until biological meaningful conclusions on the underlying building principles can be derived.

However, an interesting topological finding concerning **regulator proteins** was made: these proteins appear to have a higher **centroid value** (Fig. 36), which means that they are located towards the centre of the protein-interaction network. This would be expected for a family of proteins that integrates input signals from several different sources.

Links Mediated by Y2H Interactions

The Y2H interactions were analyzed with respect to their function to link different biological categories ranging form genomic locations, over sub-cellular localizations, to domains and functions.

Bacterial genomes are known to be functionally structured. Operons often contain functionally related genes and genes located in a conserved neighbourhood in several genomes tend to show a functional association (Overbeek et al. 1999). The association between different genomic locations has not been considered, yet. In this thesis, protein interaction based **links between different genomic locations** were analyzed (Fig. 33). Strikingly, several overrepresented links compared to randomized networks were identified. These are based on different underlying interaction patterns: clusters of interactions between neighboring genes (including homodimers), a single gene interacting with several neighboring genes at a different genomic location, or most interestingly several interactions involving various genes at two genomic locations. The most interesting link was observed between a location flanking TP0943 and a region flanking TP0046. These locations were linked by six interactions involving six distinct proteins at these two locations. TP0943, FliS, is a well-known flagellar chaperone. Interestingly, the ortholog of the neighboring gene TP0945, ribulose-5P-epimerase, which is also involved in this link, shows a motility phenotype in *E. coli* (Table 40). The orthologs of the linking genes at the location, TP0046 and TP0048, both showed a motility phenotype in *B. subtilis* (Table 41). Thus, the observed link between these

locations connects two gene clusters involved in motility. Further studies need to clarify the molecular function of this link. In summary, functional relevant links between genomic locations in bacteria can be identified. This should set the basis for the identification of such links in other bacteria, and moreover for the analysis of these links down to molecular detail.

It is generally assumed (and biologically meaningful) that protein should preferentially attach to proteins in the same **compartment** (von Mering et al. 2002). For *T. pallidum*, such an analysis is hampered by the lower number of distinct compartments in bacteria and by the unavailability of experimental localization data – a genome-wide localization study for *E. coli* has been conducted, but is unpublished (Prof. Mori, *pers. comm.*). Thus, the analysis presented in this thesis had to rely on bioinformatical predictions, for which the PSORT 2.0 algorithm was employed (Gardy et al. 2005). Most of the proteins were localized to the cytoplasm (39%), a similar percentage had an unknown localization (38%), and 17% were localized to the cytoplasmic membrane (Table 28). Cytoplasmic proteins were found to attach preferentially to other cytoplasmic proteins and membrane proteins to other membrane proteins (Fig. 34). In addition, an underrepresentation of interactions between cytoplasmic and membrane proteins was found. The anticipated over-representation of links between the same localization was found in the *T. pallidum* network, however, the limited number of localization compartments should be kept in mind.

Protein interaction networks are based on the interactions of individual domains. The *T. pallidum* network was decomposed into a **domain network** filtered for unspecifically interacting domains (Fig. 32). This is the first domain-centered network for a prokaryotic species and for the first time provides insights into prokaryotic domain interactions at a genome-wide scale. However, it should be noted that follow-up experiments are required to unambiguously identify some interacting domain pairs, e.g. the DUF180 domain (protein TP0658) was found to interact with proteins consisting of a Flagellin_C and Flagellin_N domain. Further experiments showed that only the Flagellin_C part interacts with TP0658, and thus with the DUF180 domain (chapter 3.5). The most frequent domain in the genome of *T. pallidum* is the Tpr domain (Table 27). This domain is known as a protein-interaction domain and members of a paralogous gene family carrying this domain are described as virulence factors (see introduction). As expected, this domain showed several interactions to a diverse array of domains also including self-associations. Links not discovered in the whole network can be identified in the domain network: two links between Mur_ligase and Flg_bb_rod domains are observed (Fig. 32). These links are constituted by the interactions TP0961 (FlgG-2) - TP0341 (MurC) and TP0903 (MurD) - TP0396 (FlgB). The flagellum is in principle known to associate with peptidoglycane processing enzymes, e.g. FlgJ consists of a domain involved in rod assembly and a domain involved in hydrolyzing peptidoglycan in *E. coli* and *S. enterica* (Pallen et al. 2005). The observed interactions might form a similar functional link in *T. pallidum*, which has a FlgJ ortholog only consisting of the rod assembly domain. However, it should be noted that MurC and MurD are commonly believed to localize to the cytoplasm.

To assess the higher-level organization of the bacterial cell, links between function categories were considered (Fig. 31). Such an analysis was first conducted for the yeast network (Schwikowski et al. 2000). **Self-associations of functional categories** are expected (von Mering et al. 2002). These are found for motility related proteins, proteins involved in DNA metabolism, and for cell division proteins. Especially, the links of the former to categories can be the basis for analyzing these categories in more detail. An in detail discussion of motility related proteins was presented by Rajagopala SV (Rajagopala 2006). Other interesting links such as the link between "protein synthesis" and "protein fate" and the potential regulatory link between motility genes and tRNA aminoacylation links open the route for further in detail investigations.

Comparison, Integration & Conservation

One major aim of protein interaction studies is the comparison with other data sets. The idea is to identify common patterns in different interaction sets, and finally devise a theory on the evolution of protein-protein interactions. However, these comparisons are (at the moment) hampered by the little overlap between data sets. Already, within the same species and with a similar method only a small overlap is observed, e.g. only 28% of the core complexes are conserved between to recently published coAP/MS data sets for yeast (Goll and Uetz 2006) and two yeast-two-hybrid studies for yeast showed an overlap of ~17% (Ito et al. 2001). Comparisons between different species, which are based on orthologous gene relationships, show an even smaller overlap: Suthram *et al.* found an overlap between 5% and 13% when comparing interaction networks from four eukaryotic species (yeast, fly, worm, and Plasmodium).

The **overlap** observed between the *T. pallidum* network and other networks from other species was also very small (Table 31) ranging from 0.4% (*E. coli* coAP/MS) to 5.1% (*H. pylori* yeast-two-hybrid). The smaller overlap with coAP/MS data is expected due to the methodological differences. The overlap with *H. pylori* is in a reasonable range compared to the results for eukaryotic data. Nevertheless, a larger absolute number could be expected if the whole proteome of *H. pylori* had been screened (only a partial interaction map with 261 tested baits has been generated). The overlap with the *C. jejuni* data from Parish *et al.* is small (~3%). Interestingly, Parish *et al.* retested 173 interactions from the *T. pallidum* dataset with their system and classified ~28% as positive (*pers. comm.*). Thus, the actual number of reproducible interactions between species and two different Y2H systems seems to be bigger than one would conclude from the direct comparison of data sets.

However, in addition to methodological differences and the observed high number of false negative interactions in the Y2H system, the lower overlap of inter-species comparisons is probably due to real differences between species. For understanding the evolution of protein interactions, it will be crucial to sort out these interactions; this can be done by making use of additional protein-interaction verification methods.

Here I looked at the conservation of interacting proteins throughout evolution (Fig. 38). This analysis was based on the subset of Y2H interactions supported either by bioinformatical predictions or by an overlap with any other protein-interaction dataset. Interestingly, the interaction set could be divided into different conservation classes including overall conserved interactions and interactions with one constitutive and one optional interaction partner. This analysis allows a glimpse of the variability of protein-interaction networks and arouses interest in looking at the variability of interactions for cases where both interacting partners are conserved.

Motility and Genome-wide Motility Phenotyping of E. coli

As seen in the last paragraphs, protein interactions themselves can already provide a wealth of ideas on the biology of organisms. However, the common goal is to relate these molecular properties to phenotypic effects on the organismal level, and thus, try to explain the latter by the former.

Following a top-down strategy, the first step to achieve this objective is the integration of several functional genomic datasets including molecular properties and phenotypic effects – such approaches can be termed "integrative systems biology".

For yeast, several of these datasets are available ranging from protein abundance measurements, over protein localization studies, to quantitative phenotypic profiling (http://www.yeastgenome.org/cache/genome-wide-analysis.html).

For bacteria, only a few systematic large-scale datasets are available. The most comprehensive phenotyping study was done by the "Bacillus subtilis Functional Analysis Consortium" including specific phenotyping assays for a large array of functional processes (Schumann et

al. 2000). Recently, Baba *et al.* established a systematic single gene deletion library for *E. coli* (Baba et al. 2006) which provides a basis for large scale phenotyping assays in *E. coli*.
The bacterial flagellum is probably the best studied protein complex of bacteria, motility plays a crucial role in the pathogenesis of Syphilis and many other infectious diseases (see introduction). Bacterial motility was selected and genome-wide motility phenotyping for *E. coli* based on the afore mentioned library was conducted. The intention was to find out what we can learn – even about a well-characterized functional complex –when genome-scale approaches are applied. **159 gene-deletion mutants with reduced motility** were identified (page 130). These included the majority of known motility genes, which supports the reliability of the method. The intersection of the *E. coli* and the *B. subtilis* (Schumann et al. 2000) motility phenotyping sets mainly contained known motility genes. From this, we can conclude that most of the essential conserved motility genes are already known. However, several additional genes influencing motility have been identified. These genes can have an indirect role for motility such as by synthesis of required cofactors or restructuring of peptidoglycan (Supplementary Table 29) or they might play a species-specific role in motility. An assembly factor for the bacterial flagellum, which is only present in a certain subset of bacterial species has been, for example, identified to be required for motility in *B. subtilis* (chapter 3.5).
A number of proteins were both found to interact with motility-related proteins in *T. pallidum* and have an ortholog with reduced motility in *E. coli* (Table 40). These proteins can be assumed to have a direct role in motility and include a protein involved in restructuring of peptidoglycan (AmiA), an enzyme showing a genomic location link to motility, TP0945, and conserved hypothetical proteins.
A further discussion of the implications for bacterial motility from interaction mapping is provided by Rajagopala (Rajagopala 2006).

Pathogenicity-related Genes

T. pallidum is the causative agent of Syphilis, but the molecular details of this disease are only poorly understood (see introduction) – mainly due to the impossibility to culture this spirochete. However, a set of possible virulence factors has been identified (Weinstock et al. 1998) and a set of genes with highest expression levels during an experimental rabbit infection has been characterized (Smajs et al. 2005). These genes were analyzed with respect to their interaction properties (page 120).
On **the individual gene level** the identified interactions can provide routes for further investigations, e.g. a functional link between a virulence associated capsular polysaccharide biosynthesis protein, TP0077, and a protein potentially binding to peptidoglycan, TP0297, was found. This puts the later into a virulence context and could evoke further studies on the role of this link in cell-wall metabolism. Another example is the interaction between two membrane located virulence factors, TP0971 and TP0171, which indicates also a functional link between these proteins.
On the topological level, no differences between virulence-related genes and the remaining gene were found except for a higher centroid value of regulator proteins which form a virulence associated gene class (see above).
Several **functional associations** of these virulence classes could be observed (Fig. 37). The biological relevance of these links, however, needs to be elucidated by further studies. An interesting link is formed between virulence proteins exposed on the surface and proteins highly expressed during experimental rabbit infection (Table 35). A subset of these protein pairs might provide candidates for medical intervention, e.g. by selecting pairs of proteins for combination vaccines.
Although, no definite consequences for therapeutic intervention or vaccination can be drawn from these results, they deliver further insight into the molecular details of virulence genes.

They can provide first ideas for further investigations, which is especially crucial for an organism such as *T. pallidum*, which can not be cultured or genetically manipulated.

Guilt-by-association – Functional Predictions

Another major objective of interactome studies is to derive hypotheses on the functions of previously uncharacterized proteins. The basis is that proteins rarely function alone, but nearly in all cases function in the context of other proteins. By looking at the interacting partners of a given protein certain predictions about its function can be made ("guilt-by-association" approach).
Schwikowski et al. (Schwikowski et al. 2000) derived predictions for the function of 29 proteins by considering their interactions in the interaction network of yeast; predictions were only made for proteins with at least two interacting proteins with at least one function in common. Another approach taken by Vazquez *et al.* minimizes the number of protein interactions among different functional categories (Vazquez et al. 2003).
In this thesis, the interaction partners of each protein of unknown function were analyzed with respect to their functional categories. To reduce the influence of unspecifically interacting protein categories (or categories with a large number of members), only functional links that were enriched compared to randomized networks were considered. In addition, at least 30% (TIGR classification) or 50% (GO terms) of the total number of interactions should be involved in the observed link. This filtering provided lists of genes with their **associated potential functions** (Table 29 & Table 30).
The hypothetical protein **TP0183**, for example, seems to function in regulation of "DNA replication, recombination, and repair", probably involving a small RNA, tmRNA, mediated regulatory mechanism (Keiler and Shapiro 2003).
The interactions of **TP0496**, a protein conserved in *Treponema* and *Borrelia* species, include several proteins involved in protein biosynthesis/tRNA metabolism. A link to DNA replication is provided by the interaction with DNA primase (DnaE). TP0496 is located in an operon with ROD shape-determining proteins MreB/C (von Mering et al. 2005). The interaction with the DNA replication protein DnaE is in concordance with the known link between MreB and DNA replication (Defeu Soufo and Graumann 2005). Therefore, TP0496 might function as a link between tRNA metabolism (amino acid or translational status) and DNA replication.
However, these potential functional links of these proteins need to be verified by further investigations. An example for such an investigation is given in the next chapter: the protein **TP0658** was found to be associated to bacterial motility in the interactions dataset, which motivated an in detail characterization of its function.

4.3. Individual Protein I – TP0658, a Conserved Assembly Factor for the Bacterial Flagellum

In the *T. pallidum* Y2H screen, TP0658 was the only widely conserved protein of unknown function which interacted with all three flagellin proteins of *T. pallidum* (FlaB1 = TP0868, FlaB2 = TP0792, and FlaB3 = TP0870) in a specific manner. Thus, TP0658 was selected for an in detail characterization (Titz et al. 2006a).

The Interaction between TP0658 and Flagellins is widely conserved

TP0658 is conserved in several bacterial species including spirochetes, clostridia, bacillales and delta/epsilon proteobacteria. The interaction between TP0658 and flagellin was verified biochemically for *T. pallidum* and *B. subtilis* (yviF-flagellin) (Fig. 47). In addition, an interaction between flagellin and two TP0658 orthologs in *H. pylori*, HP1377 and HP1154, was found in another large scale Y2H study (Rain et al. 2001). Here it is demonstrated that the TP0658 ortholog in *B. subtilis*, yviF, is crucial for bacterial motility (Fig. 49). This confirms an earlier observation by Golden *et al.* (Golden and Acheson 2002) who identified the *Campylobacter*

jejuni ortholog of TP0658, CJ1075, in a motility mutagenesis screen. Taken together, these findings demonstrate that TP0658 as well as its interaction with flagellin proteins, is essential for motility in many divergent bacterial species. Finally, J. Parish and R. Finley (*pers. comm.*) found the *Campylobacter jejuni* homologs of FliC and TP0658 to interact in a two-hybrid assay.
Bioinformatical analysis of flagella proteins present in species other than the classical model bacteria, *S. typhimurium* and *E. coli*, shows a divergence, for example, in respect to export chaperones (Pallen et al. 2005): FlgN (the chaperone for FlgK) is absent, for example, in *spirochetes*, FliT (the chaperone for FliD) is restricted to *proteobacteria*, and despite its six flagellin proteins, no FliS gene is present in the genome of *Caulobacter crescendus*. There is also no obvious similarity between TP0658 and FliS, so it is unlikely that their function is very similar either.

What is the molecular mechanism of TP0658's function?

In several databases, TP0658 and its orthologs are still annotated as "putative membrane protein". Although the sequence indicates a hydrophobic stretch near the middle of the protein, the presented experiments show clearly that the protein is highly soluble. Moreover, several (~45) GST-fusions of *T. pallidum* were tested for soluble expression. Of these, the TP0658 was the protein with the highest solubility (not shown). Interestingly, at least some chaperones exhibit such hydrophobic stretches as well (Deuerling and Bukau, 2004).
In particular, several observations are reminiscent of the export chaperone FliS in *S. typhimurium* (Auvray et al. 2001; Ozin et al. 2003). First, the direct interaction between flagellin and TP0658 supports physical cooperation of TP0658 and flagellin. Second, lack of TP0658 leads to impairment of motility due to loss of flagellin supporting a role of TP0658 in filament assembly and/or stabilization of flagellin in the cytosol. In fact, Golden & Acheson (Golden and Acheson 2002) showed that a mutant of *Campylobacter* CJ1075 was not only completely immotile but also had no detectable flagellin (FlaA). A direct effect on flagellin stability is also supported by artificially co-expression of TP0658 and flagellin (Fig. 49). Third, both TP0658 and FliS bind to the c-terminal part of flagellin which is implicated in polymerization (Auvray et al. 2001). However, the detailed molecular mechanism of TP0658 and FliS function remain unclear. They may act in parallel or subsequently and it cannot be excluded that TP0658 might, for example, add a further layer of regulation to the process. Finally, type III secretion chaperones (TTSCs) have been shown to prevent degradation and aggregation of their cognate substrates prior to secretion (Bennett and Hughes 2000), just as TP0658 appears to do (Fig. 49). Once secretion of the bound substrate is initiated, the TTSCs are thought to donate the substrates to the secretion apparatus. Unlike chaperones associated with virulent TTSSs, all flagella-associated TTSCs bind the carboxyterminal region of their partners (Bennett and Hughes 2000).
To unravel these distinct functions of FliS and TP0658 it will be necessary to characterize the molecular function of TP0658 in more detail and analyze to which extent both proteins can compensate for each other.

4.4. Individual Protein II – yjjG, a House-cleaning Nucleotidase *in vivo*

YjjG was found to function as an *in vivo* house cleaning phosphatase for non-canonical pyrimidine nucleotides. YjjG recognizes a range of substrates *in vivo*, prevents their incorporation into DNA and has a higher enzymatic activity towards non-canonical nucleotides than towards canonical nucleotides *in vitro*. An overview of YjjG's function in the nucleotide metabolism is shown in Fig. 53. However, the *in vivo* relevance of the substrates tested is not clear. Reactive oxygen/nitrogen species are thought to be the main sources of damage to DNA and DNA precursors (Kamiya 2003): oxidation products of pyrimidine DNA precursors include 5-formyluracil, 5-hydroxyuracil, and thymine glycol. Although their evaluation in the *in vivo* assay used in this thesis was not feasible (5-formyluracil and 5-hydroxyuracil did not show a toxic effect even at a concentration of 1mM; data not shown), monophosphorylated derivatives of these compounds are potential substrates of YjjG. A higher sensitivity towards H_2O_2, however, was not observed for the *yjjG* mutant either (data not shown). Apart from oxidative damage, YjjG could also directly protect bacteria from modified pyrimidine nucleotides acquired from environmental sources. Bacteria of the gut might have the propensity to modify the pharmacokinetics of chemotherapeutic drugs based on modified pyrimidine compounds. In summary, our findings imply that YjjG with its broad pyrimidine nucleotide activity spectrum is a house-cleaning candidate for newly identified non-canonical pyrimidine nucleotides found in the environment or as by-products of metabolism.

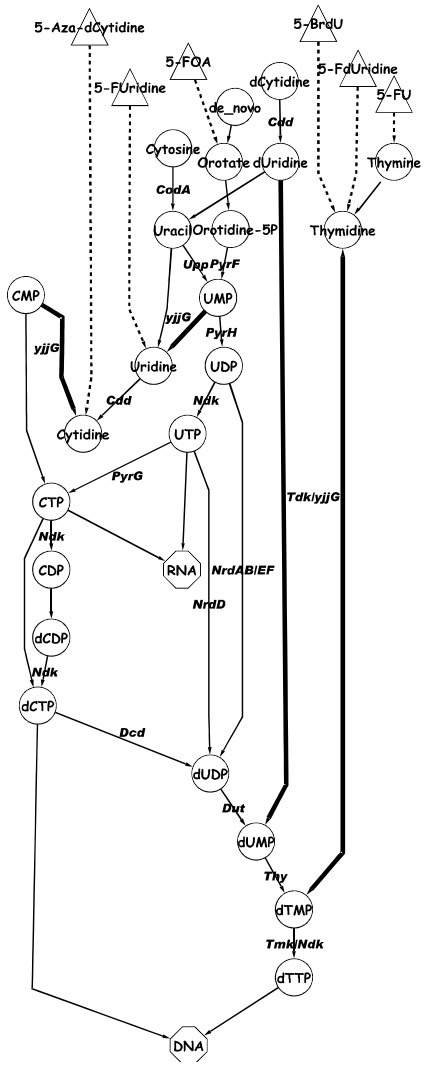


Fig. 53 Overview of nucleotide metabolism and YjjG's function. The main enzymatic reactions of pyrimidine metabolism, entry points of non canonical pyrimidine derivatives, and reactions controlled by YjjG's house-cleaning function are shown. Circles represent canonical compounds; triangles represent non-canonical compounds, and octagons DNA and RNA. Enzymatic reactions are shown by arrows. Only a selection of *E. coli* enzymes is given. Entry points of non-canonical nucleobase compounds are indicated by dashed arrows. Reactions controlled by YjjG are marked with thick lines.

An especially noteworthy feature of YjjG and its yeast homolog SDT1 is their activity against nucleotide monophosphates. All previously described house-cleaning phophatases act on nucleoside triphosphates (Galperin et al. 2006). Thus, YjjG and SDT1 do not only constitute a new homology, but also a new functional group of house-cleaning phosphatases. This clearly supports the hypothesis by Galperin et al. that the importance of the house-cleaning

function suggests that many undiscovered house-cleaning enzymes are "lurking among the unannotated 'conserved hypothetical' open reading frames found in microbial genomes" (Galperin et al. 2006).

4.5. Final Conclusions & Outlook

The protein-interaction map for *T. pallidum* presented in this thesis represents one of the first and most comprehensive interaction maps for bacteria.

Several analyses on different levels of the network revealed biological insights for this spirochete, and moreover form the basis for further investigations by "integrative systems biology" approaches. An outstanding example is the identification of protein interaction mediated links between different genomic locations, which has not been attempted and shown before.

Several insights for individual proteins have been obtained, e.g. functional predictions and associations to virulence related genes. However, in a functional proteomics study only a limited number of follow-up experiments can be conducted. The power of this approach is exemplified by the identification of a conserved assembly factor of the flagellum, TP0658. In addition, the complementary nature of phenotyping datasets is shown by the characterization of YjjG, which functions as an *in vivo* house-cleaning nucleotidase in *E. coli*.

The idea of integrating datasets of different types – to eventually reach a functional understanding of the observed molecular details – is exemplified by a whole-genome motility phenotyping study of *E. coli*.

Finally, the analysis of transcriptional activator properties demonstrates that high-throughput datasets provide a wealth of information that needs to be integrated with several other data types to draw conclusions that are not possible to reach by classical approaches.

However, functional proteomics studies raise more questions than they can answer – they generate hypotheses rather than testing them. Thus, several further investigations are needed, for example to check for functional prediction or look for the biological relevance of the identified genomic location links.

The major challenge will be to transform the presented static interaction network into a dynamic network of functional associations. The questions are: "When/under which conditions are these interactions formed?", "What are the molecular functions of these interactions?" and "How do we capture this biological knowledge in computational models?"

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6. Supplementary Tables

Supplementary Table 1 Identified Y2H activators for Yeast. The original Y2H study from which they were extracted (Uetz = (Ito et al. 2001) or Ito = (Uetz et al. 2000)) and the measured activation strengths are given. LTH is the minimal concentration of 3-AT (in mM) that is required to suppress activator activity and thus a direct measure of activation strength. bGAL is the beta-Galactosidase activity measured as described in Materials and Methods, including the Standard Error Mean (SEM) resulting from 3 measurements. Proteins annotated to have the F-GO term "transcriptional activator activity" in the YPD database (Biobase) are indicated (YPD). See also (Titz et al. 2006b).

ORF	name	source	LTH (3-AT)	bGAL (+/- SEM)	YPD
YAL014C	YAL014C	Ito	>200	0.8685+/-0.0990	
YAL040C	CLN3	Ito	50	-0.029+/-0.0399	
YAR003W	YAR003W	Ito	100	0.1138+/-0.1060	
YAR014C	YAR014C	Ito & Uetz	50	NA	
YAR042W	SWH1	Ito	25	-0.073+/-0.0191	
YAR062W	YAR062W	Ito	50	0.2152+/-0.0601	
YAR074C		Ito	NA	NA	
YBL005W-A		Ito	NA	NA	
YBL007C	SLA1	Ito	>200	0.8809+/-0.0605	
YBL010C	YBL010C	Ito	100	NA	
YBL025W	RRN10	Ito	NA	NA	
YBL032W		Uetz	NA	NA	
YBL046W	YBL046W	Ito	10	NA	
YBL049W	YBL049W	Ito	NA	NA	
YBL051C	YBL051C	Ito	100	0.4275+/-0.1067	
YBL056W	PTC3	Ito	3	NA	
YBL074C	AAR2	Ito	NA	NA	
YBL079W	NUP170	Ito	100	0.2055+/-0.0769	
YBL081W	YBL081W	Ito	>200	0.8972+/-0.0431	
YBL093C	ROX3	Ito	>200	0.5879+/-0.0490	y
YBL097W	BRN1	Ito	10	NA	
YBR012C	YBR012C	Ito	NA	NA	
YBR028C		Uetz	10	NA	
YBR030W	YBR030W	Ito	100	0.5805+/-0.1252	
YBR045C	GIP1	Ito	NA	NA	
YBR050C	REG2	Ito & Uetz	NA	NA	
YBR057C	MUM2	Ito	NA	NA	
YBR058C	UBP14	Ito	50	0.6862+/-0.0742	
YBR061C	YBR061C	Ito	200	NA	
YBR062C	YBR062C	Ito	NA	NA	
YBR072W	HSP26	Ito	50	0.6162+/-0.1196	
YBR098W	YBR098W	Ito	100	0.0312+/-0.0478	y
YBR105C	VID24	Ito	NA	NA	
YBR125C		Uetz	3	NA	
YBR138C	YBR138C	Ito	100	0.5158+/-0.0970	
YBR156C		Uetz	NA	NA	
YBR193C	MED8	Ito	>200	0.8372+/-0.1316	y
YBR211C		Uetz	NA	NA	
YBR212W	NGR1	Ito	100	NA	
YBR239C		Uetz	3	NA	
YBR240C	THI2	Ito	50	NA	
YBR250W		Uetz	3	NA	
YBR271W	YBR271W	Ito	200	0.7195+/-0.1125	
YBR284W	YBR284W	Ito	50	-0.000+/-0.0249	
YBR289W	SNF5	Ito	100	NA	y
YCL012W		Ito	NA	NA	
YCL017C	NFS1	Ito	50	-0.137+/-0.0089	
YCL032W		Uetz	3	NA	
YCL043C		Uetz	NA	NA	
YCR065W	HCM1	Ito	100	0.1958+/-0.0279	y
YCR077C	PAT1	Ito	>200	0.5859+/-0.0760	
YCR082W	YCR082W	Ito	200	0.5496+/-0.0552	
YDL005C	MED2	Ito	NA	NA	
YDL017W	CDC7	Ito	100	0.2612+/-0.0748	
YDL020C	RPN4	Ito	25	NA	y
YDL028C		Uetz	3	NA	
YDL037C	YDL037c	Ito	NA	NA	
YDL065C	PEX19	Ito	200	0.1532+/-0.0317	
YDL081C	RPP1A	Ito	200	0.1932+/-0.0225	
YDL088C	ASM4	Ito	>200	0.0355+/-0.0473	
YDL106C	GRF10	Ito	NA	NA	
YDL115C	YDL115c	Ito	NA	NA	
YDL125C		Uetz	NA	NA	
YDL130W	RPP1B	Ito	100	0.1822+/-0.0318	
YDL134C	PPH21	Ito & Uetz	100	0.1252+/-0.0366	
YDL154W	MSH5	Ito	100	-0.080+/-0.0233	
YDL161W	YDL161w	Ito	>200	0.7565+/-0.1249	
YDL165W	CDC36	Ito	50	0.3929+/-0.1141	y
YDL188C	PPH22	Ito	25	-0.003+/-0.0198	
YDL215C	GDH2	Ito	3	NA	
YDL223C		Uetz	3	NA	
YDR016C	YDR016c	Ito	100	NA	

YDR022C	CIS1	Ito	100	0.0735+/-0.0341	
YDR031W	YDR031w	Ito	200	0.4646+/-0.0889	
YDR045C	YDR045C	Ito	10	0.0372+/-0.0526	
YDR073W	SNF11	Ito	100	0.3912+/-0.0466	y
YDR075W	YDR075W	Ito & Uetz	NA	NA	
YDR081C	PDC2	Ito	>200	0.0566+/-0.0424	
YDR082W	STN1	Ito	50	0.3036+/-0.0682	
YDR098C	YDR098C	Ito	3	0.0172+/-0.0266	
YDR103W	STE5	Ito	200	NA	
YDR111C		Uetz	3	NA	
YDR118W	APC4	Ito	>200	0.2609+/-0.0465	
YDR123C	YDR123C	Ito	NA	NA	y
YDR124W	YDR124W	Ito	NA	NA	
YDR132C		Uetz	10	NA	
YDR145W	YDR145W	Ito	NA	NA	y
YDR146C	SWI5	Ito	>200	0.5196+/-0.1306	y
YDR151C	YDR151C	Ito	NA	NA	
YDR162C	YDR162C	Ito	NA	NA	
YDR164C		Uetz	NA	NA	
YDR165W		Uetz	3	NA	
YDR167W	YDR167W	Ito	NA	NA	y
YDR183W	YDR183W	Ito	NA	NA	
YDR184C	ATC1	Ito	>200	0.5882+/-0.0313	
YDR189W		Uetz	3	NA	
YDR210W	YDR210W	Ito	100	NA	
YDR213W	YDR213W	Ito	>200	0.5049+/-0.1203	y
YDR216W	ADR1	Ito	>200	0.4752+/-0.2174	y
YDR221W	YDR221W	Ito	3	NA	
YDR223W	YDR223W	Ito	>200	0.5482+/-0.0435	
YDR253C	MET32	Ito	50	0.3632+/-0.0988	
YDR260C	YDR260C	Ito	200	-0.010+/-0.0371	
YDR273W	YDR273W	Ito	100	0.5725+/-0.0730	
YDR277C	MTH1	Ito	NA	NA	
YDR291W	YDR291W	Ito	>200	0.0675+/-0.0683	
YDR299W	BFR2	Ito	>200	0.5766+/-0.0529	
YDR308C	SRB7	Ito	25	0.0699+/-0.0375	
YDR318W	YDR318W	Ito	NA	NA	
YDR320C	YDR320C	Ito	>200	0.8629+/-0.0902	
YDR328C	SKP1	Ito	3	0.0399+/-0.0280	
YDR330W	YDR330W	Ito	200	0.2609+/-0.0773	
YDR373W		Uetz	3	NA	
YDR392W	SPT3	Ito	50	0.2372+/-0.1230	y
YDR423C	CAD1	Ito	100	0.0096+/-0.0185	y
YDR443C	SSN2	Ito	>200	0.7916+/-0.0357	
YDR448W	ADA2	Ito	NA	NA	y
YDR464W	SPP41	Ito	3	0.1369+/-0.0537	
YDR484W		Uetz	NA	NA	
YDR489W	YDR489W	Ito	>200	NA	
YDR518W		Uetz	NA	NA	
YDR520C	YDR520C	Ito	>200	0.8299+/-0.0179	
YDR527W	YDR527W	Ito	NA	NA	
YDR532C	YDR532C	Ito	100	0.2726+/-0.0802	
YEL053C	MAK10	Ito	3	NA	
YER008C	SEC3	Ito	50	0.0352+/-0.0300	
YER021W	RPN3	Ito	50	0.3698+/-0.2191	
YER027C	GAL83	Ito	100	0.0962+/-0.0576	
YER033C	YER033c	Ito	100	NA	
YER040W	GLN3	Ito	>200	NA	
YER045C	YER045c	Ito	>200	0.9192+/-0.0479	y
YER051W		Uetz	200	NA	
YER059W	PCL6	Ito	200	0.0992+/-0.1759	
YER089C		Uetz	3	NA	
YER096W	YER096w	Ito	100	0.4195+/-0.0440	
YER108C		Ito	NA	NA	
YER111C	SWI4	Ito	100	0.2982+/-0.1524	y
YER118C	YER118c	Ito	100	0.7692+/-0.0578	
YER122C		Uetz	3	NA	
YER125W	RSP5	Ito	>200	0.9515+/-0.0602	
YER130C	YER130c	Ito	10	NA	
YER149C	PEA2	Ito	25	NA	
YER151C	UBP3	Ito	>200	0.8425+/-0.0947	
YER167W	BCK2	Ito	>200	0.6002+/-0.2382	
YFL029C	CAK1	Ito	200	0.5335+/-0.0385	
YFL033C	RIM15	Ito	>200	0.4306+/-0.0764	
YFL049W	YFL049W	Ito	100	0.6852+/-0.1114	
YFR033C	QCR6	Ito	25	0.0139+/-0.0445	
YFR034C	PHO4	Ito	200	0.5952+/-0.0681	y
YFR043C	YFR043C	Ito	100	-0.101+/-0.0157	
YFR046C	YFR046C	Ito	NA	NA	
YGL003C	CDH1	Ito	100	NA	
YGL015C	YGL015C	Ito	100	0.0675+/-0.0458	
YGL019W	CKB1	Ito	50	0.2105+/-0.1388	
YGL036W	YGL036W	Ito	>200	0.5912+/-0.1001	
YGL043W	DST1	Ito	100	0.1785+/-0.1442	
YGL066W	YGL066W	Ito & Uetz	50 (3 Uetz)	0.7785+/-0.1077	

YGL070C	RPB9	Ito	100	0.0272+/-0.0506	
YGL073W	HSF1	Ito	>200	NA	
YGL079W	YGL079W	Ito	200	0.2138+/-0.0565	
YGL127C	SOH1	Ito	50	0.0412+/-0.0288	
YGL134W	PCL10	Ito	25	-0.054+/-0.0140	
YGL151W	YGL151W	Ito	NA	NA	
YGL154C	LYS5	Ito	10	0.3445+/-0.1086	
YGL161C		Uetz	NA	NA	
YGL166W	CUP2	Ito	>200	0.8069+/-0.1406	y
YGL170C	YGL170C	Ito	100	0.2252+/-0.1502	
YGL172W	NUP49	Ito	100	0.5799+/-0.0877	
YGL175C	SAE2	Ito	NA	NA	
YGL181W		Uetz	3	NA	y
YGL223C	YGL223C	Ito	200	NA	
YGL227W	YGL227W	Ito	NA	NA	
YGL229C	SAP4	Ito	100	NA	
YGR052W		Uetz	3	NA	
YGR070W		Uetz	NA	NA	
YGR077C	PEX8	Ito	25	0.0188+/-0.0190	
YGR120C	YGR120C	Ito	>200	NA	
YGR130C	YGR130C	Ito	>200	0.4559+/-0.0909	
YGR160W		Uetz	25	NA	
YGR163W	YGR163W	Ito	NA	NA	
YGR188C		Uetz	3	NA	
YGR241C	YAP1802	Ito	>200	0.2015+/-0.0863	
YGR251W	YGR251W	Ito	50	NA	
YGR253C	PUP2	Ito	200	0.1598+/-0.0615	
YGR256W		Uetz	3	NA	
YGR269W	YGR269W	Ito	25	NA	
YGR274C	YGR274C	Ito	NA	NA	y
YGR288W	YGR288W	Ito	25	NA	y
YHL009C	YAP3	Ito	NA	NA	
YHL012W	YHL012W	Ito	200	NA	
YHL018W	YHL018W	Ito	3	NA	
YHR030C	SLT2	Ito	100	0.5042+/-0.0686	
YHR056C	YHR056C	Ito	25	NA	
YHR086W	NAM8	Ito	3	NA	
YHR124W	NDT80	Ito	3	0.0272+/-0.0281	
YHR135C		Uetz	3	NA	
YHR149C	YHR149C	Ito	10	NA	
YHR160C	YHR160C	Ito	>200	1.0002+/-0.0941	
YHR167W		Uetz	3	NA	
YHR170W	NMD3	Ito	3	NA	
YHR183W		Uetz	10	NA	
YHR184W	SSP1	Ito	25	NA	
YHR185C	YHR185C	Ito	25	NA	
YHR187W	IKI1	Ito	200	0.8495+/-0.0858	
YHR205W	SCH9	Ito	200	0.1552+/-0.0475	
YIL007C		Uetz	50	NA	
YIL019W	YIL019W	Ito	200	0.2692+/-0.0706	
YIL021W	RPB3	Ito	>200	0.6482+/-0.0357	
YIL034C	CAP2	Ito	100	0.2682+/-0.0399	
YIL036W	YIL036W	Ito	100	0.2162+/-0.0778	y
YIL046W		Uetz	NA	NA	
YIL062C	ARC15	Ito	100	-0.047+/-0.0183	
YIL071W		Ito	NA	NA	
YIL079C	YIL079C	Ito	>200	0.9892+/-0.0207	
YIL093C	YIL093C	Ito	3	-0.042+/-0.0378	
YIL119C	RPI1	Ito	>200	0.9349+/-0.0426	y
YIL123W	SIM1	Ito	3	NA	
YIL135C	YIL135C	Ito	3	NA	
YIL151C	YIL151C	Ito	NA	NA	
YIR010W	YIR010W	Ito	100	0.0122+/-0.0233	
YIR025W	YIR025W	Ito	3	-0.092+/-0.0238	
YJL029C	YJL029C	Ito	>200	NA	
YJL058C	YJL058C	Ito	50	0.0046+/-0.0229	
YJL069C	YJL069C	Ito	100	-0.019+/-0.0421	
YJL070C	YJL070C	Ito	NA	NA	
YJL084C	YJL084C	Ito	50	NA	
YJL098W	YJL098W	Ito	10	NA	
YJL100W		Uetz	100	NA	
YJL103C	YJL103C	Ito	50	-0.056+/-0.0198	
YJL106W	IME2	Ito	10	NA	
YJL116C	NCA3	Ito	200	0.6629+/-0.1065	
YJL126W		Uetz	3	NA	
YJL127C	SPT10	Ito	25	-0.076+/-0.0166	y
YJL146W	IDS2	Ito	>200	0.2022+/-0.1395	
YJL147C	YJL147C	Ito	3	NA	
YJL159W	HSP150	Ito	NA	NA	
YJL176C	SWI3	Ito	200	0.0189+/-0.0175	
YJL181W	YJL181W	Ito	>200	0.1689+/-0.0668	
YJL185C	YJL185C	Ito	50	0.0228+/-0.0163	
YJL187C	SWE1	Ito	25	0.0969+/-0.0519	
YJL204C		Uetz	3	NA	
YJL218W	YJL218W	Ito	100	NA	
YJR002W	MPP10	Ito	25	-0.006+/-0.0353	
YJR042W	YJR042W	Ito	NA	NA	
YJR056C		Uetz	3	NA	
YJR063W	RPA12	Ito	200	-0.011+/-0.0032	
YJR067C	YAE1	Ito	3	NA	

YJR070C	YJR070C	Ito & Uetz	200 (3 Uetz)	NA	
YJR082C	YJR082C	Ito	3	0.0038+/- 0.0197	
YJR093C	FIP1	Ito	100	-0.134+/- 0.0214	
YJR094C	IME1	Ito	200	NA	
YJR112W	NNF1	Ito	10	NA	
YJR119C	YJR119C	Ito	200	0.2019+/- 0.1009	
YJR125C	YJR125C	Ito	3	NA	
YJR141W		Uetz	10	NA	
YKL002W	YKL002W	Ito	100	NA	
YKL015W	PUT3	Ito	200	0.3072+/- 0.0846	y
YKL025C	PAN3	Ito	100	0.2319+/- 0.0485	
YKL028W	TFA1	Ito	100	0.3572+/- 0.1658	
YKL038W	YKL038W	Ito	NA	NA	y
YKL048C		Uetz	10	NA	
YKL059C	YKL059C	Ito	200	0.1292+/- 0.0985	
YKL061W	YKL061W	Ito	100	0.3545+/- 0.1920	
YKL062W	MSN4	Ito	100	0.7522+/- 0.0354	y
YKL068W	NUP100	Ito	200	0.3679+/- 0.0517	
YKL093W	MBR1	Ito	200	-0.132+/- 0.0142	
YKL109W	HAP4	Ito	200	0.6056+/- 0.0597	y
YKL135C	APL2	Ito	>200	0.1112+/- 0.0662	
YKL143W	LTV1	Ito	200	0.5272+/- 0.0376	
YKL161C	YKL161C	Ito	3	0.0465+/- 0.0765	
YKL165C	MCD4	Ito	>200	0.3156+/- 0.0892	
YKL171W	YKL171W	Ito	200	NA	
YKL173W	SNU114	Ito	100	0.1232+/- 0.0124	
YKL190W		Uetz	25	NA	
YKR017C	YKR017C	Ito	50	0.0619+/- 0.0165	
YKR021W	YKR021W	Ito	50	0.3116+/- 0.0905	
YKR022C		Uetz	100	NA	
YKR027W	YKR027W	Ito	50	0.2616+/- 0.0432	
YKR048C	NAP1	Ito	200	0.6022+/- 0.0544	
YKR060W	YKR060W	Ito	>200	NA	
YKR064W	YKR064W	Ito	200	-0.024+/- 0.0423	
YKR077W	YKR077W	Ito	>200	0.9899+/- 0.0390	
YLL013C	YLL013C	Ito	>200	0.7076+/- 0.0934	
YLR016C		Uetz	50	NA	
YLR019W	YLR019W	Ito	100	NA	
YLR024C	YLR024C	Ito	100	0.1615+/- 0.0752	
YLR038C	COX12	Ito	3	NA	
YLR053C	YLR053C	Ito	3	NA	
YLR071C	RGR1	Ito	50	NA	y
YLR085C	ARP6	Ito	25	NA	
YLR095C	YLR095C	Ito	100	0.2445+/- 0.0776	
YLR098C	CHA4	Ito	200	0.6499+/- 0.0856	y
YLR102C	APC9	Ito	100	NA	
YLR113W	HOG1	Ito	100	0.1389+/- 0.0362	
YLR119W	SRN2	Ito	3	NA	
YLR131C	ACE2	Ito	>200	NA	y
YLR135W	YLR135W	Ito	>200	0.7172+/- 0.1206	
YLR144C	ACF2	Ito	>200	NA	
YLR154C	YLR154C	Ito	3	-0.099+/- 0.0144	
YLR182W	SWI6	Ito	100	NA	y
YLR192C	YLR192C	Ito	>200	0.8849+/- 0.0641	
YLR212C	TUB4	Ito	100	0.2939+/- 0.0491	
YLR215C		Uetz	100	NA	
YLR226W		Uetz	NA	NA	
YLR228C	ECM22	Ito	>200	0.7762+/- 0.1344	y
YLR273C	PIG1	Ito	100	NA	
YLR285W	YLR285W	Ito	>200	0.9469+/- 0.0781	
YLR288C	MEC3	Ito	25	NA	
YLR300W	EXG1	Ito	25	NA	
YLR321C	SFH1	Ito	100	0.2722+/- 0.0064	
YLR331C	YLR331C	Ito	100	1.0302+/- 0.0364	
YLR371W		Uetz	3	NA	
YLR403W	SFP1	Ito	3	0.0022+/- 0.0089	
YLR417W	VPS36	Ito	25	0.0082+/- 0.0187	
YLR424W	YLR424W	Ito	100	-0.011+/- 0.0300	
YLR435W	YLR435W	Ito	10	-0.028+/- 0.0141	
YLR445W	YLR445W	Ito	200	0.1456+/- 0.0112	
YLR451W	LEU3	Ito	100	0.3956+/- 0.1238	y
YML037C	YML037C	Ito	200	0.0382+/- 0.0207	
YML058W	SML1	Ito	3	NA	
YML068W	YML068W	Ito	3	-0.098+/- 0.0059	
YML081W	YML081W	Ito	3	-0.061+/- 0.0332	
YML091C	YML091C	Ito	NA	NA	
YML099C	ARG81	Ito	100	NA	y
YML128C	YML128C	Ito	100	0.3646+/- 0.0531	
YMR004W	MVP1	Ito	>200	0.3639+/- 0.0600	
YMR022W		Uetz	3	NA	
YMR030W	YMR030W	Ito	>200	0.0425+/- 0.0698	y
YMR037C	MSN2	Ito	>200	1.1689+/- 0.1381	y
YMR048W	YMR048W	Ito	>200	0.1739+/- 0.0609	
YMR080C	NAM7	Ito	200	0.0282+/- 0.0298	

YMR081C	ISF1	Ito	200	0.2389+/-0.0471	
YMR091C	NPL6	Ito	25	NA	
YMR112C	YMR112C	Ito	100	0.2012+/-0.0585	
YMR133W	REC114	Ito	200	-0.035+/-0.0319	
YMR179W	SPT21	Ito	>200	-0.009+/-0.0390	
YMR181C	YMR181C	Ito	>200	0.8592+/-0.0775	
YMR195W	YMR195W	Ito	>200	0.3746+/-0.0845	
YMR223W	UBP8	Ito	50	0.6462+/-0.1722	
YMR227C	YMR227C	Ito	NA	NA	
YMR236W	YMR236W	Ito	NA	NA	y
YMR270C	RRN9	Ito	100	NA	
YMR277W	FCP1	Ito	200	0.1342+/-0.0405	
YMR295C	YMR295C	Ito	>200	NA	
YMR297W	PRC1	Ito	25	NA	
YMR299C	YMR299C	Ito	200	0.0979+/-0.0148	
YMR323W	YMR323W	Ito	3	-0.014+/-0.0122	
YNL004W	HRB1	Ito	3	-0.062+/-0.0235	
YNL025C	SSN8	Ito	100	0.2122+/-0.0517	
YNL027W	CRZ1	Ito	>200	0.8595+/-0.0728	
YNL032W	SIW14	Ito	200	0.7252+/-0.1191	
YNL074C	YNL074C	Ito	NA	NA	
YNL075W		Uetz	25	NA	
YNL091W	YNL091W	Ito	50	-0.014+/-0.0416	
YNL092W	YNL092W	Ito	3	-0.045+/-0.0169	
YNL103W	MET4	Ito	>200	0.7636+/-0.0770	y
YNL127W	YNL127W	Ito	3	0.0485+/-0.0240	
YNL151C	RPC31	Ito	50	-0.026+/-0.0369	
YNL161W	CBK1	Ito	100	0.3809+/-0.1267	
YNL164C	YNL164C	Ito	3	0.0162+/-0.0497	
YNL192W	YNL192W	Ito	NA	NA	
YNL199C	GCR2	Ito	100	0.5216+/-0.0662	y
YNL204C	SPS18	Ito	100	0.0242+/-0.0378	
YNL223W	YNL223W	Ito	NA	NA	
YNL225C	CNM67	Ito	100	0.1709+/-0.0875	
YNL236W	SIN4	Ito	>200	0.1229+/-0.0694	
YNL245C		Uetz	NA	NA	
YNL308C		Uetz	3	NA	
YNL309W	STB1	Ito	100	NA	y
YNL314W	DAL82	Ito	100	-0.047+/-0.0655	y
YNL330C	RPD3	Ito	10	NA	
YNR003C	RPC34	Ito	3	NA	
YNR004W	YNR004W	Ito	10	0.0165+/-0.0629	
YNR010W	CSE2	Ito	200	0.3445+/-0.0819	
YNR017W	MAS6	Ito	200	0.5209+/-0.1233	
YNR023W	SNF12	Ito	NA	NA	
YNR032W	PPG1	Ito	200	NA	
YNR063W	YNR063W	Ito	100	0.0312+/-0.0368	
YNR069C	YNR069C	Ito	>200	0.9416+/-0.3435	
YOL044W		Uetz	3	NA	
YOL051W	GAL11	Ito	200	0.9772+/-0.0244	y
YOL067C	RTG1	Ito	>200	0.5925+/-0.0651	y
YOL082W	YOL082W	Ito	NA	NA	
YOL083W	YOL083W	Ito	NA	NA	
YOL108C	INO4	Ito	100	NA	y
YOL112W	MSB4	Ito	200	0.4759+/-0.1309	
YOL135C	MED7	Ito	50	0.0815+/-0.0151	
YOL136C	PFK27	Ito	200	0.3526+/-0.0579	
YOL148C	SPT20	Ito	100	0.4402+/-0.1069	y
YOR032C	HMS1	Ito	NA	NA	
YOR066W	YOR066W	Ito	>200	0.5309+/-0.1226	
YOR069W		Uetz	NA	NA	
YOR070C	GYP1	Ito	>200	-0.070+/-0.0176	
YOR113W		Uetz	NA	NA	y
YOR128C	ADE2	Ito	NA	NA	
YOR151C	YOR151C	Ito & Uetz	NA	NA	
YOR162C	YRR1	Ito	100	0.0812+/-0.0411	y
YOR166C	YOR166C	Ito	200	0.0519+/-0.0395	
YOR174W	MED4	Ito	>200	0.1035+/-0.0747	
YOR177C		Uetz	3	NA	
YOR178C	GAC1	Ito	>200	0.5292+/-0.0982	
YOR194C	TOA1	Ito	>200	NA	
YOR197W	YOR197W	Ito	100	0.1565+/-0.0919	
YOR212W	STE4	Ito	NA	NA	
YOR262W	YOR262W	Ito	200	0.5596+/-0.0335	
YOR281C	YOR281C	Ito	100	NA	
YOR290C	SNF2	Ito	200	0.7139+/-0.1587	
YOR299W	BUD7	Ito	50	0.1079+/-0.0420	
YOR329C	SCD5	Ito	>200	0.2706+/-0.0516	
YOR339C		Uetz	NA	NA	
YOR344C	TYE7	Ito	100	0.3559+/-0.1249	y
YOR352W	YOR352W	Ito	100	0.2375+/-0.0558	
YOR355W	GDS1	Ito	100	0.2076+/-0.0304	
YOR370C	MRS6	Ito	>200	0.5295+/-0.1343	
YOR382W	YOR382W	Ito	3	-0.023+/-0.0297	

YPL011C	YPL011C	Ito	NA	NA	
YPL014W	YPL014W	Ito	3	0.0819+/-0.0381	
YPL026C	SKS1	Ito	50	-0.025+/-0.0102	
YPL038W	MET31	Ito	50	0.0242+/-0.0316	
YPL042C	SSN3	Ito	NA	NA	
YPL054W	LEE1	Ito	50	-0.041+/-0.0251	
YPL055C	YPL055C	Ito	3	-0.047+/-0.0301	
YPL075W	GCR1	Ito	50	0.0769+/-0.0356	y
YPL089C	RLM1	Ito	200	NA	
YPL105C	YPL105C	Ito	200	0.0619+/-0.0482	
YPL124W	YPL124W	Ito	NA	NA	
YPL174C	NIP100	Ito	100	-0.056+/-0.0151	
YPL184C	YPL184C	Ito	100	0.5069+/-0.1525	
YPL202C	YPL202C	Ito	NA	NA	y
YPL229W	YPL229W	Ito & Uetz	200	0.0929+/-0.0316	
YPL233W	YPL233W	Ito	200	NA	
YPL250C	YPL250C	Ito	>200	0.5319+/-0.1199	
YPL254W	HFI1	Ito	100	0.2372+/-0.1030	y
YPL256C	CLN2	Ito	NA	NA	
YPL278C	YPL278C	Ito	100	0.3419+/-0.0477	
YPR007C	YPR007C	Ito	3	-0.013+/-0.0290	
YPR008W	YPR008W	Ito	>200	0.8622+/-0.1090	
YPR040W		Uetz	3	NA	
YPR046W	MCM16	Ito	50	0.0815+/-0.0187	
YPR066W	YPR066W	Ito	NA	NA	
YPR070W	YPR070W	Ito	NA	NA	
YPR076W	YPR076W	Ito	100	0.4306+/-0.0696	
YPR103W	PRE2	Ito	100	0.0619+/-0.0151	
YPR105C		Uetz	3	NA	
YPR119W		Uetz	3	NA	
YPR144C	YPR144C	Ito & Uetz	50	NA	
YPR168W	NUT2	Ito	100	0.0442+/-0.0305	
YPR179C	YPR179C	Ito	>200	0.8885+/-0.0251	
YPR180W	AOS1	Ito	>200	-0.048+/-0.1139	
YPR187W	RPO26	Ito	100	0.0695+/-0.0532	
YPR192W	YPR192W	Ito	NA	NA	

Supplementary Table 2 Protein interactions of *T. pallidum*. All protein interactions detected for *T. pallidum* are shown. The definition lines are shortened and the prey count and subset (W=whole set; F=filtered set) is given in parenthesis.

TP0001 [chromosomal replicat...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0004 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0004 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0006 [Tp75 protein {Trepon...] - TP0281 [hypothetical protein...] (64,W)
TP0006 [Tp75 protein {Trepon...] - TP0518 [conserved hypothetic...] (70,W)
TP0006 [Tp75 protein {Trepon...] - TP0563 [hypothetical protein...] (93,W)
TP0006 [Tp75 protein {Trepon...] - TP0587 [hypothetical protein...] (23,F)
TP0006 [Tp75 protein {Trepon...] - TP0618 [hypothetical protein...] (24,F)
TP0006 [Tp75 protein {Trepon...] - TP0664 [flagellar filament o...] (34,F)
TP0006 [Tp75 protein {Trepon...] - TP0764 [conserved hypothetic...] (139,W)
TP0006 [Tp75 protein {Trepon...] - TP0788 [hypothetical protein...] (132,W)
TP0006 [Tp75 protein {Trepon...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0006 [Tp75 protein {Trepon...] - TP0946 [glucose-inhibited di...] (19,F)
TP0006 [Tp75 protein {Trepon...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0006 [Tp75 protein {Trepon...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0006 [Tp75 protein {Trepon...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0007 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0007 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0007 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0007 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0007 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0007 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0007 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0007 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0011 [tpr protein B (tprB)...] - TP0563 [hypothetical protein...] (93,W)
TP0011 [tpr protein B (tprB)...] - TP0661 [hypothetical protein...] (117,W)
TP0012 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0012 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0012 [hypothetical protein...] - TP0287 [conserved hypothetic...] (27,F)
TP0012 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0012 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0012 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0012 [hypothetical protein...] - TP0519 [response regulatory ...] (30,F)
TP0012 [hypothetical protein...] - TP0559 [conserved hypothetic...] (26,F)
TP0012 [hypothetical protein...] - TP0587 [hypothetical protein...] (23,F)
TP0012 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0012 [hypothetical protein...] - TP0664 [flagellar filament o...] (34,F)
TP0012 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0012 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0012 [hypothetical protein...] - TP0773 [periplasmic serine p...] (30,F)
TP0012 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0012 [hypothetical protein...] - TP0894 [conserved hypothetic...] (13,F)
TP0012 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0012 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0012 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0012 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0012 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0013 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0013 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0013 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0013 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0015 [phenylalanyl-tRNA sy...] - TP0258 [conserved hypothetic...] (173,W)
TP0015 [phenylalanyl-tRNA sy...] - TP0383 [conserved hypothetic...] (65,W)
TP0015 [phenylalanyl-tRNA sy...] - TP0563 [hypothetical protein...] (93,W)
TP0015 [phenylalanyl-tRNA sy...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0015 [phenylalanyl-tRNA sy...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0017 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0017 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0017 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0017 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0017 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0018 [transcription elonga...] - TP0677 [hypothetical protein...] (2,F)
TP0018 [transcription elonga...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0018 [transcription elonga...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0019 [transcription elonga...] - TP0060 [ribosomal protein L9...] (78,W)
TP0019 [transcription elonga...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0019 [transcription elonga...] - TP0281 [hypothetical protein...] (64,W)
TP0019 [transcription elonga...] - TP0563 [hypothetical protein...] (93,W)
TP0019 [transcription elonga...] - TP0741 [conserved hypothetic...] (8,F)
TP0019 [transcription elonga...] - TP0788 [hypothetical protein...] (132,W)
TP0019 [transcription elonga...] - TP0907 [conserved hypothetic...] (110,W)
TP0019 [transcription elonga...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0019 [transcription elonga...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0021 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0025 [conserved hypothetic...] - TP0928 [hypothetical protein...] (1,F)
TP0025 [conserved hypothetic...] - TP1040 [lysyl-tRNA synthetas...] (2,F)
TP0026 [flagellar motor swit...] - TP0563 [hypothetical protein...] (93,W)
TP0027 [hemolysin, putative ...] - TP0209 [ribosomal protein L3...] (27,F)
TP0027 [hemolysin, putative ...] - TP0764 [conserved hypothetic...] (139,W)
TP0029 [UDP-N-acetylglucosam...] - TP0713 [flagellar-associated...] (1,F)
TP0029 [UDP-N-acetylglucosam...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0030 [heat shock protein (...] - TP0050 [conserved hypothetic...] (10,F)
TP0030 [heat shock protein (...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0030 [heat shock protein (...] - TP0726 [flagellar protein (f...] (7,F)
TP0030 [heat shock protein (...] - TP0946 [glucose-inhibited di...] (19,F)
TP0030 [heat shock protein (...] - TP0987 [hypothetical protein...] (2,F)
TP0031 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0031 [hypothetical protein...] - TP0561 [conserved hypothetic...] (44,F)
TP0031 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0031 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0032 [conserved hypothetic...] - TP0519 [response regulatory ...] (30,F)
TP0033 [conserved hypothetic...] - TP0227 [cobalt ABC transport...] (1,F)
TP0034 [ABC transporter, per...] - TP0469 [hypothetical protein...] (1,F)
TP0034 [ABC transporter, per...] - TP0788 [hypothetical protein...] (132,W)
TP0034 [ABC transporter, per...] - TP0799 [hypothetical protein...] (2,F)
TP0035 [ABC transporter, ATP...] - TP0383 [conserved hypothetic...] (65,W)
TP0035 [ABC transporter, ATP...] - TP0398 [flagellar hook-basal...] (114,W)
TP0035 [ABC transporter, ATP...] - TP0519 [response regulatory ...] (30,F)
TP0035 [ABC transporter, ATP...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0035 [ABC transporter, ATP...] - TP0563 [hypothetical protein...] (93,W)
TP0035 [ABC transporter, ATP...] - TP0788 [hypothetical protein...] (132,W)
TP0035 [ABC transporter, ATP...] - TP0872 [flagellar filament c...] (1,F)
TP0035 [ABC transporter, ATP...] - TP0907 [conserved hypothetic...] (110,W)
TP0035 [ABC transporter, ATP...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0035 [ABC transporter, ATP...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0035 [ABC transporter, ATP...] - TP1004 [recombination protei...] (74,W)
TP0035 [ABC transporter, ATP...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0036 [ABC transporter, per...] - TP0561 [conserved hypothetic...] (44,F)
TP0037 [D-specific D-2-hydro...] - TP0764 [conserved hypothetic...] (139,W)
TP0038 [regulatory protein (...] - TP0377 [conserved hypothetic...] (11,F)
TP0038 [regulatory protein (...] - TP0398 [flagellar hook-basal...] (114,W)
TP0038 [regulatory protein (...] - TP0561 [conserved hypothetic...] (44,F)
TP0038 [regulatory protein (...] - TP0708 [hypothetical protein...] (13,F)
TP0038 [regulatory protein (...] - TP0764 [conserved hypothetic...] (139,W)
TP0038 [regulatory protein (...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0039 [hypothetical protein...] - TP0059 [hypothetical protein...] (21,F)
TP0039 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0039 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0039 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0039 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0041 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0041 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0041 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0041 [hypothetical protein...] - TP0727 [flagellar hook prote...] (5,F)
TP0041 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0042 [hypothetical protein...] - TP0334 [conserved hypothetic...] (5,F)
TP0042 [hypothetical protein...] - TP0377 [conserved hypothetic...] (11,F)
TP0042 [hypothetical protein...] - TP0561 [conserved hypothetic...] (44,F)
TP0042 [hypothetical protein...] - TP0708 [hypothetical protein...] (13,F)
TP0042 [hypothetical protein...] - TP0716 [flagellar biosynthet...] (2,F)
TP0042 [hypothetical protein...] - TP0826 [conserved hypothetic...] (1,F)
TP0042 [hypothetical protein...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0043 [soluble lytic transg...] - TP0764 [conserved hypothetic...] (139,W)
TP0044 [glucose inhibited di...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0044 [glucose inhibited di...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0044 [glucose inhibited di...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0045 [adenosine deaminase,...] - TP0060 [ribosomal protein L9...] (78,W)
TP0045 [adenosine deaminase,...] - TP0258 [conserved hypothetic...] (173,W)
TP0045 [adenosine deaminase,...] - TP0398 [flagellar hook-basal...] (114,W)
TP0045 [adenosine deaminase,...] - TP0661 [hypothetical protein...] (117,W)
TP0045 [adenosine deaminase,...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0045 [adenosine deaminase,...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0046 [hypothetical protein...] - TP0099 [uridylate kinase (sm...] (3,F)
TP0046 [hypothetical protein...] - TP0287 [conserved hypothetic...] (27,F)
TP0046 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0046 [hypothetical protein...] - TP0773 [periplasmic serine p...] (30,F)
TP0046 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0046 [hypothetical protein...] - TP0797 [1-pyrroline-5-carbox...] (5,F)
TP0046 [hypothetical protein...] - TP0894 [conserved hypothetic...] (13,F)
TP0046 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0046 [hypothetical protein...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0046 [hypothetical protein...] - TP0946 [glucose-inhibited di...] (19,F)
TP0046 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0046 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0046 [hypothetical protein...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0046 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0047 [conserved hypothetic...] - TP0024 [conserved hypothetic...] (16,F)
TP0047 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0047 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0047 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0047 [conserved hypothetic...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0047 [conserved hypothetic...] - TP0587 [hypothetical protein...] (23,F)
TP0047 [conserved hypothetic...] - TP0618 [hypothetical protein...] (24,F)
TP0047 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0047 [conserved hypothetic...] - TP0684 [methylgalactoside AB...] (15,F)
TP0047 [conserved hypothetic...] - TP0711 [conserved hypothetic...] (46,F)

TP0047 [conserved hypothetic...] - TP0757 [polypeptide deformyl...] (36,F)
TP0047 [conserved hypothetic...] - TP0773 [periplasmic serine p...] (30,F)
TP0047 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0047 [conserved hypothetic...] - TP0797 [1-pyrroline-5-carbox...] (5,F)
TP0047 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0047 [conserved hypothetic...] - TP0943 [flagellar protein (f...] (15,F)
TP0047 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0047 [conserved hypothetic...] - TP0965 [membrane fusion prot...] (14,F)
TP0047 [conserved hypothetic...] - TP0974 [hypothetical protein...] (23,F)
TP0047 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0047 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0047 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0047 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0047 [conserved hypothetic...] - TP1023 [recX protein (recX) ...] (13,F)
TP0048 [conserved hypothetic...] - TP0059 [hypothetical protein...] (21,F)
TP0048 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0048 [conserved hypothetic...] - TP0095 [hypothetical protein...] (15,F)
TP0048 [conserved hypothetic...] - TP0197 [ribosomal protein L2...] (15,F)
TP0048 [conserved hypothetic...] - TP0281 [hypothetical protein...] (64,W)
TP0048 [conserved hypothetic...] - TP0287 [conserved hypothetic...] (27,F)
TP0048 [conserved hypothetic...] - TP0341 [UDP-N-acetylmuramate...] (12,F)
TP0048 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0048 [conserved hypothetic...] - TP0397 [flagellar basal-body...] (25,F)
TP0048 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0048 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0048 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0048 [conserved hypothetic...] - TP0519 [response regulatory ...] (30,F)
TP0048 [conserved hypothetic...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0048 [conserved hypothetic...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0048 [conserved hypothetic...] - TP0559 [conserved hypothetic...] (26,F)
TP0048 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0048 [conserved hypothetic...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0048 [conserved hypothetic...] - TP0587 [hypothetical protein...] (23,F)
TP0048 [conserved hypothetic...] - TP0618 [hypothetical protein...] (24,F)
TP0048 [conserved hypothetic...] - TP0626 [exonuclease, putativ...] (12,F)
TP0048 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0048 [conserved hypothetic...] - TP0664 [flagellar filament o...] (34,F)
TP0048 [conserved hypothetic...] - TP0711 [conserved hypothetic...] (46,F)
TP0048 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0048 [conserved hypothetic...] - TP0773 [periplasmic serine p...] (30,F)
TP0048 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0048 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0048 [conserved hypothetic...] - TP0894 [conserved hypothetic...] (13,F)
TP0048 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0048 [conserved hypothetic...] - TP0943 [flagellar protein (f...] (15,F)
TP0048 [conserved hypothetic...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0048 [conserved hypothetic...] - TP0946 [glucose-inhibited di...] (19,F)
TP0048 [conserved hypothetic...] - TP0965 [membrane fusion prot...] (14,F)
TP0048 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0048 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0048 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0048 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0048 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0048 [conserved hypothetic...] - TP1023 [recX protein (recX) ...] (13,F)
TP0050 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0050 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0050 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0050 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0050 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0050 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0051 [peptide chain releas...] - TP0067 [conserved hypothetic...] (19,F)
TP0051 [peptide chain releas...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0051 [peptide chain releas...] - TP0210 [ribosomal protein S1...] (1,F)
TP0052 [protoporphyrinogen o...] - TP0764 [conserved hypothetic...] (139,W)
TP0053 [ribonucleoside-dipho...] - TP0832 [hypothetical protein...] (37,F)
TP0053 [ribonucleoside-dipho...] - TP0961 [flagellar basal-body...] (84,W)
TP0054 [conserved hypothetic...] - TP0095 [hypothetical protein...] (15,F)
TP0054 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0054 [conserved hypothetic...] - TP0519 [response regulatory ...] (30,F)
TP0054 [conserved hypothetic...] - TP0559 [conserved hypothetic...] (26,F)
TP0054 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0054 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0054 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0054 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0054 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0055 [hypothetical protein...] - TP0561 [conserved hypothetic...] (44,F)
TP0055 [hypothetical protein...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0057 [oxaloacetate decarbo...] - TP0377 [conserved hypothetic...] (11,F)
TP0057 [oxaloacetate decarbo...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0058 [replicative DNA heli...] - TP0001 [chromosomal replicat...] (3,F)
TP0058 [replicative DNA heli...] - TP0005 [DNA gyrase, subunit ...] (9,F)
TP0058 [replicative DNA heli...] - TP0046 [hypothetical protein...] (18,F)
TP0058 [replicative DNA heli...] - TP0050 [conserved hypothetic...] (10,F)
TP0058 [replicative DNA heli...] - TP0064 [hypothetical, protei...] (8,F)
TP0058 [replicative DNA heli...] - TP0066 [hypothetical protein...] (11,F)
TP0058 [replicative DNA heli...] - TP0092 [RNA polymerase sigma...] (10,F)
TP0058 [replicative DNA heli...] - TP0102 [rep helicase, single...] (1,F)
TP0058 [replicative DNA heli...] - TP0258 [conserved hypothetic...] (173,W)
TP0058 [replicative DNA heli...] - TP0288 [spore coat polysacch...] (77,W)
TP0058 [replicative DNA heli...] - TP0563 [hypothetical protein...] (93,W)
TP0058 [replicative DNA heli...] - TP0832 [hypothetical protein...] (37,F)
TP0058 [replicative DNA heli...] - TP0896 [hypothetical protein...] (1,F)
TP0058 [replicative DNA heli...] - TP0897 [tpr protein K (tprK)...] (1,F)
TP0058 [replicative DNA heli...] - TP0907 [conserved hypothetic...] (110,W)
TP0058 [replicative DNA heli...] - TP0961 [flagellar basal-body...] (84,W)
TP0058 [replicative DNA heli...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0058 [replicative DNA heli...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0058 [replicative DNA heli...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0059 [hypothetical protein...] - TP0059 [hypothetical protein...] (21,F)
TP0059 [hypothetical protein...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0059 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0059 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0059 [hypothetical protein...] - TP0286 [conserved hypothetic...] (9,F)
TP0059 [hypothetical protein...] - TP0287 [conserved hypothetic...] (27,F)
TP0059 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0059 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0059 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0059 [hypothetical protein...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0059 [hypothetical protein...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0059 [hypothetical protein...] - TP0587 [hypothetical protein...] (23,F)
TP0059 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0059 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0059 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0059 [hypothetical protein...] - TP0773 [periplasmic serine p...] (30,F)
TP0059 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0059 [hypothetical protein...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0059 [hypothetical protein...] - TP0946 [glucose-inhibited di...] (19,F)
TP0059 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0059 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0059 [hypothetical protein...] - TP0995 [cyclic nucleotide bi...] (5,F)
TP0060 [ribosomal protein L9...] - TP0398 [flagellar hook-basal...] (114,W)
TP0060 [ribosomal protein L9...] - TP0907 [conserved hypothetic...] (110,W)
TP0060 [ribosomal protein L9...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0060 [ribosomal protein L9...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0061 [ribosomal protein S1...] - TP0258 [conserved hypothetic...] (173,W)
TP0061 [ribosomal protein S1...] - TP0287 [conserved hypothetic...] (27,F)
TP0061 [ribosomal protein S1...] - TP0288 [spore coat polysacch...] (77,W)
TP0061 [ribosomal protein S1...] - TP0383 [conserved hypothetic...] (65,W)
TP0061 [ribosomal protein S1...] - TP0711 [conserved hypothetic...] (46,F)
TP0061 [ribosomal protein S1...] - TP0788 [hypothetical protein...] (132,W)
TP0061 [ribosomal protein S1...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0061 [ribosomal protein S1...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0061 [ribosomal protein S1...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0062 [single-strand DNA bi...] - TP0288 [spore coat polysacch...] (77,W)
TP0063 [ribosomal protein S6...] - TP0258 [conserved hypothetic...] (173,W)
TP0063 [ribosomal protein S6...] - TP0383 [conserved hypothetic...] (65,W)
TP0063 [ribosomal protein S6...] - TP0518 [conserved hypothetic...] (70,W)
TP0063 [ribosomal protein S6...] - TP0661 [hypothetical protein...] (117,W)
TP0063 [ribosomal protein S6...] - TP0711 [conserved hypothetic...] (46,F)
TP0063 [ribosomal protein S6...] - TP0757 [polypeptide deformyl...] (36,F)
TP0063 [ribosomal protein S6...] - TP0788 [hypothetical protein...] (132,W)
TP0063 [ribosomal protein S6...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0063 [ribosomal protein S6...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0063 [ribosomal protein S6...] - TP0997 [protease IV (sppA) {...] (8,F)
TP0063 [ribosomal protein S6...] - TP1004 [recombination protei...] (74,W)
TP0064 [hypothetical, protei...] - TP0281 [hypothetical protein...] (64,W)
TP0064 [hypothetical, protei...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0064 [hypothetical, protei...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0066 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0067 [conserved hypothetic...] - TP0095 [hypothetical protein...] (15,F)
TP0067 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0067 [conserved hypothetic...] - TP0519 [response regulatory ...] (30,F)
TP0067 [conserved hypothetic...] - TP0559 [conserved hypothetic...] (26,F)
TP0067 [conserved hypothetic...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0067 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0067 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0067 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0067 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0068 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0068 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0068 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0068 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0068 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0068 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0070 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0070 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0070 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0071 [ATP-dependent Clp pr...] - TP0398 [flagellar hook-basal...] (114,W)
TP0071 [ATP-dependent Clp pr...] - TP0465 [hypothetical protein...] (7,F)
TP0071 [ATP-dependent Clp pr...] - TP0519 [response regulatory ...] (30,F)
TP0071 [ATP-dependent Clp pr...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0071 [ATP-dependent Clp pr...] - TP1004 [recombination protei...] (74,W)
TP0072 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0072 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0072 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0073 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0073 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0074 [sugar ABC transporte...] - TP0067 [conserved hypothetic...] (19,F)
TP0074 [sugar ABC transporte...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0074 [sugar ABC transporte...] - TP0258 [conserved hypothetic...] (173,W)

TP0074 [sugar ABC transporte...] - TP0281 [hypothetical protein...] (64,W)
TP0074 [sugar ABC transporte...] - TP0398 [flagellar hook-basal...] (114,W)
TP0074 [sugar ABC transporte...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0074 [sugar ABC transporte...] - TP0519 [response regulatory ...] (30,F)
TP0074 [sugar ABC transporte...] - TP0587 [hypothetical protein...] (23,F)
TP0074 [sugar ABC transporte...] - TP0764 [conserved hypothetic...] (139,W)
TP0074 [sugar ABC transporte...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0074 [sugar ABC transporte...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0074 [sugar ABC transporte...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0074 [sugar ABC transporte...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0077 [capsular polysacchar...] - TP0060 [ribosomal protein L9...] (78,W)
TP0077 [capsular polysacchar...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0079 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0079 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0079 [conserved hypothetic...] - TP0559 [conserved hypothetic...] (26,F)
TP0079 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0079 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0079 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0080 [quinoline 2-oxidored...] - TP0518 [conserved hypothetic...] (70,W)
TP0080 [quinoline 2-oxidored...] - TP0559 [conserved hypothetic...] (26,F)
TP0080 [quinoline 2-oxidored...] - TP0788 [hypothetical protein...] (132,W)
TP0080 [quinoline 2-oxidored...] - TP0907 [conserved hypothetic...] (110,W)
TP0080 [quinoline 2-oxidored...] - TP0920 [hypothetical protein...] (7,F)
TP0080 [quinoline 2-oxidored...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0080 [quinoline 2-oxidored...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0080 [quinoline 2-oxidored...] - TP1004 [recombination protei...] (74,W)
TP0081 [conserved hypothetic...] - TP0414 [D-alanine glycine pe...] (1,F)
TP0083 [conserved hypothetic...] - TP0024 [conserved hypothetic...] (16,F)
TP0083 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0083 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0083 [conserved hypothetic...] - TP0587 [hypothetical protein...] (23,F)
TP0083 [conserved hypothetic...] - TP0773 [periplasmic serine p...] (30,F)
TP0083 [conserved hypothetic...] - TP0943 [flagellar protein (f...] (15,F)
TP0084 [hypothetical protein...] - TP0059 [hypothetical protein...] (21,F)
TP0084 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0084 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0084 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0084 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0084 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0084 [hypothetical protein...] - TP0587 [hypothetical protein...] (23,F)
TP0084 [hypothetical protein...] - TP0618 [hypothetical protein...] (24,F)
TP0084 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0084 [hypothetical protein...] - TP0664 [flagellar filament o...] (34,F)
TP0084 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0084 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0084 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0084 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0084 [hypothetical protein...] - TP1023 [recX protein (recX) ...] (13,F)
TP0085 [PTS system, nitrogen...] - TP0059 [hypothetical protein...] (21,F)
TP0085 [PTS system, nitrogen...] - TP0060 [ribosomal protein L9...] (78,W)
TP0085 [PTS system, nitrogen...] - TP0258 [conserved hypothetic...] (173,W)
TP0085 [PTS system, nitrogen...] - TP0281 [hypothetical protein...] (64,W)
TP0085 [PTS system, nitrogen...] - TP0287 [conserved hypothetic...] (27,F)
TP0085 [PTS system, nitrogen...] - TP0383 [conserved hypothetic...] (65,W)
TP0085 [PTS system, nitrogen...] - TP0398 [flagellar hook-basal...] (114,W)
TP0085 [PTS system, nitrogen...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0085 [PTS system, nitrogen...] - TP0518 [conserved hypothetic...] (70,W)
TP0085 [PTS system, nitrogen...] - TP0519 [response regulatory ...] (30,F)
TP0085 [PTS system, nitrogen...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0085 [PTS system, nitrogen...] - TP0559 [conserved hypothetic...] (26,F)
TP0085 [PTS system, nitrogen...] - TP0711 [conserved hypothetic...] (46,F)
TP0085 [PTS system, nitrogen...] - TP0764 [conserved hypothetic...] (139,W)
TP0085 [PTS system, nitrogen...] - TP0773 [periplasmic serine p...] (30,F)
TP0085 [PTS system, nitrogen...] - TP0788 [hypothetical protein...] (132,W)
TP0085 [PTS system, nitrogen...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0085 [PTS system, nitrogen...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0085 [PTS system, nitrogen...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0086 [conserved hypothetic...] - TP0024 [conserved hypothetic...] (16,F)
TP0086 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0086 [conserved hypothetic...] - TP0095 [hypothetical protein...] (15,F)
TP0086 [conserved hypothetic...] - TP0167 [cation-activated rep...] (1,F)
TP0086 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0086 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0086 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0086 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0086 [conserved hypothetic...] - TP0412 [conserved hypothetic...] (4,F)
TP0086 [conserved hypothetic...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0086 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0086 [conserved hypothetic...] - TP0513 [K+ transport protein...] (4,F)
TP0086 [conserved hypothetic...] - TP0519 [response regulatory ...] (30,F)
TP0086 [conserved hypothetic...] - TP0559 [conserved hypothetic...] (26,F)
TP0086 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0086 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0086 [conserved hypothetic...] - TP0704 [single-stranded-DNA-...] (12,F)
TP0086 [conserved hypothetic...] - TP0711 [conserved hypothetic...] (46,F)
TP0086 [conserved hypothetic...] - TP0773 [periplasmic serine p...] (30,F)
TP0086 [conserved hypothetic...] - TP0797 [1-pyrroline-5-carbox...] (5,F)
TP0086 [conserved hypothetic...] - TP0833 [hypothetical protein...] (34,F)
TP0086 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0086 [conserved hypothetic...] - TP0894 [conserved hypothetic...] (13,F)
TP0086 [conserved hypothetic...] - TP0895 [hypothetical protein...] (3,F)
TP0086 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0086 [conserved hypothetic...] - TP0965 [membrane fusion prot...] (14,F)
TP0086 [conserved hypothetic...] - TP0974 [hypothetical protein...] (23,F)
TP0086 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0086 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0086 [conserved hypothetic...] - TP0997 [protease IV (sppA) {...] (8,F)
TP0086 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0086 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0087 [conserved hypothetic...] - TP0024 [conserved hypothetic...] (16,F)
TP0087 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0087 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0087 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0087 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0087 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0087 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0087 [conserved hypothetic...] - TP0688 [immunity protein (mc...] (1,F)
TP0087 [conserved hypothetic...] - TP0773 [periplasmic serine p...] (30,F)
TP0087 [conserved hypothetic...] - TP0974 [hypothetical protein...] (23,F)
TP0087 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0088 [conserved hypothetic...] - TP0088 [conserved hypothetic...] (8,F)
TP0088 [conserved hypothetic...] - TP0832 [hypothetical protein...] (37,F)
TP0089 [cyclic nucleotide bi...] - TP0258 [conserved hypothetic...] (173,W)
TP0089 [cyclic nucleotide bi...] - TP0398 [flagellar hook-basal...] (114,W)
TP0089 [cyclic nucleotide bi...] - TP0898 [ATP-dependent nuclea...] (1,F)
TP0089 [cyclic nucleotide bi...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0089 [cyclic nucleotide bi...] - TP1004 [recombination protei...] (74,W)
TP0092 [RNA polymerase sigma...] - TP0060 [ribosomal protein L9...] (78,W)
TP0092 [RNA polymerase sigma...] - TP0258 [conserved hypothetic...] (173,W)
TP0092 [RNA polymerase sigma...] - TP0288 [spore coat polysacch...] (77,W)
TP0092 [RNA polymerase sigma...] - TP0518 [conserved hypothetic...] (70,W)
TP0092 [RNA polymerase sigma...] - TP0661 [hypothetical protein...] (117,W)
TP0092 [RNA polymerase sigma...] - TP0764 [conserved hypothetic...] (139,W)
TP0092 [RNA polymerase sigma...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0094 [phosphate acetyltran...] - TP0059 [hypothetical protein...] (21,F)
TP0094 [phosphate acetyltran...] - TP0067 [conserved hypothetic...] (19,F)
TP0094 [phosphate acetyltran...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0094 [phosphate acetyltran...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0094 [phosphate acetyltran...] - TP0258 [conserved hypothetic...] (173,W)
TP0094 [phosphate acetyltran...] - TP0281 [hypothetical protein...] (64,W)
TP0094 [phosphate acetyltran...] - TP0286 [conserved hypothetic...] (9,F)
TP0094 [phosphate acetyltran...] - TP0287 [conserved hypothetic...] (27,F)
TP0094 [phosphate acetyltran...] - TP0383 [conserved hypothetic...] (65,W)
TP0094 [phosphate acetyltran...] - TP0398 [flagellar hook-basal...] (114,W)
TP0094 [phosphate acetyltran...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0094 [phosphate acetyltran...] - TP0465 [hypothetical protein...] (7,F)
TP0094 [phosphate acetyltran...] - TP0519 [response regulatory ...] (30,F)
TP0094 [phosphate acetyltran...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0094 [phosphate acetyltran...] - TP0563 [hypothetical protein...] (93,W)
TP0094 [phosphate acetyltran...] - TP0664 [flagellar filament o...] (34,F)
TP0094 [phosphate acetyltran...] - TP0907 [conserved hypothetic...] (110,W)
TP0094 [phosphate acetyltran...] - TP0920 [hypothetical protein...] (7,F)
TP0094 [phosphate acetyltran...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0094 [phosphate acetyltran...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0094 [phosphate acetyltran...] - TP1004 [recombination protei...] (74,W)
TP0094 [phosphate acetyltran...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0095 [hypothetical protein...] - TP0559 [conserved hypothetic...] (26,F)
TP0097 [translation initiati...] - TP0059 [hypothetical protein...] (21,F)
TP0097 [translation initiati...] - TP0060 [ribosomal protein L9...] (78,W)
TP0097 [translation initiati...] - TP0078 [spore coat polysacch...] (2,F)
TP0097 [translation initiati...] - TP0177 [hypothetical protein...] (1,F)
TP0097 [translation initiati...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0097 [translation initiati...] - TP0258 [conserved hypothetic...] (173,W)
TP0097 [translation initiati...] - TP0281 [hypothetical protein...] (64,W)
TP0097 [translation initiati...] - TP0286 [conserved hypothetic...] (9,F)
TP0097 [translation initiati...] - TP0287 [conserved hypothetic...] (27,F)
TP0097 [translation initiati...] - TP0383 [conserved hypothetic...] (65,W)
TP0097 [translation initiati...] - TP0398 [flagellar hook-basal...] (114,W)
TP0097 [translation initiati...] - TP0412 [conserved hypothetic...] (4,F)
TP0097 [translation initiati...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0097 [translation initiati...] - TP0518 [conserved hypothetic...] (70,W)
TP0097 [translation initiati...] - TP0519 [response regulatory ...] (30,F)
TP0097 [translation initiati...] - TP0552 [hypothetical protein...] (3,F)
TP0097 [translation initiati...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0097 [translation initiati...] - TP0563 [hypothetical protein...] (93,W)
TP0097 [translation initiati...] - TP0587 [hypothetical protein...] (23,F)
TP0097 [translation initiati...] - TP0618 [hypothetical protein...] (24,F)
TP0097 [translation initiati...] - TP0661 [hypothetical protein...] (117,W)
TP0097 [translation initiati...] - TP0664 [flagellar filament o...] (34,F)
TP0097 [translation initiati...] - TP0684 [methylgalactoside AB...] (15,F)
TP0097 [translation initiati...] - TP0704 [single-stranded-DNA-...] (12,F)
TP0097 [translation initiati...] - TP0711 [conserved hypothetic...] (46,F)
TP0097 [translation initiati...] - TP0751 [hypothetical protein...] (7,F)
TP0097 [translation initiati...] - TP0757 [polypeptide deformyl...] (36,F)
TP0097 [translation initiati...] - TP0764 [conserved hypothetic...] (139,W)
TP0097 [translation initiati...] - TP0773 [periplasmic serine p...] (30,F)
TP0097 [translation initiati...] - TP0788 [hypothetical protein...] (132,W)
TP0097 [translation initiati...] - TP0833 [hypothetical protein...] (34,F)
TP0097 [translation initiati...] - TP0907 [conserved hypothetic...] (110,W)
TP0097 [translation initiati...] - TP0945 [ribulose-phosphate 3...] (21,F)

TP0097 [translation initiati...] - TP0946 [glucose-inhibited di...] (19,F)
TP0097 [translation initiati...] - TP0974 [hypothetical protein...] (23,F)
TP0097 [translation initiati...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0097 [translation initiati...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0097 [translation initiati...] - TP0997 [protease IV (sppA) {...] (8,F)
TP0097 [translation initiati...] - TP1004 [recombination protei...] (74,W)
TP0097 [translation initiati...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0099 [uridylate kinase (sm...] - TP0281 [hypothetical protein...] (64,W)
TP0099 [uridylate kinase (sm...] - TP0398 [flagellar hook-basal...] (114,W)
TP0099 [uridylate kinase (sm...] - TP0518 [conserved hypothetic...] (70,W)
TP0099 [uridylate kinase (sm...] - TP0764 [conserved hypothetic...] (139,W)
TP0099 [uridylate kinase (sm...] - TP0788 [hypothetical protein...] (132,W)
TP0100 [thioredoxin, putativ...] - TP0005 [DNA gyrase, subunit ...] (9,F)
TP0100 [thioredoxin, putativ...] - TP0088 [conserved hypothetic...] (8,F)
TP0100 [thioredoxin, putativ...] - TP0832 [hypothetical protein...] (37,F)
TP0100 [thioredoxin, putativ...] - TP0961 [flagellar basal-body...] (84,W)
TP0100 [thioredoxin, putativ...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0101 [cytochrome c biogene...] - TP0561 [conserved hypothetic...] (44,F)
TP0101 [cytochrome c biogene...] - TP0708 [hypothetical protein...] (13,F)
TP0101 [cytochrome c biogene...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0103 [ATP-dependent DNA he...] - TP0559 [conserved hypothetic...] (26,F)
TP0103 [ATP-dependent DNA he...] - TP0661 [hypothetical protein...] (117,W)
TP0103 [ATP-dependent DNA he...] - TP0764 [conserved hypothetic...] (139,W)
TP0103 [ATP-dependent DNA he...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0103 [ATP-dependent DNA he...] - TP1004 [recombination protei...] (74,W)
TP0104 [5'-nucleotidase (ush...] - TP0060 [ribosomal protein L9...] (78,W)
TP0104 [5'-nucleotidase (ush...] - TP0281 [hypothetical protein...] (64,W)
TP0104 [5'-nucleotidase (ush...] - TP0287 [conserved hypothetic...] (27,F)
TP0104 [5'-nucleotidase (ush...] - TP0518 [conserved hypothetic...] (70,W)
TP0104 [5'-nucleotidase (ush...] - TP0561 [conserved hypothetic...] (44,F)
TP0104 [5'-nucleotidase (ush...] - TP0764 [conserved hypothetic...] (139,W)
TP0104 [5'-nucleotidase (ush...] - TP0907 [conserved hypothetic...] (110,W)
TP0104 [5'-nucleotidase (ush...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0104 [5'-nucleotidase (ush...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0104 [5'-nucleotidase (ush...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0104 [5'-nucleotidase (ush...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0106 [carnitine transporte...] - TP0377 [conserved hypothetic...] (11,F)
TP0106 [carnitine transporte...] - TP0561 [conserved hypothetic...] (44,F)
TP0106 [carnitine transporte...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0107 [licC protein (licC) ...] - TP0764 [conserved hypothetic...] (139,W)
TP0107 [licC protein (licC) ...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0109 [rRNA methylase, puta...] - TP0764 [conserved hypothetic...] (139,W)
TP0110 [hypothetical protein...] - TP0561 [conserved hypothetic...] (44,F)
TP0110 [hypothetical protein...] - TP0708 [hypothetical protein...] (13,F)
TP0110 [hypothetical protein...] - TP0774 [Mg2+ transport prote...] (2,F)
TP0111 [RNA polymerase sigma...] - TP0764 [conserved hypothetic...] (139,W)
TP0112 [aminopeptidase C (pe...] - TP0818 [hypothetical protein...] (2,F)
TP0113 [Lambda CII stability...] - TP0661 [hypothetical protein...] (117,W)
TP0113 [Lambda CII stability...] - TP0764 [conserved hypothetic...] (139,W)
TP0113 [Lambda CII stability...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0114 [Lambda CII stability...] - TP0764 [conserved hypothetic...] (139,W)
TP0115 [phosphomethypyrimidi...] - TP0258 [conserved hypothetic...] (173,W)
TP0115 [phosphomethypyrimidi...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0117 [tpr protein C (tprC)...] - TP0209 [ribosomal protein L3...] (27,F)
TP0117 [tpr protein C (tprC)...] - TP0788 [hypothetical protein...] (132,W)
TP0119 [amino acid ABC trans...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0121 [conserved hypothetic...] - TP0121 [conserved hypothetic...] (7,F)
TP0121 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0121 [conserved hypothetic...] - TP0559 [conserved hypothetic...] (26,F)
TP0121 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0121 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0121 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0124 [conserved hypothetic...] - TP0005 [DNA gyrase, subunit ...] (9,F)
TP0124 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0124 [conserved hypothetic...] - TP0067 [conserved hypothetic...] (19,F)
TP0124 [conserved hypothetic...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0124 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0124 [conserved hypothetic...] - TP0432 [hypothetical protein...] (2,F)
TP0124 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0124 [conserved hypothetic...] - TP0704 [single-stranded-DNA-...] (12,F)
TP0124 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0124 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0124 [conserved hypothetic...] - TP0795 [hypothetical protein...] (4,F)
TP0124 [conserved hypothetic...] - TP0833 [hypothetical protein...] (34,F)
TP0126 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0128 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0128 [hypothetical protein...] - TP0067 [conserved hypothetic...] (19,F)
TP0128 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0128 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0128 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0128 [hypothetical protein...] - TP0664 [flagellar filament o...] (34,F)
TP0128 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0128 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0128 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0128 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0128 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0129 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0130 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0130 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0130 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0130 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0130 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0130 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0131 [tpr protein D (tprD)...] - TP0853 [ATP-binding protein ...] (1,F)
TP0132 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0132 [hypothetical protein...] - TP0067 [conserved hypothetic...] (19,F)
TP0132 [hypothetical protein...] - TP0095 [hypothetical protein...] (15,F)
TP0132 [hypothetical protein...] - TP0197 [ribosomal protein L2...] (15,F)
TP0132 [hypothetical protein...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0132 [hypothetical protein...] - TP0255 [ribosomal protein L3...] (2,F)
TP0132 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0132 [hypothetical protein...] - TP0287 [conserved hypothetic...] (27,F)
TP0132 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0132 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0132 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0132 [hypothetical protein...] - TP0465 [hypothetical protein...] (7,F)
TP0132 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0132 [hypothetical protein...] - TP0519 [response regulatory ...] (30,F)
TP0132 [hypothetical protein...] - TP0552 [hypothetical protein...] (3,F)
TP0132 [hypothetical protein...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0132 [hypothetical protein...] - TP0559 [conserved hypothetic...] (26,F)
TP0132 [hypothetical protein...] - TP0587 [hypothetical protein...] (23,F)
TP0132 [hypothetical protein...] - TP0618 [hypothetical protein...] (24,F)
TP0132 [hypothetical protein...] - TP0641 [histidyl-tRNA synthe...] (9,F)
TP0132 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0132 [hypothetical protein...] - TP0664 [flagellar filament o...] (34,F)
TP0132 [hypothetical protein...] - TP0684 [methylgalactoside AB...] (15,F)
TP0132 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0132 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0132 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0132 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0132 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0132 [hypothetical protein...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0132 [hypothetical protein...] - TP0946 [glucose-inhibited di...] (19,F)
TP0132 [hypothetical protein...] - TP0974 [hypothetical protein...] (23,F)
TP0132 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0132 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0132 [hypothetical protein...] - TP0997 [protease IV (sppA) {...] (8,F)
TP0132 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0132 [hypothetical protein...] - TP1023 [recX protein (recX) ...] (13,F)
TP0133 [hypothetical protein...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0133 [hypothetical protein...] - TP0640 [methyl-accepting che...] (5,F)
TP0133 [hypothetical protein...] - TP0832 [hypothetical protein...] (37,F)
TP0134 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0134 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0135 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0135 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0135 [hypothetical protein...] - TP0965 [membrane fusion prot...] (14,F)
TP0135 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0136 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0136 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0136 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0140 [K+ transport protein...] - TP0661 [hypothetical protein...] (117,W)
TP0140 [K+ transport protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0140 [K+ transport protein...] - TP0788 [hypothetical protein...] (132,W)
TP0140 [K+ transport protein...] - TP0939 [pyruvate oxidoreduct...] (12,F)
TP0140 [K+ transport protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0140 [K+ transport protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0140 [K+ transport protein...] - TP1004 [recombination protei...] (74,W)
TP0142 [thiamine ABC transpo...] - TP0281 [hypothetical protein...] (64,W)
TP0142 [thiamine ABC transpo...] - TP0518 [conserved hypothetic...] (70,W)
TP0142 [thiamine ABC transpo...] - TP0764 [conserved hypothetic...] (139,W)
TP0142 [thiamine ABC transpo...] - TP0907 [conserved hypothetic...] (110,W)
TP0142 [thiamine ABC transpo...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0142 [thiamine ABC transpo...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0142 [thiamine ABC transpo...] - TP1004 [recombination protei...] (74,W)
TP0142 [thiamine ABC transpo...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0148 [hypothetical protein...] - TP0561 [conserved hypothetic...] (44,F)
TP0149 [hypothetical protein...] - TP0708 [hypothetical protein...] (13,F)
TP0149 [hypothetical protein...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0150 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0150 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0150 [hypothetical protein...] - TP0519 [response regulatory ...] (30,F)
TP0150 [hypothetical protein...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0150 [hypothetical protein...] - TP0641 [histidyl-tRNA synthe...] (9,F)
TP0150 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0150 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0150 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0150 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0150 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0150 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0150 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0151 [conserved hypothetic...] - TP0561 [conserved hypothetic...] (44,F)
TP0151 [conserved hypothetic...] - TP0658 [transmembrane protei...] (5,F)
TP0151 [conserved hypothetic...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0153 [conserved hypothetic...] - TP0561 [conserved hypothetic...] (44,F)
TP0153 [conserved hypothetic...] - TP0610 [tpr protein H (tprH)...] (1,F)

TP0154 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0154 [conserved hypothetic...] - TP0209 [ribosomal protein L3...] (27,F)
TP0154 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0154 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0154 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0155 [conserved hypothetic...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0157 [conserved hypothetic...] - TP0024 [conserved hypothetic...] (16,F)
TP0157 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0157 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0157 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0157 [conserved hypothetic...] - TP0559 [conserved hypothetic...] (26,F)
TP0157 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0157 [conserved hypothetic...] - TP0773 [periplasmic serine p...] (30,F)
TP0157 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0157 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0157 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0157 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0157 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0157 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0158 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0158 [conserved hypothetic...] - TP0197 [ribosomal protein L2...] (15,F)
TP0158 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0158 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0158 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0158 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0158 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0158 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0158 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0158 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0158 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0158 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0162 [Holliday junction DN...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0162 [Holliday junction DN...] - TP0543 [Holliday junction DN...] (1,F)
TP0163 [ABC transporter, per...] - TP0206 [ribosomal protein S5...] (1,F)
TP0163 [ABC transporter, per...] - TP0550 [thiophene and furan ...] (1,F)
TP0163 [ABC transporter, per...] - TP0832 [hypothetical protein...] (37,F)
TP0163 [ABC transporter, per...] - TP0833 [hypothetical protein...] (34,F)
TP0163 [ABC transporter, per...] - TP0907 [conserved hypothetic...] (110,W)
TP0163 [ABC transporter, per...] - TP0961 [flagellar basal-body...] (84,W)
TP0163 [ABC transporter, per...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0163 [ABC transporter, per...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0164 [ABC transporter, ATP...] - TP0504 [hypothetical protein...] (1,F)
TP0164 [ABC transporter, ATP...] - TP0764 [conserved hypothetic...] (139,W)
TP0164 [ABC transporter, ATP...] - TP0842 [methionine aminopept...] (3,F)
TP0164 [ABC transporter, ATP...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0165 [ABC transporter, per...] - TP0249 [flagellar filament o...] (1,F)
TP0165 [ABC transporter, per...] - TP0880 [membrane spanning pr...] (1,F)
TP0165 [ABC transporter, per...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0167 [cation-activated rep...] - TP0046 [hypothetical protein...] (18,F)
TP0167 [cation-activated rep...] - TP0288 [spore coat polysacch...] (77,W)
TP0167 [cation-activated rep...] - TP0661 [hypothetical protein...] (117,W)
TP0167 [cation-activated rep...] - TP0832 [hypothetical protein...] (37,F)
TP0167 [cation-activated rep...] - TP0961 [flagellar basal-body...] (84,W)
TP0167 [cation-activated rep...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0170 [pfs protein (pfs) {T...] - TP0661 [hypothetical protein...] (117,W)
TP0170 [pfs protein (pfs) {T...] - TP0764 [conserved hypothetic...] (139,W)
TP0170 [pfs protein (pfs) {T...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0177 [hypothetical protein...] - TP0067 [conserved hypothetic...] (19,F)
TP0183 [hypothetical protein...] - TP0001 [chromosomal replicat...] (3,F)
TP0183 [hypothetical protein...] - TP0024 [conserved hypothetic...] (16,F)
TP0183 [hypothetical protein...] - TP0066 [hypothetical protein...] (11,F)
TP0183 [hypothetical protein...] - TP0092 [RNA polymerase sigma...] (10,F)
TP0183 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0183 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0183 [hypothetical protein...] - TP0354 [thymidylate kinase (...] (8,F)
TP0183 [hypothetical protein...] - TP0380 [DNA repair helicase,...] (5,F)
TP0183 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0183 [hypothetical protein...] - TP0421 [conserved hypothetic...] (4,F)
TP0183 [hypothetical protein...] - TP0514 [excinuclease ABC, su...] (7,F)
TP0183 [hypothetical protein...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0183 [hypothetical protein...] - TP0626 [exonuclease, putativ...] (12,F)
TP0183 [hypothetical protein...] - TP0648 [conserved hypothetic...] (3,F)
TP0183 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0183 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0183 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0183 [hypothetical protein...] - TP0939 [pyruvate oxidoreduct...] (12,F)
TP0183 [hypothetical protein...] - TP0946 [glucose-inhibited di...] (19,F)
TP0183 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0183 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0183 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0183 [hypothetical protein...] - TP1023 [recX protein (recX) ...] (13,F)
TP0184 [small protein (smpB)...] - TP0764 [conserved hypothetic...] (139,W)
TP0185 [signal peptidase I (...] - TP0644 [lysyl-tRNA synthetas...] (1,F)
TP0185 [signal peptidase I (...] - TP0661 [hypothetical protein...] (117,W)
TP0185 [signal peptidase I (...] - TP0764 [conserved hypothetic...] (139,W)
TP0185 [signal peptidase I (...] - TP0788 [hypothetical protein...] (132,W)
TP0187 [translation elongati...] - TP0067 [conserved hypothetic...] (19,F)
TP0187 [translation elongati...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0188 [ribosomal protein S1...] - TP0398 [flagellar hook-basal...] (114,W)
TP0188 [ribosomal protein S1...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0188 [ribosomal protein S1...] - TP0519 [response regulatory ...] (30,F)
TP0188 [ribosomal protein S1...] - TP0661 [hypothetical protein...] (117,W)
TP0192 [ribosomal protein L2...] - TP0756 [methionyl-tRNA formy...] (1,F)
TP0193 [ribosomal protein S1...] - TP0764 [conserved hypothetic...] (139,W)
TP0194 [ribosomal protein L2...] - TP0258 [conserved hypothetic...] (173,W)
TP0194 [ribosomal protein L2...] - TP0288 [spore coat polysacch...] (77,W)
TP0194 [ribosomal protein L2...] - TP0661 [hypothetical protein...] (117,W)
TP0194 [ribosomal protein L2...] - TP0764 [conserved hypothetic...] (139,W)
TP0194 [ribosomal protein L2...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0195 [ribosomal protein S3...] - TP0398 [flagellar hook-basal...] (114,W)
TP0195 [ribosomal protein S3...] - TP0559 [conserved hypothetic...] (26,F)
TP0195 [ribosomal protein S3...] - TP0764 [conserved hypothetic...] (139,W)
TP0197 [ribosomal protein L2...] - TP0661 [hypothetical protein...] (117,W)
TP0197 [ribosomal protein L2...] - TP0711 [conserved hypothetic...] (46,F)
TP0202 [ribosomal protein S1...] - TP0661 [hypothetical protein...] (117,W)
TP0202 [ribosomal protein S1...] - TP0711 [conserved hypothetic...] (46,F)
TP0202 [ribosomal protein S1...] - TP0788 [hypothetical protein...] (132,W)
TP0202 [ribosomal protein S1...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0207 [ribosomal protein L1...] - TP0258 [conserved hypothetic...] (173,W)
TP0208 [preprotein transloca...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0209 [ribosomal protein L3...] - TP0258 [conserved hypothetic...] (173,W)
TP0209 [ribosomal protein L3...] - TP0398 [flagellar hook-basal...] (114,W)
TP0209 [ribosomal protein L3...] - TP0518 [conserved hypothetic...] (70,W)
TP0209 [ribosomal protein L3...] - TP0519 [response regulatory ...] (30,F)
TP0209 [ribosomal protein L3...] - TP0974 [hypothetical protein...] (23,F)
TP0209 [ribosomal protein L3...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0210 [ribosomal protein S1...] - TP0258 [conserved hypothetic...] (173,W)
TP0210 [ribosomal protein S1...] - TP0383 [conserved hypothetic...] (65,W)
TP0211 [ribosomal protein S1...] - TP0398 [flagellar hook-basal...] (114,W)
TP0212 [DNA-directed RNA pol...] - TP0059 [hypothetical protein...] (21,F)
TP0212 [DNA-directed RNA pol...] - TP0060 [ribosomal protein L9...] (78,W)
TP0212 [DNA-directed RNA pol...] - TP0383 [conserved hypothetic...] (65,W)
TP0213 [ribosomal protein L1...] - TP0398 [flagellar hook-basal...] (114,W)
TP0214 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0214 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0216 [heat shock protein 7...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0216 [heat shock protein 7...] - TP1004 [recombination protei...] (74,W)
TP0218 [sigma factor SigG re...] - TP0269 [conserved hypothetic...] (3,F)
TP0218 [sigma factor SigG re...] - TP0377 [conserved hypothetic...] (11,F)
TP0218 [sigma factor SigG re...] - TP0561 [conserved hypothetic...] (44,F)
TP0218 [sigma factor SigG re...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0222 [hypothetical protein...] - TP0561 [conserved hypothetic...] (44,F)
TP0222 [hypothetical protein...] - TP0708 [hypothetical protein...] (13,F)
TP0222 [hypothetical protein...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0223 [aspartate aminotrans...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0224 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0224 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0224 [hypothetical protein...] - TP0287 [conserved hypothetic...] (27,F)
TP0224 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0225 [leucine-rich repeat ...] - TP0258 [conserved hypothetic...] (173,W)
TP0225 [leucine-rich repeat ...] - TP0398 [flagellar hook-basal...] (114,W)
TP0225 [leucine-rich repeat ...] - TP0788 [hypothetical protein...] (132,W)
TP0227 [cobalt ABC transport...] - TP0398 [flagellar hook-basal...] (114,W)
TP0227 [cobalt ABC transport...] - TP0404 [hypothetical protein...] (1,F)
TP0227 [cobalt ABC transport...] - TP0894 [conserved hypothetic...] (13,F)
TP0227 [cobalt ABC transport...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0227 [cobalt ABC transport...] - TP1004 [recombination protei...] (74,W)
TP0228 [biotin synthase, put...] - TP0034 [ABC transporter, per...] (1,F)
TP0229 [DNA polymerase, bact...] - TP0258 [conserved hypothetic...] (173,W)
TP0229 [DNA polymerase, bact...] - TP0764 [conserved hypothetic...] (139,W)
TP0229 [DNA polymerase, bact...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0229 [DNA polymerase, bact...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0232 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0232 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0232 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0232 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0232 [hypothetical protein...] - TP0974 [hypothetical protein...] (23,F)
TP0232 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0232 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0233 [anti-sigma F factor ...] - TP0258 [conserved hypothetic...] (173,W)
TP0233 [anti-sigma F factor ...] - TP0764 [conserved hypothetic...] (139,W)
TP0233 [anti-sigma F factor ...] - TP0966 [hypothetical protein...] (1,F)
TP0233 [anti-sigma F factor ...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0233 [anti-sigma F factor ...] - TP1003 [hypothetical protein...] (1,F)
TP0234 [ribosomal protein L3...] - TP0258 [conserved hypothetic...] (173,W)
TP0234 [ribosomal protein L3...] - TP0281 [hypothetical protein...] (64,W)
TP0234 [ribosomal protein L3...] - TP0398 [flagellar hook-basal...] (114,W)
TP0234 [ribosomal protein L3...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0234 [ribosomal protein L3...] - TP0518 [conserved hypothetic...] (70,W)
TP0234 [ribosomal protein L3...] - TP0519 [response regulatory ...] (30,F)
TP0234 [ribosomal protein L3...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0234 [ribosomal protein L3...] - TP0587 [hypothetical protein...] (23,F)
TP0234 [ribosomal protein L3...] - TP0661 [hypothetical protein...] (117,W)
TP0234 [ribosomal protein L3...] - TP0664 [flagellar filament o...] (34,F)
TP0234 [ribosomal protein L3...] - TP0711 [conserved hypothetic...] (46,F)
TP0234 [ribosomal protein L3...] - TP0764 [conserved hypothetic...] (139,W)
TP0234 [ribosomal protein L3...] - TP0788 [hypothetical protein...] (132,W)
TP0234 [ribosomal protein L3...] - TP0946 [glucose-inhibited di...] (19,F)
TP0234 [ribosomal protein L3...] - TP0974 [hypothetical protein...] (23,F)
TP0234 [ribosomal protein L3...] - TP0993 [rare lipoprotein A, ...] (285,W)

TP0234 [ribosomal protein L3...] - TP1004 [recombination protei...] (74,W)
TP0234 [ribosomal protein L3...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0234 [ribosomal protein L3...] - TP1023 [recX protein (recX) ...] (13,F)
TP0235 [preprotein transloca...] - TP0561 [conserved hypothetic...] (44,F)
TP0236 [transcription antite...] - TP0258 [conserved hypothetic...] (173,W)
TP0237 [ribosomal protein L1...] - TP0258 [conserved hypothetic...] (173,W)
TP0237 [ribosomal protein L1...] - TP0288 [spore coat polysacch...] (77,W)
TP0237 [ribosomal protein L1...] - TP0398 [flagellar hook-basal...] (114,W)
TP0237 [ribosomal protein L1...] - TP0518 [conserved hypothetic...] (70,W)
TP0237 [ribosomal protein L1...] - TP0519 [response regulatory ...] (30,F)
TP0237 [ribosomal protein L1...] - TP0559 [conserved hypothetic...] (26,F)
TP0237 [ribosomal protein L1...] - TP0661 [hypothetical protein...] (117,W)
TP0237 [ribosomal protein L1...] - TP0664 [flagellar filament o...] (34,F)
TP0237 [ribosomal protein L1...] - TP0711 [conserved hypothetic...] (46,F)
TP0237 [ribosomal protein L1...] - TP0764 [conserved hypothetic...] (139,W)
TP0237 [ribosomal protein L1...] - TP0773 [periplasmic serine p...] (30,F)
TP0237 [ribosomal protein L1...] - TP0788 [hypothetical protein...] (132,W)
TP0237 [ribosomal protein L1...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0247 [N-acetylmuramoyl-L-a...] - TP0067 [conserved hypothetic...] (19,F)
TP0247 [N-acetylmuramoyl-L-a...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0247 [N-acetylmuramoyl-L-a...] - TP0150 [hypothetical protein...] (1,F)
TP0247 [N-acetylmuramoyl-L-a...] - TP0382 [hypothetical protein...] (1,F)
TP0248 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0248 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0251 [DNA-binding protein ...] - TP0974 [hypothetical protein...] (23,F)
TP0252 [apolipoprotein N-acy...] - TP0258 [conserved hypothetic...] (173,W)
TP0252 [apolipoprotein N-acy...] - TP0281 [hypothetical protein...] (64,W)
TP0252 [apolipoprotein N-acy...] - TP0287 [conserved hypothetic...] (27,F)
TP0252 [apolipoprotein N-acy...] - TP0383 [conserved hypothetic...] (65,W)
TP0252 [apolipoprotein N-acy...] - TP0398 [flagellar hook-basal...] (114,W)
TP0252 [apolipoprotein N-acy...] - TP0518 [conserved hypothetic...] (70,W)
TP0252 [apolipoprotein N-acy...] - TP0764 [conserved hypothetic...] (139,W)
TP0252 [apolipoprotein N-acy...] - TP0788 [hypothetical protein...] (132,W)
TP0252 [apolipoprotein N-acy...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0252 [apolipoprotein N-acy...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0252 [apolipoprotein N-acy...] - TP1004 [recombination protei...] (74,W)
TP0252 [apolipoprotein N-acy...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0255 [ribosomal protein L3...] - TP0281 [hypothetical protein...] (64,W)
TP0255 [ribosomal protein L3...] - TP0383 [conserved hypothetic...] (65,W)
TP0255 [ribosomal protein L3...] - TP0398 [flagellar hook-basal...] (114,W)
TP0255 [ribosomal protein L3...] - TP0641 [histidyl-tRNA synthe...] (9,F)
TP0255 [ribosomal protein L3...] - TP0661 [hypothetical protein...] (117,W)
TP0255 [ribosomal protein L3...] - TP0664 [flagellar filament o...] (34,F)
TP0255 [ribosomal protein L3...] - TP0711 [conserved hypothetic...] (46,F)
TP0255 [ribosomal protein L3...] - TP0757 [polypeptide deformyl...] (36,F)
TP0255 [ribosomal protein L3...] - TP0764 [conserved hypothetic...] (139,W)
TP0255 [ribosomal protein L3...] - TP0907 [conserved hypothetic...] (110,W)
TP0255 [ribosomal protein L3...] - TP1004 [recombination protei...] (74,W)
TP0256 [CDP-diacylglycerol--...] - TP0708 [hypothetical protein...] (13,F)
TP0256 [CDP-diacylglycerol--...] - TP0765 [cell division protei...] (2,F)
TP0256 [CDP-diacylglycerol--...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0258 [conserved hypothetic...] - TP0059 [hypothetical protein...] (21,F)
TP0258 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0258 [conserved hypothetic...] - TP0197 [ribosomal protein L2...] (15,F)
TP0258 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0258 [conserved hypothetic...] - TP0281 [hypothetical protein...] (64,W)
TP0258 [conserved hypothetic...] - TP0329 [serine hydroxymethyl...] (1,F)
TP0258 [conserved hypothetic...] - TP0341 [UDP-N-acetylmuramate...] (12,F)
TP0258 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0258 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0258 [conserved hypothetic...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0258 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0258 [conserved hypothetic...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0258 [conserved hypothetic...] - TP0559 [conserved hypothetic...] (26,F)
TP0258 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0258 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0258 [conserved hypothetic...] - TP0664 [flagellar filament o...] (34,F)
TP0258 [conserved hypothetic...] - TP0673 [glutamyl-tRNA synthe...] (1,F)
TP0258 [conserved hypothetic...] - TP0711 [conserved hypothetic...] (46,F)
TP0258 [conserved hypothetic...] - TP0773 [periplasmic serine p...] (30,F)
TP0258 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0258 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0258 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0258 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0258 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0258 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0258 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0258 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0260 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0260 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0260 [hypothetical protein...] - TP0664 [flagellar filament o...] (34,F)
TP0260 [hypothetical protein...] - TP0684 [methylgalactoside AB...] (15,F)
TP0260 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0260 [hypothetical protein...] - TP0833 [hypothetical protein...] (34,F)
TP0266 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0267 [conserved hypothetic...] - TP0833 [hypothetical protein...] (34,F)
TP0268 [conserved hypothetic...] - TP0059 [hypothetical protein...] (21,F)
TP0268 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0268 [conserved hypothetic...] - TP0334 [conserved hypothetic...] (5,F)
TP0268 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0268 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0268 [conserved hypothetic...] - TP0587 [hypothetical protein...] (23,F)
TP0268 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0268 [conserved hypothetic...] - TP0664 [flagellar filament o...] (34,F)
TP0268 [conserved hypothetic...] - TP0711 [conserved hypothetic...] (46,F)
TP0268 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0268 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0268 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0268 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0268 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0268 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0270 [polynucleotide adeny...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0270 [polynucleotide adeny...] - TP0661 [hypothetical protein...] (117,W)
TP0270 [polynucleotide adeny...] - TP0813 [hypothetical protein...] (3,F)
TP0271 [chromosome partition...] - TP0046 [hypothetical protein...] (18,F)
TP0271 [chromosome partition...] - TP0183 [hypothetical protein...] (1,F)
TP0271 [chromosome partition...] - TP0198 [ribosomal protein S1...] (1,F)
TP0271 [chromosome partition...] - TP0305 [CTP synthase (pyrG) ...] (4,F)
TP0271 [chromosome partition...] - TP0463 [hypothetical protein...] (8,F)
TP0271 [chromosome partition...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0271 [chromosome partition...] - TP0764 [conserved hypothetic...] (139,W)
TP0271 [chromosome partition...] - TP0832 [hypothetical protein...] (37,F)
TP0271 [chromosome partition...] - TP0961 [flagellar basal-body...] (84,W)
TP0271 [chromosome partition...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0272 [SpoOJ regulator (soj...] - TP0060 [ribosomal protein L9...] (78,W)
TP0272 [SpoOJ regulator (soj...] - TP0188 [ribosomal protein S1...] (2,F)
TP0272 [SpoOJ regulator (soj...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0272 [SpoOJ regulator (soj...] - TP0833 [hypothetical protein...] (34,F)
TP0272 [SpoOJ regulator (soj...] - TP0843 [heat shock protein, ...] (3,F)
TP0273 [hypothetical protein...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0273 [hypothetical protein...] - TP0972 [conserved hypothetic...] (1,F)
TP0275 [UDP-N-acetyl-D-manno...] - TP0059 [hypothetical protein...] (21,F)
TP0275 [UDP-N-acetyl-D-manno...] - TP0258 [conserved hypothetic...] (173,W)
TP0275 [UDP-N-acetyl-D-manno...] - TP0281 [hypothetical protein...] (64,W)
TP0275 [UDP-N-acetyl-D-manno...] - TP0398 [flagellar hook-basal...] (114,W)
TP0275 [UDP-N-acetyl-D-manno...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0275 [UDP-N-acetyl-D-manno...] - TP0587 [hypothetical protein...] (23,F)
TP0276 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0276 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0280 [hypothetical protein...] - TP0059 [hypothetical protein...] (21,F)
TP0280 [hypothetical protein...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0280 [hypothetical protein...] - TP0287 [conserved hypothetic...] (27,F)
TP0280 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0280 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0280 [hypothetical protein...] - TP0995 [cyclic nucleotide bi...] (5,F)
TP0280 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0282 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0282 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0282 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0282 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0282 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0282 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0282 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0283 [lipopolysaccharide c...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0284 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0284 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0284 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0284 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0284 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0284 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0284 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0287 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0287 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0287 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0287 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0287 [conserved hypothetic...] - TP0894 [conserved hypothetic...] (13,F)
TP0287 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0287 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0287 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0287 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0290 [conserved hypothetic...] - TP0040 [methyl-accepting che...] (1,F)
TP0290 [conserved hypothetic...] - TP0044 [glucose inhibited di...] (3,F)
TP0290 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0295 [xylulokinase (xylB) ...] - TP0640 [methyl-accepting che...] (5,F)
TP0295 [xylulokinase (xylB) ...] - TP0723 [hypothetical protein...] (1,F)
TP0296 [conserved hypothetic...] - TP0557 [conserved hypothetic...] (1,F)
TP0296 [conserved hypothetic...] - TP0578 [cell division protei...] (1,F)
TP0296 [conserved hypothetic...] - TP0591 [HPr kinase (ptsK) {B...] (1,F)
TP0296 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0297 [conserved hypothetic...] - TP0077 [capsular polysacchar...] (1,F)
TP0297 [conserved hypothetic...] - TP0236 [transcription antite...] (5,F)
TP0297 [conserved hypothetic...] - TP0738 [conserved hypothetic...] (1,F)
TP0298 [exported protein (tp...] - TP0258 [conserved hypothetic...] (173,W)
TP0298 [exported protein (tp...] - TP0287 [conserved hypothetic...] (27,F)
TP0298 [exported protein (tp...] - TP0288 [spore coat polysacch...] (77,W)
TP0298 [exported protein (tp...] - TP0383 [conserved hypothetic...] (65,W)
TP0298 [exported protein (tp...] - TP0518 [conserved hypothetic...] (70,W)
TP0298 [exported protein (tp...] - TP0563 [hypothetical protein...] (93,W)
TP0298 [exported protein (tp...] - TP0661 [hypothetical protein...] (117,W)

TP0298 [exported protein (tp...] - TP0757 [polypeptide deformyl...] (36,F)
TP0298 [exported protein (tp...] - TP0788 [hypothetical protein...] (132,W)
TP0301 [conserved hypothetic...] - TP0561 [conserved hypothetic...] (44,F)
TP0301 [conserved hypothetic...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0302 [conserved hypothetic...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0303 [DNA mismatch repair ...] - TP0661 [hypothetical protein...] (117,W)
TP0307 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0307 [conserved hypothetic...] - TP0209 [ribosomal protein L3...] (27,F)
TP0307 [conserved hypothetic...] - TP0396 [flagellar basal-body...] (15,F)
TP0307 [conserved hypothetic...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0307 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0307 [conserved hypothetic...] - TP0741 [conserved hypothetic...] (8,F)
TP0307 [conserved hypothetic...] - TP0946 [glucose-inhibited di...] (19,F)
TP0308 [amino acid ABC trans...] - TP0961 [flagellar basal-body...] (84,W)
TP0308 [amino acid ABC trans...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0308 [amino acid ABC trans...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0312 [conserved hypothetic...] - TP0561 [conserved hypothetic...] (44,F)
TP0313 [tpr protein E (tprE)...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0314 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0320 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0320 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0320 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0320 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0320 [hypothetical protein...] - TP0626 [exonuclease, putativ...] (12,F)
TP0320 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0320 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0320 [hypothetical protein...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0320 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0320 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0322 [ribose/galactose ABC...] - TP0561 [conserved hypothetic...] (44,F)
TP0328 [DNA mismatch repair ...] - TP0060 [ribosomal protein L9...] (78,W)
TP0328 [DNA mismatch repair ...] - TP0095 [hypothetical protein...] (15,F)
TP0328 [DNA mismatch repair ...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0328 [DNA mismatch repair ...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0328 [DNA mismatch repair ...] - TP0661 [hypothetical protein...] (117,W)
TP0328 [DNA mismatch repair ...] - TP0764 [conserved hypothetic...] (139,W)
TP0328 [DNA mismatch repair ...] - TP0907 [conserved hypothetic...] (110,W)
TP0328 [DNA mismatch repair ...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0328 [DNA mismatch repair ...] - TP0946 [glucose-inhibited di...] (19,F)
TP0328 [DNA mismatch repair ...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0329 [serine hydroxymethyl...] - TP0788 [hypothetical protein...] (132,W)
TP0330 [cell division protei...] - TP0127 [hypothetical protein...] (1,F)
TP0330 [cell division protei...] - TP0330 [cell division protei...] (2,F)
TP0330 [cell division protei...] - TP0387 [cell division protei...] (1,F)
TP0330 [cell division protei...] - TP0499 [rod shape-determinin...] (1,F)
TP0330 [cell division protei...] - TP0641 [histidyl-tRNA synthe...] (9,F)
TP0330 [cell division protei...] - TP0870 [flagellar filament 3...] (79,W)
TP0330 [cell division protei...] - TP0891 [translation initiati...] (1,F)
TP0330 [cell division protei...] - TP0961 [flagellar basal-body...] (84,W)
TP0333 [conserved hypothetic...] - TP0281 [hypothetical protein...] (64,W)
TP0333 [conserved hypothetic...] - TP0397 [flagellar basal-body...] (25,F)
TP0333 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0333 [conserved hypothetic...] - TP0465 [hypothetical protein...] (7,F)
TP0333 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0333 [conserved hypothetic...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0333 [conserved hypothetic...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0333 [conserved hypothetic...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0333 [conserved hypothetic...] - TP0587 [hypothetical protein...] (23,F)
TP0333 [conserved hypothetic...] - TP0618 [hypothetical protein...] (24,F)
TP0333 [conserved hypothetic...] - TP0626 [exonuclease, putativ...] (12,F)
TP0333 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0333 [conserved hypothetic...] - TP0664 [flagellar filament o...] (34,F)
TP0333 [conserved hypothetic...] - TP0711 [conserved hypothetic...] (46,F)
TP0333 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0333 [conserved hypothetic...] - TP0833 [hypothetical protein...] (34,F)
TP0333 [conserved hypothetic...] - TP0834 [tyrosyl-tRNA synthet...] (1,F)
TP0333 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0333 [conserved hypothetic...] - TP0940 [hypothetical protein...] (1,F)
TP0333 [conserved hypothetic...] - TP0946 [glucose-inhibited di...] (19,F)
TP0333 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0333 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0333 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0334 [conserved hypothetic...] - TP0784 [hypothetical protein...] (1,F)
TP0334 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0338 [hypothetical protein...] - TP0377 [conserved hypothetic...] (11,F)
TP0338 [hypothetical protein...] - TP0708 [hypothetical protein...] (13,F)
TP0338 [hypothetical protein...] - TP0716 [flagellar biosynthet...] (2,F)
TP0339 [conserved hypothetic...] - TP0632 [tryptophanyl-tRNA sy...] (1,F)
TP0339 [conserved hypothetic...] - TP0687 [DNA recombinase (rec...] (2,F)
TP0339 [conserved hypothetic...] - TP0728 [flagellar hook assem...] (1,F)
TP0339 [conserved hypothetic...] - TP0869 [hypothetical protein...] (1,F)
TP0341 [UDP-N-acetylmuramate...] - TP0209 [ribosomal protein L3...] (27,F)
TP0341 [UDP-N-acetylmuramate...] - TP0288 [spore coat polysacch...] (77,W)
TP0341 [UDP-N-acetylmuramate...] - TP0761 [hypothetical protein...] (1,F)
TP0341 [UDP-N-acetylmuramate...] - TP0907 [conserved hypothetic...] (110,W)
TP0341 [UDP-N-acetylmuramate...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0342 [cytidylate kinase (c...] - TP0661 [hypothetical protein...] (117,W)
TP0343 [A/G-specific adenine...] - TP0470 [conserved hypothetic...] (1,F)
TP0343 [A/G-specific adenine...] - TP0598 [hypothetical protein...] (1,F)
TP0343 [A/G-specific adenine...] - TP0661 [hypothetical protein...] (117,W)
TP0343 [A/G-specific adenine...] - TP0664 [flagellar filament o...] (34,F)
TP0343 [A/G-specific adenine...] - TP0788 [hypothetical protein...] (132,W)
TP0343 [A/G-specific adenine...] - TP0870 [flagellar filament 3...] (79,W)
TP0343 [A/G-specific adenine...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0343 [A/G-specific adenine...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0344 [transcription-repair...] - TP0046 [hypothetical protein...] (18,F)
TP0344 [transcription-repair...] - TP0505 [hexokinase (hxk) {Sc...] (1,F)
TP0344 [transcription-repair...] - TP0514 [excinuclease ABC, su...] (7,F)
TP0344 [transcription-repair...] - TP0563 [hypothetical protein...] (93,W)
TP0344 [transcription-repair...] - TP0832 [hypothetical protein...] (37,F)
TP0344 [transcription-repair...] - TP0833 [hypothetical protein...] (34,F)
TP0344 [transcription-repair...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0345 [phospho-N-acetylmura...] - TP0209 [ribosomal protein L3...] (27,F)
TP0345 [phospho-N-acetylmura...] - TP0420 [hypothetical protein...] (1,F)
TP0345 [phospho-N-acetylmura...] - TP0561 [conserved hypothetic...] (44,F)
TP0345 [phospho-N-acetylmura...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0350 [glutamate-5-semialde...] - TP0939 [pyruvate oxidoreduct...] (12,F)
TP0350 [glutamate-5-semialde...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0351 [glutamate 5-kinase (...] - TP0661 [hypothetical protein...] (117,W)
TP0351 [glutamate 5-kinase (...] - TP0757 [polypeptide deformyl...] (36,F)
TP0351 [glutamate 5-kinase (...] - TP0764 [conserved hypothetic...] (139,W)
TP0351 [glutamate 5-kinase (...] - TP0788 [hypothetical protein...] (132,W)
TP0351 [glutamate 5-kinase (...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0354 [thymidylate kinase (...] - TP0097 [translation initiati...] (3,F)
TP0354 [thymidylate kinase (...] - TP0870 [flagellar filament 3...] (79,W)
TP0354 [thymidylate kinase (...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0356 [RNA-binding protein,...] - TP0850 [translation initiati...] (1,F)
TP0359 [hypothetical protein...] - TP0024 [conserved hypothetic...] (16,F)
TP0359 [hypothetical protein...] - TP0059 [hypothetical protein...] (21,F)
TP0359 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0359 [hypothetical protein...] - TP0197 [ribosomal protein L2...] (15,F)
TP0359 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0359 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0359 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0359 [hypothetical protein...] - TP0354 [thymidylate kinase (...] (8,F)
TP0359 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0359 [hypothetical protein...] - TP0397 [flagellar basal-body...] (25,F)
TP0359 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0359 [hypothetical protein...] - TP0443 [conserved hypothetic...] (6,F)
TP0359 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0359 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0359 [hypothetical protein...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0359 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0359 [hypothetical protein...] - TP0587 [hypothetical protein...] (23,F)
TP0359 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0359 [hypothetical protein...] - TP0664 [flagellar filament o...] (34,F)
TP0359 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0359 [hypothetical protein...] - TP0726 [flagellar protein (f...] (7,F)
TP0359 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0359 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0359 [hypothetical protein...] - TP0807 [ribosomal protein L3...] (4,F)
TP0359 [hypothetical protein...] - TP0833 [hypothetical protein...] (34,F)
TP0359 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0359 [hypothetical protein...] - TP0959 [hypothetical protein...] (1,F)
TP0359 [hypothetical protein...] - TP0974 [hypothetical protein...] (23,F)
TP0359 [hypothetical protein...] - TP0981 [sensory transduction...] (5,F)
TP0359 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0359 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0359 [hypothetical protein...] - TP0997 [protease IV (sppA) {...] (8,F)
TP0359 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0359 [hypothetical protein...] - TP1023 [recX protein (recX) ...] (13,F)
TP0360 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0362 [ribosomal protein L2...] - TP0059 [hypothetical protein...] (21,F)
TP0362 [ribosomal protein L2...] - TP0518 [conserved hypothetic...] (70,W)
TP0367 [chromosome segregati...] - TP0050 [conserved hypothetic...] (10,F)
TP0367 [chromosome segregati...] - TP0060 [ribosomal protein L9...] (78,W)
TP0367 [chromosome segregati...] - TP0064 [hypothetical, protei...] (8,F)
TP0367 [chromosome segregati...] - TP0066 [hypothetical protein...] (11,F)
TP0367 [chromosome segregati...] - TP0764 [conserved hypothetic...] (139,W)
TP0367 [chromosome segregati...] - TP0772 [hypothetical protein...] (3,F)
TP0367 [chromosome segregati...] - TP0832 [hypothetical protein...] (37,F)
TP0367 [chromosome segregati...] - TP0870 [flagellar filament 3...] (79,W)
TP0367 [chromosome segregati...] - TP0961 [flagellar basal-body...] (84,W)
TP0368 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0368 [hypothetical protein...] - TP0209 [ribosomal protein L3...] (27,F)
TP0368 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0368 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0368 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0368 [hypothetical protein...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0368 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0368 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0368 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0368 [hypothetical protein...] - TP0842 [methionine aminopept...] (3,F)
TP0370 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0370 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0370 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0370 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0370 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0370 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)

TP0371 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0371 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0372 [general stress prote...] - TP0258 [conserved hypothetic...] (173,W)
TP0372 [general stress prote...] - TP0907 [conserved hypothetic...] (110,W)
TP0372 [general stress prote...] - TP0961 [flagellar basal-body...] (84,W)
TP0372 [general stress prote...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0372 [general stress prote...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0373 [conserved hypothetic...] - TP0409 [hypothetical protein...] (1,F)
TP0373 [conserved hypothetic...] - TP0733 [hypothetical protein...] (1,F)
TP0374 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0374 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0374 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0374 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0374 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0374 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0374 [hypothetical protein...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0376 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0376 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0376 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0376 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0376 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0376 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0376 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0376 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0377 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0377 [conserved hypothetic...] - TP0209 [ribosomal protein L3...] (27,F)
TP0377 [conserved hypothetic...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0378 [flagellar protein, p...] - TP0002 [DNA polymerase III, ...] (4,F)
TP0378 [flagellar protein, p...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0380 [DNA repair helicase,...] - TP0095 [hypothetical protein...] (15,F)
TP0380 [DNA repair helicase,...] - TP0121 [conserved hypothetic...] (7,F)
TP0380 [DNA repair helicase,...] - TP0258 [conserved hypothetic...] (173,W)
TP0380 [DNA repair helicase,...] - TP0288 [spore coat polysacch...] (77,W)
TP0380 [DNA repair helicase,...] - TP0398 [flagellar hook-basal...] (114,W)
TP0380 [DNA repair helicase,...] - TP0421 [conserved hypothetic...] (4,F)
TP0380 [DNA repair helicase,...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0380 [DNA repair helicase,...] - TP0449 [hypothetical protein...] (51,W)
TP0380 [DNA repair helicase,...] - TP0487 [hypothetical protein...] (1,F)
TP0380 [DNA repair helicase,...] - TP0518 [conserved hypothetic...] (70,W)
TP0380 [DNA repair helicase,...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0380 [DNA repair helicase,...] - TP0559 [conserved hypothetic...] (26,F)
TP0380 [DNA repair helicase,...] - TP0661 [hypothetical protein...] (117,W)
TP0380 [DNA repair helicase,...] - TP0704 [single-stranded-DNA-...] (12,F)
TP0380 [DNA repair helicase,...] - TP0764 [conserved hypothetic...] (139,W)
TP0380 [DNA repair helicase,...] - TP0773 [periplasmic serine p...] (30,F)
TP0380 [DNA repair helicase,...] - TP0788 [hypothetical protein...] (132,W)
TP0380 [DNA repair helicase,...] - TP0870 [flagellar filament 3...] (79,W)
TP0380 [DNA repair helicase,...] - TP0939 [pyruvate oxidoreduct...] (12,F)
TP0380 [DNA repair helicase,...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0380 [DNA repair helicase,...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0380 [DNA repair helicase,...] - TP1004 [recombination protei...] (74,W)
TP0380 [DNA repair helicase,...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0381 [hypothetical protein...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0383 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0383 [conserved hypothetic...] - TP0856 [hypothetical protein...] (1,F)
TP0383 [conserved hypothetic...] - TP0938 [hypothetical protein...] (1,F)
TP0383 [conserved hypothetic...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0384 [conserved hypothetic...] - TP0068 [conserved hypothetic...] (1,F)
TP0384 [conserved hypothetic...] - TP0396 [flagellar basal-body...] (15,F)
TP0384 [conserved hypothetic...] - TP0832 [hypothetical protein...] (37,F)
TP0386 [UDP-N-acetylmuramoyl...] - TP0383 [conserved hypothetic...] (65,W)
TP0387 [cell division protei...] - TP0236 [transcription antite...] (5,F)
TP0387 [cell division protei...] - TP0260 [hypothetical protein...] (5,F)
TP0387 [cell division protei...] - TP0561 [conserved hypothetic...] (44,F)
TP0387 [cell division protei...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0387 [cell division protei...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0387 [cell division protei...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0388 [cell division protei...] - TP0109 [rRNA methylase, puta...] (1,F)
TP0389 [cell division protei...] - TP0066 [hypothetical protein...] (11,F)
TP0389 [cell division protei...] - TP0092 [RNA polymerase sigma...] (10,F)
TP0389 [cell division protei...] - TP0260 [hypothetical protein...] (5,F)
TP0389 [cell division protei...] - TP0380 [DNA repair helicase,...] (5,F)
TP0389 [cell division protei...] - TP0559 [conserved hypothetic...] (26,F)
TP0389 [cell division protei...] - TP0563 [hypothetical protein...] (93,W)
TP0389 [cell division protei...] - TP0579 [hypothetical protein...] (5,F)
TP0389 [cell division protei...] - TP0764 [conserved hypothetic...] (139,W)
TP0389 [cell division protei...] - TP0832 [hypothetical protein...] (37,F)
TP0389 [cell division protei...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0390 [cell division protei...] - TP0046 [hypothetical protein...] (18,F)
TP0390 [cell division protei...] - TP0060 [ribosomal protein L9...] (78,W)
TP0390 [cell division protei...] - TP0288 [spore coat polysacch...] (77,W)
TP0390 [cell division protei...] - TP0907 [conserved hypothetic...] (110,W)
TP0390 [cell division protei...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0390 [cell division protei...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0391 [integrase/recombinas...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0391 [integrase/recombinas...] - TP0788 [hypothetical protein...] (132,W)
TP0391 [integrase/recombinas...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0394 [DNA topoisomerase I ...] - TP0208 [preprotein transloca...] (2,F)
TP0394 [DNA topoisomerase I ...] - TP0763 [hypothetical protein...] (2,F)
TP0395 [integrase/recombinas...] - TP0661 [hypothetical protein...] (117,W)
TP0398 [flagellar hook-basal...] - TP0005 [DNA gyrase, subunit ...] (9,F)
TP0398 [flagellar hook-basal...] - TP0026 [flagellar motor swit...] (8,F)
TP0398 [flagellar hook-basal...] - TP0046 [hypothetical protein...] (18,F)
TP0398 [flagellar hook-basal...] - TP0050 [conserved hypothetic...] (10,F)
TP0398 [flagellar hook-basal...] - TP0064 [hypothetical, protei...] (8,F)
TP0398 [flagellar hook-basal...] - TP0066 [hypothetical protein...] (11,F)
TP0398 [flagellar hook-basal...] - TP0092 [RNA polymerase sigma...] (10,F)
TP0398 [flagellar hook-basal...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0398 [flagellar hook-basal...] - TP0162 [Holliday junction DN...] (3,F)
TP0398 [flagellar hook-basal...] - TP0258 [conserved hypothetic...] (173,W)
TP0398 [flagellar hook-basal...] - TP0288 [spore coat polysacch...] (77,W)
TP0398 [flagellar hook-basal...] - TP0383 [conserved hypothetic...] (65,W)
TP0398 [flagellar hook-basal...] - TP0396 [flagellar basal-body...] (15,F)
TP0398 [flagellar hook-basal...] - TP0398 [flagellar hook-basal...] (114,W)
TP0398 [flagellar hook-basal...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0398 [flagellar hook-basal...] - TP0563 [hypothetical protein...] (93,W)
TP0398 [flagellar hook-basal...] - TP0579 [hypothetical protein...] (5,F)
TP0398 [flagellar hook-basal...] - TP0629 [hypothetical protein...] (6,F)
TP0398 [flagellar hook-basal...] - TP0661 [hypothetical protein...] (117,W)
TP0398 [flagellar hook-basal...] - TP0764 [conserved hypothetic...] (139,W)
TP0398 [flagellar hook-basal...] - TP0788 [hypothetical protein...] (132,W)
TP0398 [flagellar hook-basal...] - TP0832 [hypothetical protein...] (37,F)
TP0398 [flagellar hook-basal...] - TP0870 [flagellar filament 3...] (79,W)
TP0398 [flagellar hook-basal...] - TP0907 [conserved hypothetic...] (110,W)
TP0398 [flagellar hook-basal...] - TP0961 [flagellar basal-body...] (84,W)
TP0398 [flagellar hook-basal...] - TP0979 [conserved hypothetic...] (1,F)
TP0398 [flagellar hook-basal...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0398 [flagellar hook-basal...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0399 [flagellar basal-body...] - TP0026 [flagellar motor swit...] (8,F)
TP0399 [flagellar basal-body...] - TP0561 [conserved hypothetic...] (44,F)
TP0399 [flagellar basal-body...] - TP0708 [hypothetical protein...] (13,F)
TP0399 [flagellar basal-body...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0400 [flagellar motor swit...] - TP0014 [hypothetical protein...] (2,F)
TP0400 [flagellar motor swit...] - TP0026 [flagellar motor swit...] (8,F)
TP0400 [flagellar motor swit...] - TP0060 [ribosomal protein L9...] (78,W)
TP0400 [flagellar motor swit...] - TP0066 [hypothetical protein...] (11,F)
TP0400 [flagellar motor swit...] - TP0091 [cysteinyl-tRNA synth...] (1,F)
TP0400 [flagellar motor swit...] - TP0092 [RNA polymerase sigma...] (10,F)
TP0400 [flagellar motor swit...] - TP0209 [ribosomal protein L3...] (27,F)
TP0400 [flagellar motor swit...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0400 [flagellar motor swit...] - TP0399 [flagellar basal-body...] (2,F)
TP0400 [flagellar motor swit...] - TP0443 [conserved hypothetic...] (6,F)
TP0400 [flagellar motor swit...] - TP0563 [hypothetical protein...] (93,W)
TP0400 [flagellar motor swit...] - TP0648 [conserved hypothetic...] (3,F)
TP0400 [flagellar motor swit...] - TP0665 [hypothetical protein...] (1,F)
TP0400 [flagellar motor swit...] - TP0743 [ribosomal protein L2...] (2,F)
TP0400 [flagellar motor swit...] - TP0764 [conserved hypothetic...] (139,W)
TP0400 [flagellar motor swit...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0401 [flagellar assembly p...] - TP0026 [flagellar motor swit...] (8,F)
TP0402 [flagellum-specific A...] - TP0413 [phosphoglucomutase {...] (2,F)
TP0402 [flagellum-specific A...] - TP0640 [methyl-accepting che...] (5,F)
TP0402 [flagellum-specific A...] - TP0833 [hypothetical protein...] (34,F)
TP0402 [flagellum-specific A...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0403 [flagellar protein, p...] - TP0288 [spore coat polysacch...] (77,W)
TP0403 [flagellar protein, p...] - TP0563 [hypothetical protein...] (93,W)
TP0403 [flagellar protein, p...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0403 [flagellar protein, p...] - TP0764 [conserved hypothetic...] (139,W)
TP0403 [flagellar protein, p...] - TP0832 [hypothetical protein...] (37,F)
TP0403 [flagellar protein, p...] - TP0868 [flagellar filament 3...] (1,F)
TP0403 [flagellar protein, p...] - TP0961 [flagellar basal-body...] (84,W)
TP0403 [flagellar protein, p...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0403 [flagellar protein, p...] - TP1004 [recombination protei...] (74,W)
TP0407 [phosphoglycolate pho...] - TP0398 [flagellar hook-basal...] (114,W)
TP0407 [phosphoglycolate pho...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0409 [hypothetical protein...] - TP0059 [hypothetical protein...] (21,F)
TP0409 [hypothetical protein...] - TP0197 [ribosomal protein L2...] (15,F)
TP0409 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0409 [hypothetical protein...] - TP0587 [hypothetical protein...] (23,F)
TP0409 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0409 [hypothetical protein...] - TP0773 [periplasmic serine p...] (30,F)
TP0409 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0409 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0409 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0409 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0410 [protein-export membr...] - TP0281 [hypothetical protein...] (64,W)
TP0410 [protein-export membr...] - TP0287 [conserved hypothetic...] (27,F)
TP0410 [protein-export membr...] - TP0383 [conserved hypothetic...] (65,W)
TP0410 [protein-export membr...] - TP0518 [conserved hypothetic...] (70,W)
TP0410 [protein-export membr...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0410 [protein-export membr...] - TP0587 [hypothetical protein...] (23,F)
TP0410 [protein-export membr...] - TP0661 [hypothetical protein...] (117,W)
TP0410 [protein-export membr...] - TP0788 [hypothetical protein...] (132,W)
TP0410 [protein-export membr...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0411 [protein-export membr...] - TP0561 [conserved hypothetic...] (44,F)
TP0411 [protein-export membr...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0412 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0412 [conserved hypothetic...] - TP0067 [conserved hypothetic...] (19,F)
TP0412 [conserved hypothetic...] - TP0121 [conserved hypothetic...] (7,F)
TP0412 [conserved hypothetic...] - TP0209 [ribosomal protein L3...] (27,F)
TP0412 [conserved hypothetic...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)

TP0412 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0412 [conserved hypothetic...] - TP0281 [hypothetical protein...] (64,W)
TP0412 [conserved hypothetic...] - TP0287 [conserved hypothetic...] (27,F)
TP0412 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0412 [conserved hypothetic...] - TP0341 [UDP-N-acetylmuramate...] (12,F)
TP0412 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0412 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0412 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0412 [conserved hypothetic...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0412 [conserved hypothetic...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0412 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0412 [conserved hypothetic...] - TP0664 [flagellar filament o...] (34,F)
TP0412 [conserved hypothetic...] - TP0711 [conserved hypothetic...] (46,F)
TP0412 [conserved hypothetic...] - TP0757 [polypeptide deformyl...] (36,F)
TP0412 [conserved hypothetic...] - TP0773 [periplasmic serine p...] (30,F)
TP0412 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0412 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0412 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0412 [conserved hypothetic...] - TP0943 [flagellar protein (f...] (15,F)
TP0412 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0412 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0412 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0412 [conserved hypothetic...] - TP0997 [protease IV (sppA) {...] (8,F)
TP0412 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0412 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0413 [phosphoglucomutase {...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0414 [D-alanine glycine pe...] - TP0561 [conserved hypothetic...] (44,F)
TP0414 [D-alanine glycine pe...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0418 [galactokinase {Homo ...] - TP0067 [conserved hypothetic...] (19,F)
TP0418 [galactokinase {Homo ...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0418 [galactokinase {Homo ...] - TP0095 [hypothetical protein...] (15,F)
TP0418 [galactokinase {Homo ...] - TP0661 [hypothetical protein...] (117,W)
TP0418 [galactokinase {Homo ...] - TP0684 [methylgalactoside AB...] (15,F)
TP0418 [galactokinase {Homo ...] - TP0711 [conserved hypothetic...] (46,F)
TP0418 [galactokinase {Homo ...] - TP0757 [polypeptide deformyl...] (36,F)
TP0418 [galactokinase {Homo ...] - TP0907 [conserved hypothetic...] (110,W)
TP0418 [galactokinase {Homo ...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0419 [survival protein, pu...] - TP0046 [hypothetical protein...] (18,F)
TP0421 [conserved hypothetic...] - TP0095 [hypothetical protein...] (15,F)
TP0421 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0421 [conserved hypothetic...] - TP0711 [conserved hypothetic...] (46,F)
TP0421 [conserved hypothetic...] - TP0939 [pyruvate oxidoreduct...] (12,F)
TP0424 [V-type ATPase, subun...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0427 [V-type ATPase, subun...] - TP0243 [ribosomal protein S1...] (1,F)
TP0427 [V-type ATPase, subun...] - TP0328 [DNA mismatch repair ...] (1,F)
TP0430 [V-type ATPase, subun...] - TP0561 [conserved hypothetic...] (44,F)
TP0432 [hypothetical protein...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0434 [hypothetical protein...] - TP0059 [hypothetical protein...] (21,F)
TP0434 [hypothetical protein...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0434 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0434 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0434 [hypothetical protein...] - TP0287 [conserved hypothetic...] (27,F)
TP0434 [hypothetical protein...] - TP0341 [UDP-N-acetylmuramate...] (12,F)
TP0434 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0434 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0434 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0434 [hypothetical protein...] - TP0463 [hypothetical protein...] (8,F)
TP0434 [hypothetical protein...] - TP0465 [hypothetical protein...] (7,F)
TP0434 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0434 [hypothetical protein...] - TP0519 [response regulatory ...] (30,F)
TP0434 [hypothetical protein...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0434 [hypothetical protein...] - TP0559 [conserved hypothetic...] (26,F)
TP0434 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0434 [hypothetical protein...] - TP0618 [hypothetical protein...] (24,F)
TP0434 [hypothetical protein...] - TP0641 [histidyl-tRNA synthe...] (9,F)
TP0434 [hypothetical protein...] - TP0684 [methylgalactoside AB...] (15,F)
TP0434 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0434 [hypothetical protein...] - TP0727 [flagellar hook prote...] (5,F)
TP0434 [hypothetical protein...] - TP0741 [conserved hypothetic...] (8,F)
TP0434 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0434 [hypothetical protein...] - TP0773 [periplasmic serine p...] (30,F)
TP0434 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0434 [hypothetical protein...] - TP0807 [ribosomal protein L3...] (4,F)
TP0434 [hypothetical protein...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0434 [hypothetical protein...] - TP0946 [glucose-inhibited di...] (19,F)
TP0434 [hypothetical protein...] - TP0974 [hypothetical protein...] (23,F)
TP0434 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0434 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0434 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0434 [hypothetical protein...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0434 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0434 [hypothetical protein...] - TP1023 [recX protein (recX) ...] (13,F)
TP0435 [lipoprotein, 17 kDa ...] - TP0046 [hypothetical protein...] (18,F)
TP0435 [lipoprotein, 17 kDa ...] - TP0050 [conserved hypothetic...] (10,F)
TP0435 [lipoprotein, 17 kDa ...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0435 [lipoprotein, 17 kDa ...] - TP0258 [conserved hypothetic...] (173,W)
TP0435 [lipoprotein, 17 kDa ...] - TP0287 [conserved hypothetic...] (27,F)
TP0435 [lipoprotein, 17 kDa ...] - TP0288 [spore coat polysacch...] (77,W)
TP0435 [lipoprotein, 17 kDa ...] - TP0396 [flagellar basal-body...] (15,F)
TP0435 [lipoprotein, 17 kDa ...] - TP0467 [hypothetical protein...] (2,F)
TP0435 [lipoprotein, 17 kDa ...] - TP0563 [hypothetical protein...] (93,W)
TP0435 [lipoprotein, 17 kDa ...] - TP0629 [hypothetical protein...] (6,F)
TP0435 [lipoprotein, 17 kDa ...] - TP0661 [hypothetical protein...] (117,W)
TP0435 [lipoprotein, 17 kDa ...] - TP0726 [flagellar protein (f...] (7,F)
TP0435 [lipoprotein, 17 kDa ...] - TP0741 [conserved hypothetic...] (8,F)
TP0435 [lipoprotein, 17 kDa ...] - TP0757 [polypeptide deformyl...] (36,F)
TP0435 [lipoprotein, 17 kDa ...] - TP0788 [hypothetical protein...] (132,W)
TP0435 [lipoprotein, 17 kDa ...] - TP0832 [hypothetical protein...] (37,F)
TP0435 [lipoprotein, 17 kDa ...] - TP0907 [conserved hypothetic...] (110,W)
TP0435 [lipoprotein, 17 kDa ...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0437 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0437 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0439 [purine-binding chemo...] - TP0258 [conserved hypothetic...] (173,W)
TP0439 [purine-binding chemo...] - TP0764 [conserved hypothetic...] (139,W)
TP0439 [purine-binding chemo...] - TP0788 [hypothetical protein...] (132,W)
TP0441 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0443 [conserved hypothetic...] - TP0029 [UDP-N-acetylglucosam...] (1,F)
TP0443 [conserved hypothetic...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0443 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0443 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0443 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0443 [conserved hypothetic...] - TP0711 [conserved hypothetic...] (46,F)
TP0443 [conserved hypothetic...] - TP0773 [periplasmic serine p...] (30,F)
TP0443 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0443 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0443 [conserved hypothetic...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0443 [conserved hypothetic...] - TP0946 [glucose-inhibited di...] (19,F)
TP0443 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0443 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0443 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0443 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0443 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0443 [conserved hypothetic...] - TP1023 [recX protein (recX) ...] (13,F)
TP0446 [gcpE protein (gcpE) ...] - TP0398 [flagellar hook-basal...] (114,W)
TP0446 [gcpE protein (gcpE) ...] - TP0764 [conserved hypothetic...] (139,W)
TP0451 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0451 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0451 [hypothetical protein...] - TP0974 [hypothetical protein...] (23,F)
TP0451 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0451 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0451 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0451 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0452 [isoleucyl-tRNA synth...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0452 [isoleucyl-tRNA synth...] - TP0185 [signal peptidase I (...] (1,F)
TP0452 [isoleucyl-tRNA synth...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0453 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0453 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0453 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0453 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0455 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0455 [conserved hypothetic...] - TP0209 [ribosomal protein L3...] (27,F)
TP0455 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0455 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0455 [conserved hypothetic...] - TP0397 [flagellar basal-body...] (25,F)
TP0455 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0455 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0455 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0455 [conserved hypothetic...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0455 [conserved hypothetic...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0455 [conserved hypothetic...] - TP0559 [conserved hypothetic...] (26,F)
TP0455 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0455 [conserved hypothetic...] - TP0626 [exonuclease, putativ...] (12,F)
TP0455 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0455 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0455 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0455 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0455 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0455 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0455 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0457 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0457 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0457 [conserved hypothetic...] - TP0281 [hypothetical protein...] (64,W)
TP0457 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0457 [conserved hypothetic...] - TP0397 [flagellar basal-body...] (25,F)
TP0457 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0457 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0457 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0457 [conserved hypothetic...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0457 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0457 [conserved hypothetic...] - TP0773 [periplasmic serine p...] (30,F)
TP0457 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0457 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0457 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0457 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0457 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0457 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0457 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0457 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0458 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0459 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)

TP0459 [conserved hypothetic...] - TP0067 [conserved hypothetic...] (19,F)
TP0459 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0459 [conserved hypothetic...] - TP0281 [hypothetical protein...] (64,W)
TP0459 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0459 [conserved hypothetic...] - TP0336 [comE protein, putati...] (1,F)
TP0459 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0459 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0459 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0459 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0459 [conserved hypothetic...] - TP0757 [polypeptide deformyl...] (36,F)
TP0459 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0459 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0459 [conserved hypothetic...] - TP0874 [conserved hypothetic...] (1,F)
TP0459 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0459 [conserved hypothetic...] - TP0982 [glpG protein, putati...] (1,F)
TP0459 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0459 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0461 [hypothetical protein...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0461 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0461 [hypothetical protein...] - TP0287 [conserved hypothetic...] (27,F)
TP0461 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0461 [hypothetical protein...] - TP0443 [conserved hypothetic...] (6,F)
TP0462 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0462 [hypothetical protein...] - TP0286 [conserved hypothetic...] (9,F)
TP0462 [hypothetical protein...] - TP0287 [conserved hypothetic...] (27,F)
TP0462 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0462 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0462 [hypothetical protein...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0462 [hypothetical protein...] - TP0641 [histidyl-tRNA synthe...] (9,F)
TP0462 [hypothetical protein...] - TP0684 [methylgalactoside AB...] (15,F)
TP0462 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0462 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0462 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0462 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0463 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0464 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0464 [conserved hypothetic...] - TP0712 [ATP-binding protein ...] (1,F)
TP0464 [conserved hypothetic...] - TP0739 [conserved hypothetic...] (1,F)
TP0464 [conserved hypothetic...] - TP0832 [hypothetical protein...] (37,F)
TP0465 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0465 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0465 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0466 [hypothetical protein...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0467 [hypothetical protein...] - TP0287 [conserved hypothetic...] (27,F)
TP0467 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0467 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0467 [hypothetical protein...] - TP0965 [membrane fusion prot...] (14,F)
TP0467 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0467 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0467 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0468 [conserved hypothetic...] - TP0757 [polypeptide deformyl...] (36,F)
TP0468 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0468 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0469 [hypothetical protein...] - TP0833 [hypothetical protein...] (34,F)
TP0469 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0471 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0471 [hypothetical protein...] - TP0421 [conserved hypothetic...] (4,F)
TP0471 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0472 [excinuclease ABC, su...] - TP0258 [conserved hypothetic...] (173,W)
TP0472 [excinuclease ABC, su...] - TP0661 [hypothetical protein...] (117,W)
TP0472 [excinuclease ABC, su...] - TP0894 [conserved hypothetic...] (13,F)
TP0472 [excinuclease ABC, su...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0472 [excinuclease ABC, su...] - TP1004 [recombination protei...] (74,W)
TP0473 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0474 [conserved hypothetic...] - TP0462 [hypothetical protein...] (1,F)
TP0474 [conserved hypothetic...] - TP0481 [hypothetical protein...] (1,F)
TP0474 [conserved hypothetic...] - TP0489 [conserved hypothetic...] (1,F)
TP0474 [conserved hypothetic...] - TP0510 [GTP-binding membrane...] (1,F)
TP0474 [conserved hypothetic...] - TP0533 [V-type ATPase, subun...] (1,F)
TP0474 [conserved hypothetic...] - TP0651 [conserved hypothetic...] (1,F)
TP0474 [conserved hypothetic...] - TP0794 [S-adenosylmethionine...] (1,F)
TP0474 [conserved hypothetic...] - TP0798 [methionyl-tRNA synth...] (1,F)
TP0474 [conserved hypothetic...] - TP0864 [conserved hypothetic...] (1,F)
TP0474 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0478 [glucose-6-phosphate ...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0479 [hypothetical protein...] - TP0067 [conserved hypothetic...] (19,F)
TP0481 [hypothetical protein...] - TP0968 [hypothetical protein...] (1,F)
TP0481 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0481 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0484 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0484 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0484 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0484 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0484 [hypothetical protein...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0485 [adenylate cyclase {A...] - TP0060 [ribosomal protein L9...] (78,W)
TP0485 [adenylate cyclase {A...] - TP0518 [conserved hypothetic...] (70,W)
TP0485 [adenylate cyclase {A...] - TP0563 [hypothetical protein...] (93,W)
TP0485 [adenylate cyclase {A...] - TP0907 [conserved hypothetic...] (110,W)
TP0485 [adenylate cyclase {A...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0485 [adenylate cyclase {A...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0485 [adenylate cyclase {A...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0490 [conserved hypothetic...] - TP0371 [conserved hypothetic...] (1,F)
TP0490 [conserved hypothetic...] - TP0920 [hypothetical protein...] (7,F)
TP0492 [DNA primase (dnaE) {...] - TP0024 [conserved hypothetic...] (16,F)
TP0492 [DNA primase (dnaE) {...] - TP0066 [hypothetical protein...] (11,F)
TP0492 [DNA primase (dnaE) {...] - TP0088 [conserved hypothetic...] (8,F)
TP0492 [DNA primase (dnaE) {...] - TP0092 [RNA polymerase sigma...] (10,F)
TP0492 [DNA primase (dnaE) {...] - TP0095 [hypothetical protein...] (15,F)
TP0492 [DNA primase (dnaE) {...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0492 [DNA primase (dnaE) {...] - TP0168 [phosphoglycerate mut...] (1,F)
TP0492 [DNA primase (dnaE) {...] - TP0197 [ribosomal protein L2...] (15,F)
TP0492 [DNA primase (dnaE) {...] - TP0258 [conserved hypothetic...] (173,W)
TP0492 [DNA primase (dnaE) {...] - TP0288 [spore coat polysacch...] (77,W)
TP0492 [DNA primase (dnaE) {...] - TP0305 [CTP synthase (pyrG) ...] (4,F)
TP0492 [DNA primase (dnaE) {...] - TP0380 [DNA repair helicase,...] (5,F)
TP0492 [DNA primase (dnaE) {...] - TP0398 [flagellar hook-basal...] (114,W)
TP0492 [DNA primase (dnaE) {...] - TP0519 [response regulatory ...] (30,F)
TP0492 [DNA primase (dnaE) {...] - TP0648 [conserved hypothetic...] (3,F)
TP0492 [DNA primase (dnaE) {...] - TP0661 [hypothetical protein...] (117,W)
TP0492 [DNA primase (dnaE) {...] - TP0751 [hypothetical protein...] (7,F)
TP0492 [DNA primase (dnaE) {...] - TP0764 [conserved hypothetic...] (139,W)
TP0492 [DNA primase (dnaE) {...] - TP0788 [hypothetical protein...] (132,W)
TP0492 [DNA primase (dnaE) {...] - TP0797 [1-pyrroline-5-carbox...] (5,F)
TP0492 [DNA primase (dnaE) {...] - TP0832 [hypothetical protein...] (37,F)
TP0492 [DNA primase (dnaE) {...] - TP0833 [hypothetical protein...] (34,F)
TP0492 [DNA primase (dnaE) {...] - TP0877 [conserved hypothetic...] (4,F)
TP0492 [DNA primase (dnaE) {...] - TP0907 [conserved hypothetic...] (110,W)
TP0492 [DNA primase (dnaE) {...] - TP0939 [pyruvate oxidoreduct...] (12,F)
TP0492 [DNA primase (dnaE) {...] - TP0942 [hypothetical protein...] (1,F)
TP0492 [DNA primase (dnaE) {...] - TP0961 [flagellar basal-body...] (84,W)
TP0492 [DNA primase (dnaE) {...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0492 [DNA primase (dnaE) {...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0492 [DNA primase (dnaE) {...] - TP1006 [DNA gyrase, subunit ...] (1,F)
TP0495 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0495 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0495 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0496 [conserved hypothetic...] - TP0492 [DNA primase (dnaE) {...] (1,F)
TP0496 [conserved hypothetic...] - TP0889 [tRNA pseudouridine 5...] (1,F)
TP0496 [conserved hypothetic...] - TP0909 [ribosomal protein L1...] (1,F)
TP0496 [conserved hypothetic...] - TP0973 [phenylalanyl-tRNA sy...] (1,F)
TP0496 [conserved hypothetic...] - TP0985 [aspartyl-tRNA synthe...] (2,F)
TP0496 [conserved hypothetic...] - TP1008 [ribonucleoside-dipho...] (2,F)
TP0497 [rod shape-determinin...] - TP0001 [chromosomal replicat...] (3,F)
TP0497 [rod shape-determinin...] - TP0060 [ribosomal protein L9...] (78,W)
TP0497 [rod shape-determinin...] - TP0088 [conserved hypothetic...] (8,F)
TP0497 [rod shape-determinin...] - TP0209 [ribosomal protein L3...] (27,F)
TP0497 [rod shape-determinin...] - TP0258 [conserved hypothetic...] (173,W)
TP0497 [rod shape-determinin...] - TP0260 [hypothetical protein...] (5,F)
TP0497 [rod shape-determinin...] - TP0334 [conserved hypothetic...] (5,F)
TP0497 [rod shape-determinin...] - TP0629 [hypothetical protein...] (6,F)
TP0497 [rod shape-determinin...] - TP0764 [conserved hypothetic...] (139,W)
TP0497 [rod shape-determinin...] - TP0788 [hypothetical protein...] (132,W)
TP0497 [rod shape-determinin...] - TP0807 [ribosomal protein L3...] (4,F)
TP0497 [rod shape-determinin...] - TP0832 [hypothetical protein...] (37,F)
TP0497 [rod shape-determinin...] - TP0907 [conserved hypothetic...] (110,W)
TP0497 [rod shape-determinin...] - TP0961 [flagellar basal-body...] (84,W)
TP0497 [rod shape-determinin...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0497 [rod shape-determinin...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0498 [rod shape-determinin...] - TP0258 [conserved hypothetic...] (173,W)
TP0498 [rod shape-determinin...] - TP0288 [spore coat polysacch...] (77,W)
TP0498 [rod shape-determinin...] - TP0397 [flagellar basal-body...] (25,F)
TP0498 [rod shape-determinin...] - TP0473 [hypothetical protein...] (1,F)
TP0498 [rod shape-determinin...] - TP0870 [flagellar filament 3...] (79,W)
TP0498 [rod shape-determinin...] - TP0884 [conserved hypothetic...] (1,F)
TP0498 [rod shape-determinin...] - TP0907 [conserved hypothetic...] (110,W)
TP0498 [rod shape-determinin...] - TP0961 [flagellar basal-body...] (84,W)
TP0498 [rod shape-determinin...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0499 [rod shape-determinin...] - TP0561 [conserved hypothetic...] (44,F)
TP0500 [penicillin-binding p...] - TP0012 [hypothetical protein...] (1,F)
TP0500 [penicillin-binding p...] - TP0252 [apolipoprotein N-acy...] (1,F)
TP0500 [penicillin-binding p...] - TP0907 [conserved hypothetic...] (110,W)
TP0500 [penicillin-binding p...] - TP0961 [flagellar basal-body...] (84,W)
TP0500 [penicillin-binding p...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0500 [penicillin-binding p...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0500 [penicillin-binding p...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0500 [penicillin-binding p...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0501 [rod shape-determinin...] - TP0113 [Lambda CII stability...] (2,F)
TP0501 [rod shape-determinin...] - TP0258 [conserved hypothetic...] (173,W)
TP0501 [rod shape-determinin...] - TP0377 [conserved hypothetic...] (11,F)
TP0501 [rod shape-determinin...] - TP0561 [conserved hypothetic...] (44,F)
TP0501 [rod shape-determinin...] - TP0563 [hypothetical protein...] (93,W)
TP0501 [rod shape-determinin...] - TP0708 [hypothetical protein...] (13,F)
TP0501 [rod shape-determinin...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0501 [rod shape-determinin...] - TP0961 [flagellar basal-body...] (84,W)
TP0501 [rod shape-determinin...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0501 [rod shape-determinin...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0501 [rod shape-determinin...] - TP0998 [sodium/proton-depend...] (1,F)
TP0503 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)

TP0503 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0503 [hypothetical protein...] - TP0396 [flagellar basal-body...] (15,F)
TP0503 [hypothetical protein...] - TP0397 [flagellar basal-body...] (25,F)
TP0503 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0503 [hypothetical protein...] - TP0463 [hypothetical protein...] (8,F)
TP0503 [hypothetical protein...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0503 [hypothetical protein...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0503 [hypothetical protein...] - TP0559 [conserved hypothetic...] (26,F)
TP0503 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0503 [hypothetical protein...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0503 [hypothetical protein...] - TP0587 [hypothetical protein...] (23,F)
TP0503 [hypothetical protein...] - TP0618 [hypothetical protein...] (24,F)
TP0503 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0503 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0503 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0503 [hypothetical protein...] - TP0797 [1-pyrroline-5-carbox...] (5,F)
TP0503 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0503 [hypothetical protein...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0503 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0503 [hypothetical protein...] - TP0974 [hypothetical protein...] (23,F)
TP0503 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0503 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0504 [hypothetical protein...] - TP0067 [conserved hypothetic...] (19,F)
TP0504 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0504 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0504 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0505 [hexokinase (hxk) {Sc...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0506 [trigger factor (tig)...] - TP0086 [conserved hypothetic...] (1,F)
TP0506 [trigger factor (tig)...] - TP0605 [translation elongati...] (1,F)
TP0507 [ATP-dependent Clp pr...] - TP0060 [ribosomal protein L9...] (78,W)
TP0507 [ATP-dependent Clp pr...] - TP0362 [ribosomal protein L2...] (2,F)
TP0507 [ATP-dependent Clp pr...] - TP0377 [conserved hypothetic...] (11,F)
TP0507 [ATP-dependent Clp pr...] - TP0563 [hypothetical protein...] (93,W)
TP0507 [ATP-dependent Clp pr...] - TP0907 [conserved hypothetic...] (110,W)
TP0507 [ATP-dependent Clp pr...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0507 [ATP-dependent Clp pr...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0508 [ATP-dependent Clp pr...] - TP0060 [ribosomal protein L9...] (78,W)
TP0508 [ATP-dependent Clp pr...] - TP0961 [flagellar basal-body...] (84,W)
TP0508 [ATP-dependent Clp pr...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0509 [alkyl hydroperoxide ...] - TP0258 [conserved hypothetic...] (173,W)
TP0509 [alkyl hydroperoxide ...] - TP0764 [conserved hypothetic...] (139,W)
TP0511 [transcription factor...] - TP0258 [conserved hypothetic...] (173,W)
TP0511 [transcription factor...] - TP0788 [hypothetical protein...] (132,W)
TP0511 [transcription factor...] - TP0907 [conserved hypothetic...] (110,W)
TP0511 [transcription factor...] - TP0961 [flagellar basal-body...] (84,W)
TP0511 [transcription factor...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0511 [transcription factor...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0516 [virulence factor (mv...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0516 [virulence factor (mv...] - TP0305 [CTP synthase (pyrG) ...] (4,F)
TP0517 [Holliday junction nu...] - TP0258 [conserved hypothetic...] (173,W)
TP0517 [Holliday junction nu...] - TP0288 [spore coat polysacch...] (77,W)
TP0517 [Holliday junction nu...] - TP0294 [phosphoribosyl pyrop...] (3,F)
TP0517 [Holliday junction nu...] - TP0341 [UDP-N-acetylmuramate...] (12,F)
TP0517 [Holliday junction nu...] - TP0383 [conserved hypothetic...] (65,W)
TP0517 [Holliday junction nu...] - TP0397 [flagellar basal-body...] (25,F)
TP0517 [Holliday junction nu...] - TP0449 [hypothetical protein...] (51,W)
TP0517 [Holliday junction nu...] - TP0518 [conserved hypothetic...] (70,W)
TP0517 [Holliday junction nu...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0517 [Holliday junction nu...] - TP0661 [hypothetical protein...] (117,W)
TP0517 [Holliday junction nu...] - TP0664 [flagellar filament o...] (34,F)
TP0517 [Holliday junction nu...] - TP0684 [methylgalactoside AB...] (15,F)
TP0517 [Holliday junction nu...] - TP0704 [single-stranded-DNA-...] (12,F)
TP0517 [Holliday junction nu...] - TP0711 [conserved hypothetic...] (46,F)
TP0517 [Holliday junction nu...] - TP0757 [polypeptide deformyl...] (36,F)
TP0517 [Holliday junction nu...] - TP0773 [periplasmic serine p...] (30,F)
TP0517 [Holliday junction nu...] - TP0788 [hypothetical protein...] (132,W)
TP0517 [Holliday junction nu...] - TP0870 [flagellar filament 3...] (79,W)
TP0517 [Holliday junction nu...] - TP0907 [conserved hypothetic...] (110,W)
TP0517 [Holliday junction nu...] - TP0943 [flagellar protein (f...] (15,F)
TP0517 [Holliday junction nu...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0519 [response regulatory ...] - TP0352 [hypothetical protein...] (1,F)
TP0519 [response regulatory ...] - TP0519 [response regulatory ...] (30,F)
TP0521 [DNA polymerase III, ...] - TP0764 [conserved hypothetic...] (139,W)
TP0521 [DNA polymerase III, ...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0521 [DNA polymerase III, ...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0525 [translation elongati...] - TP0764 [conserved hypothetic...] (139,W)
TP0526 [ATP-dependent helica...] - TP0067 [conserved hypothetic...] (19,F)
TP0526 [ATP-dependent helica...] - TP0192 [ribosomal protein L2...] (1,F)
TP0526 [ATP-dependent helica...] - TP0258 [conserved hypothetic...] (173,W)
TP0526 [ATP-dependent helica...] - TP0559 [conserved hypothetic...] (26,F)
TP0526 [ATP-dependent helica...] - TP0764 [conserved hypothetic...] (139,W)
TP0526 [ATP-dependent helica...] - TP0788 [hypothetical protein...] (132,W)
TP0526 [ATP-dependent helica...] - TP0892 [N utilization substa...] (1,F)
TP0526 [ATP-dependent helica...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0526 [ATP-dependent helica...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0526 [ATP-dependent helica...] - TP1023 [recX protein (recX) ...] (13,F)
TP0527 [V-type ATPase, subun...] - TP0059 [hypothetical protein...] (21,F)
TP0527 [V-type ATPase, subun...] - TP0060 [ribosomal protein L9...] (78,W)
TP0527 [V-type ATPase, subun...] - TP0197 [ribosomal protein L2...] (15,F)
TP0527 [V-type ATPase, subun...] - TP0288 [spore coat polysacch...] (77,W)
TP0527 [V-type ATPase, subun...] - TP0383 [conserved hypothetic...] (65,W)
TP0527 [V-type ATPase, subun...] - TP0396 [flagellar basal-body...] (15,F)
TP0527 [V-type ATPase, subun...] - TP0398 [flagellar hook-basal...] (114,W)
TP0527 [V-type ATPase, subun...] - TP0449 [hypothetical protein...] (51,W)
TP0527 [V-type ATPase, subun...] - TP0563 [hypothetical protein...] (93,W)
TP0527 [V-type ATPase, subun...] - TP0661 [hypothetical protein...] (117,W)
TP0527 [V-type ATPase, subun...] - TP0764 [conserved hypothetic...] (139,W)
TP0527 [V-type ATPase, subun...] - TP0870 [flagellar filament 3...] (79,W)
TP0527 [V-type ATPase, subun...] - TP0907 [conserved hypothetic...] (110,W)
TP0527 [V-type ATPase, subun...] - TP0961 [flagellar basal-body...] (84,W)
TP0527 [V-type ATPase, subun...] - TP0965 [membrane fusion prot...] (14,F)
TP0527 [V-type ATPase, subun...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0527 [V-type ATPase, subun...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0527 [V-type ATPase, subun...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0528 [V-type ATPase, subun...] - TP0060 [ribosomal protein L9...] (78,W)
TP0528 [V-type ATPase, subun...] - TP0288 [spore coat polysacch...] (77,W)
TP0528 [V-type ATPase, subun...] - TP0383 [conserved hypothetic...] (65,W)
TP0528 [V-type ATPase, subun...] - TP0661 [hypothetical protein...] (117,W)
TP0528 [V-type ATPase, subun...] - TP0961 [flagellar basal-body...] (84,W)
TP0528 [V-type ATPase, subun...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0528 [V-type ATPase, subun...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0530 [V-type ATPase, subun...] - TP0258 [conserved hypothetic...] (173,W)
TP0530 [V-type ATPase, subun...] - TP0288 [spore coat polysacch...] (77,W)
TP0530 [V-type ATPase, subun...] - TP0398 [flagellar hook-basal...] (114,W)
TP0530 [V-type ATPase, subun...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0530 [V-type ATPase, subun...] - TP0563 [hypothetical protein...] (93,W)
TP0530 [V-type ATPase, subun...] - TP0661 [hypothetical protein...] (117,W)
TP0530 [V-type ATPase, subun...] - TP0870 [flagellar filament 3...] (79,W)
TP0530 [V-type ATPase, subun...] - TP0961 [flagellar basal-body...] (84,W)
TP0530 [V-type ATPase, subun...] - TP0974 [hypothetical protein...] (23,F)
TP0530 [V-type ATPase, subun...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0530 [V-type ATPase, subun...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0531 [V-type ATPase, subun...] - TP0258 [conserved hypothetic...] (173,W)
TP0531 [V-type ATPase, subun...] - TP0383 [conserved hypothetic...] (65,W)
TP0531 [V-type ATPase, subun...] - TP0398 [flagellar hook-basal...] (114,W)
TP0531 [V-type ATPase, subun...] - TP0449 [hypothetical protein...] (51,W)
TP0531 [V-type ATPase, subun...] - TP0518 [conserved hypothetic...] (70,W)
TP0531 [V-type ATPase, subun...] - TP0563 [hypothetical protein...] (93,W)
TP0531 [V-type ATPase, subun...] - TP0661 [hypothetical protein...] (117,W)
TP0531 [V-type ATPase, subun...] - TP0764 [conserved hypothetic...] (139,W)
TP0531 [V-type ATPase, subun...] - TP0907 [conserved hypothetic...] (110,W)
TP0531 [V-type ATPase, subun...] - TP0961 [flagellar basal-body...] (84,W)
TP0531 [V-type ATPase, subun...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0533 [V-type ATPase, subun...] - TP0377 [conserved hypothetic...] (11,F)
TP0533 [V-type ATPase, subun...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0537 [triosephosphate isom...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0538 [phosphoglycerate kin...] - TP0961 [flagellar basal-body...] (84,W)
TP0539 [hypothetical protein...] - TP0397 [flagellar basal-body...] (25,F)
TP0539 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0539 [hypothetical protein...] - TP0687 [DNA recombinase (rec...] (2,F)
TP0539 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0539 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0540 [anti-sigma F factor ...] - TP0288 [spore coat polysacch...] (77,W)
TP0540 [anti-sigma F factor ...] - TP0563 [hypothetical protein...] (93,W)
TP0540 [anti-sigma F factor ...] - TP0661 [hypothetical protein...] (117,W)
TP0540 [anti-sigma F factor ...] - TP0704 [single-stranded-DNA-...] (12,F)
TP0540 [anti-sigma F factor ...] - TP0764 [conserved hypothetic...] (139,W)
TP0540 [anti-sigma F factor ...] - TP0961 [flagellar basal-body...] (84,W)
TP0541 [GTP-binding protein ...] - TP0658 [transmembrane protei...] (5,F)
TP0541 [GTP-binding protein ...] - TP0704 [single-stranded-DNA-...] (12,F)
TP0542 [pyrophosphate--fruct...] - TP0258 [conserved hypothetic...] (173,W)
TP0542 [pyrophosphate--fruct...] - TP0398 [flagellar hook-basal...] (114,W)
TP0542 [pyrophosphate--fruct...] - TP0788 [hypothetical protein...] (132,W)
TP0544 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0544 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0544 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0547 [penicillin tolerance...] - TP0287 [conserved hypothetic...] (27,F)
TP0547 [penicillin tolerance...] - TP0288 [spore coat polysacch...] (77,W)
TP0547 [penicillin tolerance...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0547 [penicillin tolerance...] - TP0449 [hypothetical protein...] (51,W)
TP0547 [penicillin tolerance...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0547 [penicillin tolerance...] - TP0764 [conserved hypothetic...] (139,W)
TP0547 [penicillin tolerance...] - TP0870 [flagellar filament 3...] (79,W)
TP0547 [penicillin tolerance...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0547 [penicillin tolerance...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0547 [penicillin tolerance...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0551 [phosphatase {Trepone...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0552 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0552 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0552 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0552 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0552 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0552 [hypothetical protein...] - TP0397 [flagellar basal-body...] (25,F)
TP0552 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0552 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0552 [hypothetical protein...] - TP0559 [conserved hypothetic...] (26,F)
TP0552 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0552 [hypothetical protein...] - TP0626 [exonuclease, putativ...] (12,F)
TP0552 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0552 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)

TP0552 [hypothetical protein...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0552 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0552 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0552 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0552 [hypothetical protein...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0555 [glutamate/ aspartate...] - TP0561 [conserved hypothetic...] (44,F)
TP0557 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0557 [conserved hypothetic...] - TP0655 [spermidine/putrescin...] (1,F)
TP0557 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0558 [conserved hypothetic...] - TP0234 [ribosomal protein L3...] (1,F)
TP0558 [conserved hypothetic...] - TP0274 [deoxycytidylate deam...] (1,F)
TP0558 [conserved hypothetic...] - TP0561 [conserved hypothetic...] (44,F)
TP0558 [conserved hypothetic...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0559 [conserved hypothetic...] - TP0559 [conserved hypothetic...] (26,F)
TP0561 [conserved hypothetic...] - TP0561 [conserved hypothetic...] (44,F)
TP0561 [conserved hypothetic...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0561 [conserved hypothetic...] - TP0920 [hypothetical protein...] (7,F)
TP0561 [conserved hypothetic...] - TP0985 [aspartyl-tRNA synthe...] (2,F)
TP0562 [spore coat polysacch...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0563 [hypothetical protein...] - TP0014 [hypothetical protein...] (2,F)
TP0563 [hypothetical protein...] - TP0024 [conserved hypothetic...] (16,F)
TP0563 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0563 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0563 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0563 [hypothetical protein...] - TP0341 [UDP-N-acetylmuramate...] (12,F)
TP0563 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0563 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0563 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0563 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0563 [hypothetical protein...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0563 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0563 [hypothetical protein...] - TP0664 [flagellar filament o...] (34,F)
TP0563 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0563 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0563 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0563 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0563 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0563 [hypothetical protein...] - TP0943 [flagellar protein (f...] (15,F)
TP0563 [hypothetical protein...] - TP0946 [glucose-inhibited di...] (19,F)
TP0563 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0563 [hypothetical protein...] - TP0974 [hypothetical protein...] (23,F)
TP0563 [hypothetical protein...] - TP0981 [sensory transduction...] (5,F)
TP0563 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0563 [hypothetical protein...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0563 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0563 [hypothetical protein...] - TP1023 [recX protein (recX) ...] (13,F)
TP0564 [hypothetical protein...] - TP0561 [conserved hypothetic...] (44,F)
TP0564 [hypothetical protein...] - TP0675 [hypothetical protein...] (2,F)
TP0564 [hypothetical protein...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0564 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0565 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0565 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0565 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0567 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0567 [conserved hypothetic...] - TP0421 [conserved hypothetic...] (4,F)
TP0567 [conserved hypothetic...] - TP0675 [hypothetical protein...] (2,F)
TP0567 [conserved hypothetic...] - TP0708 [hypothetical protein...] (13,F)
TP0567 [conserved hypothetic...] - TP0832 [hypothetical protein...] (37,F)
TP0567 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0567 [conserved hypothetic...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0567 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0567 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0571 [Tp70 protein {Trepon...] - TP0059 [hypothetical protein...] (21,F)
TP0571 [Tp70 protein {Trepon...] - TP0060 [ribosomal protein L9...] (78,W)
TP0571 [Tp70 protein {Trepon...] - TP0281 [hypothetical protein...] (64,W)
TP0571 [Tp70 protein {Trepon...] - TP0398 [flagellar hook-basal...] (114,W)
TP0571 [Tp70 protein {Trepon...] - TP0711 [conserved hypothetic...] (46,F)
TP0573 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0573 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0573 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0578 [cell division protei...] - TP0046 [hypothetical protein...] (18,F)
TP0578 [cell division protei...] - TP0066 [hypothetical protein...] (11,F)
TP0578 [cell division protei...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0578 [cell division protei...] - TP0258 [conserved hypothetic...] (173,W)
TP0578 [cell division protei...] - TP0288 [spore coat polysacch...] (77,W)
TP0578 [cell division protei...] - TP0380 [DNA repair helicase,...] (5,F)
TP0578 [cell division protei...] - TP0563 [hypothetical protein...] (93,W)
TP0578 [cell division protei...] - TP0764 [conserved hypothetic...] (139,W)
TP0578 [cell division protei...] - TP0788 [hypothetical protein...] (132,W)
TP0578 [cell division protei...] - TP0832 [hypothetical protein...] (37,F)
TP0578 [cell division protei...] - TP0870 [flagellar filament 3...] (79,W)
TP0578 [cell division protei...] - TP0907 [conserved hypothetic...] (110,W)
TP0578 [cell division protei...] - TP0961 [flagellar basal-body...] (84,W)
TP0578 [cell division protei...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0578 [cell division protei...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0579 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0580 [conserved hypothetic...] - TP0099 [uridylate kinase (sm...] (3,F)
TP0582 [conserved hypothetic...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0582 [conserved hypothetic...] - TP0342 [cytidylate kinase (c...] (1,F)
TP0582 [conserved hypothetic...] - TP0368 [hypothetical protein...] (1,F)
TP0582 [conserved hypothetic...] - TP0397 [flagellar basal-body...] (25,F)
TP0582 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0582 [conserved hypothetic...] - TP0685 [methylgalactoside AB...] (1,F)
TP0582 [conserved hypothetic...] - TP0698 [hypothetical protein...] (1,F)
TP0582 [conserved hypothetic...] - TP0765 [cell division protei...] (2,F)
TP0582 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0582 [conserved hypothetic...] - TP0965 [membrane fusion prot...] (14,F)
TP0582 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0582 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0582 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0582 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0583 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0583 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0583 [hypothetical protein...] - TP0396 [flagellar basal-body...] (15,F)
TP0583 [hypothetical protein...] - TP0397 [flagellar basal-body...] (25,F)
TP0583 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0583 [hypothetical protein...] - TP0587 [hypothetical protein...] (23,F)
TP0583 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0583 [hypothetical protein...] - TP0664 [flagellar filament o...] (34,F)
TP0583 [hypothetical protein...] - TP0741 [conserved hypothetic...] (8,F)
TP0583 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0583 [hypothetical protein...] - TP0773 [periplasmic serine p...] (30,F)
TP0583 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0586 [leucyl-tRNA syntheta...] - TP0060 [ribosomal protein L9...] (78,W)
TP0586 [leucyl-tRNA syntheta...] - TP0258 [conserved hypothetic...] (173,W)
TP0586 [leucyl-tRNA syntheta...] - TP0281 [hypothetical protein...] (64,W)
TP0586 [leucyl-tRNA syntheta...] - TP0397 [flagellar basal-body...] (25,F)
TP0586 [leucyl-tRNA syntheta...] - TP0449 [hypothetical protein...] (51,W)
TP0586 [leucyl-tRNA syntheta...] - TP0870 [flagellar filament 3...] (79,W)
TP0586 [leucyl-tRNA syntheta...] - TP0907 [conserved hypothetic...] (110,W)
TP0586 [leucyl-tRNA syntheta...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0587 [hypothetical protein...] - TP0587 [hypothetical protein...] (23,F)
TP0587 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0587 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0587 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0588 [conserved hypothetic...] - TP0120 [amino acid ABC trans...] (1,F)
TP0588 [conserved hypothetic...] - TP0134 [hypothetical protein...] (1,F)
TP0588 [conserved hypothetic...] - TP0148 [hypothetical protein...] (1,F)
TP0588 [conserved hypothetic...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0588 [conserved hypothetic...] - TP0483 [hypothetical protein...] (1,F)
TP0588 [conserved hypothetic...] - TP0676 [hypothetical protein...] (2,F)
TP0588 [conserved hypothetic...] - TP0678 [hypothetical protein...] (1,F)
TP0588 [conserved hypothetic...] - TP0948 [spoIIIJ-associated p...] (1,F)
TP0589 [phosphocarrier prote...] - TP0398 [flagellar hook-basal...] (114,W)
TP0589 [phosphocarrier prote...] - TP0576 [peptide chain releas...] (1,F)
TP0589 [phosphocarrier prote...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0591 [HPr kinase (ptsK) {B...] - TP0257 [glycerophosphodieste...] (3,F)
TP0591 [HPr kinase (ptsK) {B...] - TP0286 [conserved hypothetic...] (9,F)
TP0591 [HPr kinase (ptsK) {B...] - TP0449 [hypothetical protein...] (51,W)
TP0591 [HPr kinase (ptsK) {B...] - TP0661 [hypothetical protein...] (117,W)
TP0591 [HPr kinase (ptsK) {B...] - TP0870 [flagellar filament 3...] (79,W)
TP0591 [HPr kinase (ptsK) {B...] - TP0939 [pyruvate oxidoreduct...] (12,F)
TP0592 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0592 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0592 [hypothetical protein...] - TP0583 [hypothetical protein...] (1,F)
TP0593 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0593 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0593 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0593 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0593 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0593 [hypothetical protein...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0593 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0597 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0597 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0597 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0597 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0597 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0597 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0597 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0597 [hypothetical protein...] - TP0974 [hypothetical protein...] (23,F)
TP0597 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0597 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0597 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0598 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0598 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0598 [hypothetical protein...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0600 [zinc protease, putat...] - TP0561 [conserved hypothetic...] (44,F)
TP0603 [conserved hypothetic...] - TP0111 [RNA polymerase sigma...] (1,F)
TP0603 [conserved hypothetic...] - TP0284 [hypothetical protein...] (1,F)
TP0603 [conserved hypothetic...] - TP0424 [V-type ATPase, subun...] (1,F)
TP0604 [ribosome recycling f...] - TP0060 [ribosomal protein L9...] (78,W)
TP0604 [ribosome recycling f...] - TP0214 [hypothetical protein...] (2,F)
TP0604 [ribosome recycling f...] - TP0258 [conserved hypothetic...] (173,W)
TP0604 [ribosome recycling f...] - TP0288 [spore coat polysacch...] (77,W)
TP0604 [ribosome recycling f...] - TP0398 [flagellar hook-basal...] (114,W)
TP0604 [ribosome recycling f...] - TP0449 [hypothetical protein...] (51,W)
TP0604 [ribosome recycling f...] - TP0563 [hypothetical protein...] (93,W)
TP0604 [ribosome recycling f...] - TP0771 [conserved hypothetic...] (1,F)
TP0604 [ribosome recycling f...] - TP0788 [hypothetical protein...] (132,W)
TP0607 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)

TP0610 [tpr protein H (tprH)...] - TP0209 [ribosomal protein L3...] (27,F)
TP0611 [ABC transporter, ATP...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0612 [conserved hypothetic...] - TP0209 [ribosomal protein L3...] (27,F)
TP0612 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0615 [nitrogen fixation pr...] - TP0258 [conserved hypothetic...] (173,W)
TP0615 [nitrogen fixation pr...] - TP0563 [hypothetical protein...] (93,W)
TP0615 [nitrogen fixation pr...] - TP0661 [hypothetical protein...] (117,W)
TP0615 [nitrogen fixation pr...] - TP0788 [hypothetical protein...] (132,W)
TP0615 [nitrogen fixation pr...] - TP0907 [conserved hypothetic...] (110,W)
TP0615 [nitrogen fixation pr...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0615 [nitrogen fixation pr...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0617 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0621 [tpr protein J (tprJ)...] - TP0258 [conserved hypothetic...] (173,W)
TP0622 [hypothetical protein...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0622 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0622 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0622 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0622 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0622 [hypothetical protein...] - TP0519 [response regulatory ...] (30,F)
TP0622 [hypothetical protein...] - TP0641 [histidyl-tRNA synthe...] (9,F)
TP0622 [hypothetical protein...] - TP0660 [flagellar hook-assoc...] (4,F)
TP0622 [hypothetical protein...] - TP0684 [methylgalactoside AB...] (15,F)
TP0622 [hypothetical protein...] - TP0704 [single-stranded-DNA-...] (12,F)
TP0622 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0622 [hypothetical protein...] - TP0751 [hypothetical protein...] (7,F)
TP0622 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0624 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0625 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0626 [exonuclease, putativ...] - TP0258 [conserved hypothetic...] (173,W)
TP0626 [exonuclease, putativ...] - TP0661 [hypothetical protein...] (117,W)
TP0626 [exonuclease, putativ...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0627 [exonuclease (sbcC) {...] - TP0561 [conserved hypothetic...] (44,F)
TP0627 [exonuclease (sbcC) {...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0628 [conserved hypothetic...] - TP0176 [hypothetical protein...] (1,F)
TP0628 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0628 [conserved hypothetic...] - TP0314 [hypothetical protein...] (2,F)
TP0628 [conserved hypothetic...] - TP0413 [phosphoglucomutase {...] (2,F)
TP0628 [conserved hypothetic...] - TP0515 [conserved hypothetic...] (1,F)
TP0628 [conserved hypothetic...] - TP0677 [hypothetical protein...] (2,F)
TP0628 [conserved hypothetic...] - TP0735 [glutamate synthase (...] (2,F)
TP0628 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0628 [conserved hypothetic...] - TP0894 [conserved hypothetic...] (13,F)
TP0628 [conserved hypothetic...] - TP0987 [hypothetical protein...] (2,F)
TP0628 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0628 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0628 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0628 [conserved hypothetic...] - TP1039 [adenine phosphoribos...] (1,F)
TP0630 [chemotaxis protein m...] - TP0026 [flagellar motor swit...] (8,F)
TP0630 [chemotaxis protein m...] - TP0046 [hypothetical protein...] (18,F)
TP0630 [chemotaxis protein m...] - TP0064 [hypothetical, protei...] (8,F)
TP0630 [chemotaxis protein m...] - TP0088 [conserved hypothetic...] (8,F)
TP0630 [chemotaxis protein m...] - TP0092 [RNA polymerase sigma...] (10,F)
TP0630 [chemotaxis protein m...] - TP0121 [conserved hypothetic...] (7,F)
TP0630 [chemotaxis protein m...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0630 [chemotaxis protein m...] - TP0162 [Holliday junction DN...] (3,F)
TP0630 [chemotaxis protein m...] - TP0209 [ribosomal protein L3...] (27,F)
TP0630 [chemotaxis protein m...] - TP0288 [spore coat polysacch...] (77,W)
TP0630 [chemotaxis protein m...] - TP0305 [CTP synthase (pyrG) ...] (4,F)
TP0630 [chemotaxis protein m...] - TP0330 [cell division protei...] (2,F)
TP0630 [chemotaxis protein m...] - TP0396 [flagellar basal-body...] (15,F)
TP0630 [chemotaxis protein m...] - TP0398 [flagellar hook-basal...] (114,W)
TP0630 [chemotaxis protein m...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0630 [chemotaxis protein m...] - TP0764 [conserved hypothetic...] (139,W)
TP0630 [chemotaxis protein m...] - TP0832 [hypothetical protein...] (37,F)
TP0630 [chemotaxis protein m...] - TP0851 [hypothetical protein...] (1,F)
TP0630 [chemotaxis protein m...] - TP0870 [flagellar filament 3...] (79,W)
TP0630 [chemotaxis protein m...] - TP0877 [conserved hypothetic...] (4,F)
TP0630 [chemotaxis protein m...] - TP0961 [flagellar basal-body...] (84,W)
TP0630 [chemotaxis protein m...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0630 [chemotaxis protein m...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0630 [chemotaxis protein m...] - TP1004 [recombination protei...] (74,W)
TP0630 [chemotaxis protein m...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0631 [protein-glutamate me...] - TP0258 [conserved hypothetic...] (173,W)
TP0631 [protein-glutamate me...] - TP0288 [spore coat polysacch...] (77,W)
TP0631 [protein-glutamate me...] - TP0764 [conserved hypothetic...] (139,W)
TP0631 [protein-glutamate me...] - TP0832 [hypothetical protein...] (37,F)
TP0631 [protein-glutamate me...] - TP0961 [flagellar basal-body...] (84,W)
TP0631 [protein-glutamate me...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0632 [tryptophanyl-tRNA sy...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0634 [DNA ligase (lig) {Th...] - TP0060 [ribosomal protein L9...] (78,W)
TP0634 [DNA ligase (lig) {Th...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0634 [DNA ligase (lig) {Th...] - TP0258 [conserved hypothetic...] (173,W)
TP0634 [DNA ligase (lig) {Th...] - TP0341 [UDP-N-acetylmuramate...] (12,F)
TP0634 [DNA ligase (lig) {Th...] - TP0461 [hypothetical protein...] (3,F)
TP0634 [DNA ligase (lig) {Th...] - TP0514 [excinuclease ABC, su...] (7,F)
TP0634 [DNA ligase (lig) {Th...] - TP0519 [response regulatory ...] (30,F)
TP0634 [DNA ligase (lig) {Th...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0634 [DNA ligase (lig) {Th...] - TP0618 [hypothetical protein...] (24,F)
TP0634 [DNA ligase (lig) {Th...] - TP0661 [hypothetical protein...] (117,W)
TP0634 [DNA ligase (lig) {Th...] - TP0684 [methylgalactoside AB...] (15,F)
TP0634 [DNA ligase (lig) {Th...] - TP0711 [conserved hypothetic...] (46,F)
TP0634 [DNA ligase (lig) {Th...] - TP0757 [polypeptide deformyl...] (36,F)
TP0634 [DNA ligase (lig) {Th...] - TP0939 [pyruvate oxidoreduct...] (12,F)
TP0634 [DNA ligase (lig) {Th...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0636 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0636 [conserved hypothetic...] - TP0773 [periplasmic serine p...] (30,F)
TP0636 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0637 [tRNA delta(2)-isopen...] - TP0060 [ribosomal protein L9...] (78,W)
TP0637 [tRNA delta(2)-isopen...] - TP0397 [flagellar basal-body...] (25,F)
TP0637 [tRNA delta(2)-isopen...] - TP0398 [flagellar hook-basal...] (114,W)
TP0637 [tRNA delta(2)-isopen...] - TP0870 [flagellar filament 3...] (79,W)
TP0638 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0640 [methyl-accepting che...] - TP0064 [hypothetical, protei...] (8,F)
TP0640 [methyl-accepting che...] - TP0088 [conserved hypothetic...] (8,F)
TP0640 [methyl-accepting che...] - TP0288 [spore coat polysacch...] (77,W)
TP0640 [methyl-accepting che...] - TP0397 [flagellar basal-body...] (25,F)
TP0640 [methyl-accepting che...] - TP0764 [conserved hypothetic...] (139,W)
TP0640 [methyl-accepting che...] - TP0832 [hypothetical protein...] (37,F)
TP0641 [histidyl-tRNA synthe...] - TP0258 [conserved hypothetic...] (173,W)
TP0641 [histidyl-tRNA synthe...] - TP0383 [conserved hypothetic...] (65,W)
TP0641 [histidyl-tRNA synthe...] - TP0398 [flagellar hook-basal...] (114,W)
TP0641 [histidyl-tRNA synthe...] - TP0518 [conserved hypothetic...] (70,W)
TP0641 [histidyl-tRNA synthe...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0641 [histidyl-tRNA synthe...] - TP0641 [histidyl-tRNA synthe...] (9,F)
TP0641 [histidyl-tRNA synthe...] - TP0704 [single-stranded-DNA-...] (12,F)
TP0641 [histidyl-tRNA synthe...] - TP0764 [conserved hypothetic...] (139,W)
TP0641 [histidyl-tRNA synthe...] - TP0788 [hypothetical protein...] (132,W)
TP0641 [histidyl-tRNA synthe...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0642 [phosphomannomutase (...] - TP0060 [ribosomal protein L9...] (78,W)
TP0642 [phosphomannomutase (...] - TP0449 [hypothetical protein...] (51,W)
TP0643 [DNA polymerase III, ...] - TP0397 [flagellar basal-body...] (25,F)
TP0644 [lysyl-tRNA synthetas...] - TP0661 [hypothetical protein...] (117,W)
TP0644 [lysyl-tRNA synthetas...] - TP0664 [flagellar filament o...] (34,F)
TP0647 [seryl-tRNA synthetas...] - TP0563 [hypothetical protein...] (93,W)
TP0647 [seryl-tRNA synthetas...] - TP0788 [hypothetical protein...] (132,W)
TP0648 [conserved hypothetic...] - TP0024 [conserved hypothetic...] (16,F)
TP0648 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0648 [conserved hypothetic...] - TP0095 [hypothetical protein...] (15,F)
TP0648 [conserved hypothetic...] - TP0197 [ribosomal protein L2...] (15,F)
TP0648 [conserved hypothetic...] - TP0209 [ribosomal protein L3...] (27,F)
TP0648 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0648 [conserved hypothetic...] - TP0341 [UDP-N-acetylmuramate...] (12,F)
TP0648 [conserved hypothetic...] - TP0354 [thymidylate kinase (...] (8,F)
TP0648 [conserved hypothetic...] - TP0443 [conserved hypothetic...] (6,F)
TP0648 [conserved hypothetic...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0648 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0648 [conserved hypothetic...] - TP0461 [hypothetical protein...] (3,F)
TP0648 [conserved hypothetic...] - TP0513 [K+ transport protein...] (4,F)
TP0648 [conserved hypothetic...] - TP0514 [excinuclease ABC, su...] (7,F)
TP0648 [conserved hypothetic...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0648 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0648 [conserved hypothetic...] - TP0582 [conserved hypothetic...] (1,F)
TP0648 [conserved hypothetic...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0648 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0648 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0648 [conserved hypothetic...] - TP0894 [conserved hypothetic...] (13,F)
TP0648 [conserved hypothetic...] - TP0895 [hypothetical protein...] (3,F)
TP0648 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0648 [conserved hypothetic...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0648 [conserved hypothetic...] - TP0939 [pyruvate oxidoreduct...] (12,F)
TP0648 [conserved hypothetic...] - TP0943 [flagellar protein (f...] (15,F)
TP0648 [conserved hypothetic...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0648 [conserved hypothetic...] - TP0965 [membrane fusion prot...] (14,F)
TP0648 [conserved hypothetic...] - TP0974 [hypothetical protein...] (23,F)
TP0648 [conserved hypothetic...] - TP0981 [sensory transduction...] (5,F)
TP0648 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0648 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0648 [conserved hypothetic...] - TP0997 [protease IV (sppA) {...] (8,F)
TP0648 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0648 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0648 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0649 [hemolysin (tlyC) {Bo...] - TP0258 [conserved hypothetic...] (173,W)
TP0649 [hemolysin (tlyC) {Bo...] - TP0398 [flagellar hook-basal...] (114,W)
TP0649 [hemolysin (tlyC) {Bo...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0649 [hemolysin (tlyC) {Bo...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0650 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0650 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0650 [conserved hypothetic...] - TP0681 [alanine racemase (al...] (1,F)
TP0650 [conserved hypothetic...] - TP0757 [polypeptide deformyl...] (36,F)
TP0650 [conserved hypothetic...] - TP0807 [ribosomal protein L3...] (4,F)
TP0650 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0651 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0651 [conserved hypothetic...] - TP0156 [conserved hypothetic...] (1,F)
TP0651 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0651 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0651 [conserved hypothetic...] - TP0397 [flagellar basal-body...] (25,F)
TP0651 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0651 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0651 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0651 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)

TP0651 [conserved hypothetic...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0651 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0651 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0651 [conserved hypothetic...] - TP0894 [conserved hypothetic...] (13,F)
TP0651 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0651 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0651 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0651 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0651 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0653 [spermidine/putrescin...] - TP0398 [flagellar hook-basal...] (114,W)
TP0653 [spermidine/putrescin...] - TP0561 [conserved hypothetic...] (44,F)
TP0653 [spermidine/putrescin...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0654 [spermidine/putrescin...] - TP0397 [flagellar basal-body...] (25,F)
TP0655 [spermidine/putrescin...] - TP0281 [hypothetical protein...] (64,W)
TP0655 [spermidine/putrescin...] - TP0397 [flagellar basal-body...] (25,F)
TP0655 [spermidine/putrescin...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0655 [spermidine/putrescin...] - TP0449 [hypothetical protein...] (51,W)
TP0655 [spermidine/putrescin...] - TP0661 [hypothetical protein...] (117,W)
TP0655 [spermidine/putrescin...] - TP0741 [conserved hypothetic...] (8,F)
TP0655 [spermidine/putrescin...] - TP0870 [flagellar filament 3...] (79,W)
TP0655 [spermidine/putrescin...] - TP0907 [conserved hypothetic...] (110,W)
TP0656 [hypothetical protein...] - TP0059 [hypothetical protein...] (21,F)
TP0656 [hypothetical protein...] - TP0067 [conserved hypothetic...] (19,F)
TP0656 [hypothetical protein...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0656 [hypothetical protein...] - TP0180 [hypothetical protein...] (1,F)
TP0656 [hypothetical protein...] - TP0197 [ribosomal protein L2...] (15,F)
TP0656 [hypothetical protein...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0656 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0656 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0656 [hypothetical protein...] - TP0286 [conserved hypothetic...] (9,F)
TP0656 [hypothetical protein...] - TP0287 [conserved hypothetic...] (27,F)
TP0656 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0656 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0656 [hypothetical protein...] - TP0443 [conserved hypothetic...] (6,F)
TP0656 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0656 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0656 [hypothetical protein...] - TP0519 [response regulatory ...] (30,F)
TP0656 [hypothetical protein...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0656 [hypothetical protein...] - TP0587 [hypothetical protein...] (23,F)
TP0656 [hypothetical protein...] - TP0618 [hypothetical protein...] (24,F)
TP0656 [hypothetical protein...] - TP0641 [histidyl-tRNA synthe...] (9,F)
TP0656 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0656 [hypothetical protein...] - TP0664 [flagellar filament o...] (34,F)
TP0656 [hypothetical protein...] - TP0741 [conserved hypothetic...] (8,F)
TP0656 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0656 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0656 [hypothetical protein...] - TP0773 [periplasmic serine p...] (30,F)
TP0656 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0656 [hypothetical protein...] - TP0894 [conserved hypothetic...] (13,F)
TP0656 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0656 [hypothetical protein...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0656 [hypothetical protein...] - TP0946 [glucose-inhibited di...] (19,F)
TP0656 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0656 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0656 [hypothetical protein...] - TP0995 [cyclic nucleotide bi...] (5,F)
TP0656 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0657 [carbon storage regul...] - TP0226 [hypothetical protein...] (1,F)
TP0657 [carbon storage regul...] - TP0258 [conserved hypothetic...] (173,W)
TP0657 [carbon storage regul...] - TP0518 [conserved hypothetic...] (70,W)
TP0658 [transmembrane protei...] - TP0620 [tpr protein I (tprI)...] (1,F)
TP0658 [transmembrane protei...] - TP0736 [hydrogenase, gamma c...] (1,F)
TP0658 [transmembrane protei...] - TP0831 [arginyl-tRNA synthet...] (1,F)
TP0658 [transmembrane protei...] - TP0939 [pyruvate oxidoreduct...] (12,F)
TP0658 [transmembrane protei...] - TP0941 [hypothetical protein...] (1,F)
TP0658 [transmembrane protei...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0659 [flagellar hook-assoc...] - TP0002 [DNA polymerase III, ...] (4,F)
TP0659 [flagellar hook-assoc...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0659 [flagellar hook-assoc...] - TP0258 [conserved hypothetic...] (173,W)
TP0659 [flagellar hook-assoc...] - TP0563 [hypothetical protein...] (93,W)
TP0659 [flagellar hook-assoc...] - TP0726 [flagellar protein (f...] (7,F)
TP0659 [flagellar hook-assoc...] - TP0764 [conserved hypothetic...] (139,W)
TP0659 [flagellar hook-assoc...] - TP0788 [hypothetical protein...] (132,W)
TP0659 [flagellar hook-assoc...] - TP0832 [hypothetical protein...] (37,F)
TP0659 [flagellar hook-assoc...] - TP0907 [conserved hypothetic...] (110,W)
TP0659 [flagellar hook-assoc...] - TP0961 [flagellar basal-body...] (84,W)
TP0659 [flagellar hook-assoc...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0659 [flagellar hook-assoc...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0659 [flagellar hook-assoc...] - TP1004 [recombination protei...] (74,W)
TP0660 [flagellar hook-assoc...] - TP0024 [conserved hypothetic...] (16,F)
TP0660 [flagellar hook-assoc...] - TP0060 [ribosomal protein L9...] (78,W)
TP0660 [flagellar hook-assoc...] - TP0067 [conserved hypothetic...] (19,F)
TP0660 [flagellar hook-assoc...] - TP0258 [conserved hypothetic...] (173,W)
TP0660 [flagellar hook-assoc...] - TP0288 [spore coat polysacch...] (77,W)
TP0660 [flagellar hook-assoc...] - TP0383 [conserved hypothetic...] (65,W)
TP0660 [flagellar hook-assoc...] - TP0398 [flagellar hook-basal...] (114,W)
TP0660 [flagellar hook-assoc...] - TP0465 [hypothetical protein...] (7,F)
TP0660 [flagellar hook-assoc...] - TP0518 [conserved hypothetic...] (70,W)
TP0660 [flagellar hook-assoc...] - TP0563 [hypothetical protein...] (93,W)
TP0660 [flagellar hook-assoc...] - TP0626 [exonuclease, putativ...] (12,F)
TP0660 [flagellar hook-assoc...] - TP0661 [hypothetical protein...] (117,W)
TP0660 [flagellar hook-assoc...] - TP0788 [hypothetical protein...] (132,W)
TP0661 [hypothetical protein...] - TP0024 [conserved hypothetic...] (16,F)
TP0661 [hypothetical protein...] - TP0059 [hypothetical protein...] (21,F)
TP0661 [hypothetical protein...] - TP0121 [conserved hypothetic...] (7,F)
TP0661 [hypothetical protein...] - TP0188 [ribosomal protein S1...] (2,F)
TP0661 [hypothetical protein...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0661 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0661 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0661 [hypothetical protein...] - TP0286 [conserved hypothetic...] (9,F)
TP0661 [hypothetical protein...] - TP0287 [conserved hypothetic...] (27,F)
TP0661 [hypothetical protein...] - TP0354 [thymidylate kinase (...] (8,F)
TP0661 [hypothetical protein...] - TP0359 [hypothetical protein...] (2,F)
TP0661 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0661 [hypothetical protein...] - TP0397 [flagellar basal-body...] (25,F)
TP0661 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0661 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0661 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0661 [hypothetical protein...] - TP0513 [K+ transport protein...] (4,F)
TP0661 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0661 [hypothetical protein...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0661 [hypothetical protein...] - TP0559 [conserved hypothetic...] (26,F)
TP0661 [hypothetical protein...] - TP0587 [hypothetical protein...] (23,F)
TP0661 [hypothetical protein...] - TP0618 [hypothetical protein...] (24,F)
TP0661 [hypothetical protein...] - TP0626 [exonuclease, putativ...] (12,F)
TP0661 [hypothetical protein...] - TP0660 [flagellar hook-assoc...] (4,F)
TP0661 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0661 [hypothetical protein...] - TP0664 [flagellar filament o...] (34,F)
TP0661 [hypothetical protein...] - TP0684 [methylgalactoside AB...] (15,F)
TP0661 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0661 [hypothetical protein...] - TP0741 [conserved hypothetic...] (8,F)
TP0661 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0661 [hypothetical protein...] - TP0773 [periplasmic serine p...] (30,F)
TP0661 [hypothetical protein...] - TP0803 [hypothetical protein...] (2,F)
TP0661 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0661 [hypothetical protein...] - TP0932 [hypothetical protein...] (1,F)
TP0661 [hypothetical protein...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0661 [hypothetical protein...] - TP0946 [glucose-inhibited di...] (19,F)
TP0661 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0661 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0661 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0662 [fructose-bisphosphat...] - TP0398 [flagellar hook-basal...] (114,W)
TP0662 [fructose-bisphosphat...] - TP0870 [flagellar filament 3...] (79,W)
TP0662 [fructose-bisphosphat...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0662 [fructose-bisphosphat...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0663 [outer membrane prote...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0664 [flagellar filament o...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0664 [flagellar filament o...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0664 [flagellar filament o...] - TP0258 [conserved hypothetic...] (173,W)
TP0664 [flagellar filament o...] - TP0764 [conserved hypothetic...] (139,W)
TP0664 [flagellar filament o...] - TP0961 [flagellar basal-body...] (84,W)
TP0664 [flagellar filament o...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0666 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0668 [conserved hypothetic...] - TP0561 [conserved hypothetic...] (44,F)
TP0668 [conserved hypothetic...] - TP0751 [hypothetical protein...] (7,F)
TP0668 [conserved hypothetic...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0669 [DNA polymerase III, ...] - TP0398 [flagellar hook-basal...] (114,W)
TP0669 [DNA polymerase III, ...] - TP0518 [conserved hypothetic...] (70,W)
TP0670 [D-alanine--D-alanine...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0671 [sn-1,2-diacylglycero...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0673 [glutamyl-tRNA synthe...] - TP0258 [conserved hypothetic...] (173,W)
TP0673 [glutamyl-tRNA synthe...] - TP0788 [hypothetical protein...] (132,W)
TP0676 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0676 [hypothetical protein...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0676 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0676 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0676 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0676 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0676 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0676 [hypothetical protein...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0679 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0679 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0679 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0679 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0679 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0679 [hypothetical protein...] - TP0833 [hypothetical protein...] (34,F)
TP0679 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0679 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0679 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0679 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0686 [methylgalactoside AB...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0686 [methylgalactoside AB...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0687 [DNA recombinase (rec...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0687 [DNA recombinase (rec...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0687 [DNA recombinase (rec...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0688 [immunity protein (mc...] - TP0060 [ribosomal protein L9...] (78,W)
TP0688 [immunity protein (mc...] - TP0258 [conserved hypothetic...] (173,W)
TP0688 [immunity protein (mc...] - TP0281 [hypothetical protein...] (64,W)
TP0688 [immunity protein (mc...] - TP0398 [flagellar hook-basal...] (114,W)
TP0688 [immunity protein (mc...] - TP0618 [hypothetical protein...] (24,F)
TP0688 [immunity protein (mc...] - TP0757 [polypeptide deformyl...] (36,F)

TP0688 [immunity protein (mc...] - TP0764 [conserved hypothetic...] (139,W)
TP0688 [immunity protein (mc...] - TP0788 [hypothetical protein...] (132,W)
TP0688 [immunity protein (mc...] - TP0974 [hypothetical protein...] (23,F)
TP0688 [immunity protein (mc...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0688 [immunity protein (mc...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0690 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0691 [conserved hypothetic...] - TP0197 [ribosomal protein L2...] (15,F)
TP0691 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0691 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0691 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0691 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0693 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0694 [5,10-methenyltetrahy...] - TP0833 [hypothetical protein...] (34,F)
TP0694 [5,10-methenyltetrahy...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0695 [phosphoribosylglycin...] - TP0661 [hypothetical protein...] (117,W)
TP0695 [phosphoribosylglycin...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0696 [nicotinamidase, puta...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0699 [hypothetical protein...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0699 [hypothetical protein...] - TP0833 [hypothetical protein...] (34,F)
TP0699 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0699 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0699 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0700 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0700 [hypothetical protein...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0700 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0700 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0700 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0700 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0700 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0700 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0700 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0702 [conserved hypothetic...] - TP0269 [conserved hypothetic...] (3,F)
TP0702 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0706 [conserved hypothetic...] - TP0519 [response regulatory ...] (30,F)
TP0706 [conserved hypothetic...] - TP0664 [flagellar filament o...] (34,F)
TP0706 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0706 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0708 [hypothetical protein...] - TP0036 [ABC transporter, per...] (1,F)
TP0708 [hypothetical protein...] - TP0561 [conserved hypothetic...] (44,F)
TP0708 [hypothetical protein...] - TP0708 [hypothetical protein...] (13,F)
TP0708 [hypothetical protein...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0709 [RNA polymerase sigma...] - TP0974 [hypothetical protein...] (23,F)
TP0711 [conserved hypothetic...] - TP0126 [hypothetical protein...] (1,F)
TP0713 [flagellar-associated...] - TP0711 [conserved hypothetic...] (46,F)
TP0713 [flagellar-associated...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0714 [flagellar biosynthes...] - TP0377 [conserved hypothetic...] (11,F)
TP0714 [flagellar biosynthes...] - TP0708 [hypothetical protein...] (13,F)
TP0715 [flagellar biosynthet...] - TP0561 [conserved hypothetic...] (44,F)
TP0715 [flagellar biosynthet...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0716 [flagellar biosynthet...] - TP0561 [conserved hypothetic...] (44,F)
TP0716 [flagellar biosynthet...] - TP0725 [flagellar motor rota...] (2,F)
TP0716 [flagellar biosynthet...] - TP0774 [Mg2+ transport prote...] (2,F)
TP0716 [flagellar biosynthet...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0717 [flagellar biosynthet...] - TP0561 [conserved hypothetic...] (44,F)
TP0717 [flagellar biosynthet...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0719 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0720 [flagellar motor swit...] - TP0026 [flagellar motor swit...] (8,F)
TP0720 [flagellar motor swit...] - TP0048 [conserved hypothetic...] (1,F)
TP0720 [flagellar motor swit...] - TP0066 [hypothetical protein...] (11,F)
TP0720 [flagellar motor swit...] - TP0088 [conserved hypothetic...] (8,F)
TP0720 [flagellar motor swit...] - TP0100 [thioredoxin, putativ...] (3,F)
TP0720 [flagellar motor swit...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0720 [flagellar motor swit...] - TP0193 [ribosomal protein S1...] (1,F)
TP0720 [flagellar motor swit...] - TP0209 [ribosomal protein L3...] (27,F)
TP0720 [flagellar motor swit...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0720 [flagellar motor swit...] - TP0258 [conserved hypothetic...] (173,W)
TP0720 [flagellar motor swit...] - TP0287 [conserved hypothetic...] (27,F)
TP0720 [flagellar motor swit...] - TP0288 [spore coat polysacch...] (77,W)
TP0720 [flagellar motor swit...] - TP0397 [flagellar basal-body...] (25,F)
TP0720 [flagellar motor swit...] - TP0563 [hypothetical protein...] (93,W)
TP0720 [flagellar motor swit...] - TP0579 [hypothetical protein...] (5,F)
TP0720 [flagellar motor swit...] - TP0629 [hypothetical protein...] (6,F)
TP0720 [flagellar motor swit...] - TP0660 [flagellar hook-assoc...] (4,F)
TP0720 [flagellar motor swit...] - TP0700 [hypothetical protein...] (1,F)
TP0720 [flagellar motor swit...] - TP0764 [conserved hypothetic...] (139,W)
TP0720 [flagellar motor swit...] - TP0772 [hypothetical protein...] (3,F)
TP0720 [flagellar motor swit...] - TP0782 [hypothetical protein...] (2,F)
TP0720 [flagellar motor swit...] - TP0788 [hypothetical protein...] (132,W)
TP0720 [flagellar motor swit...] - TP0832 [hypothetical protein...] (37,F)
TP0720 [flagellar motor swit...] - TP0833 [hypothetical protein...] (34,F)
TP0720 [flagellar motor swit...] - TP0843 [heat shock protein, ...] (3,F)
TP0720 [flagellar motor swit...] - TP0870 [flagellar filament 3...] (79,W)
TP0720 [flagellar motor swit...] - TP0907 [conserved hypothetic...] (110,W)
TP0720 [flagellar motor swit...] - TP0961 [flagellar basal-body...] (84,W)
TP0720 [flagellar motor swit...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0720 [flagellar motor swit...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0720 [flagellar motor swit...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0721 [flagellar motor swit...] - TP0026 [flagellar motor swit...] (8,F)
TP0721 [flagellar motor swit...] - TP0066 [hypothetical protein...] (11,F)
TP0721 [flagellar motor swit...] - TP0092 [RNA polymerase sigma...] (10,F)
TP0721 [flagellar motor swit...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0722 [flagellar protein (f...] - TP0260 [hypothetical protein...] (5,F)
TP0722 [flagellar protein (f...] - TP0561 [conserved hypothetic...] (44,F)
TP0722 [flagellar protein (f...] - TP0832 [hypothetical protein...] (37,F)
TP0722 [flagellar protein (f...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0724 [flagellar motor rota...] - TP0832 [hypothetical protein...] (37,F)
TP0724 [flagellar motor rota...] - TP0961 [flagellar basal-body...] (84,W)
TP0725 [flagellar motor rota...] - TP0725 [flagellar motor rota...] (2,F)
TP0725 [flagellar motor rota...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0727 [flagellar hook prote...] - TP0209 [ribosomal protein L3...] (27,F)
TP0727 [flagellar hook prote...] - TP0292 [outer membrane prote...] (1,F)
TP0728 [flagellar hook assem...] - TP0005 [DNA gyrase, subunit ...] (9,F)
TP0728 [flagellar hook assem...] - TP0046 [hypothetical protein...] (18,F)
TP0728 [flagellar hook assem...] - TP0050 [conserved hypothetic...] (10,F)
TP0728 [flagellar hook assem...] - TP0100 [thioredoxin, putativ...] (3,F)
TP0728 [flagellar hook assem...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0728 [flagellar hook assem...] - TP0258 [conserved hypothetic...] (173,W)
TP0728 [flagellar hook assem...] - TP0396 [flagellar basal-body...] (15,F)
TP0728 [flagellar hook assem...] - TP0398 [flagellar hook-basal...] (114,W)
TP0728 [flagellar hook assem...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0728 [flagellar hook assem...] - TP0563 [hypothetical protein...] (93,W)
TP0728 [flagellar hook assem...] - TP0579 [hypothetical protein...] (5,F)
TP0728 [flagellar hook assem...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0728 [flagellar hook assem...] - TP0629 [hypothetical protein...] (6,F)
TP0728 [flagellar hook assem...] - TP0661 [hypothetical protein...] (117,W)
TP0728 [flagellar hook assem...] - TP0726 [flagellar protein (f...] (7,F)
TP0728 [flagellar hook assem...] - TP0727 [flagellar hook prote...] (5,F)
TP0728 [flagellar hook assem...] - TP0764 [conserved hypothetic...] (139,W)
TP0728 [flagellar hook assem...] - TP0788 [hypothetical protein...] (132,W)
TP0728 [flagellar hook assem...] - TP0832 [hypothetical protein...] (37,F)
TP0728 [flagellar hook assem...] - TP0870 [flagellar filament 3...] (79,W)
TP0728 [flagellar hook assem...] - TP0907 [conserved hypothetic...] (110,W)
TP0728 [flagellar hook assem...] - TP0961 [flagellar basal-body...] (84,W)
TP0728 [flagellar hook assem...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0728 [flagellar hook assem...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0730 [conserved hypothetic...] - TP0067 [conserved hypothetic...] (19,F)
TP0733 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0738 [conserved hypothetic...] - TP0024 [conserved hypothetic...] (16,F)
TP0738 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0738 [conserved hypothetic...] - TP0067 [conserved hypothetic...] (19,F)
TP0738 [conserved hypothetic...] - TP0078 [spore coat polysacch...] (2,F)
TP0738 [conserved hypothetic...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0738 [conserved hypothetic...] - TP0095 [hypothetical protein...] (15,F)
TP0738 [conserved hypothetic...] - TP0097 [translation initiati...] (3,F)
TP0738 [conserved hypothetic...] - TP0113 [Lambda CII stability...] (2,F)
TP0738 [conserved hypothetic...] - TP0197 [ribosomal protein L2...] (15,F)
TP0738 [conserved hypothetic...] - TP0199 [ribosomal protein L1...] (1,F)
TP0738 [conserved hypothetic...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0738 [conserved hypothetic...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0738 [conserved hypothetic...] - TP0255 [ribosomal protein L3...] (2,F)
TP0738 [conserved hypothetic...] - TP0257 [glycerophosphodieste...] (3,F)
TP0738 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0738 [conserved hypothetic...] - TP0281 [hypothetical protein...] (64,W)
TP0738 [conserved hypothetic...] - TP0286 [conserved hypothetic...] (9,F)
TP0738 [conserved hypothetic...] - TP0334 [conserved hypothetic...] (5,F)
TP0738 [conserved hypothetic...] - TP0341 [UDP-N-acetylmuramate...] (12,F)
TP0738 [conserved hypothetic...] - TP0354 [thymidylate kinase (...] (8,F)
TP0738 [conserved hypothetic...] - TP0359 [hypothetical protein...] (2,F)
TP0738 [conserved hypothetic...] - TP0375 [hypothetical protein...] (1,F)
TP0738 [conserved hypothetic...] - TP0393 [smf protein (smf) {B...] (1,F)
TP0738 [conserved hypothetic...] - TP0397 [flagellar basal-body...] (25,F)
TP0738 [conserved hypothetic...] - TP0408 [hypothetical protein...] (1,F)
TP0738 [conserved hypothetic...] - TP0412 [conserved hypothetic...] (4,F)
TP0738 [conserved hypothetic...] - TP0443 [conserved hypothetic...] (6,F)
TP0738 [conserved hypothetic...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0738 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0738 [conserved hypothetic...] - TP0465 [hypothetical protein...] (7,F)
TP0738 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0738 [conserved hypothetic...] - TP0519 [response regulatory ...] (30,F)
TP0738 [conserved hypothetic...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0738 [conserved hypothetic...] - TP0552 [hypothetical protein...] (3,F)
TP0738 [conserved hypothetic...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0738 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0738 [conserved hypothetic...] - TP0569 [aminopeptidase P {Ho...] (1,F)
TP0738 [conserved hypothetic...] - TP0587 [hypothetical protein...] (23,F)
TP0738 [conserved hypothetic...] - TP0607 [hypothetical protein...] (1,F)
TP0738 [conserved hypothetic...] - TP0618 [hypothetical protein...] (24,F)
TP0738 [conserved hypothetic...] - TP0626 [exonuclease, putativ...] (12,F)
TP0738 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0738 [conserved hypothetic...] - TP0664 [flagellar filament o...] (34,F)
TP0738 [conserved hypothetic...] - TP0704 [single-stranded-DNA-...] (12,F)
TP0738 [conserved hypothetic...] - TP0711 [conserved hypothetic...] (46,F)
TP0738 [conserved hypothetic...] - TP0757 [polypeptide deformyl...] (36,F)
TP0738 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0738 [conserved hypothetic...] - TP0773 [periplasmic serine p...] (30,F)
TP0738 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0738 [conserved hypothetic...] - TP0833 [hypothetical protein...] (34,F)
TP0738 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0738 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0738 [conserved hypothetic...] - TP0943 [flagellar protein (f...] (15,F)

TP0738 [conserved hypothetic...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0738 [conserved hypothetic...] - TP0946 [glucose-inhibited di...] (19,F)
TP0738 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0738 [conserved hypothetic...] - TP0965 [membrane fusion prot...] (14,F)
TP0738 [conserved hypothetic...] - TP0981 [sensory transduction...] (5,F)
TP0738 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0738 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0738 [conserved hypothetic...] - TP0997 [protease IV (sppA) {...] (8,F)
TP0738 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0738 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0738 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0738 [conserved hypothetic...] - TP1023 [recX protein (recX) ...] (13,F)
TP0739 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0739 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0740 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0741 [conserved hypothetic...] - TP0046 [hypothetical protein...] (18,F)
TP0741 [conserved hypothetic...] - TP0209 [ribosomal protein L3...] (27,F)
TP0741 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0741 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0743 [ribosomal protein L2...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0744 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0744 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0744 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0744 [conserved hypothetic...] - TP0943 [flagellar protein (f...] (15,F)
TP0744 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0744 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0744 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0744 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0744 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0744 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0744 [conserved hypothetic...] - TP1020 [glu-tRNA amidotransf...] (2,F)
TP0747 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0747 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0747 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0747 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0747 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0748 [cytoplasmic filament...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0751 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0751 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0751 [hypothetical protein...] - TP0684 [methylgalactoside AB...] (15,F)
TP0751 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0751 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0751 [hypothetical protein...] - TP0939 [pyruvate oxidoreduct...] (12,F)
TP0751 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0751 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0752 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0752 [hypothetical protein...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0752 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0752 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0752 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0752 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0752 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0752 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0753 [hypothetical protein...] - TP0561 [conserved hypothetic...] (44,F)
TP0753 [hypothetical protein...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0754 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0754 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0754 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0755 [PTS system, nitrogen...] - TP0619 [hypothetical protein...] (2,F)
TP0756 [methionyl-tRNA formy...] - TP0060 [ribosomal protein L9...] (78,W)
TP0756 [methionyl-tRNA formy...] - TP0258 [conserved hypothetic...] (173,W)
TP0756 [methionyl-tRNA formy...] - TP0383 [conserved hypothetic...] (65,W)
TP0756 [methionyl-tRNA formy...] - TP0398 [flagellar hook-basal...] (114,W)
TP0756 [methionyl-tRNA formy...] - TP0657 [carbon storage regul...] (1,F)
TP0756 [methionyl-tRNA formy...] - TP0757 [polypeptide deformyl...] (36,F)
TP0756 [methionyl-tRNA formy...] - TP0764 [conserved hypothetic...] (139,W)
TP0756 [methionyl-tRNA formy...] - TP0788 [hypothetical protein...] (132,W)
TP0756 [methionyl-tRNA formy...] - TP0833 [hypothetical protein...] (34,F)
TP0756 [methionyl-tRNA formy...] - TP0974 [hypothetical protein...] (23,F)
TP0756 [methionyl-tRNA formy...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0756 [methionyl-tRNA formy...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0756 [methionyl-tRNA formy...] - TP0995 [cyclic nucleotide bi...] (5,F)
TP0756 [methionyl-tRNA formy...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0756 [methionyl-tRNA formy...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0757 [polypeptide deformyl...] - TP0684 [methylgalactoside AB...] (15,F)
TP0757 [polypeptide deformyl...] - TP0788 [hypothetical protein...] (132,W)
TP0757 [polypeptide deformyl...] - TP0833 [hypothetical protein...] (34,F)
TP0757 [polypeptide deformyl...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0759 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0760 [penicillin-binding p...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0761 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0763 [hypothetical protein...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0766 [hypothetical protein...] - TP0619 [hypothetical protein...] (2,F)
TP0766 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0768 [membrane protein (tm...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0771 [conserved hypothetic...] - TP0209 [ribosomal protein L3...] (27,F)
TP0771 [conserved hypothetic...] - TP0522 [hypothetical protein...] (1,F)
TP0772 [hypothetical protein...] - TP0017 [conserved hypothetic...] (1,F)
TP0772 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0772 [hypothetical protein...] - TP0334 [conserved hypothetic...] (5,F)
TP0772 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0772 [hypothetical protein...] - TP0396 [flagellar basal-body...] (15,F)
TP0772 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0772 [hypothetical protein...] - TP0701 [DNA-directed RNA pol...] (3,F)
TP0772 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0772 [hypothetical protein...] - TP0795 [hypothetical protein...] (4,F)
TP0772 [hypothetical protein...] - TP0818 [hypothetical protein...] (2,F)
TP0777 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0777 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0778 [beta-lactamase regul...] - TP0258 [conserved hypothetic...] (173,W)
TP0778 [beta-lactamase regul...] - TP0907 [conserved hypothetic...] (110,W)
TP0778 [beta-lactamase regul...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0778 [beta-lactamase regul...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0779 [dedA protein (dedA) ...] - TP0050 [conserved hypothetic...] (10,F)
TP0779 [dedA protein (dedA) ...] - TP0354 [thymidylate kinase (...] (8,F)
TP0779 [dedA protein (dedA) ...] - TP0380 [DNA repair helicase,...] (5,F)
TP0779 [dedA protein (dedA) ...] - TP0563 [hypothetical protein...] (93,W)
TP0779 [dedA protein (dedA) ...] - TP0618 [hypothetical protein...] (24,F)
TP0779 [dedA protein (dedA) ...] - TP0764 [conserved hypothetic...] (139,W)
TP0779 [dedA protein (dedA) ...] - TP0832 [hypothetical protein...] (37,F)
TP0779 [dedA protein (dedA) ...] - TP0833 [hypothetical protein...] (34,F)
TP0779 [dedA protein (dedA) ...] - TP0907 [conserved hypothetic...] (110,W)
TP0779 [dedA protein (dedA) ...] - TP0961 [flagellar basal-body...] (84,W)
TP0782 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0782 [hypothetical protein...] - TP0341 [UDP-N-acetylmuramate...] (12,F)
TP0782 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0782 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0782 [hypothetical protein...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0782 [hypothetical protein...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0782 [hypothetical protein...] - TP0626 [exonuclease, putativ...] (12,F)
TP0785 [conserved hypothetic...] - TP0397 [flagellar basal-body...] (25,F)
TP0785 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0785 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0785 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0785 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0786 [ABC transporter, ATP...] - TP0258 [conserved hypothetic...] (173,W)
TP0786 [ABC transporter, ATP...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0787 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0787 [hypothetical protein...] - TP0920 [hypothetical protein...] (7,F)
TP0787 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0787 [hypothetical protein...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0788 [hypothetical protein...] - TP0121 [conserved hypothetic...] (7,F)
TP0789 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0789 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0789 [hypothetical protein...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0790 [antibiotic transport...] - TP0518 [conserved hypothetic...] (70,W)
TP0790 [antibiotic transport...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0790 [antibiotic transport...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0791 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0791 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0791 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0791 [hypothetical protein...] - TP0995 [cyclic nucleotide bi...] (5,F)
TP0792 [flagellar filament 3...] - TP0064 [hypothetical, protei...] (8,F)
TP0792 [flagellar filament 3...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0792 [flagellar filament 3...] - TP0658 [transmembrane protei...] (5,F)
TP0792 [flagellar filament 3...] - TP0764 [conserved hypothetic...] (139,W)
TP0792 [flagellar filament 3...] - TP0832 [hypothetical protein...] (37,F)
TP0792 [flagellar filament 3...] - TP0961 [flagellar basal-body...] (84,W)
TP0793 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0793 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0793 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0793 [hypothetical protein...] - TP0833 [hypothetical protein...] (34,F)
TP0793 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0793 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0793 [hypothetical protein...] - TP1023 [recX protein (recX) ...] (13,F)
TP0794 [S-adenosylmethionine...] - TP0002 [DNA polymerase III, ...] (4,F)
TP0794 [S-adenosylmethionine...] - TP0046 [hypothetical protein...] (18,F)
TP0794 [S-adenosylmethionine...] - TP0955 [hypothetical protein...] (1,F)
TP0794 [S-adenosylmethionine...] - TP0961 [flagellar basal-body...] (84,W)
TP0795 [hypothetical protein...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0795 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0795 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0795 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0795 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0795 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0795 [hypothetical protein...] - TP0727 [flagellar hook prote...] (5,F)
TP0795 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0795 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0795 [hypothetical protein...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0795 [hypothetical protein...] - TP0946 [glucose-inhibited di...] (19,F)
TP0795 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0795 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0795 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0798 [methionyl-tRNA synth...] - TP0258 [conserved hypothetic...] (173,W)
TP0798 [methionyl-tRNA synth...] - TP0281 [hypothetical protein...] (64,W)
TP0798 [methionyl-tRNA synth...] - TP0288 [spore coat polysacch...] (77,W)
TP0798 [methionyl-tRNA synth...] - TP0383 [conserved hypothetic...] (65,W)
TP0798 [methionyl-tRNA synth...] - TP0398 [flagellar hook-basal...] (114,W)
TP0798 [methionyl-tRNA synth...] - TP0518 [conserved hypothetic...] (70,W)

TP0798 [methionyl-tRNA synth...] - TP0764 [conserved hypothetic...] (139,W)
TP0798 [methionyl-tRNA synth...] - TP0965 [membrane fusion prot...] (14,F)
TP0798 [methionyl-tRNA synth...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0798 [methionyl-tRNA synth...] - TP0992 [conserved hypothetic...] (1,F)
TP0798 [methionyl-tRNA synth...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0798 [methionyl-tRNA synth...] - TP1004 [recombination protei...] (74,W)
TP0800 [serine-type D-Ala-D-...] - TP0258 [conserved hypothetic...] (173,W)
TP0800 [serine-type D-Ala-D-...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0802 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0802 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0802 [hypothetical protein...] - TP0286 [conserved hypothetic...] (9,F)
TP0802 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0802 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0802 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0802 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0802 [hypothetical protein...] - TP0519 [response regulatory ...] (30,F)
TP0802 [hypothetical protein...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0802 [hypothetical protein...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0802 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0802 [hypothetical protein...] - TP0626 [exonuclease, putativ...] (12,F)
TP0802 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0802 [hypothetical protein...] - TP0664 [flagellar filament o...] (34,F)
TP0802 [hypothetical protein...] - TP0684 [methylgalactoside AB...] (15,F)
TP0802 [hypothetical protein...] - TP0757 [polypeptide deformyl...] (36,F)
TP0802 [hypothetical protein...] - TP0773 [periplasmic serine p...] (30,F)
TP0803 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0803 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0803 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0803 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0803 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0803 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0803 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0803 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0803 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0803 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0804 [sugar ABC transporte...] - TP0044 [glucose inhibited di...] (3,F)
TP0805 [exoribonuclease II (...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0805 [exoribonuclease II (...] - TP0258 [conserved hypothetic...] (173,W)
TP0805 [exoribonuclease II (...] - TP0383 [conserved hypothetic...] (65,W)
TP0805 [exoribonuclease II (...] - TP0518 [conserved hypothetic...] (70,W)
TP0805 [exoribonuclease II (...] - TP0661 [hypothetical protein...] (117,W)
TP0805 [exoribonuclease II (...] - TP0751 [hypothetical protein...] (7,F)
TP0805 [exoribonuclease II (...] - TP0764 [conserved hypothetic...] (139,W)
TP0805 [exoribonuclease II (...] - TP0788 [hypothetical protein...] (132,W)
TP0805 [exoribonuclease II (...] - TP0813 [hypothetical protein...] (3,F)
TP0805 [exoribonuclease II (...] - TP0833 [hypothetical protein...] (34,F)
TP0805 [exoribonuclease II (...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0805 [exoribonuclease II (...] - TP1004 [recombination protei...] (74,W)
TP0806 [femA protein, putati...] - TP0398 [flagellar hook-basal...] (114,W)
TP0806 [femA protein, putati...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0806 [femA protein, putati...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0807 [ribosomal protein L3...] - TP0197 [ribosomal protein L2...] (15,F)
TP0807 [ribosomal protein L3...] - TP0258 [conserved hypothetic...] (173,W)
TP0807 [ribosomal protein L3...] - TP0281 [hypothetical protein...] (64,W)
TP0807 [ribosomal protein L3...] - TP0398 [flagellar hook-basal...] (114,W)
TP0807 [ribosomal protein L3...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0807 [ribosomal protein L3...] - TP0449 [hypothetical protein...] (51,W)
TP0807 [ribosomal protein L3...] - TP0618 [hypothetical protein...] (24,F)
TP0807 [ribosomal protein L3...] - TP0661 [hypothetical protein...] (117,W)
TP0807 [ribosomal protein L3...] - TP0664 [flagellar filament o...] (34,F)
TP0807 [ribosomal protein L3...] - TP0711 [conserved hypothetic...] (46,F)
TP0807 [ribosomal protein L3...] - TP0773 [periplasmic serine p...] (30,F)
TP0807 [ribosomal protein L3...] - TP0788 [hypothetical protein...] (132,W)
TP0807 [ribosomal protein L3...] - TP0870 [flagellar filament 3...] (79,W)
TP0807 [ribosomal protein L3...] - TP0907 [conserved hypothetic...] (110,W)
TP0807 [ribosomal protein L3...] - TP0961 [flagellar basal-body...] (84,W)
TP0807 [ribosomal protein L3...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0807 [ribosomal protein L3...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0807 [ribosomal protein L3...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0807 [ribosomal protein L3...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0809 [ribonuclease III (rn...] - TP0398 [flagellar hook-basal...] (114,W)
TP0809 [ribonuclease III (rn...] - TP0661 [hypothetical protein...] (117,W)
TP0809 [ribonuclease III (rn...] - TP0711 [conserved hypothetic...] (46,F)
TP0809 [ribonuclease III (rn...] - TP0870 [flagellar filament 3...] (79,W)
TP0809 [ribonuclease III (rn...] - TP0961 [flagellar basal-body...] (84,W)
TP0809 [ribonuclease III (rn...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0810 [DNA adenine methyltr...] - TP0258 [conserved hypothetic...] (173,W)
TP0813 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0814 [thioredoxin reductas...] - TP0294 [phosphoribosyl pyrop...] (3,F)
TP0814 [thioredoxin reductas...] - TP0362 [ribosomal protein L2...] (2,F)
TP0814 [thioredoxin reductas...] - TP0661 [hypothetical protein...] (117,W)
TP0814 [thioredoxin reductas...] - TP0773 [periplasmic serine p...] (30,F)
TP0814 [thioredoxin reductas...] - TP0813 [hypothetical protein...] (3,F)
TP0814 [thioredoxin reductas...] - TP0870 [flagellar filament 3...] (79,W)
TP0814 [thioredoxin reductas...] - TP0961 [flagellar basal-body...] (84,W)
TP0814 [thioredoxin reductas...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0814 [thioredoxin reductas...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0816 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0816 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0816 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0816 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0816 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0818 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0818 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0818 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0819 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0819 [conserved hypothetic...] - TP0095 [hypothetical protein...] (15,F)
TP0819 [conserved hypothetic...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0819 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0819 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0819 [conserved hypothetic...] - TP0341 [UDP-N-acetylmuramate...] (12,F)
TP0819 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0819 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0819 [conserved hypothetic...] - TP0399 [flagellar basal-body...] (2,F)
TP0819 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0819 [conserved hypothetic...] - TP0512 [conserved hypothetic...] (1,F)
TP0819 [conserved hypothetic...] - TP0513 [K+ transport protein...] (4,F)
TP0819 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0819 [conserved hypothetic...] - TP0640 [methyl-accepting che...] (5,F)
TP0819 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0819 [conserved hypothetic...] - TP0664 [flagellar filament o...] (34,F)
TP0819 [conserved hypothetic...] - TP0670 [D-alanine--D-alanine...] (1,F)
TP0819 [conserved hypothetic...] - TP0704 [single-stranded-DNA-...] (12,F)
TP0819 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0819 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0819 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0819 [conserved hypothetic...] - TP0920 [hypothetical protein...] (7,F)
TP0819 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0819 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0819 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0819 [conserved hypothetic...] - TP1002 [conserved hypothetic...] (1,F)
TP0819 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0820 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0820 [hypothetical protein...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0820 [hypothetical protein...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0820 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0820 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0820 [hypothetical protein...] - TP0463 [hypothetical protein...] (8,F)
TP0820 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0820 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0823 [desulfoferrodoxin (r...] - TP1037 [hemolysin III (hlyII...] (1,F)
TP0824 [transketolase B (tkt...] - TP0768 [membrane protein (tm...] (1,F)
TP0824 [transketolase B (tkt...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0824 [transketolase B (tkt...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0826 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0826 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0826 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0826 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0826 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0826 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0826 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0826 [conserved hypothetic...] - TP1020 [glu-tRNA amidotransf...] (2,F)
TP0827 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0827 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0827 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0829 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0829 [conserved hypothetic...] - TP0412 [conserved hypothetic...] (4,F)
TP0829 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0829 [conserved hypothetic...] - TP0518 [conserved hypothetic...] (70,W)
TP0829 [conserved hypothetic...] - TP0519 [response regulatory ...] (30,F)
TP0829 [conserved hypothetic...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0829 [conserved hypothetic...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0829 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0829 [conserved hypothetic...] - TP0626 [exonuclease, putativ...] (12,F)
TP0829 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0829 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0829 [conserved hypothetic...] - TP0833 [hypothetical protein...] (34,F)
TP0829 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0829 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0829 [conserved hypothetic...] - TP0943 [flagellar protein (f...] (15,F)
TP0829 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0829 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0830 [pseudouridylate synt...] - TP0288 [spore coat polysacch...] (77,W)
TP0830 [pseudouridylate synt...] - TP0907 [conserved hypothetic...] (110,W)
TP0830 [pseudouridylate synt...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0830 [pseudouridylate synt...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0831 [arginyl-tRNA synthet...] - TP0788 [hypothetical protein...] (132,W)
TP0831 [arginyl-tRNA synthet...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0831 [arginyl-tRNA synthet...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0833 [hypothetical protein...] - TP0024 [conserved hypothetic...] (16,F)
TP0833 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0833 [hypothetical protein...] - TP0080 [quinoline 2-oxidored...] (13,F)
TP0833 [hypothetical protein...] - TP0209 [ribosomal protein L3...] (27,F)
TP0833 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0833 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0833 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0833 [hypothetical protein...] - TP0514 [excinuclease ABC, su...] (7,F)
TP0833 [hypothetical protein...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0833 [hypothetical protein...] - TP0559 [conserved hypothetic...] (26,F)
TP0833 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)

TP0833 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP0833 [hypothetical protein...] - TP0664 [flagellar filament o...] (34,F)
TP0833 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0833 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0833 [hypothetical protein...] - TP0833 [hypothetical protein...] (34,F)
TP0833 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0833 [hypothetical protein...] - TP0943 [flagellar protein (f...] (15,F)
TP0833 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0836 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0840 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0840 [conserved hypothetic...] - TP0281 [hypothetical protein...] (64,W)
TP0840 [conserved hypothetic...] - TP0397 [flagellar basal-body...] (25,F)
TP0840 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0840 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0840 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0840 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0840 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0840 [conserved hypothetic...] - TP0894 [conserved hypothetic...] (13,F)
TP0840 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0840 [conserved hypothetic...] - TP0965 [membrane fusion prot...] (14,F)
TP0840 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0840 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0840 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0840 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0840 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0841 [periplasmic serine p...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0842 [methionine aminopept...] - TP0258 [conserved hypothetic...] (173,W)
TP0842 [methionine aminopept...] - TP0294 [phosphoribosyl pyrop...] (3,F)
TP0842 [methionine aminopept...] - TP0354 [thymidylate kinase (...] (8,F)
TP0842 [methionine aminopept...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0844 [glyceraldehyde 3-pho...] - TP0449 [hypothetical protein...] (51,W)
TP0844 [glyceraldehyde 3-pho...] - TP0870 [flagellar filament 3...] (79,W)
TP0845 [P23 protein, putativ...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0845 [P23 protein, putativ...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0846 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0847 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0847 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0848 [ribosomal protein L2...] - TP0764 [conserved hypothetic...] (139,W)
TP0849 [ribosomal protein L3...] - TP0258 [conserved hypothetic...] (173,W)
TP0849 [ribosomal protein L3...] - TP0398 [flagellar hook-basal...] (114,W)
TP0850 [translation initiati...] - TP0095 [hypothetical protein...] (15,F)
TP0850 [translation initiati...] - TP0258 [conserved hypothetic...] (173,W)
TP0850 [translation initiati...] - TP0449 [hypothetical protein...] (51,W)
TP0850 [translation initiati...] - TP0661 [hypothetical protein...] (117,W)
TP0850 [translation initiati...] - TP0664 [flagellar filament o...] (34,F)
TP0850 [translation initiati...] - TP0788 [hypothetical protein...] (132,W)
TP0850 [translation initiati...] - TP0870 [flagellar filament 3...] (79,W)
TP0850 [translation initiati...] - TP0906 [conserved hypothetic...] (1,F)
TP0850 [translation initiati...] - TP0907 [conserved hypothetic...] (110,W)
TP0850 [translation initiati...] - TP0943 [flagellar protein (f...] (15,F)
TP0850 [translation initiati...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0856 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0856 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0856 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0856 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0858 [hypothetical protein...] - TP0046 [hypothetical protein...] (18,F)
TP0858 [hypothetical protein...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0860 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0864 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0864 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0866 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0866 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0866 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0866 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0866 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0866 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0867 [hypothetical protein...] - TP0002 [DNA polymerase III, ...] (4,F)
TP0868 [flagellar filament 3...] - TP0050 [conserved hypothetic...] (10,F)
TP0868 [flagellar filament 3...] - TP0658 [transmembrane protei...] (5,F)
TP0868 [flagellar filament 3...] - TP0832 [hypothetical protein...] (37,F)
TP0869 [hypothetical protein...] - TP0124 [conserved hypothetic...] (1,F)
TP0869 [hypothetical protein...] - TP0208 [preprotein transloca...] (2,F)
TP0869 [hypothetical protein...] - TP0225 [leucine-rich repeat ...] (1,F)
TP0869 [hypothetical protein...] - TP0701 [DNA-directed RNA pol...] (3,F)
TP0870 [flagellar filament 3...] - TP0005 [DNA gyrase, subunit ...] (9,F)
TP0870 [flagellar filament 3...] - TP0046 [hypothetical protein...] (18,F)
TP0870 [flagellar filament 3...] - TP0050 [conserved hypothetic...] (10,F)
TP0870 [flagellar filament 3...] - TP0053 [ribonucleoside-dipho...] (1,F)
TP0870 [flagellar filament 3...] - TP0060 [ribosomal protein L9...] (78,W)
TP0870 [flagellar filament 3...] - TP0066 [hypothetical protein...] (11,F)
TP0870 [flagellar filament 3...] - TP0174 [hypothetical protein...] (1,F)
TP0870 [flagellar filament 3...] - TP0257 [glycerophosphodieste...] (3,F)
TP0870 [flagellar filament 3...] - TP0258 [conserved hypothetic...] (173,W)
TP0870 [flagellar filament 3...] - TP0288 [spore coat polysacch...] (77,W)
TP0870 [flagellar filament 3...] - TP0383 [conserved hypothetic...] (65,W)
TP0870 [flagellar filament 3...] - TP0396 [flagellar basal-body...] (15,F)
TP0870 [flagellar filament 3...] - TP0398 [flagellar hook-basal...] (114,W)
TP0870 [flagellar filament 3...] - TP0518 [conserved hypothetic...] (70,W)
TP0870 [flagellar filament 3...] - TP0563 [hypothetical protein...] (93,W)
TP0870 [flagellar filament 3...] - TP0629 [hypothetical protein...] (6,F)
TP0870 [flagellar filament 3...] - TP0630 [chemotaxis protein m...] (1,F)
TP0870 [flagellar filament 3...] - TP0640 [methyl-accepting che...] (5,F)
TP0870 [flagellar filament 3...] - TP0658 [transmembrane protei...] (5,F)
TP0870 [flagellar filament 3...] - TP0661 [hypothetical protein...] (117,W)
TP0870 [flagellar filament 3...] - TP0702 [conserved hypothetic...] (2,F)
TP0870 [flagellar filament 3...] - TP0711 [conserved hypothetic...] (46,F)
TP0870 [flagellar filament 3...] - TP0760 [penicillin-binding p...] (1,F)
TP0870 [flagellar filament 3...] - TP0764 [conserved hypothetic...] (139,W)
TP0870 [flagellar filament 3...] - TP0788 [hypothetical protein...] (132,W)
TP0870 [flagellar filament 3...] - TP0832 [hypothetical protein...] (37,F)
TP0870 [flagellar filament 3...] - TP0870 [flagellar filament 3...] (79,W)
TP0870 [flagellar filament 3...] - TP0873 [hypothetical protein...] (1,F)
TP0870 [flagellar filament 3...] - TP0907 [conserved hypothetic...] (110,W)
TP0870 [flagellar filament 3...] - TP0943 [flagellar protein (f...] (15,F)
TP0870 [flagellar filament 3...] - TP0961 [flagellar basal-body...] (84,W)
TP0870 [flagellar filament 3...] - TP0981 [sensory transduction...] (5,F)
TP0870 [flagellar filament 3...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0870 [flagellar filament 3...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0873 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0873 [hypothetical protein...] - TP0197 [ribosomal protein L2...] (15,F)
TP0873 [hypothetical protein...] - TP0209 [ribosomal protein L3...] (27,F)
TP0873 [hypothetical protein...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0873 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0873 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0873 [hypothetical protein...] - TP0354 [thymidylate kinase (...] (8,F)
TP0873 [hypothetical protein...] - TP0833 [hypothetical protein...] (34,F)
TP0873 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0873 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0873 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0874 [conserved hypothetic...] - TP0463 [hypothetical protein...] (8,F)
TP0874 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0875 [conserved hypothetic...] - TP0046 [hypothetical protein...] (18,F)
TP0875 [conserved hypothetic...] - TP0060 [ribosomal protein L9...] (78,W)
TP0875 [conserved hypothetic...] - TP0240 [ribosomal protein L7...] (2,F)
TP0875 [conserved hypothetic...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0875 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0875 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0876 [conserved hypothetic...] - TP0024 [conserved hypothetic...] (16,F)
TP0876 [conserved hypothetic...] - TP0097 [translation initiati...] (3,F)
TP0876 [conserved hypothetic...] - TP0121 [conserved hypothetic...] (7,F)
TP0876 [conserved hypothetic...] - TP0247 [N-acetylmuramoyl-L-a...] (20,F)
TP0876 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0876 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP0876 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0876 [conserved hypothetic...] - TP0586 [leucyl-tRNA syntheta...] (16,F)
TP0876 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0876 [conserved hypothetic...] - TP0751 [hypothetical protein...] (7,F)
TP0876 [conserved hypothetic...] - TP0757 [polypeptide deformyl...] (36,F)
TP0876 [conserved hypothetic...] - TP0803 [hypothetical protein...] (2,F)
TP0876 [conserved hypothetic...] - TP0895 [hypothetical protein...] (3,F)
TP0876 [conserved hypothetic...] - TP0943 [flagellar protein (f...] (15,F)
TP0876 [conserved hypothetic...] - TP0974 [hypothetical protein...] (23,F)
TP0876 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0876 [conserved hypothetic...] - TP0991 [rubredoxin {Clostrid...] (1,F)
TP0876 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0876 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0876 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0877 [conserved hypothetic...] - TP0461 [hypothetical protein...] (3,F)
TP0880 [membrane spanning pr...] - TP0833 [hypothetical protein...] (34,F)
TP0881 [ABC transporter, ATP...] - TP0383 [conserved hypothetic...] (65,W)
TP0881 [ABC transporter, ATP...] - TP0398 [flagellar hook-basal...] (114,W)
TP0881 [ABC transporter, ATP...] - TP0518 [conserved hypothetic...] (70,W)
TP0881 [ABC transporter, ATP...] - TP0764 [conserved hypothetic...] (139,W)
TP0881 [ABC transporter, ATP...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0881 [ABC transporter, ATP...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0881 [ABC transporter, ATP...] - TP1004 [recombination protei...] (74,W)
TP0881 [ABC transporter, ATP...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0884 [conserved hypothetic...] - TP0561 [conserved hypothetic...] (44,F)
TP0891 [translation initiati...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0893 [conserved hypothetic...] - TP0209 [ribosomal protein L3...] (27,F)
TP0895 [hypothetical protein...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0895 [hypothetical protein...] - TP0236 [transcription antite...] (5,F)
TP0895 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0895 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0895 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0895 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0895 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0895 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0896 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0896 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0897 [tpr protein K (tprK)...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0902 [carboxylesterase (es...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0903 [UDP-N-acetylmuramoyl...] - TP0064 [hypothetical, protei...] (8,F)
TP0903 [UDP-N-acetylmuramoyl...] - TP0092 [RNA polymerase sigma...] (10,F)
TP0903 [UDP-N-acetylmuramoyl...] - TP0100 [thioredoxin, putativ...] (3,F)
TP0903 [UDP-N-acetylmuramoyl...] - TP0288 [spore coat polysacch...] (77,W)
TP0903 [UDP-N-acetylmuramoyl...] - TP0396 [flagellar basal-body...] (15,F)
TP0903 [UDP-N-acetylmuramoyl...] - TP0398 [flagellar hook-basal...] (114,W)
TP0903 [UDP-N-acetylmuramoyl...] - TP0563 [hypothetical protein...] (93,W)

TP0903 [UDP-N-acetylmuramoyl...] - TP0618 [hypothetical protein...] (24,F)
TP0903 [UDP-N-acetylmuramoyl...] - TP0661 [hypothetical protein...] (117,W)
TP0903 [UDP-N-acetylmuramoyl...] - TP0711 [conserved hypothetic...] (46,F)
TP0903 [UDP-N-acetylmuramoyl...] - TP0788 [hypothetical protein...] (132,W)
TP0903 [UDP-N-acetylmuramoyl...] - TP0832 [hypothetical protein...] (37,F)
TP0903 [UDP-N-acetylmuramoyl...] - TP0870 [flagellar filament 3...] (79,W)
TP0903 [UDP-N-acetylmuramoyl...] - TP0907 [conserved hypothetic...] (110,W)
TP0903 [UDP-N-acetylmuramoyl...] - TP0961 [flagellar basal-body...] (84,W)
TP0903 [UDP-N-acetylmuramoyl...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0903 [UDP-N-acetylmuramoyl...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0903 [UDP-N-acetylmuramoyl...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0905 [ribosomal protein S1...] - TP0060 [ribosomal protein L9...] (78,W)
TP0905 [ribosomal protein S1...] - TP0236 [transcription antite...] (5,F)
TP0905 [ribosomal protein S1...] - TP0258 [conserved hypothetic...] (173,W)
TP0905 [ribosomal protein S1...] - TP0281 [hypothetical protein...] (64,W)
TP0905 [ribosomal protein S1...] - TP0288 [spore coat polysacch...] (77,W)
TP0905 [ribosomal protein S1...] - TP0518 [conserved hypothetic...] (70,W)
TP0905 [ribosomal protein S1...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0905 [ribosomal protein S1...] - TP0618 [hypothetical protein...] (24,F)
TP0905 [ribosomal protein S1...] - TP0961 [flagellar basal-body...] (84,W)
TP0906 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0907 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0909 [ribosomal protein L1...] - TP0764 [conserved hypothetic...] (139,W)
TP0909 [ribosomal protein L1...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0911 [conserved hypothetic...] - TP0281 [hypothetical protein...] (64,W)
TP0912 [conserved hypothetic...] - TP0704 [single-stranded-DNA-...] (12,F)
TP0912 [conserved hypothetic...] - TP0833 [hypothetical protein...] (34,F)
TP0912 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0913 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0913 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0913 [conserved hypothetic...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0914 [conserved hypothetic...] - TP0095 [hypothetical protein...] (15,F)
TP0914 [conserved hypothetic...] - TP0214 [hypothetical protein...] (2,F)
TP0914 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0914 [conserved hypothetic...] - TP0291 [hypothetical protein...] (1,F)
TP0914 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP0914 [conserved hypothetic...] - TP0661 [hypothetical protein...] (117,W)
TP0914 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0914 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0914 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0914 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0914 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0914 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0915 [conserved hypothetic...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0915 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP0915 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0915 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0915 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0916 [hypothetical protein...] - TP0618 [hypothetical protein...] (24,F)
TP0917 [Mg2+ transport prote...] - TP1016 [basic membrane prote...] (1,F)
TP0918 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0918 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0921 [NADH oxidase {Strept...] - TP0726 [flagellar protein (f...] (7,F)
TP0921 [NADH oxidase {Strept...] - TP0788 [hypothetical protein...] (132,W)
TP0924 [tex protein (tex) {B...] - TP0833 [hypothetical protein...] (34,F)
TP0924 [tex protein (tex) {B...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0925 [flavodoxin {Clostrid...] - TP0209 [ribosomal protein L3...] (27,F)
TP0926 [signal peptidase I, ...] - TP0209 [ribosomal protein L3...] (27,F)
TP0928 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0928 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0928 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0929 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0929 [hypothetical protein...] - TP0099 [uridylate kinase (sm...] (3,F)
TP0929 [hypothetical protein...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0929 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0929 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0929 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0929 [hypothetical protein...] - TP0396 [flagellar basal-body...] (15,F)
TP0929 [hypothetical protein...] - TP0398 [flagellar hook-basal...] (114,W)
TP0929 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0929 [hypothetical protein...] - TP0463 [hypothetical protein...] (8,F)
TP0929 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0929 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0929 [hypothetical protein...] - TP0618 [hypothetical protein...] (24,F)
TP0929 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0929 [hypothetical protein...] - TP0870 [flagellar filament 3...] (79,W)
TP0929 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0929 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0929 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0929 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0929 [hypothetical protein...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0932 [hypothetical protein...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0932 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0932 [hypothetical protein...] - TP0281 [hypothetical protein...] (64,W)
TP0932 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0932 [hypothetical protein...] - TP0383 [conserved hypothetic...] (65,W)
TP0932 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0932 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0932 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0932 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0932 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0932 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0932 [hypothetical protein...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0933 [UDP-N-acetylmuramoyl...] - TP0833 [hypothetical protein...] (34,F)
TP0935 [N-acetylphosphinothr...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0936 [hemolysin, putative ...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0937 [conserved hypothetic...] - TP0920 [hypothetical protein...] (7,F)
TP0937 [conserved hypothetic...] - TP1009 [glycerol-3-phosphate...] (1,F)
TP0939 [pyruvate oxidoreduct...] - TP0060 [ribosomal protein L9...] (78,W)
TP0939 [pyruvate oxidoreduct...] - TP0258 [conserved hypothetic...] (173,W)
TP0939 [pyruvate oxidoreduct...] - TP0281 [hypothetical protein...] (64,W)
TP0939 [pyruvate oxidoreduct...] - TP0288 [spore coat polysacch...] (77,W)
TP0939 [pyruvate oxidoreduct...] - TP0396 [flagellar basal-body...] (15,F)
TP0939 [pyruvate oxidoreduct...] - TP0398 [flagellar hook-basal...] (114,W)
TP0939 [pyruvate oxidoreduct...] - TP0449 [hypothetical protein...] (51,W)
TP0939 [pyruvate oxidoreduct...] - TP0518 [conserved hypothetic...] (70,W)
TP0939 [pyruvate oxidoreduct...] - TP0563 [hypothetical protein...] (93,W)
TP0939 [pyruvate oxidoreduct...] - TP0757 [polypeptide deformyl...] (36,F)
TP0939 [pyruvate oxidoreduct...] - TP0764 [conserved hypothetic...] (139,W)
TP0939 [pyruvate oxidoreduct...] - TP0907 [conserved hypothetic...] (110,W)
TP0939 [pyruvate oxidoreduct...] - TP0961 [flagellar basal-body...] (84,W)
TP0939 [pyruvate oxidoreduct...] - TP0965 [membrane fusion prot...] (14,F)
TP0939 [pyruvate oxidoreduct...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0939 [pyruvate oxidoreduct...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0939 [pyruvate oxidoreduct...] - TP1004 [recombination protei...] (74,W)
TP0939 [pyruvate oxidoreduct...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0940 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0940 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0940 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0940 [hypothetical protein...] - TP0618 [hypothetical protein...] (24,F)
TP0940 [hypothetical protein...] - TP0788 [hypothetical protein...] (132,W)
TP0940 [hypothetical protein...] - TP0833 [hypothetical protein...] (34,F)
TP0940 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0940 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0940 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0940 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0940 [hypothetical protein...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0940 [hypothetical protein...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0940 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0941 [hypothetical protein...] - TP0060 [ribosomal protein L9...] (78,W)
TP0941 [hypothetical protein...] - TP0233 [anti-sigma F factor ...] (13,F)
TP0941 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0941 [hypothetical protein...] - TP0519 [response regulatory ...] (30,F)
TP0941 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0941 [hypothetical protein...] - TP0618 [hypothetical protein...] (24,F)
TP0941 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0941 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0941 [hypothetical protein...] - TP0974 [hypothetical protein...] (23,F)
TP0941 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0941 [hypothetical protein...] - TP1013 [chaperonin (groES) {...] (14,F)
TP0943 [flagellar protein (f...] - TP0060 [ribosomal protein L9...] (78,W)
TP0943 [flagellar protein (f...] - TP0197 [ribosomal protein L2...] (15,F)
TP0943 [flagellar protein (f...] - TP0209 [ribosomal protein L3...] (27,F)
TP0943 [flagellar protein (f...] - TP0258 [conserved hypothetic...] (173,W)
TP0943 [flagellar protein (f...] - TP0383 [conserved hypothetic...] (65,W)
TP0943 [flagellar protein (f...] - TP0398 [flagellar hook-basal...] (114,W)
TP0943 [flagellar protein (f...] - TP0660 [flagellar hook-assoc...] (4,F)
TP0943 [flagellar protein (f...] - TP0661 [hypothetical protein...] (117,W)
TP0943 [flagellar protein (f...] - TP0788 [hypothetical protein...] (132,W)
TP0943 [flagellar protein (f...] - TP0870 [flagellar filament 3...] (79,W)
TP0943 [flagellar protein (f...] - TP0907 [conserved hypothetic...] (110,W)
TP0943 [flagellar protein (f...] - TP0943 [flagellar protein (f...] (15,F)
TP0943 [flagellar protein (f...] - TP0945 [ribulose-phosphate 3...] (21,F)
TP0943 [flagellar protein (f...] - TP0961 [flagellar basal-body...] (84,W)
TP0943 [flagellar protein (f...] - TP0974 [hypothetical protein...] (23,F)
TP0943 [flagellar protein (f...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0943 [flagellar protein (f...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0944 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0945 [ribulose-phosphate 3...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0946 [glucose-inhibited di...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0946 [glucose-inhibited di...] - TP0258 [conserved hypothetic...] (173,W)
TP0946 [glucose-inhibited di...] - TP0288 [spore coat polysacch...] (77,W)
TP0946 [glucose-inhibited di...] - TP0514 [excinuclease ABC, su...] (7,F)
TP0946 [glucose-inhibited di...] - TP0661 [hypothetical protein...] (117,W)
TP0946 [glucose-inhibited di...] - TP0870 [flagellar filament 3...] (79,W)
TP0946 [glucose-inhibited di...] - TP0961 [flagellar basal-body...] (84,W)
TP0946 [glucose-inhibited di...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0946 [glucose-inhibited di...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0947 [peptidyl-prolyl cis-...] - TP0281 [hypothetical protein...] (64,W)
TP0947 [peptidyl-prolyl cis-...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0947 [peptidyl-prolyl cis-...] - TP0563 [hypothetical protein...] (93,W)
TP0947 [peptidyl-prolyl cis-...] - TP0618 [hypothetical protein...] (24,F)
TP0947 [peptidyl-prolyl cis-...] - TP0661 [hypothetical protein...] (117,W)
TP0947 [peptidyl-prolyl cis-...] - TP0664 [flagellar filament o...] (34,F)
TP0947 [peptidyl-prolyl cis-...] - TP0684 [methylgalactoside AB...] (15,F)
TP0947 [peptidyl-prolyl cis-...] - TP0727 [flagellar hook prote...] (5,F)
TP0947 [peptidyl-prolyl cis-...] - TP0757 [polypeptide deformyl...] (36,F)

TP0947 [peptidyl-prolyl cis-...] - TP0788 [hypothetical protein...] (132,W)
TP0947 [peptidyl-prolyl cis-...] - TP0833 [hypothetical protein...] (34,F)
TP0947 [peptidyl-prolyl cis-...] - TP0870 [flagellar filament 3...] (79,W)
TP0947 [peptidyl-prolyl cis-...] - TP0907 [conserved hypothetic...] (110,W)
TP0947 [peptidyl-prolyl cis-...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0948 [spoIIIJ-associated p...] - TP0463 [hypothetical protein...] (8,F)
TP0948 [spoIIIJ-associated p...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0953 [pheromone shutdown p...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0953 [pheromone shutdown p...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0954 [conserved hypothetic...] - TP0044 [glucose inhibited di...] (3,F)
TP0956 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0957 [Tp33 protein {Trepon...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0958 [dicarboxylate transp...] - TP0833 [hypothetical protein...] (34,F)
TP0958 [dicarboxylate transp...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0959 [hypothetical protein...] - TP0005 [DNA gyrase, subunit ...] (9,F)
TP0959 [hypothetical protein...] - TP0046 [hypothetical protein...] (18,F)
TP0959 [hypothetical protein...] - TP0088 [conserved hypothetic...] (8,F)
TP0959 [hypothetical protein...] - TP0162 [Holliday junction DN...] (3,F)
TP0959 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0959 [hypothetical protein...] - TP0260 [hypothetical protein...] (5,F)
TP0959 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0959 [hypothetical protein...] - TP0467 [hypothetical protein...] (2,F)
TP0959 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0959 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0959 [hypothetical protein...] - TP0832 [hypothetical protein...] (37,F)
TP0959 [hypothetical protein...] - TP0907 [conserved hypothetic...] (110,W)
TP0959 [hypothetical protein...] - TP0961 [flagellar basal-body...] (84,W)
TP0959 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0959 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0960 [flagellar basal-body...] - TP0832 [hypothetical protein...] (37,F)
TP0961 [flagellar basal-body...] - TP0005 [DNA gyrase, subunit ...] (9,F)
TP0961 [flagellar basal-body...] - TP0024 [conserved hypothetic...] (16,F)
TP0961 [flagellar basal-body...] - TP0026 [flagellar motor swit...] (8,F)
TP0961 [flagellar basal-body...] - TP0050 [conserved hypothetic...] (10,F)
TP0961 [flagellar basal-body...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0961 [flagellar basal-body...] - TP0236 [transcription antite...] (5,F)
TP0961 [flagellar basal-body...] - TP0287 [conserved hypothetic...] (27,F)
TP0961 [flagellar basal-body...] - TP0288 [spore coat polysacch...] (77,W)
TP0961 [flagellar basal-body...] - TP0314 [hypothetical protein...] (2,F)
TP0961 [flagellar basal-body...] - TP0341 [UDP-N-acetylmuramate...] (12,F)
TP0961 [flagellar basal-body...] - TP0397 [flagellar basal-body...] (25,F)
TP0961 [flagellar basal-body...] - TP0664 [flagellar filament o...] (34,F)
TP0961 [flagellar basal-body...] - TP0726 [flagellar protein (f...] (7,F)
TP0961 [flagellar basal-body...] - TP0751 [hypothetical protein...] (7,F)
TP0961 [flagellar basal-body...] - TP0757 [polypeptide deformyl...] (36,F)
TP0961 [flagellar basal-body...] - TP0764 [conserved hypothetic...] (139,W)
TP0961 [flagellar basal-body...] - TP0772 [hypothetical protein...] (3,F)
TP0961 [flagellar basal-body...] - TP0773 [periplasmic serine p...] (30,F)
TP0961 [flagellar basal-body...] - TP0782 [hypothetical protein...] (2,F)
TP0961 [flagellar basal-body...] - TP0788 [hypothetical protein...] (132,W)
TP0961 [flagellar basal-body...] - TP0832 [hypothetical protein...] (37,F)
TP0961 [flagellar basal-body...] - TP0870 [flagellar filament 3...] (79,W)
TP0961 [flagellar basal-body...] - TP0877 [conserved hypothetic...] (4,F)
TP0961 [flagellar basal-body...] - TP0907 [conserved hypothetic...] (110,W)
TP0961 [flagellar basal-body...] - TP0911 [conserved hypothetic...] (1,F)
TP0961 [flagellar basal-body...] - TP0961 [flagellar basal-body...] (84,W)
TP0961 [flagellar basal-body...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0961 [flagellar basal-body...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0962 [conserved hypothetic...] - TP0209 [ribosomal protein L3...] (27,F)
TP0962 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0962 [conserved hypothetic...] - TP0281 [hypothetical protein...] (64,W)
TP0962 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0962 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0962 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0962 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0962 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0963 [conserved hypothetic...] - TP0383 [conserved hypothetic...] (65,W)
TP0963 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0963 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0963 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0963 [conserved hypothetic...] - TP0965 [membrane fusion prot...] (14,F)
TP0963 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0963 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0965 [membrane fusion prot...] - TP0514 [excinuclease ABC, su...] (7,F)
TP0965 [membrane fusion prot...] - TP0563 [hypothetical protein...] (93,W)
TP0965 [membrane fusion prot...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0966 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0968 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0968 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0968 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0968 [hypothetical protein...] - TP1004 [recombination protei...] (74,W)
TP0969 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP0969 [hypothetical protein...] - TP0288 [spore coat polysacch...] (77,W)
TP0969 [hypothetical protein...] - TP0518 [conserved hypothetic...] (70,W)
TP0969 [hypothetical protein...] - TP0563 [hypothetical protein...] (93,W)
TP0969 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0969 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0969 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0969 [hypothetical protein...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0971 [membrane antigen, pa...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP0973 [phenylalanyl-tRNA sy...] - TP0764 [conserved hypothetic...] (139,W)
TP0973 [phenylalanyl-tRNA sy...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0974 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0976 [hypothetical protein...] - TP0432 [hypothetical protein...] (2,F)
TP0976 [hypothetical protein...] - TP0701 [DNA-directed RNA pol...] (3,F)
TP0976 [hypothetical protein...] - TP0764 [conserved hypothetic...] (139,W)
TP0976 [hypothetical protein...] - TP0799 [hypothetical protein...] (2,F)
TP0976 [hypothetical protein...] - TP0876 [conserved hypothetic...] (1,F)
TP0978 [signal peptidase II ...] - TP0060 [ribosomal protein L9...] (78,W)
TP0978 [signal peptidase II ...] - TP0258 [conserved hypothetic...] (173,W)
TP0978 [signal peptidase II ...] - TP0377 [conserved hypothetic...] (11,F)
TP0978 [signal peptidase II ...] - TP0907 [conserved hypothetic...] (110,W)
TP0978 [signal peptidase II ...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0978 [signal peptidase II ...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0978 [signal peptidase II ...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0981 [sensory transduction...] - TP0005 [DNA gyrase, subunit ...] (9,F)
TP0981 [sensory transduction...] - TP0046 [hypothetical protein...] (18,F)
TP0981 [sensory transduction...] - TP0061 [ribosomal protein S1...] (1,F)
TP0981 [sensory transduction...] - TP0064 [hypothetical, protei...] (8,F)
TP0981 [sensory transduction...] - TP0089 [cyclic nucleotide bi...] (1,F)
TP0981 [sensory transduction...] - TP0092 [RNA polymerase sigma...] (10,F)
TP0981 [sensory transduction...] - TP0160 [prolyl-tRNA syntheta...] (15,F)
TP0981 [sensory transduction...] - TP0258 [conserved hypothetic...] (173,W)
TP0981 [sensory transduction...] - TP0288 [spore coat polysacch...] (77,W)
TP0981 [sensory transduction...] - TP0396 [flagellar basal-body...] (15,F)
TP0981 [sensory transduction...] - TP0530 [V-type ATPase, subun...] (19,F)
TP0981 [sensory transduction...] - TP0563 [hypothetical protein...] (93,W)
TP0981 [sensory transduction...] - TP0661 [hypothetical protein...] (117,W)
TP0981 [sensory transduction...] - TP0764 [conserved hypothetic...] (139,W)
TP0981 [sensory transduction...] - TP0832 [hypothetical protein...] (37,F)
TP0981 [sensory transduction...] - TP0843 [heat shock protein, ...] (3,F)
TP0981 [sensory transduction...] - TP0870 [flagellar filament 3...] (79,W)
TP0981 [sensory transduction...] - TP0877 [conserved hypothetic...] (4,F)
TP0981 [sensory transduction...] - TP0907 [conserved hypothetic...] (110,W)
TP0981 [sensory transduction...] - TP0961 [flagellar basal-body...] (84,W)
TP0981 [sensory transduction...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0981 [sensory transduction...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0981 [sensory transduction...] - TP1004 [recombination protei...] (74,W)
TP0981 [sensory transduction...] - TP1005 [DNA polymerase III, ...] (44,F)
TP0981 [sensory transduction...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0982 [glpG protein, putati...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0983 [hypothetical protein...] - TP0445 [4-methyl-5(b-hydroxy...] (30,F)
TP0983 [hypothetical protein...] - TP0449 [hypothetical protein...] (51,W)
TP0983 [hypothetical protein...] - TP0519 [response regulatory ...] (30,F)
TP0983 [hypothetical protein...] - TP0711 [conserved hypothetic...] (46,F)
TP0983 [hypothetical protein...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0983 [hypothetical protein...] - TP1008 [ribonucleoside-dipho...] (2,F)
TP0984 [heat shock protein 9...] - TP0060 [ribosomal protein L9...] (78,W)
TP0984 [heat shock protein 9...] - TP0258 [conserved hypothetic...] (173,W)
TP0984 [heat shock protein 9...] - TP0288 [spore coat polysacch...] (77,W)
TP0984 [heat shock protein 9...] - TP0398 [flagellar hook-basal...] (114,W)
TP0984 [heat shock protein 9...] - TP0563 [hypothetical protein...] (93,W)
TP0984 [heat shock protein 9...] - TP0907 [conserved hypothetic...] (110,W)
TP0984 [heat shock protein 9...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0984 [heat shock protein 9...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0984 [heat shock protein 9...] - TP1004 [recombination protei...] (74,W)
TP0984 [heat shock protein 9...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0985 [aspartyl-tRNA synthe...] - TP0258 [conserved hypothetic...] (173,W)
TP0985 [aspartyl-tRNA synthe...] - TP0281 [hypothetical protein...] (64,W)
TP0985 [aspartyl-tRNA synthe...] - TP0383 [conserved hypothetic...] (65,W)
TP0985 [aspartyl-tRNA synthe...] - TP0398 [flagellar hook-basal...] (114,W)
TP0985 [aspartyl-tRNA synthe...] - TP0518 [conserved hypothetic...] (70,W)
TP0985 [aspartyl-tRNA synthe...] - TP0554 [phosphoglycolate pho...] (33,F)
TP0985 [aspartyl-tRNA synthe...] - TP0561 [conserved hypothetic...] (44,F)
TP0985 [aspartyl-tRNA synthe...] - TP0618 [hypothetical protein...] (24,F)
TP0985 [aspartyl-tRNA synthe...] - TP0661 [hypothetical protein...] (117,W)
TP0985 [aspartyl-tRNA synthe...] - TP0664 [flagellar filament o...] (34,F)
TP0985 [aspartyl-tRNA synthe...] - TP0711 [conserved hypothetic...] (46,F)
TP0985 [aspartyl-tRNA synthe...] - TP0735 [glutamate synthase (...] (2,F)
TP0985 [aspartyl-tRNA synthe...] - TP0757 [polypeptide deformyl...] (36,F)
TP0985 [aspartyl-tRNA synthe...] - TP0764 [conserved hypothetic...] (139,W)
TP0985 [aspartyl-tRNA synthe...] - TP0773 [periplasmic serine p...] (30,F)
TP0985 [aspartyl-tRNA synthe...] - TP0788 [hypothetical protein...] (132,W)
TP0985 [aspartyl-tRNA synthe...] - TP0833 [hypothetical protein...] (34,F)
TP0985 [aspartyl-tRNA synthe...] - TP0907 [conserved hypothetic...] (110,W)
TP0985 [aspartyl-tRNA synthe...] - TP0939 [pyruvate oxidoreduct...] (12,F)
TP0985 [aspartyl-tRNA synthe...] - TP0965 [membrane fusion prot...] (14,F)
TP0985 [aspartyl-tRNA synthe...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0985 [aspartyl-tRNA synthe...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP0985 [aspartyl-tRNA synthe...] - TP1004 [recombination protei...] (74,W)
TP0985 [aspartyl-tRNA synthe...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP0986 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP0986 [conserved hypothetic...] - TP0917 [Mg2+ transport prote...] (49,F)
TP0986 [conserved hypothetic...] - TP0925 [flavodoxin {Clostrid...] (1,F)
TP0986 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP0986 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP0988 [conserved hypothetic...] - TP0561 [conserved hypothetic...] (44,F)
TP0988 [conserved hypothetic...] - TP0676 [hypothetical protein...] (2,F)
TP0989 [P26 {Borrelia burgdo...] - TP0398 [flagellar hook-basal...] (114,W)

TP0989 [P26 {Borrelia burgdo...] - TP0518 [conserved hypothetic...] (70,W)
TP0989 [P26 {Borrelia burgdo...] - TP0764 [conserved hypothetic...] (139,W)
TP0989 [P26 {Borrelia burgdo...] - TP0907 [conserved hypothetic...] (110,W)
TP0991 [rubredoxin {Clostrid...] - TP0907 [conserved hypothetic...] (110,W)
TP0991 [rubredoxin {Clostrid...] - TP1004 [recombination protei...] (74,W)
TP0992 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP0992 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0992 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP0992 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP0994 [conserved hypothetic...] - TP0287 [conserved hypothetic...] (27,F)
TP0994 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP0994 [conserved hypothetic...] - TP0579 [hypothetical protein...] (5,F)
TP0994 [conserved hypothetic...] - TP0622 [hypothetical protein...] (1,F)
TP0994 [conserved hypothetic...] - TP0631 [protein-glutamate me...] (1,F)
TP0994 [conserved hypothetic...] - TP0763 [hypothetical protein...] (2,F)
TP0994 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP0994 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP0994 [conserved hypothetic...] - TP0976 [hypothetical protein...] (1,F)
TP0994 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP1002 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP1002 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP1002 [conserved hypothetic...] - TP0757 [polypeptide deformyl...] (36,F)
TP1002 [conserved hypothetic...] - TP0788 [hypothetical protein...] (132,W)
TP1002 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP1002 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP1002 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP1002 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP1004 [recombination protei...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP1004 [recombination protei...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP1005 [DNA polymerase III, ...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP1005 [DNA polymerase III, ...] - TP0661 [hypothetical protein...] (117,W)
TP1005 [DNA polymerase III, ...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP1005 [DNA polymerase III, ...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP1005 [DNA polymerase III, ...] - TP1005 [DNA polymerase III, ...] (44,F)
TP1006 [DNA gyrase, subunit ...] - TP0004 [hypothetical protein...] (2,F)
TP1006 [DNA gyrase, subunit ...] - TP0764 [conserved hypothetic...] (139,W)
TP1007 [thymidylate synthase...] - TP0060 [ribosomal protein L9...] (78,W)
TP1007 [thymidylate synthase...] - TP0398 [flagellar hook-basal...] (114,W)
TP1007 [thymidylate synthase...] - TP0563 [hypothetical protein...] (93,W)
TP1007 [thymidylate synthase...] - TP0788 [hypothetical protein...] (132,W)
TP1007 [thymidylate synthase...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP1007 [thymidylate synthase...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP1010 [nucleoside-diphospha...] - TP0060 [ribosomal protein L9...] (78,W)
TP1010 [nucleoside-diphospha...] - TP0258 [conserved hypothetic...] (173,W)
TP1010 [nucleoside-diphospha...] - TP0383 [conserved hypothetic...] (65,W)
TP1010 [nucleoside-diphospha...] - TP0563 [hypothetical protein...] (93,W)
TP1010 [nucleoside-diphospha...] - TP0788 [hypothetical protein...] (132,W)
TP1011 [peptidyl-tRNA hydrol...] - TP0258 [conserved hypothetic...] (173,W)
TP1011 [peptidyl-tRNA hydrol...] - TP0764 [conserved hypothetic...] (139,W)
TP1011 [peptidyl-tRNA hydrol...] - TP0788 [hypothetical protein...] (132,W)
TP1011 [peptidyl-tRNA hydrol...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP1013 [chaperonin (groES) {...] - TP0463 [hypothetical protein...] (8,F)
TP1017 [alanyl-tRNA syntheta...] - TP0004 [hypothetical protein...] (2,F)
TP1018 [conserved hypothetic...] - TP0154 [conserved hypothetic...] (1,F)
TP1018 [conserved hypothetic...] - TP0422 [hypothetical protein...] (1,F)
TP1018 [conserved hypothetic...] - TP0506 [trigger factor (tig)...] (1,F)
TP1018 [conserved hypothetic...] - TP0702 [conserved hypothetic...] (2,F)
TP1018 [conserved hypothetic...] - TP0956 [hypothetical protein...] (1,F)
TP1018 [conserved hypothetic...] - TP1040 [lysyl-tRNA synthetas...] (2,F)
TP1020 [glu-tRNA amidotransf...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP1023 [recX protein (recX) ...] - TP0518 [conserved hypothetic...] (70,W)
TP1023 [recX protein (recX) ...] - TP0563 [hypothetical protein...] (93,W)
TP1023 [recX protein (recX) ...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP1024 [ribosomal protein S9...] - TP0059 [hypothetical protein...] (21,F)
TP1024 [ribosomal protein S9...] - TP0060 [ribosomal protein L9...] (78,W)
TP1024 [ribosomal protein S9...] - TP0258 [conserved hypothetic...] (173,W)
TP1024 [ribosomal protein S9...] - TP0398 [flagellar hook-basal...] (114,W)
TP1024 [ribosomal protein S9...] - TP0743 [ribosomal protein L2...] (2,F)
TP1024 [ribosomal protein S9...] - TP0764 [conserved hypothetic...] (139,W)
TP1024 [ribosomal protein S9...] - TP0894 [conserved hypothetic...] (13,F)
TP1024 [ribosomal protein S9...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP1024 [ribosomal protein S9...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP1024 [ribosomal protein S9...] - TP1004 [recombination protei...] (74,W)
TP1032 [hypothetical protein...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP1032 [hypothetical protein...] - TP0258 [conserved hypothetic...] (173,W)
TP1032 [hypothetical protein...] - TP0661 [hypothetical protein...] (117,W)
TP1032 [hypothetical protein...] - TP0795 [hypothetical protein...] (4,F)
TP1032 [hypothetical protein...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP1033 [conserved hypothetic...] - TP0119 [amino acid ABC trans...] (1,F)
TP1033 [conserved hypothetic...] - TP0175 [hypothetical protein...] (1,F)
TP1033 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP1033 [conserved hypothetic...] - TP0288 [spore coat polysacch...] (77,W)
TP1033 [conserved hypothetic...] - TP0398 [flagellar hook-basal...] (114,W)
TP1033 [conserved hypothetic...] - TP0449 [hypothetical protein...] (51,W)
TP1033 [conserved hypothetic...] - TP0563 [hypothetical protein...] (93,W)
TP1033 [conserved hypothetic...] - TP0764 [conserved hypothetic...] (139,W)
TP1033 [conserved hypothetic...] - TP0870 [flagellar filament 3...] (79,W)
TP1033 [conserved hypothetic...] - TP0907 [conserved hypothetic...] (110,W)
TP1033 [conserved hypothetic...] - TP0961 [flagellar basal-body...] (84,W)
TP1033 [conserved hypothetic...] - TP0989 [P26 {Borrelia burgdo...] (180,W)
TP1033 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP1033 [conserved hypothetic...] - TP1004 [recombination protei...] (74,W)
TP1033 [conserved hypothetic...] - TP1005 [DNA polymerase III, ...] (44,F)
TP1033 [conserved hypothetic...] - TP1019 [glu-tRNA amidotransf...] (65,W)
TP1034 [conserved hypothetic...] - TP0043 [soluble lytic transg...] (1,F)
TP1034 [conserved hypothetic...] - TP0240 [ribosomal protein L7...] (2,F)
TP1034 [conserved hypothetic...] - TP0258 [conserved hypothetic...] (173,W)
TP1034 [conserved hypothetic...] - TP0269 [conserved hypothetic...] (3,F)
TP1034 [conserved hypothetic...] - TP0332 [hypothetical protein...] (1,F)
TP1034 [conserved hypothetic...] - TP0561 [conserved hypothetic...] (44,F)
TP1034 [conserved hypothetic...] - TP0842 [methionine aminopept...] (3,F)
TP1034 [conserved hypothetic...] - TP0903 [UDP-N-acetylmuramoyl...] (1,F)
TP1034 [conserved hypothetic...] - TP0917 [Mg2+ transport prote...] (49,F)
TP1034 [conserved hypothetic...] - TP0993 [rare lipoprotein A, ...] (285,W)
TP1037 [hemolysin III (hlyII...] - TP0281 [hypothetical protein...] (64,W)
TP1037 [hemolysin III (hlyII...] - TP0398 [flagellar hook-basal...] (114,W)
TP1037 [hemolysin III (hlyII...] - TP0661 [hypothetical protein...] (117,W)
TP1037 [hemolysin III (hlyII...] - TP0764 [conserved hypothetic...] (139,W)
TP1038 [bacterioferrin (TpF1...] - TP0171 [lipoprotein, 15 kDa ...] (17,F)
TP1038 [bacterioferrin (TpF1...] - TP0302 [conserved hypothetic...] (1,F)
TP1038 [bacterioferrin (TpF1...] - TP0795 [hypothetical protein...] (4,F)

Supplementary Table 3 PPI-links between predicted (PSORT2.0) subcellular locations

Location A	Location B	Z-Value	Number of Interactions
CytoplasmicMembrane	CytoplasmicMembrane	10.1	53
Cytoplasmic	Cytoplasmic	2.8	359
OuterMembrane	Unknown (Multiple Locations)	1.4	1
OuterMembrane	Unknown	1.3	13
Periplasmic	Unknown	1.1	38
CytoplasmicMembrane	Extracellular	1.0	1
Unknown	Unknown	0.9	264
OuterMembrane	Periplasmic	0.5	1
Cytoplasmic	Periplasmic	0.3	40
Unknown	Unknown (Multiple Locations)	0.3	13
Periplasmic	Unknown (Multiple Locations)	0.1	1
CytoplasmicMembrane	Unknown (Multiple Locations)	0.1	3
Extracellular	Unknown	-0.1	2
Cytoplasmic	Extracellular	-0.2	2
Cytoplasmic	Unknown	-0.3	584
Cytoplasmic	OuterMembrane	-0.5	11
Cytoplasmic	Unknown (Multiple Locations)	-0.6	12
CytoplasmicMembrane	Periplasmic	-1.7	5
CytoplasmicMembrane	Unknown	-2.3	123
Cytoplasmic	CytoplasmicMembrane	-5.2	107

Supplementary Table 4 TPA interactions vs. predicted interologs.

#	bait	description	prey	description	interologs	TPA dataset	compared with	orthology
1	TP0025	conserved hypothetical protein {Borrelia burgdorferi}	TP1040	lysyl-tRNA synthetase (lysS) {Escherichia coli}	CJ0401-CJ0463	filtered	CJE all	MBGD
					B1494-B2890 B2821-B2890	filtered	ECO II SAI	MBGD
					B1494-B2890 B2890-B2821	filtered	ECO II SPK	MBGD
2	TP0030	heat shock protein (groEL) {Treponema pallidum}	TP0160	prolyl-tRNA synthetase (proS) {Escherichia coli}	B0194-B4143	filtered	ECO II SPK	MBGD
					B0194-B4143	filtered	ECO II SPK	COG
3	TP0030	heat shock protein (groEL) {Treponema pallidum}	TP0946	glucose-inhibited division protein B (gidB) {Escherichia coli}	CJ1221-CJ0997	filtered	CJE all	COG
					CJ1221-CJ0997	filtered	CJE all	MBGD
					CJ1221-CJ0997	filtered	CJE HCF	COG
					CJ1221-CJ0997	filtered	CJE HCF	MBGD
4	TP0048	conserved hypothetical protein {Borrelia burgdorferi}	TP0870	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	HP1542-HP0601	all	HPY	MBGD
					HP1542-HP0601	all	HPY	COG
5	TP0058	replicative DNA helicase (dnaB) {Bacillus subtilis}	TP0092	RNA polymerase sigma factor E (rpoE) {Mycobacterium leprae}	B2573-B4052	filtered	ECO II SPK	MBGD
					B2573-B4052	filtered	ECO II SPK	COG
6	TP0068	conserved hypothetical protein {Synechocystis PCC6803}	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	CJ1157-CJ1713	filtered	CJE all	COG
					CJ1157-CJ1713	filtered	CJE all	MBGD
7	TP0094	phosphate acetyltransferase (pta) {Methanosarcina thermophila}	TP0067	conserved hypothetical protein {Borrelia burgdorferi}	B2463-B3530	filtered	ECO II SAI	COG
					B3530-B2463	filtered	ECO II SPK	COG
8	TP0094	phosphate acetyltransferase (pta) {Methanosarcina thermophila}	TP0519	response regulatory protein (atoC) {Borrelia burgdorferi}	B2297-B2731	filtered	ECO II SAI	MBGD
9	TP0094	phosphate acetyltransferase (pta) {Methanosarcina thermophila}	TP0920	hypothetical protein	B2463-B3530	filtered	ECO II SAI	COG
					B3530-B2463	filtered	ECO II SPK	COG
10	TP0100	thioredoxin, putative {Bradyrhizobium japonicum}	TP0005	DNA gyrase, subunit A (gyrA) {Bacillus subtilis}	CJ0147C-CJ1027C	filtered	CJE all	COG
11	TP0154	conserved hypothetical protein {Borrelia burgdorferi}	TP0060	ribosomal protein L9 (rplI) {Bacillus subtilis}	B1086-B4203	all	ECO I SPK	COG

12	TP0162	Holliday junction DNA helicase (ruvB) {Haemophilus influenzae}	TP0543	Holliday junction DNA helicase (ruvA) {Haemophilus influenzae}	CJ1362-CJ0799C CJ0799C-CJ1362	filtered	CJE all	COG
					CJ1362-CJ0799C CJ0799C-CJ1362	filtered	CJE all	MBGD
					CJ1362-CJ0799C CJ0799C-CJ1362	filtered	CJE HCF	COG
					CJ1362-CJ0799C CJ0799C-CJ1362	filtered	CJE HCF	MBGD
13	TP0192	ribosomal protein L2 (rplB) {Borrelia burgdorferi}	TP0756	methionyl-tRNA formyltransferase (fmt) {Haemophilus influenzae}	B2255-B3317	filtered	ECO II SPK	COG
14	TP0330	cell division protein (ftsH) {Mycoplasma genitalium}	TP0330	cell division protein (ftsH) {Mycoplasma genitalium}	B3178-B3178	filtered	ECO I SPK	COG
15	TP0344	transcription-repair coupling factor (trcF) {Borrelia burgdorferi}	TP0514	excinuclease ABC, subunit A (uvrA) {Bacillus subtilis}	HP0705-HP1541	filtered	HPY	MBGD
					HP0705-HP1541	filtered	HPY	COG
16	TP0459	conserved hypothetical protein {Borrelia burgdorferi}	TP0060	ribosomal protein L9 (rplI) {Bacillus subtilis}	B1269-B4203	all	ECO I SPK	MBGD
					B1269-B4203	all	ECO I SPK	COG
17	TP0468	conserved hypothetical protein {Bacillus subtilis}	TP0757	polypeptide deformylase (def) {Synechocystis PCC6803}	CJ0191C-CJ1679 CJ1679-CJ0191C	filtered	CJE all	COG
					CJ0191C-CJ1679 CJ1679-CJ0191C	filtered	CJE HCF	COG
18	TP0472	excinuclease ABC, subunit C (uvrC) {Methanobacterium thermoautotrophicum}	TP0894	conserved hypothetical protein {Synechocystic PCC6803}	HP0879-HP0821	filtered	HPY	COG
19	TP0507	ATP-dependent Clp protease proteolytic component (clpP) {Haemophilus influenzae}	TP0362	ribosomal protein L28 (rpmB) {Treponema pallidum}	B0437-B3637	filtered	ECO I SPK	MBGD
					B0437-B3637	filtered	ECO I SPK	COG
					CJ0192C-CJ0712	filtered	CJE all	COG
					CJ0192C-CJ0712	filtered	CJE all	MBGD
20	TP0519	response regulatory protein (atoC) {Borrelia burgdorferi}	TP0519	response regulatory protein (atoC) {Borrelia burgdorferi}	B2554-B2554 B2869-B2869	filtered	ECO I SPK	MBGD
					B2554-B2554	filtered	ECO I SPK	COG
21	TP0526	ATP-dependent helicase (hrpA) {Borrelia burgdorferi}	TP0892	N utilization substance protein A (nusA) {Borrelia burgdorferi}	B1413-B3169	filtered	ECO II SAI	MBGD
					B1413-B3169	filtered	ECO II SAI	COG
22	TP0622	hypothetical protein	TP0641	histidyl-tRNA synthetase (hisS) {Borrelia burgdorferi}	B2514-B3530	filtered	ECO II SAI	COG
					B2514-B3530	filtered	ECO II SPK	COG
23	TP0622	hypothetical protein	TP0684	Glucose/galactose-binding lipoprotein precursor	B2150-B2851	filtered	ECO I SAI	COG
24	TP0641	histidyl-tRNA synthetase (hisS) {Borrelia burgdorferi}	TP0641	histidyl-tRNA synthetase (hisS) {Borrelia burgdorferi}	CJ0765C-CJ0765C	filtered	CJE all	COG

					CJ0765C-CJ0765C	filtered	CJE all	MBGD
					B2514-B2514	filtered	ECO I SPK	MBGD
					B2514-B2514	filtered	ECO I SPK	COG
					CJ0765C-CJ0765C	filtered	CJE HCF	COG
					CJ0765C-CJ0765C	filtered	CJE HCF	MBGD
25	TP0642	phosphomannomutase (manB) {Bacillus subtilis}	TP0060	ribosomal protein L9 (rplI) {Bacillus subtilis}	B3176-B4203	all	ECO II SAI	MBGD
					B3176-B4203	all	ECO II SAI	COG
26	TP0648	conserved hypothetical protein {Borrelia burgdorferi}	TP0894	conserved hypothetical protein {Synechocystic PCC6803}	HP0879-HP0275 HP0879-HP1274	filtered	HPY	COG
27	TP0648	conserved hypothetical protein {Borrelia burgdorferi}	TP0943	flagellar protein (fliS) {Bacillus subtilis}	HP0753-HP1274	filtered	HPY	COG
28	TP0648	conserved hypothetical protein {Borrelia burgdorferi}	TP0965	membrane fusion protein, putative {Haemophilus influenzae}	CJ0606-CJ0390	filtered	CJE all	COG
					CJ0606-CJ0390	filtered	CJE HCF	COG
29	TP0659	flagellar hook-associated protein 3 (flgL) {Borrelia burgdorferi}	TP0160	prolyl-tRNA synthetase (proS) {Escherichia coli}	B0194-B1923	filtered	ECO II SAI	COG
					B1923-B0194	filtered	ECO II SPK	COG
30	TP0659	flagellar hook-associated protein 3 (flgL) {Borrelia burgdorferi}	TP1004	recombination protein (recR) {Haemophilus influenzae}	CJ0720C-CJ1263	all	CJE all	COG
					CJ0720C-CJ1263	all	CJE HCF	COG
31	TP0728	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	TP0100	thioredoxin, putative {Bradyrhizobium japonicum}	CJ0042-CJ0864	filtered	CJE all	COG
32	TP0738	conserved hypothetical protein {Bacillus subtilis}	TP0199	ribosomal protein L14 (rplN) {Borrelia burgdorferi}	CJ1697C-CJ1405	filtered	CJE all	COG
					CJ1697C-CJ1405	filtered	CJE all	MBGD
					B0637-B3310	filtered	ECO I SPK	MBGD
					B0637-B3310	filtered	ECO I SPK	COG
					CJ1697C-CJ1405	filtered	CJE HCF	COG
					CJ1697C-CJ1405	filtered	CJE HCF	MBGD
33	TP0756	methionyl-tRNA formyltransferase (fmt) {Haemophilus influenzae}	TP0060	ribosomal protein L9 (rplI) {Bacillus subtilis}	B3288-B4203	all	ECO II SPK	MBGD
					B3288-B4203	all	ECO II SPK	COG
34	TP0782	hypothetical protein	TP0554	phosphoglycolate phosphatase (gph) {Haemophilus influenzae}	CJ1275C-CJ1477C CJ1275C-CJ1233	filtered	CJE all	COG
					CJ1275C-CJ1477C	filtered	CJE HCF	COG
35	TP0792	flagellar filament 33 kDa core protein (flaB2) {Treponema pallidum}	TP0160	prolyl-tRNA synthetase (proS) {Escherichia coli}	B0194-B1923	filtered	ECO II SAI	MBGD
					B0194-B1923	filtered	ECO II SAI	COG
					B1923-B0194	filtered	ECO II SPK	MBGD
					B1923-B0194	filtered	ECO II SPK	COG

36	TP0792	flagellar filament 33 kDa core protein (flaB2) {Treponema pallidum}	TP0658	transmembrane protein, putative {Bacillus subtilis}	CJ0720C-CJ1075	filtered	CJE all	COG
					HP0601-HP1154 HP0601-HP1377	filtered	HPY	MBGD
					HP0601-HP1154 HP0601-HP1377	filtered	HPY	COG
37	TP0840	conserved hypothetical integral membrane protein {Archaeoglobus fulgidus}	TP0870	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	CJ0720C-CJ0987C	all	CJE all	COG
38	TP0840	conserved hypothetical integral membrane protein {Archaeoglobus fulgidus}	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	CJ1157-CJ0484	filtered	CJE all	COG
39	TP0868	flagellar filament 34.5 kDa core protein (flaB1) {Treponema pallidum}	TP0658	transmembrane protein, putative {Bacillus subtilis}	CJ0720C-CJ1075	filtered	CJE all	COG
					HP0601-HP1154 HP0601-HP1377	filtered	HPY	MBGD
					HP0601-HP1154 HP0601-HP1377	filtered	HPY	COG
40	TP0870	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	TP0053	ribonucleoside-diphosphate reductase, subunit beta (nrdB) {Helicobacter pylori}	B1083-B2676	filtered	ECO II SAI	COG
					B1083-B2676	all	ECO II SAI	COG
41	TP0870	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	TP0640	methyl-accepting chemotaxis protein (mcp2) {Treponema pallidum}	CJ0720C-CJ1190C CJ0720C-CJ0246C	filtered	CJE all	COG
					B1923-B3072	filtered	ECO II SAI	MBGD
					B1923-B3072	filtered	ECO II SAI	COG
					CJ0720C-CJ1190C CJ0720C-CJ0246C	filtered	CJE HCF	COG
42	TP0870	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	TP0658	transmembrane protein, putative {Bacillus subtilis}	CJ0720C-CJ1075	filtered	CJE all	COG
					HP0601-HP1154 HP0601-HP1377	filtered	HPY	MBGD
					HP0601-HP1154 HP0601-HP1377	filtered	HPY	COG
43	TP0870	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	TP0702	conserved hypothetical protein {Borrelia burgdorferi}	CJ0720C-CJ1087C	filtered	CJE all	COG
					CJ0720C-CJ1087C	filtered	CJE HCF	COG
44	TP0870	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	TP0943	flagellar protein (fliS) {Bacillus subtilis}	CJ1338C-CJ0549 CJ0720C-CJ0549 CJ1339C-CJ0549	filtered	CJE all	COG
					CJ1338C-CJ0549 CJ1339C-CJ0549	filtered	CJE all	MBGD
					HP0601-HP0753 HP0753-HP0115	filtered	HPY	MBGD
					HP0601-HP0753 HP0753-HP0115	filtered	HPY	COG
					CJ1338C-CJ0549 CJ0720C-CJ0549 CJ1339C-CJ0549	filtered	CJE HCF	COG
					CJ1338C-CJ0549 CJ1339C-CJ0549	filtered	CJE HCF	MBGD
45	TP0870	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	TP0981	sensory transduction histidine kinase, putative	B1490-B1923	filtered	ECO II SAI	MBGD

				{Synechocystis PCC6803}				
					B1490-B1923 B1490-B1923	filtered	ECO II SAI	COG
46	TP0875	conserved hypothetical protein {Synechocystis PCC6803}	TP0240	ribosomal protein L7/L12 (rplL) {Haemophilus influenzae}	B4168-B3986	filtered	ECO I SPK	MBGD
					B4168-B3986	filtered	ECO I SPK	COG
47	TP0903	UDP-N-acetylmuramoylalanine--D-glutamate ligase (murD) {Borrelia burgdorferi}	TP0100	thioredoxin, putative {Bradyrhizobium japonicum}	B2582-B0088	filtered	ECO I SPK	COG
48	TP0905	ribosomal protein S16 (rpsP) {Bacillus subtilis}	TP0236	transcription antitermination protein (nusG) {Borrelia burgdorferi}	B3982-B2609	filtered	ECO I SPK	MBGD
					B3982-B2609	filtered	ECO I SPK	COG
49	TP0939	pyruvate oxidoreductase {Synechocystis PCC6803}	TP0396	flagellar basal-body rod protein (flgB) {Treponema denticola}	HP1559-HP0589	filtered	HPY	COG
50	TP0939	pyruvate oxidoreductase {Synechocystis PCC6803}	TP0961	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	CJ0536-CJ0697	all	CJE all	COG
					CJ0536-CJ0697	all	CJE HCF	COG
51	TP0943	flagellar protein (fliS) {Bacillus subtilis}	TP0870	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	CJ1338C-CJ0549 CJ0720C-CJ0549 CJ1339C-CJ0549	all	CJE all	COG
					CJ1338C-CJ0549 CJ1339C-CJ0549	all	CJE all	MBGD
					HP0601-HP0753 HP0753-HP0115	all	HPY	MBGD
					HP0601-HP0753 HP0753-HP0115	all	HPY	COG
					CJ1338C-CJ0549 CJ0720C-CJ0549 CJ1339C-CJ0549	all	CJE HCF	COG
					CJ1338C-CJ0549 CJ1339C-CJ0549	all	CJE HCF	MBGD
52	TP0954	conserved hypothetical protein {Methanobacterium thermoautotrophicum}	TP0044	glucose inhibited division protein A (gidA) {Borrelia burgdorferi}	B3530-B3741	filtered	ECO II SAI	MBGD
					B3530-B3741	filtered	ECO II SAI	COG
					B3741-B3530	filtered	ECO II SPK	MBGD
					B3741-B3530	filtered	ECO II SPK	COG
53	TP0963	conserved hypothetical integral membrane protein {Bacillus subtilis} _	TP0870	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	CJ0720C-CJ1662	all	CJE all	COG
					CJ0720C-CJ1662	all	CJE HCF	COG
54	TP0963	conserved hypothetical integral membrane protein {Bacillus subtilis} _	TP0961	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	CJ0697-CJ1662	all	CJE all	COG
55	TP0981	sensory transduction histidine kinase, putative {Synechocystis PCC6803}	TP0005	DNA gyrase, subunit A (gyrA) {Bacillus subtilis}	CJ0643-CJ1027C	filtered	CJE all	MBGD
56	TP0981	sensory transduction histidine kinase, putative {Synechocystis	TP0870	flagellar filament 31 kDa core protein (flaB3) {Treponema	B1490-B1923	all	ECO II SAI	MBGD

		PCC6803}		pallidum}				
					B1490-B1923 B1490-B1923	all	ECO II SAI	COG
57	TP0985	aspartyl-tRNA synthetase (aspS) {Borrelia burgdorferi}	TP0735	glutamate synthase (gltA) {Pyrococcus sp.}	B1866-B3213	filtered	ECO I SPK	MBGD
					B1866-B3213	filtered	ECO I SPK	COG
58	TP0985	aspartyl-tRNA synthetase (aspS) {Borrelia burgdorferi}	TP0965	membrane fusion protein, putative {Haemophilus influenzae}	B1866-B3513	filtered	ECO II SAI	COG
59	TP0986	conserved hypothetical integral membrane protein {Helicobacter pylori}	TP0870	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	CJ0720C-CJ1544C CJ0720C-CJ0385C	all	CJE all	COG
					CJ0720C-CJ1544C	all	CJE HCF	COG
60	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	CJ1157-CJ1157	filtered	CJE all	COG
					CJ1157-CJ1157	filtered	CJE all	MBGD
					B0470-B0470	filtered	ECO I SPK	MBGD
					B0470-B0470	filtered	ECO I SPK	COG
					CJ1157-CJ1157	filtered	CJE HCF	COG
					CJ1157-CJ1157	filtered	CJE HCF	MBGD

Supplementary Table 5 Interologs retested with H. pylori orthologs. "+" indicates positive result and "(+)" was not marked as positive due to Y2H activation in control.

bait	description	prey	description	bait ortholog	prey ortholog	Interolog reproduced
TP0044	glucose inhibited division protein A (gidA) {Borrelia burgdorferi}	TP0512	conserved hypothetical protein {Rhodobacter capsulatus}	HP0213	HP1020	
TP0058	replicative DNA helicase (dnaB) {Bacillus subtilis}	TP0001	chromosomal replication initiator protein (dnaA) {Borrelia burgdorferi}	HP1362	HP1529	
TP0058	replicative DNA helicase (dnaB) {Bacillus subtilis}	TP0005	DNA gyrase, subunit A (gyrA) {Bacillus subtilis}	HP1362	HP0701	
TP0058	replicative DNA helicase (dnaB) {Bacillus subtilis}	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	HP1362	HP0717	
TP0271	chromosome partitioning protein (parB) {Caulobacter crescentus}	TP0198	ribosomal protein S17 (rpsQ) {Bacillus stearothermophilus}	HP1138	HP1310	
TP0271	chromosome partitioning protein (parB) {Caulobacter crescentus}	TP0305	CTP synthase (pyrG) {Synechocystis PCC6803}	HP1138	HP0349	
TP0271	chromosome partitioning protein (parB) {Caulobacter crescentus}	TP0386	UDP-N-acetylmuramoylalanyl-D-glutamyl-2,6-diaminopimelate--D-alanyl-D-alanine ligase (murF) {Synechocystis PCC6803}	HP1138	HP0740	
TP0271	chromosome partitioning protein (parB) {Caulobacter crescentus}	TP0586	leucyl-tRNA synthetase (leuS) {Borrelia burgdorferi}	HP1138	HP1547	(+)
TP0272	SpoOJ regulator (soj) {Bacillus subtilis}	TP0060	ribosomal protein L9 (rplI) {Bacillus subtilis}	HP1139	HP0514	
TP0272	SpoOJ regulator (soj) {Bacillus subtilis}	TP0188	ribosomal protein S10 (rpsJ) {Borrelia burgdorferi}	HP1139	HP1320	
TP0272	SpoOJ regulator (soj) {Bacillus subtilis}	TP0247	N-acetylmuramoyl-L-alanine amidase (amiA) {Escherichia coli}	HP1139	HP0772	+
TP0296	conserved hypothetical protein {Pseudomonas putida}	TP0578	cell division protein (ftsY) {Bacillus subtilis}	HP0831	HP0763	
TP0339	conserved hypothetical protein {Borrelia burgdorferi}	TP0632	tryptophanyl-tRNA synthetase (trsA) {Borrelia burgdorferi}	HP0745	HP1253	
TP0339	conserved hypothetical protein {Borrelia burgdorferi}	TP0728	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	HP0745	HP0907	

TP0384	conserved hypothetical protein {Borrelia burgdorferi}	TP0396	flagellar basal-body rod protein (flgB) {Treponema denticola}	HP0707	HP1559
TP0387	cell division protein (ftsW) {Borrelia burgdorferi}	TP0236	transcription antitermination protein (nusG) {Borrelia burgdorferi}	HP1560	HP1203
TP0387	cell division protein (ftsW) {Borrelia burgdorferi}	TP0270	polynucleotide adenylyltransferase (pcnA) {Borrelia burgdorferi}	HP1560	HP0640
TP0390	cell division protein (ftsZ) {Borrelia burgdorferi}	TP0001	chromosomal replication initiator protein (dnaA) {Borrelia burgdorferi}	HP0979	HP1529
TP0390	cell division protein (ftsZ) {Borrelia burgdorferi}	TP0060	ribosomal protein L9 (rplI) {Bacillus subtilis}	HP0979	HP0514
TP0464	conserved hypothetical protein {Haemophilus influenzae}	TP0477	glucose-6-phosphate dehydrogenase isozyme (devB) {Actinobacillus actinomycetemcomitans}	HP0747	HP1102
TP0464	conserved hypothetical protein {Haemophilus influenzae}	TP0712	ATP-binding protein (ylxH) {Treponema pallidum}	HP0747	HP1034
TP0464	conserved hypothetical protein {Haemophilus influenzae}	TP0888	riboflavin kinase/FMN adenylyltransferase (ribF) {Escherichia coli}	HP0747	HP1087
TP0492	DNA primase (dnaE) {Clostridium acetobutylicum}	TP0001	chromosomal replication initiator protein (dnaA) {Borrelia burgdorferi}	HP0012	HP1529
TP0492	DNA primase (dnaE) {Clostridium acetobutylicum}	TP0005	DNA gyrase, subunit A (gyrA) {Bacillus subtilis}	HP0012	HP0701
TP0492	DNA primase (dnaE) {Clostridium acetobutylicum}	TP0160	prolyl-tRNA synthetase (proS) {Escherichia coli}	HP0012	HP0238
TP0492	DNA primase (dnaE) {Clostridium acetobutylicum}	TP0305	CTP synthase (pyrG) {Synechocystis PCC6803}	HP0012	HP0349
TP0492	DNA primase (dnaE) {Clostridium acetobutylicum}	TP0396	flagellar basal-body rod protein (flgB) {Treponema denticola}	HP0012	HP1559
TP0492	DNA primase (dnaE) {Clostridium acetobutylicum}	TP0519	response regulatory protein (atoC) {Borrelia burgdorferi}	HP0012	HP0703
TP0492	DNA primase (dnaE) {Clostridium acetobutylicum}	TP0797	1-pyrroline-5-carboxylate reductase (proC) {Treponema pallidum}	HP0012	HP1158
TP0492	DNA primase (dnaE) {Clostridium acetobutylicum}	TP0939	pyruvate oxidoreductase {Synechocystis PCC6803}	HP0012	HP1111
TP0492	DNA primase (dnaE) {Clostridium acetobutylicum}	TP1006	DNA gyrase, subunit B (gyrB) {Treponema pallidum}	HP0012	HP0501
TP0497	rod shape-determining protein (mreB) {Borrelia burgdorferi}	TP0001	chromosomal replication initiator protein (dnaA) {Borrelia burgdorferi}	HP1373	HP1529
TP0497	rod shape-determining protein (mreB) {Borrelia burgdorferi}	TP0060	ribosomal protein L9 (rplI) {Bacillus subtilis}	HP1373	HP0514

TP0501	rod shape-determining protein (rodA) {Borrelia burgdorferi}	TP0113	Lambda CII stability-governing protein (hflK) {Treponema pallidum}	HP0743	HP0248	
TP0506	trigger factor (tig) {Borrelia burgdorferi}	TP0605	translation elongation factor TS (tsf) {Spirulina platensis}	HP0795	HP1555	
TP0506	trigger factor (tig) {Borrelia burgdorferi}	TP0712	ATP-binding protein (ylxH) {Treponema pallidum}	HP0795	HP1034	
TP0578	cell division protein (ftsY) {Bacillus subtilis}	TP0160	prolyl-tRNA synthetase (proS) {Escherichia coli}	HP0763	HP0238	+
TP0582	conserved hypothetical integral membrane protein {Borrelia burgdorferi}	TP0160	prolyl-tRNA synthetase (proS) {Escherichia coli}	HP0787	HP0238	+
TP0582	conserved hypothetical integral membrane protein {Borrelia burgdorferi}	TP0397	flagellar basal-body rod protein (flgC) {Treponema denticola}	HP0787	HP1558	
TP0582	conserved hypothetical integral membrane protein {Borrelia burgdorferi}	TP0765	cell division protein (ftsH) {Helicobacter pylori}	HP0787	HP1069	
TP0582	conserved hypothetical integral membrane protein {Borrelia burgdorferi}	TP0965	membrane fusion protein, putative {Haemophilus influenzae}	HP0787	HP0606	
TP0582	conserved hypothetical integral membrane protein {Borrelia burgdorferi}	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	HP0787	HP0717	
TP0658	transmembrane protein, putative {Bacillus subtilis}	TP0831	arginyl-tRNA synthetase (argS) {Borrelia burgdorferi}}	HP1154	HP0319	
TP0658	transmembrane protein, putative {Bacillus subtilis}	TP0939	pyruvate oxidoreductase {Synechocystis PCC6803}	HP1154	HP1111	(+)
TP0720	flagellar motor switch protein (fliY) {Treponema pallidum}	TP0048	conserved hypothetical protein {Borrelia burgdorferi}	HP1030	HP1542	
TP0720	flagellar motor switch protein (fliY) {Treponema pallidum}	TP0160	prolyl-tRNA synthetase (proS) {Escherichia coli}	HP1030	HP0238	+
TP0720	flagellar motor switch protein (fliY) {Treponema pallidum}	TP0193	ribosomal protein S19 (rpsS) {Borrelia burgdorferi}	HP1030	HP1315	
TP0720	flagellar motor switch protein (fliY) {Treponema pallidum}	TP0397	flagellar basal-body rod protein (flgC) {Treponema denticola}	HP1030	HP1558	
TP0720	flagellar motor switch protein (fliY) {Treponema pallidum}	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	HP1030	HP0717	
TP0728	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	TP0005	DNA gyrase, subunit A (gyrA) {Bacillus subtilis}	HP0907	HP0701	
TP0728	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	TP0160	prolyl-tRNA synthetase (proS) {Escherichia coli}	HP0907	HP0238	

TP0728	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	TP0396	flagellar basal-body rod protein (flgB) {Treponema denticola}	HP0907	HP1559	
TP0728	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	TP0586	leucyl-tRNA synthetase (leuS) {Borrelia burgdorferi}	HP0907	HP1547	
TP0754	conserved hypothetical protein {Haemophilus influenzae}	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	HP0269	HP0717	+
TP0765	cell division protein (ftsH) {Helicobacter pylori}	TP0814	thioredoxin reductase (trxB) {Bacillus subtilis}	HP1069	HP0825	
TP0794	S-adenosylmethionine synthetase (metK) {Escherichia coli}	TP0002	DNA polymerase III, subunit beta (dnaN) {Pseudomonas putida}	HP0197	HP0500	
TP0875	conserved hypothetical protein {Synechocystis PCC6803}	TP0060	ribosomal protein L9 (rplI) {Bacillus subtilis}	HP0716	HP0514	
TP0875	conserved hypothetical protein {Synechocystis PCC6803}	TP0240	ribosomal protein L7/L12 (rplL) {Haemophilus influenzae}	HP0716	HP1199	
TP0875	conserved hypothetical protein {Synechocystis PCC6803}	TP0247	N-acetylmuramoyl-L-alanine amidase (amiA) {Escherichia coli}	HP0716	HP0772	
TP0903	UDP-N-acetylmuramoylalanine--D-glutamate ligase (murD) {Borrelia burgdorferi}	TP0001	chromosomal replication initiator protein (dnaA) {Borrelia burgdorferi}	HP0494	HP1529	
TP0903	UDP-N-acetylmuramoylalanine--D-glutamate ligase (murD) {Borrelia burgdorferi}	TP0396	flagellar basal-body rod protein (flgB) {Treponema denticola}	HP0494	HP1559	
TP0905	ribosomal protein S16 (rpsP) {Bacillus subtilis}	TP0060	ribosomal protein L9 (rplI) {Bacillus subtilis}	HP1151	HP0514	
TP0905	ribosomal protein S16 (rpsP) {Bacillus subtilis}	TP0236	transcription antitermination protein (nusG) {Borrelia burgdorferi}	HP1151	HP1203	
TP0905	ribosomal protein S16 (rpsP) {Bacillus subtilis}	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	HP1151	HP0717	
TP0939	pyruvate oxidoreductase {Synechocystis PCC6803}	TP0396	flagellar basal-body rod protein (flgB) {Treponema denticola}	HP1111	HP1559	
TP0946	glucose-inhibited division protein B (gidB) {Escherichia coli}	TP0160	prolyl-tRNA synthetase (proS) {Escherichia coli}	HP1063	HP0238	(+)
TP0946	glucose-inhibited division protein B (gidB) {Escherichia coli}	TP0514	excinuclease ABC, subunit A (uvrA) {Bacillus subtilis}	HP1063	HP0705	

TP0965	membrane fusion protein, putative {Haemophilus influenzae}	TP0514	excinuclease ABC, subunit A (uvrA) {Bacillus subtilis}	HP0606	HP0705
TP0965	membrane fusion protein, putative {Haemophilus influenzae}	TP0965	membrane fusion protein, putative {Haemophilus influenzae}	HP0606	HP0606
TP0999	cell division protein, putative {Borrelia burgdorferi}	TP0051	peptide chain release factor 1 (prfA) {Borrelia burgdorferi}	HP1090	HP0077
TP0999	cell division protein, putative {Borrelia burgdorferi}	TP0186	oxygen-independent coproporphyrinogen III oxidase, putative {Bacillus subtilis}	HP1090	HP1226

Supplementary Table 6 MCODE complexes identified in ECO MORI SAI network (>2 proteins).

Complex	Score (Density* #Proteins)	Proteins	Interactions	Protein names
1	5,963	27	161	b1962, b0383, b3168, b1942, b2898, b1478, b0804, b0346, b0800, b3077, b0949, b4297, b2712, b0239, b0335, b0284, b2049, b1048, b3311, b2026, b1552, b4382, b3924, b1655, b3880, b0861, b4017
2	5,125	32	164	b1923, b4351, b3998, b4464, b3945, b4362, b0084, b2920, b1710, b3056, b0414, b3895, b2506, b3520, b0297, b1270, b1569, b3058, b1918, b1266, b1257, b1820, b4162, b1462, b1118, b0300, b0231, b2929, b3072, b0646, b1418, b3462
3	4,111	36	148	b0264, b3349, b1161, b0345, b0311, b1490, b4294, b3271, b3185, b0225, b0624, b3293, b1164, b1275, b1751, b0956, b0582, b4371, b2480, b2394, b0016, b0632, b0997, b4375, b4355, b1886, b2301, b0074, b3149, b0360, b0868, b4277, b0255, b1736, b1810, b0274
4	4	9	36	b1024, b2614, b2471, b0413, b2017, b1221, b1638, b2461, b4480
5	3,504	113	396	b0012, b0623, b2566, b4312, b0191, b1213, b0846, b0988, b4200, b0148, b3609, b3499, b3600, b2485, b0707, b3803, b0963, b4366, b0982, b2296, b2551, b3158, b1276, b1547, b1834, b3780, b1881, b4041, b0676, b4479, b0382, b2779, b0602, b0042, b3453, b1807, b2213, b3990, b1799, b4263, b2759, b3223, b0393, b1356, b2601, b2431, b3100, b2581, b3838, b2993, b2131, b3947, b0376, b0717, b1712, b3066, b3067, b1727, b3905, b3054, b2494, b0626, b3203, b2976, b3181, b3923, b3836, b3928, b2528, b0974, b2915, b3922, b3901, b1651, b3183, b3866, b0190, b1679, b1477, b3021, b0469, b1379, b3555, b1809, b2124, b3125, b3157, b3859, b0921, b3516, b1123, b1114, b2529, b1647, b0568, b4209, b3042, b1084, b3065, b1467, b1779, b0957, b0929, b0724, b3846, b1926, b0200, b0654, b1450, b1568, b1209, b2478, b2222
6	3,5	16	56	b1090, b0127, b1368, b2425, b1624, b0273, b3688, b0406, b3086, b3623, b3431, b4014, b2944, b4192, b1264, b3440
7	3,227	22	71	b4059, b2509, b4191, b0182, b2382, b2812, b3347, b1683, b3731, b0172, b1682, b0437, b4170, b0214, b0436, b1072, b0328, b4113, b0944, b0438, b1131, b0547

8	2,712	344	933	b2872, b0109, b3469, b3794, b3237, b2369, b0121, b0123, b1876, b3287, b3407, b1435, b1612, b0635, b2155, b2965, b2903, b3393, b0143, b0145, b1625, b3889, b0005, b2783, b1217, b2511, b2491, b3316, b4346, b2259, b2631, b1198, b1664, b2518, b4266, b0569, b3626, b1200, b4280, b1203, b3845, b1272, b0995, b4141, b4329, b0620, b0907, b2532, b2224, b4316, b1288, b2076, b1258, b1260, b0060, b0695, b3894, b4034, b1833, b1482, b2821, b2355, b2428, b0641, b3616, b4469, b0903, b1995, b0150, b4348, b2916, b3619, b2541, b3250, b3942, b1968, b3338, b0043, b2893, b0126, b1870, b0939, b4398, b3082, b3636, b3154, b2290, b0728, b2387, b0550, b1686, b3170, b1045, b1064, b3133, b0083, b2672, b0699, b2520, b1531, b3003, b1424, b3387, b1215, b3032, b0251, b3604, b2427, b4283, b2364, b3789, b0925, b2285, b3573, b1165, b0524, b1524, b0525, b4324, b2914, b2831, b3590, b4201, b1724, b0449, b2619, b0893, b2095, b3240, b1622, b4233, b0034, b2122, b2930, b1461, b1842, b1086, b4174, b0937, b1389, b2251, b2207, b0303, b0642, b3486, b4070, b1059, b3594, b3857, b3860, b0215, b0227, b1271, b1269, b3725, b3856, b1618, b0177, b3606, b3865, b1007, b1589, b4470, b3106, b4202, b0826, b3247, b1286, b3967, b1509, b3234, b1082, b1083, b1070, b2676, b2303, b4396, b4179, b2583, b2896, b3022, b2732, b2082, b0233, b2988, b1294, b0678, b1171, b3437, b2867, b3165, b3396, b2255, b3418, b2733, b0651, b2079, b3404, b2078, b0369, b2685, b1611, b2629, b3352, b2997, b1388, b0984, b1637, b3821, b3753, b3143, b4384, b1676, b4061, b0054, b2060, b0491, b1352, b2064, b1026, b0541, b0299, b0372, b2458, b3835, b2468, b3884, b3665, b0021, b4478, b0447, b4274, b1944, b4006, b3029, b1915, b3014, b4245, b2940, b1432, b2134, b3833, b3929, b3195, b2111, b2125, b0330, b1922, b0223, b2777, b0285, b0427, b2716, b3430, b3533, b0594, b0593, b4033, b0588, b1889, b3983, b4285, b0523, b2895, b1183, b1560, b0585, b2284, b1617, b0630, b3703, b0116, b3220, b4049, b2282, b3030, b1508, b2287, b1613, b3679, b2660, b0403, b0480, b2338, b1458, b1530, b1199, b3936, b2519, b3476, b2463, b2836, b1069, b0768, b2996, b3102, b0928, b1457, b0073, b1731, b2650, b0327, b2671, b0876, b2101, b0149, b3256, b0415, b1860, b3920, b1394, b1792, b4108, b0537, b4310, b3800, b4166, b3517, b0117, b1074, b3565, b1702, b1857, b1849, b1519, b1931, b1081, b4331, b2806, b0008, b1973, b4287, b3530, b0688, b2906, b0950, b4383, b4271, b0516, b0566, b0323, b1247, b1725, b1723
9	2,571	7	18	b1273, b1953, b3937, b0464, b2953, b0230, b1777
10	2,5	6	15	b3700, b0093, b1218, b3337, b2747, b2750
11	2,5	6	15	b1512, b1452, b0476, b2572, b2548, b0910
12	2,5	6	15	b0298, b1806, b0540, b2474, b1554, b0373
13	2,2	15	33	b1786, b3041, b2493, b2437, b0258, b2151, b2502, b4098, b0531, b1028, b2462, b2624, b2848, b1522, b0036
14	2,1	10	21	b4087, b2935, b0357, b4466, b0829, b3644, b2545, b2029, b3933, b2628
15	2	5	10	b0146, b3973, b3405, b3917, b3194
16	2	5	10	b0990, b1347, b0122, b0493, b3354
17	2	5	10	b2141, b3049, b1811, b4455, b1419
18	1,889	9	17	b3397, b0053, b2820, b2908, b2698, b0033, b4038, b1146, b2300
19	1,819	83	151	b0763, b2523, b2039, b2273, b2708, b0551, b2434, b3931, b1761, b2430, b4340, b4254, b4235, b4264, b0276, b1022, b0173, b2829, b4486, b0799, b1019, b3788, b1414, b1096, b1097, b2499, b2165, b1808, b2592, b2697, b1972, b3329, b0254, b2863, b4029, b4253, b3129, b0460, b1179, b3236, b4081, b3940, b2206, b3611, b0099, b4172, b1744, b2166, b1772, b1470, b1253, b2802, b2080, b3167, b3384, b3321, b4223, b0736, b1718, b0426, b2517, b0035, b3094, b2297, b1495, b2765, b0981, b2992, b2476, b3801, b0754, b3458, b3342, b2220, b3017, b2576, b2594, b0905, b0803, b0235, b2586, b1709, b2253
20	1,778	9	16	b0889, b1291, b3591, b1742, b0180, b1983, b2585, b0885, b2744
21	1,62	71	115	b1693, b0960, b0221, b3305, b0051, b1749, b3696, b3745, b0304, b3241, b0085, b2819, b3912, b2763, b4135, b2938, b0375, b1501, b0592, b0441, b3605, b0892, b2100, b1144, b1174, b3868, b2917, b0257, b2782, b2890, b1919, b0068, b0062, b2066, b3551, b3830, b1232, b3918, b1485, b1236, b2042, b1982, b1513, b3460, b3935, b0481, b0170, b3875, b1107, b3414, b3992, b2113, b0617, b1426, b2942, b0380, b0704, b2937, b4215, b2866, b3402, b2780, b2869, b0267, b2675, b2817, b2745, b2114, b4220, b0571, b1284

22	1,568	37	58	b4401, b1892, b4146, b4241, b4045, b4217, b3502, b2323, b2582, b4387, b3525, b1176, b0959, b0710, b2847, b1675, b1541, b0732, b2950, b0240, b0945, b0973, b3484, b0705, b1460, b2194, b2515, b1797, b2209, b0735, b4392, b1848, b1960, b1110, b0968, b2620, b4046
23	1,545	11	17	b0039, b1410, b2870, b1343, b3746, b1120, b1855, b1783, b2452, b3699, b3749
24	1,545	11	17	b0037, b3135, b0512, b2913, b3829, b2216, b1177, b3813, b4305, b0519, b3051
25	1,5	4	6	b2467, b2028, b1763, b3903
26	1,5	4	6	b1750, b0421, b2575, b0217
27	1,5	4	6	b4378, b2687, b2952, b3152
28	1,5	4	6	b2140, b1614, b2235, b1116
29	1,5	4	6	b2320, b1873, b3289, b1814
30	1,5	4	6	b0506, b0785, b3560, b0831
31	1,5	4	6	b2489, b3932, b2958, b2986
32	1,5	8	12	b3309, b3890, b0539, b3737, b0881, b1518, b4224, b2849
33	1,5	4	6	b2286, b0526, b2905, b3182
34	1,5	4	6	b1872, b2311, b0366, b2087
35	1,5	4	6	b4112, b2795, b2715, b4119
36	1,5	4	6	b3046, b2632, b2854, b2718
37	1,5	4	6	b2607, b3018, b2481, b0192
38	1,5	4	6	b3708, b1536, b2268, b1317
39	1,492	118	176	b2891, b3982, b1827, b3540, b1687, b1423, b4399, b0720, b1507, b2020, b2700, b3482, b2232, b2507, b3034, b4221, b0492, b0700, b3648, b0544, b3774, b3313, b2516, b3558, b0496, b2788, b4095, b1885, b1635, b4236, b1523, b2068, b3341, b3984, b0077, b2240, b3635, b3630, b3288, b3296, b2460, b1671, b2610, b2032, b3689, b1345, b0677, b3385, b1897, b0508, b0636, b0658, b2315, b1866, b1261, b0247, b3863, b2081, b2702, b1539, b2167, b0462, b0884, b2132, b2234, b1719, b2956, b2970, b0472, b4019, b3290, b4482, b3467, b2669, b1023, b1949, b4129, b0026, b3426, b1609, b3872, b2662, b0628, b3421, b0727, b3251, b0849, b4377, b1222, b3806, b4088, b3625, b0355, b3008, b4322, b1301, b3848, b0827, b2603, b2556, b0824, b4238, b0038, b0497, b3593, b3340, b4005, b3997, b2162, b1066, b2281, b0575, b2729, b2379, b2138, b4358, b3744, b1259
40	1,4	35	49	b2294, b0351, b2781, b1349, b0863, b1765, b0859, b3764, b1014, b3825, b2887, b1338, b0777, b1193, b2436, b2316, b3390, b2979, b3646, b1333, b1336, b0596, b2969, b3734, b0567, b2984, b0607, b0694, b2980, b3631, b3423, b3781, b1175, b1334, b3115
41	1,375	8	11	b3686, b3779, b0337, b2525, b1046, b1430, b3687, b2337
42	1,353	17	23	b0090, b0405, b3567, b0279, b0755, b1594, b2103, b2569, b4196, b2710, b2760, b3432, b2053, b4144, b0167, b4213, b1491
43	1,25	4	5	b0812, b1680, b1065, b0608
44	1,25	4	5	b4472, b2784, b1902, b1584
45	1,2	5	6	b0107, b2825, b2946, b2948, b1348
46	1,2	5	6	b4394, b3911, b3053, b3189, b1184
47	1,2	5	6	b3570, b3355, b0031, b0807, b4333

Supplementary Table 7 Y2H interactions supported by StringDB (COG) at medium confidence level

	bait	prey	definition bait	definition prey	combined score	genomic context score
1	TP0054	TP0095	conserved hypothetical protein {Escherichia coli}	hypothetical protein	410	247
2	TP0058	TP0001	replicative DNA helicase (dnaB) {Bacillus subtilis}	chromosomal replication initiator protein (dnaA) {Borrelia burgdorferi}	997	199
3	TP0058	TP0005	replicative DNA helicase (dnaB) {Bacillus subtilis}	DNA gyrase, subunit A (gyrA) {Bacillus subtilis}	742	173
4	TP0058	TP1005	replicative DNA helicase (dnaB) {Bacillus subtilis}	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	963	195
5	TP0067	TP1005	conserved hypothetical protein {Borrelia burgdorferi}	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	745	89
6	TP0103	TP1004	ATP-dependent DNA helicase, putative {Escherichia coli}	recombination protein (recR) {Haemophilus influenzae}	842	0
7	TP0124	TP0005	conserved hypothetical GTP-binding protein {Borrelia burgdorferi}	DNA gyrase, subunit A (gyrA) {Bacillus subtilis}	807	0
8	TP0124	TP0067	conserved hypothetical GTP-binding protein {Borrelia burgdorferi}	conserved hypothetical protein {Borrelia burgdorferi}	461	308
9	TP0162	TP0543	Holliday junction DNA helicase (ruvB) {Haemophilus influenzae}	Holliday junction DNA helicase (ruvA) {Haemophilus influenzae}	999	963
10	TP0290	TP0044	conserved hypothetical protein {Lactobacillus sake}	glucose inhibited division protein A (gidA) {Borrelia burgdorferi}	477	0
11	TP0328	TP0095	DNA mismatch repair protein (mutS) {Borrelia burgdorferi}	hypothetical protein	711	0
12	TP0343	TP0470	A/G-specific adenine glycosylase, putative {Helicobacter pylori}	conserved hypothetical protein {Synechocystis PCC6803}	469	0
13	TP0344	TP0514	transcription-repair coupling factor (trcF) {Borrelia burgdorferi}	excinuclease ABC, subunit A (uvrA) {Bacillus subtilis}	946	0
14	TP0380	TP0095	DNA repair helicase, putative {Saccharomyces cerevisiae}	hypothetical protein	551	0
15	TP0386	TP0383	UDP-N-acetylmuramoylalanyl-D-glutamyl-2,6-diaminopimelate--D-alanyl-D-alanine ligase (murF) {Synechocystis PCC6803}	conserved hypothetical protein {Enterococcus hirae}	934	863
16	TP0387	TP0993	cell division protein (ftsW) {Borrelia burgdorferi}	rare lipoprotein A, putative {Borrelia burgdorferi}	546	546
17	TP0398	TP0026	flagellar hook-basal body co mplex protein (fliE) {Treponema denticola}	flagellar motor switch protein (fliG) {Treponema denticola}	998	985
18	TP0398	TP0396	flagellar hook-basal body co mplex protein (fliE) {Treponema denticola}	flagellar basal-body rod protein (flgB) {Treponema denticola}	999	991
19	TP0398	TP0870	flagellar hook-basal body co mplex protein (fliE) {Treponema denticola}	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	991	956
20	TP0398	TP0961	flagellar hook-basal body co mplex protein (fliE) {Treponema denticola}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	998	961
21	TP0399	TP0026	flagellar basal-body M ring protein (fliF) {Treponema denticola}	flagellar motor switch protein (fliG) {Treponema denticola}	999	994
22	TP0400	TP0399	flagellar motor switch protein (fliG) {Treponema denticola}	flagellar basal-body M ring protein (fliF) {Treponema denticola}	999	994
23	TP0401	TP0026	flagellar assembly protein (fliH) {Treponema denticola}	flagellar motor switch protein (fliG) {Treponema denticola}	995	982
24	TP0402	TP0640	flagellum-specific ATP synthase (fliI) {Treponema denticola}	methyl-accepting chemotaxis protein (mcp2) {Treponema pallidum}	434	433
25	TP0403	TP0868	flagellar protein, putative {Treponema denticola}	flagellar filament 34.5 kDa core protein (flaB1) {Treponema pallidum}	933	796
26	TP0403	TP0961	flagellar protein, putative {Treponema denticola}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	922	739
27	TP0421	TP0095	conserved hypothetical protein {Borrelia burgdorferi}	hypothetical protein	522	432
28	TP0471	TP0421	hypothetical protein	conserved hypothetical protein {Borrelia burgdorferi}	522	432
29	TP0496	TP0909	conserved hypothetical protein {Borrelia burgdorferi}	ribosomal protein L19 (rplS) {Borrelia burgdorferi}	495	89
30	TP0497	TP0334	rod shape-determining protein (mreB) {Borrelia burgdorferi}	conserved hypothetical protein {Bacillus subtilis}	409	408
31	TP0497	TP0961	rod shape-determining protein (mreB) {Borrelia	flagellar basal-body rod protein	667	396

			burgdorferi}	(flgG) {Borrelia burgdorferi}		
32	TP0500	TP0993	penicillin-binding protein (pbp) {Borrelia burgdorferi}	rare lipoprotein A, putative {Borrelia burgdorferi}	734	734
33	TP0501	TP0993	rod shape-determining protein (rodA) {Borrelia burgdorferi}	rare lipoprotein A, putative {Borrelia burgdorferi}	546	546
34	TP0517	TP0704	Holliday junction nuclease (ruvC) {Escherichia coli}	single-stranded-DNA-specific exonuclease (recJ) {Borrelia burgdorferi}	764	107
35	TP0526	TP0067	ATP-dependent helicase (hrpA) {Borrelia burgdorferi}	conserved hypothetical protein {Borrelia burgdorferi}	906	312
36	TP0526	TP0192	ATP-dependent helicase (hrpA) {Borrelia burgdorferi}	ribosomal protein L2 (rplB) {Borrelia burgdorferi}	671	0
37	TP0578	TP0380	cell division protein (ftsY) {Bacillus subtilis}	DNA repair helicase, putative {Saccharomyces cerevisiae}	618	0
38	TP0604	TP0060	ribosome recycling factor {Bacillus subtilis}	ribosomal protein L9 (rplI) {Bacillus subtilis}	649	0
39	TP0630	TP0026	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}	flagellar motor switch protein (fliG) {Treponema denticola}	652	652
40	TP0630	TP0396	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}	flagellar basal-body rod protein (flgB) {Treponema denticola}	713	713
41	TP0630	TP0398	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}	flagellar hook-basal body co mplex protein (fliE) {Treponema denticola}	631	631
42	TP0630	TP0764	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}	conserved hypothetical protein {Borrelia burgdorferi}	404	294
43	TP0630	TP0870	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	943	873
44	TP0630	TP0877	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}	conserved hypothetical protein {Borrelia burgdorferi}	404	294
45	TP0630	TP0961	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	804	803
46	TP0631	TP0961	protein-glutamate methylesterase (cheB) {Salmonella choleraesuis}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	520	519
47	TP0640	TP0764	methyl-accepting chemotaxis protein (mcp2) {Treponema pallidum}	conserved hypothetical protein {Borrelia burgdorferi}	887	886
48	TP0648	TP0354	conserved hypothetical protein {Borrelia burgdorferi}	thymidylate kinase (tmk) {Methanococcus jannaschii}	408	86
49	TP0648	TP0461	conserved hypothetical protein {Borrelia burgdorferi}	hypothetical protein	609	607
50	TP0648	TP0764	conserved hypothetical protein {Borrelia burgdorferi}	conserved hypothetical protein {Borrelia burgdorferi}	492	491
51	TP0648	TP0965	conserved hypothetical protein {Borrelia burgdorferi}	membrane fusion protein, putative {Haemophilus influenzae}	531	531
52	TP0648	TP0981	conserved hypothetical protein {Borrelia burgdorferi}	sensory transduction histidine kinase, putative {Synechocystis PCC6803}	722	692
53	TP0648	TP1005	conserved hypothetical protein {Borrelia burgdorferi}	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	745	89
54	TP0659	TP0764	flagellar hook-associated protein 3 (flgL) {Borrelia burgdorferi}	conserved hypothetical protein {Borrelia burgdorferi}	476	475
55	TP0659	TP0961	flagellar hook-associated protein 3 (flgL) {Borrelia burgdorferi}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	998	991
56	TP0660	TP0398	flagellar hook-associated protein 1 (flgK) {Borrelia burgdorferi}	flagellar hook-basal body co mplex protein (fliE) {Treponema denticola}	977	936
57	TP0713	TP0711	flagellar-associated GTP-binding protein (flhF) {Treponema pallidum}	conserved hypothetical protein {Borrelia burgdorferi}	512	512
58	TP0716	TP0725	flagellar biosynthetic protein (fliR) {Treponema pallidum}	flagellar motor rotation protein (motA) {Treponema pallidum}	998	978
59	TP0720	TP0026	flagellar motor switch protein (fliY) {Treponema pallidum}	flagellar motor switch protein (fliG) {Treponema denticola}	999	990
60	TP0720	TP0397	flagellar motor switch protein (fliY) {Treponema pallidum}	flagellar basal-body rod protein (flgC) {Treponema denticola}	937	926
61	TP0720	TP0660	flagellar motor switch protein (fliY) {Treponema pallidum}	flagellar hook-associated protein 1 (flgK) {Borrelia burgdorferi}	945	894
62	TP0720	TP0870	flagellar motor switch protein (fliY) {Treponema pallidum}	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	911	910
63	TP0720	TP0961	flagellar motor switch protein (fliY) {Treponema pallidum}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	874	874
64	TP0721	TP0026	flagellar motor switch protein (fliM) {Treponema pallidum}	flagellar motor switch protein (fliG) {Treponema denticola}	999	984
65	TP0724	TP0961	flagellar motor rotation protein (motB) {Treponema pallidum}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	928	928
66	TP0728	TP0396	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	flagellar basal-body rod protein (flgB) {Treponema denticola}	998	994

67	TP0728	TP0398	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	flagellar hook-basal body co mplex protein (fliE) {Treponema denticola}	996	984
68	TP0728	TP0726	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	flagellar protein (flbD) {Treponema pallidum}	768	768
69	TP0728	TP0727	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	flagellar hook protein (flgE) {Treponema pallidum}	999	998
70	TP0728	TP0870	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	998	993
71	TP0728	TP0961	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	998	994
72	TP0730	TP0067	conserved hypothetical protein {Caenorhabditis elegans}	conserved hypothetical protein {Borrelia burgdorferi}	501	162
73	TP0738	TP0993	conserved hypothetical protein {Bacillus subtilis}	rare lipoprotein A, putative {Borrelia burgdorferi}	499	499
74	TP0756	TP0757	methionyl-tRNA formyltransferase (fmt) {Haemophilus influenzae}	polypeptide deformylase (def) {Synechocystis PCC6803}	994	891
75	TP0760	TP0993	penicillin-binding protein (pbp) {Borrelia burgdorferi}	rare lipoprotein A, putative {Borrelia burgdorferi}	734	734
76	TP0792	TP0658	flagellar filament 33 kDa core protein (flaB2) {Treponema pallidum}	transmembrane protein, putative {Bacillus subtilis}	973	902
77	TP0792	TP0764	flagellar filament 33 kDa core protein (flaB2) {Treponema pallidum}	conserved hypothetical protein {Borrelia burgdorferi}	476	475
78	TP0792	TP0961	flagellar filament 33 kDa core protein (flaB2) {Treponema pallidum}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	998	991
79	TP0840	TP0965	conserved hypothetical integral membrane protein {Archaeoglobus fulgidus}	membrane fusion protein, putative {Haemophilus influenzae}	731	593
80	TP0868	TP0658	flagellar filament 34.5 kDa core protein (flaB1) {Treponema pallidum}	transmembrane protein, putative {Bacillus subtilis}	973	902
81	TP0870	TP0396	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	flagellar basal-body rod protein (flgB) {Treponema denticola}	997	979
82	TP0870	TP0398	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	flagellar hook-basal body co mplex protein (fliE) {Treponema denticola}	991	956
83	TP0870	TP0630	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}	943	873
84	TP0870	TP0640	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	methyl-accepting chemotaxis protein (mcp2) {Treponema pallidum}	779	322
85	TP0870	TP0658	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	transmembrane protein, putative {Bacillus subtilis}	973	902
86	TP0870	TP0702	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	conserved hypothetical protein {Borrelia burgdorferi}	593	123
87	TP0870	TP0764	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	conserved hypothetical protein {Borrelia burgdorferi}	476	475
88	TP0870	TP0943	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	flagellar protein (fliS) {Bacillus subtilis}	999	991
89	TP0870	TP0961	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	998	991
90	TP0875	TP0247	conserved hypothetical protein {Synechocystis PCC6803}	N-acetylmuramoyl-L-alanine amidase (amiA) {Escherichia coli}	758	758
91	TP0915	TP0764	conserved hypothetical protein {Borrelia burgdorferi}	conserved hypothetical protein {Borrelia burgdorferi}	492	491
92	TP0943	TP0398	flagellar protein (fliS) {Bacillus subtilis}	flagellar hook-basal body co mplex protein (fliE) {Treponema denticola}	959	910
93	TP0943	TP0660	flagellar protein (fliS) {Bacillus subtilis}	flagellar hook-associated protein 1 (flgK) {Borrelia burgdorferi}	991	925
94	TP0943	TP0870	flagellar protein (fliS) {Bacillus subtilis}	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	999	991
95	TP0943	TP0961	flagellar protein (fliS) {Bacillus subtilis}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	920	857
96	TP0959	TP0961	hypothetical protein	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	974	902
97	TP0961	TP0026	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	flagellar motor switch protein (fliG) {Treponema denticola}	971	941
98	TP0961	TP0397	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	flagellar basal-body rod protein (flgC) {Treponema denticola}	999	993
99	TP0961	TP0726	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	flagellar protein (flbD) {Treponema pallidum}	467	467
100	TP0961	TP0773	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}	periplasmic serine protease DO (htrA) {Haemophilus influenzae}	401	0
101	TP0961	TP0870	flagellar basal-body rod protein (flgG) {Borrelia	flagellar filament 31 kDa core	998	991

			burgdorferi}	protein (flaB3) {Treponema pallidum}		
102	TP0963	TP0965	conserved hypothetical integral membrane protein {Bacillus subtilis} _	membrane fusion protein, putative {Haemophilus influenzae}	976	943
103	TP0981	TP0092	sensory transduction histidine kinase, putative {Synechocystis PCC6803}	RNA polymerase sigma factor E (rpoE) {Mycobacterium leprae}	667	667
104	TP0981	TP0764	sensory transduction histidine kinase, putative {Synechocystis PCC6803}	conserved hypothetical protein {Borrelia burgdorferi}	911	910
105	TP0981	TP0877	sensory transduction histidine kinase, putative {Synechocystis PCC6803}	conserved hypothetical protein {Borrelia burgdorferi}	911	910
106	TP0984	TP1004	heat shock protein 90 (htpG) {Borrelia burgdorferi}	recombination protein (recR) {Haemophilus influenzae}	622	187

Supplementary Table 8 Functional Classes present in (whole)*T. pallidum* network compared to genome.

TIGR subrole	# in network	# in genome	% in network	% in genome	ratio
No Data	190	283	35.4	37.4	0.9
Conserved	140	176	23.9	20.4	1.2
Other	36	60	5.2	6.1	0.9
Ribosomal proteins: synthesis and modification	32	54	4.6	5.5	0.8
DNA replication, recombination, and repair	39	49	5.7	4.9	1.1
Chemotaxis and motility	38	45	5.5	4.5	1.2
General	26	35	3.7	3.5	1.1
Biosynthesis and degradation of murein sacculus and peptidoglycan	18	26	2.5	2.6	1.0
tRNA aminoacylation	20	25	2.8	2.5	1.1
Degradation of proteins, peptides, and glycopeptides	11	20	1.5	2.0	0.8
Amino acids, peptides and amines	10	15	1.4	1.5	1.0
Carbohydrates, organic alcohols, and acids	7	14	1.0	1.4	0.7
Protein and peptide secretion and trafficking	10	14	1.4	1.4	1.0
Cations and iron carrying compounds	10	13	1.4	1.3	1.1
Translation factors	10	13	1.4	1.3	1.1
ATP-proton motive force interconversion	8	13	1.1	1.3	0.9
Unknown substrate	8	12	1.1	1.2	1.0
Glycolysis/gluconeogenesis	7	12	1.0	1.2	0.8
Protein folding and stabilization	6	11	0.8	1.1	0.8
Toxin production and resistance	8	11	1.1	1.1	1.0
Cell division	8	10	1.1	1.0	1.1
Biosynthesis and degradation of surface polysaccharides and lipopolysaccharides	7	10	1.0	1.0	1.0
DNA-dependent RNA polymerase	5	9	0.7	0.9	0.8
Transcription factors	5	8	0.7	0.8	0.9
Salvage of nucleosides and nucleotides	4	8	0.6	0.8	0.7
Electron transport	6	7	0.8	0.7	1.2
Pentose phosphate pathway	2	6	0.3	0.6	0.5
Biosynthesis	2	5	0.3	0.5	0.6
Sugars	4	5	0.6	0.5	1.1
Nucleotide and nucleoside interconversions	4	5	0.6	0.5	1.1
Degradation	2	5	0.3	0.5	0.6
tRNA and rRNA base modification	3	4	0.4	0.4	1.1
RNA processing	2	4	0.3	0.4	0.7
2-Deoxyribonucleotide metabolism	3	4	0.4	0.4	1.1
Glutamate family	4	4	0.6	0.4	1.4
Nitrogen fixation	0	3	0.0	0.3	0.0
Degradation of RNA	1	3	0.1	0.3	0.5
Folic acid	1	3	0.1	0.3	0.5
Adaptations to atypical conditions	3	3	0.4	0.3	1.4
Aerobic	3	3	0.4	0.3	1.4
Biosynthesis and degradation of polysaccharides	2	2	0.3	0.2	1.4
Fermentation	1	2	0.1	0.2	0.7
Detoxification	2	2	0.3	0.2	1.4
Protein modification and repair	2	2	0.3	0.2	1.4
Thiamine	2	2	0.3	0.2	1.4
Pathogenesis	2	2	0.3	0.2	1.4

Purine ribonucleotide biosynthesis	2	2	0.3	0.2	1.4
Biotin	1	2	0.1	0.2	0.7
Degradation of DNA	1	2	0.1	0.2	0.7
Aspartate family	1	2	0.1	0.2	0.7
Sugar-nucleotide biosynthesis and conversions	1	1	0.1	0.1	1.4
Menaquinone and ubiquinone	0	1	0.0	0.1	0.0
Serine family	1	1	0.1	0.1	1.4
Anaerobic	1	1	0.1	0.1	1.4
Heme, porphyrin, and cobalamin	0	1	0.0	0.1	0.0
Pyridine nucleotides	0	1	0.0	0.1	0.0
Riboflavin, FMN, and FAD	0	1	0.0	0.1	0.0
Surface structures	1	1	0.1	0.1	1.4
DNA transformation	1	1	0.1	0.1	1.4
Pyrimidine ribonucleotide biosynthesis	1	1	0.1	0.1	1.4
Entner-Doudoroff	0	1	0.0	0.1	0.0

Supplementary Table 9 Functional Classes present in filtered *T. pallidum* network compared to whole genome.

TIGR subrole	**# in network**	**# in genome**	**% in network**	**% in genome**	**ratio**
Chemotaxis and motility	37	45	6.6	4.5	1.4
General	16	35	2.7	3.5	0.8
Biosynthesis and degradation of polysaccharides	1	2	0.2	0.2	0.9
Protein folding and stabilization	4	11	0.7	1.1	0.6
tRNA and rRNA base modification	2	4	0.3	0.4	0.9
Sugar-nucleotide biosynthesis and conversions	1	1	0.2	0.1	1.7
Amino acids, peptides and amines	9	15	1.5	1.5	1.0
Menaquinone and ubiquinone	0	1	0.0	0.1	0.0
Transcription factors	4	8	0.7	0.8	0.9
Serine family	1	1	0.2	0.1	1.7
Cell division	8	10	1.3	1.0	1.4
Anaerobic	1	1	0.2	0.1	1.7
Pentose phosphate pathway	1	6	0.2	0.6	0.3
Fermentation	1	2	0.2	0.2	0.9
Cations and iron carrying compounds	10	13	1.7	1.3	1.3
Nitrogen fixation	0	3	0.0	0.3	0.0
Biosynthesis and degradation of murein sacculus and peptidoglycan	15	26	2.6	2.6	1.0
DNA-dependent RNA polymerase	5	9	0.8	0.9	1.0
Degradation of RNA	1	3	0.2	0.3	0.6
Folic acid	1	3	0.2	0.3	0.6
Heme, porphyrin, and cobalamin	0	1	0.0	0.1	0.0
Adaptations to atypical conditions	3	3	0.5	0.3	1.7
Carbohydrates, organic alcohols, and acids	7	14	1.2	1.4	0.9
Pyridine nucleotides	0	1	0.0	0.1	0.0
Detoxification	1	2	0.2	0.2	0.9
Protein modification and repair	2	2	0.3	0.2	1.7
Toxin production and resistance	4	11	0.7	1.1	0.6
Translation factors	9	13	1.5	1.3	1.2
Thiamine	1	2	0.2	0.2	0.9
RNA processing	2	4	0.3	0.4	0.9

Ribosomal proteins: synthesis and modification	25	54	4.3	5.5	0.8
Protein and peptide secretion and trafficking	10	14	1.7	1.4	1.2
Biosynthesis	2	5	0.3	0.5	0.7
2-Deoxyribonucleotide metabolism	3	4	0.5	0.4	1.3
Pathogenesis	2	2	0.3	0.2	1.7
Purine ribonucleotide biosynthesis	1	2	0.2	0.2	0.9
Salvage of nucleosides and nucleotides	2	8	0.3	0.8	0.4
Biotin	1	2	0.2	0.2	0.9
Sugars	3	5	0.5	0.5	1.0
Unknown substrate	5	12	0.8	1.2	0.7
Biosynthesis and degradation of surface polysaccharides and lipopolysaccharides	3	10	0.5	1.0	0.5
Nucleotide and nucleoside interconversions	3	5	0.5	0.5	1.0
Riboflavin, FMN, and FAD	0	1	0.0	0.1	0.0
Degradation of proteins, peptides, and glycopeptides	9	20	1.5	2.0	0.8
Degradation of DNA	1	2	0.2	0.2	0.9
Glutamate family	4	4	0.7	0.4	1.7
No Data	155	283	34.8	37.4	0.9
Aerobic	2	3	0.3	0.3	1.2
Degradation	1	5	0.2	0.5	0.3
DNA replication, recombination, and repair	32	49	5.6	4.9	1.1
Aspartate family	0	2	0.0	0.2	0.0
Glycolysis/gluconeogenesis	3	12	0.5	1.2	0.4
Electron transport	6	7	1.0	0.7	1.5
Surface structures	0	1	0.0	0.1	0.0
Conserved	128	176	27.1	20.4	1.3
ATP-proton motive force interconversion	6	13	1.0	1.3	0.8
DNA transformation	1	1	0.2	0.1	1.7
Pyrimidine ribonucleotide biosynthesis	1	1	0.2	0.1	1.7
Entner-Doudoroff	0	1	0.0	0.1	0.0
Other	28	60	4.9	6.1	0.8
tRNA aminoacylation	17	25	2.9	2.5	1.2

Supplementary Table 10 Functional Associations. TIGR Main Roles.

TIGR Main Role 1	TIGR Main Role 2	Z-Value	# Y2H interactions
Cellular processes	Cellular processes	3.65	34
Biosynthesis of cofactors, prosthetic groups, and carriers	No Data	3.34	16
Fatty acid and phospholipid metabolism	Transport and binding proteins	3.30	2
Protein fate	Protein synthesis	3.09	19
DNA metabolism	DNA metabolism	2.63	16
No Data	Regulatory functions	2.46	31
Biosynthesis of cofactors, prosthetic groups, and carriers	Transport and binding proteins	2.45	4
Central intermediary metabolism	No Data	2.44	9
Cell envelope	Transcription	2.31	4
Cellular processes	Protein synthesis	2.26	38
No Data	Transcription	2.11	13

Supplementary Table 11 Functional Associations. TIGR subroles.

TIGR SUBROLE 1	TIGR SUBROLE 2	Z-Value	# Y2H interactions
Cell division	Cell division	6.92	2
Chemotaxis and motility	Chemotaxis and motility	4.90	31
Biosynthesis	Cations and iron carrying compounds	4.76	2
Other	Pathogenesis	4.06	2
Carbohydrates, organic alcohols, and acids	Protein folding and stabilization	3.94	2
No Data	Thiamine	3.47	15
Amino acids, peptides and amines	Cations and iron carrying compounds	3.44	3
DNA replication, recombination, and repair	Glycolysis/gluconeogenesis	3.37	2
Amino acids, peptides and amines	Conserved	3.33	10
Sugars	Unknown substrate	3.10	2
Protein and peptide secretion and trafficking	tRNA aminoacylation	2.83	3
Conserved	Degradation of proteins, peptides, and glycopeptides	2.72	21
DNA replication, recombination, and repair	DNA replication, recombination, and repair	2.66	16
Degradation of RNA	No Data	2.63	3
Cations and iron carrying compounds	Protein and peptide secretion and trafficking	2.54	3

Ribosomal proteins: synthesis and modification	Thiamine	2.46	3
Degradation of proteins, peptides, and glycopeptides	Ribosomal proteins: synthesis and modification	2.38	4
Conserved	Salvage of nucleosides and nucleotides	2.19	2
Chemotaxis and motility	tRNA aminoacylation	2.12	14
No Data	Pentose phosphate pathway	2.12	9
Biosynthesis and degradation of murein sacculus and peptidoglycan	Conserved	2.03	27

Supplementary Table 12 Functional Associations. GO slim terms.

GO term 1	GO term 2	Z-Value	# Y2H interactions
ion transporter activity (GO:0015075)	membrane (GO:0016020)	8.41	42
ion transport (GO:0006811)	membrane (GO:0016020)	7.36	42
motor activity (GO:0003774)	motor activity (GO:0003774)	6.94	10
motor activity (GO:0003774)	response to abiotic stimulus (GO:0009628)	6.09	12
motor activity (GO:0003774)	response to external stimulus (GO:0009605)	5.85	9
cell motility (GO:0006928)	response to abiotic stimulus (GO:0009628)	5.56	16
cell motility (GO:0006928)	response to external stimulus (GO:0009605)	5.33	12
protein transporter activity (GO:0008565)	ion transporter activity (GO:0015075)	5.20	5
response to abiotic stimulus (GO:0009628)	cell part (GO:0044464)	5.06	20
response to external stimulus (GO:0009605)	response to external stimulus (GO:0009605)	4.91	4
binding (GO:0005488)	intracellular membrane-bound organelle (GO:0043231)	4.84	10
response to external stimulus (GO:0009605)	cell part (GO:0044464)	4.70	15
ion transport (GO:0006811)	ion transport (GO:0006811)	4.57	8
motor activity (GO:0003774)	cell part (GO:0044464)	4.56	19
motor activity (GO:0003774)	cell motility (GO:0006928)	4.55	13
ion transport (GO:0006811)	protein transporter activity (GO:0008565)	4.51	5
ion transport (GO:0006811)	ion transporter activity (GO:0015075)	4.47	8
ion transporter activity (GO:0015075)	establishment of protein localization (GO:0045184)	4.28	5
response to endogenous stimulus (GO:0009719)	response to extracellular stimulus (GO:0009991)	4.23	3
chromosome (GO:0005694)	intracellular membrane-bound organelle (GO:0043231)	4.15	3
binding (GO:0005488)	biopolymer modification (GO:0043412)	4.14	7
DNA binding (GO:0003677)	DNA binding (GO:0003677)	4.09	11

molecular function unknown (GO:0005554)	intracellular part (GO:0044424)	4.04	7
DNA binding (GO:0003677)	intracellular membrane-bound organelle (GO:0043231)	3.90	7
intracellular membrane-bound organelle (GO:0043231)	biopolymer modification (GO:0043412)	3.89	2
cell part (GO:0044464)	cell part (GO:0044464)	3.87	25
catalytic activity (GO:0003824)	intracellular membrane-bound organelle (GO:0043231)	3.87	7
response to external stimulus (GO:0009605)	response to abiotic stimulus (GO:0009628)	3.85	5
binding (GO:0005488)	protein complex (GO:0043234)	3.84	14
DNA binding (GO:0003677)	energy derivation by oxidation of organic compounds (GO:0015980)	3.84	2
DNA binding (GO:0003677)	helicase activity (GO:0004386)	3.83	7
helicase activity (GO:0004386)	DNA metabolism (GO:0006259)	3.82	10
cell motility (GO:0006928)	cell part (GO:0044464)	3.80	23
ion transport (GO:0006811)	establishment of protein localization (GO:0045184)	3.80	5
response to stress (GO:0006950)	response to extracellular stimulus (GO:0009991)	3.76	3
DNA binding (GO:0003677)	chromosome (GO:0005694)	3.71	7
response to abiotic stimulus (GO:0009628)	response to abiotic stimulus (GO:0009628)	3.60	5
ion transporter activity (GO:0015075)	ion transporter activity (GO:0015075)	3.57	5
electron transport (GO:0006118)	cellular biosynthesis (GO:0044249)	3.55	7
membrane (GO:0016020)	protein catabolism (GO:0030163)	3.55	2
nucleic acid binding (GO:0003676)	response to extracellular stimulus (GO:0009991)	3.52	4
binding (GO:0005488)	nucleotidyltransferase activity (GO:0016779)	3.51	13
ion transporter activity (GO:0015075)	cell organization and biogenesis (GO:0016043)	3.48	4
cell motility (GO:0006928)	cell motility (GO:0006928)	3.48	13
unlocalized protein complex (GO:0005941)	response to endogenous stimulus (GO:0009719)	3.46	2
ion transporter activity (GO:0015075)	secretion (GO:0046903)	3.44	5
chromosome (GO:0005694)	chromosome (GO:0005694)	3.43	2
(GO:0016070)	secondary metabolism (GO:0019748)	3.42	2
helicase activity (GO:0004386)	helicase activity (GO:0004386)	3.41	2
catalytic activity (GO:0003824)	protein complex (GO:0043234)	3.40	9
nucleic acid binding (GO:0003676)	energy derivation by oxidation of organic compounds (GO:0015980)	3.40	2
transporter activity (GO:0005215)	ion transporter activity (GO:0015075)	3.39	5
helicase activity (GO:0004386)	response to extracellular stimulus (GO:0009991)	3.39	2
helicase activity (GO:0004386)	response to endogenous stimulus (GO:0009719)	3.39	5
ion transport (GO:0006811)	cell organization and biogenesis (GO:0016043)	3.35	4

intracellular (GO:0005622)	transcription regulator activity (GO:0030528)	3.34	7
transporter activity (GO:0005215)	ion transport (GO:0006811)	3.31	5
lipid metabolism (GO:0006629)	ion transporter activity (GO:0015075)	3.30	4
response to endogenous stimulus (GO:0009719)	response to endogenous stimulus (GO:0009719)	3.30	5
binding (GO:0005488)	DNA metabolism (GO:0006259)	3.29	23
nucleic acid binding (GO:0003676)	unlocalized protein complex (GO:0005941)	3.28	3
helicase activity (GO:0004386)	chromosome (GO:0005694)	3.28	3
molecular function unknown (GO:0005554)	catabolism (GO:0009056)	3.27	2
catalytic activity (GO:0003824)	DNA metabolism (GO:0006259)	3.26	15
electron transport (GO:0006118)	kinase activity (GO:0016301)	3.25	4
structural molecule activity (GO:0005198)	response to abiotic stimulus (GO:0009628)	3.24	13
catalytic activity (GO:0003824)	nucleotidyltransferase activity (GO:0016779)	3.22	8
membrane (GO:0016020)	cell homeostasis (GO:0019725)	3.21	2
lipid metabolism (GO:0006629)	ion transport (GO:0006811)	3.20	4
protein biosynthesis (GO:0006412)	peptidase activity (GO:0008233)	3.20	13
protein biosynthesis (GO:0006412)	cellular protein metabolism (GO:0044267)	3.18	20
nucleic acid binding (GO:0003676)	catalytic activity (GO:0003824)	3.18	13
transport (GO:0006810)	ion transporter activity (GO:0015075)	3.16	11
DNA binding (GO:0003677)	protein complex (GO:0043234)	3.16	11
catabolism (GO:0009056)	ion transporter activity (GO:0015075)	3.15	3
nucleic acid binding (GO:0003676)	cellular physiological process (GO:0050875)	3.14	2
oxidoreductase activity (GO:0016491)	cellular biosynthesis (GO:0044249)	3.13	7
cellular morphogenesis (GO:0000902)	nuclease activity (GO:0004518)	3.10	6
DNA metabolism (GO:0006259)	energy derivation by oxidation of organic compounds (GO:0015980)	3.08	2
helicase activity (GO:0004386)	response to stress (GO:0006950)	3.08	5
nucleotide binding (GO:0000166)	binding (GO:0005488)	3.07	38
unlocalized protein complex (GO:0005941)	response to stress (GO:0006950)	3.07	2
ion transport (GO:0006811)	secretion (GO:0046903)	3.06	5
ion transport (GO:0006811)	catabolism (GO:0009056)	3.05	3
nucleic acid binding (GO:0003676)	response to endogenous stimulus (GO:0009719)	3.03	10
amino acid and derivative metabolism (GO:0006519)	oxidoreductase activity (GO:0016491)	3.03	5
response to endogenous stimulus (GO:0009719)	hydrolase activity (GO:0016787)	3.01	20
binding (GO:0005488)	(GO:0016070)	3.01	14

structural molecule activity (GO:0005198)	generation of precursor metabolites and energy (GO:0006091)	3.00	3
membrane (GO:0016020)	biopolymer catabolism (GO:0043285)	3.00	2

Supplementary Table 13 Paralogous gene families and their interactions. TIGR paralogous families downloaded in August 2006. The members of each family are given. For each family the number of total interactions (total # ints) and the number of interactions overlapping between different members of the same paralogous gene family (overlapping # ints) is given.

Paralog family	**Locus**	**Gene Symbol**	**Common Name**	**total # ints**	**overlapping # ints**
gtp family_01	TP0008		hypothetical protein	2	
	TP0014		hypothetical protein		
gtp family_02	TP0011	tprB	tpr protein B	6	2
	TP0117	tprC	tpr protein C		
	TP0131	tprD	tpr protein D		
	TP0313	tprE	tpr protein E		
	TP0316	tprF	tpr protein F, authentic frameshift		
	TP0317	tprG	tpr protein G		
	TP0610	tprH	tpr protein H		
	TP0620	tprI	tpr protein I		
	TP0621	tprJ	tpr protein J		
	TP0897	tprK	tpr protein K		
gtp family_03	TP0024		conserved hypothetical protein	16	
	TP0139		conserved hypothetical protein		
gtp family_04	TP0026	fliG-1	flagellar motor switch protein	20	2
	TP0400	fliG-2	flagellar motor switch protein		
gtp family_05	TP0034		ABC transporter, periplasmic binding protein	8	
	TP0163	troA	ABC transporter, periplasmic binding protein		
gtp family_06	TP0035		ABC transporter, ATP-binding protein	11	
	TP0120	abc	amino acid ABC transporter, ATP-binding protein		
	TP0142		thiamine ABC transporter, ATP-binding protein, putative		
	TP0164	troB	ABC transporter, ATP-binding protein		
	TP0227		cobalt ABC transporter, ATP-binding protein		
	TP0300	rbsA-1	ribose/galactose ABC transporter, ATP-binding protein		
	TP0321	rbsA-2	ribose/galactose ABC transporter, ATP-binding protein		
	TP0581		ABC transporter, ATP-binding protein		
	TP0652	potA	spermidine/putrescine ABC transporter, ATP-binding protein		
	TP0685	mglA	methylgalactoside ABC transporter, ATP binding		

			protein	
	TP0786		ABC transporter, ATP-binding protein, putative	
	TP0804	ugpC	sugar ABC transporter, ATP-binding protein	
	TP0881	natA	ABC transporter, ATP-binding protein	
	TP0964		ABC transporter, ATP-binding protein	
gtp family_07	TP0036		ABC transporter, permease protein	5
	TP0165	troC	ABC transporter, permease protein	
	TP0166	troD	ABC transporter, permease protein	
gtp family_08	TP0040	mcp1	methyl-accepting chemotaxis protein	10
	TP0488	mcp2-1	methyl-accepting chemotaxis protein	
	TP0639	mcp2-2	methyl-accepting chemotaxis protein	
	TP0640	mcp2-3	methyl-accepting chemotaxis protein	
gtp family_09	TP0051	prfA	peptide chain release factor 1	4
	TP0576	prfB	peptide chain release factor 2	
gtp family_10	TP0082	fhlA	formate hydrogenlyase transcriptional activator	32
	TP0519	atoC	response regulatory protein	
gtp family_11	TP0089		cyclic nucleotide binding protein	2
	TP0262	crp	catabolite gene activator	
gtp family_12	TP0102	rep	rep helicase, single-stranded DNA-dependent ATPase	1
	TP1028	uvrD	DNA helicase II	
gtp family_13	TP0126		hypothetical protein	2
	TP0733		hypothetical protein	
gtp family_14	TP0127		hypothetical protein	29
	TP0314		hypothetical protein	
	TP0315		hypothetical protein	
	TP0617		hypothetical protein	
	TP0618		hypothetical protein	
	TP0619		hypothetical protein	
gtp family_15	TP0133		hypothetical protein	20
	TP0134		hypothetical protein	
	TP0136		hypothetical protein	
	TP0462		hypothetical protein	
	TP0463		hypothetical protein	
gtp family_16	TP0252		apolipoprotein N-acyltransferase, putative	2
	TP0417	cutE	apolipoprotein N-acyltransferase	
gtp family_17	TP0268		conserved hypothetical protein	8
	TP0820		hypothetical protein	
gtp family_18	TP0270	pcnA	polynucleotide adenylyltransferase	2
	TP0596	pcnB	polynucleotide adenylyltransferase	
gtp family_19	TP0298	tpn38b	exported protein	2
	TP0319	tmpC	membrane lipoprotein	

gtp family_20	TP0308	hisJ	amino acid ABC transporter, periplasmic binding protein		
	TP0309		amino acid ABC transporter, periplasmic binding protein		
gtp family_21	TP0346		hypothetical protein		
	TP0347		hypothetical protein		
gtp family_22	TP0364	cheW-1	purine-binding chemotaxis protein		
	TP0439	cheW-2	purine-binding chemotaxis protein		
gtp family_23	TP0387	ftsW	cell division protein	12	4
	TP0501	rodA	rod shape-determining protein		
gtp family_24	TP0391	codV	integrase/recombinase	1	
	TP0395	xprB	integrase/recombinase		
gtp family_25	TP0402	fliI	flagellum-specific ATP synthase	5	
	TP0426	atpA-1	V-type ATPase, subunit A		
	TP0427	atpB-1	V-type ATPase, subunit B		
	TP0528	atpB-2	V-type ATPase, subunit B		
	TP0529	atpA-2	V-type ATPase, subunit A		
gtp family_26	TP0414	dagA	D-alanine glycine permease	4	
	TP0998		sodium/proton-dependent alanine transporter		
gtp family_27	TP0416	ffh	signal recognition particle protein	6	
	TP0578	ftsY	signal recognition particle-docking protein FtsY		
gtp family_28	TP0450	fusA-1	translation elongation factor G		
	TP0767	fusA-2	translation elongation factor G		
gtp family_29	TP0471		hypothetical protein	2	
	TP0915		conserved hypothetical protein		
gtp family_30	TP0479		hypothetical protein	1	
	TP0697		hypothetical protein		
gtp family_31	TP0493	rpoD	RNA polymerase sigma-70 factor	1	
	TP0709		RNA polymerase sigma-28 factor		
	TP1012	sigA	RNA polymerase sigma-43 factor		
gtp family_32	TP0507	clpP-1	ATP-dependent Clp protease proteolytic component	2	
	TP1041	clpP-2	ATP-dependent Clp protease proteolytic component		
gtp family_33	TP0546		periplasmic serine protease, putative	31	
	TP0773	htrA-1	periplasmic serine protease DO		
	TP0841	htrA-2	periplasmic serine protease DO		
gtp family_34	TP0548		hypothetical protein	3	
	TP0856		hypothetical protein		
	TP0858		hypothetical protein		
	TP0859		hypothetical protein		
	TP0860		hypothetical protein		
	TP0865		hypothetical protein		
gtp family_35	TP0580		conserved hypothetical	11	

			integral membrane protein		
	TP0582		conserved hypothetical integral membrane protein		
gtp family_36	TP0663		outer membrane protein, putative	36	
	TP0664	flaA-2	flagellar filament outer layer protein		
gtp family_37	TP0702		conserved hypothetical protein	6	
	TP0706		conserved hypothetical protein		
	TP0864		conserved hypothetical protein		
gtp family_38	TP0764		conserved hypothetical protein	2	
	TP0912		conserved hypothetical protein		
gtp family_39	TP0792	flaB2	flagellar filament 33 kDa core protein	27	8
	TP0868	flaB1	flagellar filament 34.5 kDa core protein		
	TP0870	flaB3	flagellar filament 31 kDa core protein		
gtp family_40	TP0960	flgG-1	flagellar basal-body rod protein	21	2
	TP0961	flgG-2	flagellar basal-body rod protein		
gtp family_41	TP0962		conserved hypothetical integral membrane protein	2	
	TP0963		conserved hypothetical integral membrane protein		
gtp family_42	TP0966		hypothetical protein	2	
	TP0967		hypothetical protein		
	TP0968		hypothetical protein		
	TP0969		hypothetical protein		

Supplementary Table 14 Interactions of paralogous gene families II. Paralogous families as downloaded from TIGR-CMR in October 2006 are analyzed.

paralogous family (annotation)	interacting ORF	annotation	#	interactions
gtp fam_PF00271 (helicases)	TP0559	conserved hypothetical protein	3	TP0380-TP0559 TP0103-TP0559 TP0526-TP0559
gtp fam_PF04055 (radical SAM superfamily)	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	3	TP0754-TP1005 TP0121-TP1005 TP0068-TP1005
gtp fam_PF01547 (bacterial solute binding protein)	TP0445	4-methyl-5(b-hydroxyethyl)-thiazole monophosphate biosynthesis enzyme (thiJ) {Borrelia burgdorferi}	2	TP0074-TP0445 TP0655-TP0445
gtp fam_PF00460 (Flagella rod protein)	TP0772	hypothetical protein	2	TP0772-TP0396 TP0961-TP0772
gtp fam_PF00460 (Flagella rod protein)	TP0832	hypothetical protein	2	TP0960-TP0832 TP0961-TP0832
gtp fam_PF00460 (Flagella rod protein)	TP0728	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}	2	TP0728-TP0727 TP0728-TP0396
gtp fam_51 (flagellins)	TP0832	hypothetical protein	3	TP0792-TP0832 TP0868-TP0832 TP0870-TP0832
gtp fam_51 (flagellins)	TP0658	transmembrane protein, putative {Bacillus subtilis}	3	TP0868-TP0658 TP0870-TP0658 TP0792-TP0658
gtp fam_51 (flagellins)	TP0050	conserved hypothetical protein {Borrelia burgdorferi}	2	TP0868-TP0050 TP0870-TP0050
gtp fam_PF00575 (S1 RNA binding)	TP0833	hypothetical protein	2	TP0097-TP0833 TP0924-TP0833
gtp fam_PF01052 (SpoA)	TP0066	hypothetical protein	2	TP0720-TP0066 TP0721-TP0066
gtp fam_PF01052 (SpoA)	TP0026	flagellar motor switch protein (fliG) {Treponema denticola}	2	TP0720-TP0026 TP0721-TP0026
gtp fam_PF02687 (FtsX)	TP0965	membrane fusion protein, putative {Haemophilus influenzae}	2	TP0582-TP0965 TP0963-TP0965
gtp fam_28 (fliG)	TP0399	flagellar basal-body M ring protein (fliF) {Treponema denticola}	2	TP0400-TP0399 TP0399-TP0026
gtp fam_PF02254 (TrkA-N)	TP0086	conserved hypothetical protein {Borrelia burgdorferi}	2	TP0086-TP0513 TP0086-TP0024
gtp fam_PF02254 (TrkA-N)	TP0661	hypothetical protein	2	TP0661-TP0513 TP0661-TP0024
gtp fam_PF02254	TP0648	conserved hypothetical protein {Borrelia	2	TP0648-TP0513

(TrkA-N)		burgdorferi}		TP0648-TP0024
gtp fam_PF01098 (FtsW/RodA)	TP0917	Mg2+ transport protein (mgtE) {Borrelia burgdorferi}	2	TP0501-TP0917 TP0387-TP0917
gtp fam_PF01098 (FtsW/RodA)	TP0561	conserved hypothetical protein {Escherichia coli}	2	TP0501-TP0561 TP0387-TP0561
gtp fam_PF02722 (MOSP_C)	TP0209	ribosomal protein L36 (rpmJ) {Chlorella vulgaris}	2	TP0117-TP0209 TP0610-TP0209
gtp fam_PF00004 (AAA)	TP0330	cell division protein (ftsH) {Mycoplasma genitalium}	2	TP0330-TP0330 TP0330-TP0330
gtp fam_PF00004 (AAA)	TP0171	lipoprotein, 15 kDa (tpp15) {Treponema pallidum}	2	TP0162-TP0171 TP1005-TP0171
gtp fam_PF00004 (AAA)	TP0630	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}	3	TP0630-TP0162 TP0630-TP0330 TP0630-TP1005
gtp fam_PF00004 (AAA)	TP0582	conserved hypothetical integral membrane protein {Borrelia burgdorferi}	2	TP0582-TP1005 TP0582-TP0765
gtp fam_PF00004 (AAA)	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	2	TP1005-TP1005 TP1005-TP1005
gtp fam_PF02653 (permease component)	TP0561	conserved hypothetical protein {Escherichia coli}	2	TP0322-TP0561 TP0301-TP0561
gtp fam_PF02653 (permease component)	TP0917	Mg2+ transport protein (mgtE) {Borrelia burgdorferi}	2	TP0301-TP0917 TP0302-TP0917
gtp fam_PF00226 (DnaJ)	TP0981	sensory transduction histidine kinase, putative {Synechocystis PCC6803}	2	TP0563-TP0981 TP0981-TP0843
gtp fam_PF00515 (TPR 1)	TP0080	quinoline 2-oxidoreductase {Pseudomonas putida}	2	TP0820-TP0080 TP0080-TP0920
gtp fam_PF00515 (TPR 1)	TP0559	conserved hypothetical protein {Archaeoglobus fulgidus}	2	TP0067-TP0559 TP0095-TP0559
gtp fam_PF00515 (TPR 1)	TP0738	conserved hypothetical protein {Bacillus subtilis}	2	TP0738-TP0067 TP0738-TP0095
gtp fam_PF00515 (TPR 1)	TP0094	phosphate acetyltransferase (pta) {Methanosarcina thermophila}	2	TP0094-TP0067 TP0094-TP0920
gtp fam_PF00515 (TPR 1)	TP0418	galactokinase {Homo sapiens}	2	TP0418-TP0067 TP0418-TP0095
gtp fam_PF00515 (TPR 1)	TP0095	hypothetical protein	2	TP0067-TP0095 TP0648-TP0095
gtp fam_PF00515 (TPR 1)	TP0492	DNA primase (dnaE) {Clostridium acetobutylicum}	3	TP0492-TP0648 TP0492-TP0095 TP0496-TP0492
gtp fam_PF00515 (TPR 1)	TP0819	conserved hypothetical protein {Borrelia burgdorferi}	2	TP0819-TP0095 TP0819-TP0920
gtp fam_PF00515 (TPR 1)	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	2	TP0067-TP1005 TP0648-TP1005

gtp fam_PF00515 (TPR 1)	TP0132	hypothetical protein	2	TP0132-TP0067 TP0132-TP0095
gtp fam_PF00515 (TPR 1)	TP0421	conserved hypothetical protein {Borrelia burgdorferi}	2	TP0421-TP0095 TP0471-TP0421
gtp fam_PF00515 (TPR 1)	TP0247	N-acetylmuramoyl-L-alanine amidase (amiA) {Escherichia coli}	2	TP0820-TP0247 TP0247-TP0067
gtp fam_PF00515 (TPR 1)	TP0586	leucyl-tRNA synthetase (leuS) {Borrelia burgdorferi}	2	TP0067-TP0586 TP0648-TP0586
gtp fam_PF01066 (CDP-OH_P_transf)	TP0917	Mg2+ transport protein (mgtE) {Borrelia burgdorferi}	2	TP0671-TP0917 TP0256-TP0917

Supplementary Table 15 Domain Interactions. Domain information for *T. pallidum* proteins was taken from Pfam database {ref}. The number of interactions (#Y2H links) between two proteins with the respective domains is shown. To estimate the significance a Z-value was calculated (a threshold of 2 was chosen), which indicates the "enrichment" of a specific domain-domain link compared to a distribution of 1000 randomized networks. Due to the limited number of Y2H links the calculated significance cannot be assured for all domain pairs.

Pfam Domain 1		Pfam Domain 2		# Y2H links	Z-Value	Y2H interactions (domains)
PF01514	YscJ_FliF	PF01706	FliG_C	2	9.99	TP0400(PF01706)-TP0399(PF01514) TP0399(PF01514)-TP0026(PF01706)
PF00700	Flagellin_C	PF02623	DUF180	3	9.56	TP0868(PF00700)-TP0658(PF02623) TP0870(PF00700)-TP0658(PF02623) TP0792(PF00700)-TP0658(PF02623)
PF00669	Flagellin_N	PF02623	DUF180	3	9.05	TP0868(PF00669)-TP0658(PF02623) TP0870(PF00669)-TP0658(PF02623) TP0792(PF00669)-TP0658(PF02623)
PF00226	DnaJ	PF00990	GGDEF	2	7.79	TP0563(PF00226)-TP0981(PF00990) TP0981(PF00990)-TP0843(PF00226)
PF01926	MMR_HSR1	PF02272	DHHA1	2	7.40	TP0124(PF01926)-TP0704(PF02272) TP0541(PF01926)-TP0704(PF02272)
PF00364	Biotin_lipoyl	PF02687	FtsX	2	6.97	TP0582(PF02687)-TP0965(PF00364) TP0963(PF02687)-TP0965(PF00364)
PF01368	DHH	PF01926	MMR_HSR1	2	6.85	TP0124(PF01926)-TP0704(PF01368) TP0541(PF01926)-TP0704(PF01368)
PF00004	AAA	PF04055	Radical_SAM	3	5.54	TP0754(PF04055)-TP1005(PF00004) TP0121(PF04055)-TP1005(PF00004) TP0068(PF04055)-TP1005(PF00004)
PF00004	AAA	PF04205	FMN_bind	2	5.44	TP0162(PF00004)-TP0171(PF04205) TP1005(PF00004)-TP0171(PF04205)
PF01052	SpoA	PF01706	FliG_C	2	5.41	TP0720(PF01052)-TP0026(PF01706) TP0721(PF01052)-TP0026(PF01706)
PF01547	SBP_bac_1	PF01965	DJ-1_PfpI	2	4.94	TP0074(PF01547)-TP0445(PF01965) TP0655(PF01547)-TP0445(PF01965)
PF00460	Flg_bb_rod	PF03963	FlgD	2	4.56	TP0728(PF03963)-TP0727(PF00460) TP0728(PF03963)-TP0396(PF00460)
PF02653	BPD_transp_2	PF04536	DUF477	2	4.51	TP0322(PF02653)-TP0561(PF04536) TP0301(PF02653)-TP0561(PF04536)
PF01769	MgtE	PF02653	BPD_transp_2	2	4.39	TP0301(PF02653)-TP0917(PF01769) TP0302(PF02653)-TP0917(PF01769)
PF02653	BPD_transp_2	PF03448	MgtE_N	2	4.39	TP0301(PF02653)-TP0917(PF03448) TP0302(PF02653)-TP0917(PF03448)
PF00004	AAA	PF01739	CheR	3	4.36	TP0630(PF01739)-TP0162(PF00004) TP0630(PF01739)-TP0330(PF00004) TP0630(PF01739)-TP1005(PF00004)
PF00004	AAA	PF03705	CheR_N	3	4.36	TP0630(PF03705)-TP0162(PF00004) TP0630(PF03705)-TP0330(PF00004) TP0630(PF03705)-TP1005(PF00004)
PF00571	CBS	PF02653	BPD_transp_2	2	4.34	TP0301(PF02653)-TP0917(PF00571) TP0302(PF02653)-TP0917(PF00571)
PF00271	Helicase_C	PF02568	ThiI	3	4.30	TP0380(PF00271)-TP0559(PF02568) TP0103(PF00271)-TP0559(PF02568) TP0526(PF00271)-TP0559(PF02568)

PF00271	Helicase_C	PF02926	THUMP	3	4.30	TP0380(PF00271)-TP0559(PF02926) TP0103(PF00271)-TP0559(PF02926) TP0526(PF00271)-TP0559(PF02926)
PF00571	CBS	PF01066	CDP-OH_P_transf	2	4.28	TP0671(PF01066)-TP0917(PF00571) TP0256(PF01066)-TP0917(PF00571)
PF01066	CDP-OH_P_transf	PF01769	MgtE	2	4.28	TP0671(PF01066)-TP0917(PF01769) TP0256(PF01066)-TP0917(PF01769)
PF01066	CDP-OH_P_transf	PF03448	MgtE_N	2	4.28	TP0671(PF01066)-TP0917(PF03448) TP0256(PF01066)-TP0917(PF03448)
PF00156	Pribosyltran	PF00700	Flagellin_C	2	3.94	TP0868(PF00700)-TP0050(PF00156) TP0870(PF00700)-TP0050(PF00156)
PF02254	TrkA_N	PF07238	PilZ	2	3.93	TP0086(PF07238)-TP0513(PF02254) TP0086(PF07238)-TP0024(PF02254)
PF02080	TrkA_C	PF07238	PilZ	2	3.93	TP0086(PF07238)-TP0513(PF02080) TP0086(PF07238)-TP0024(PF02080)
PF00515	TPR_1	PF01436	NHL	2	3.84	TP0421(PF01436)-TP0095(PF00515) TP0471(PF00515)-TP0421(PF01436)
PF01436	NHL	PF07719	TPR_2	2	3.84	TP0421(PF01436)-TP0095(PF07719) TP0471(PF07719)-TP0421(PF01436)
PF02938	GAD	PF04536	DUF477	2	3.78	TP0561(PF04536)-TP0985(PF02938) TP0985(PF02938)-TP0561(PF04536)
PF01336	tRNA_anti	PF04536	DUF477	2	3.78	TP0561(PF04536)-TP0985(PF01336) TP0985(PF01336)-TP0561(PF04536)
PF00152	tRNA-synt_2	PF04536	DUF477	2	3.77	TP0561(PF04536)-TP0985(PF00152) TP0985(PF00152)-TP0561(PF04536)
PF00669	Flagellin_N	PF04073	YbaK	2	3.67	TP0792(PF00669)-TP0160(PF04073) TP0659(PF00669)-TP0160(PF04073)
PF00156	Pribosyltran	PF00669	Flagellin_N	2	3.64	TP0868(PF00669)-TP0050(PF00156) TP0870(PF00669)-TP0050(PF00156)
PF01807	zf-CHC2	PF07719	TPR_2	3	3.30	TP0492(PF01807)-TP0648(PF07719) TP0492(PF01807)-TP0095(PF07719) TP0496(PF07719)-TP0492(PF01807)
PF07719	TPR_2	PF08275	Toprim_N	3	3.30	TP0492(PF08275)-TP0648(PF07719) TP0492(PF08275)-TP0095(PF07719) TP0496(PF07719)-TP0492(PF08275)
PF01098	FTSW_RODA_SPOVE	PF04536	DUF477	2	3.20	TP0501(PF01098)-TP0561(PF04536) TP0387(PF01098)-TP0561(PF04536)
PF00571	CBS	PF01098	FTSW_RODA_SPOVE	2	3.06	TP0501(PF01098)-TP0917(PF00571) TP0387(PF01098)-TP0917(PF00571)
PF01098	FTSW_RODA_SPOVE	PF03448	MgtE_N	2	3.06	TP0501(PF01098)-TP0917(PF03448) TP0387(PF01098)-TP0917(PF03448)
PF01098	FTSW_RODA_SPOVE	PF01769	MgtE	2	3.06	TP0501(PF01098)-TP0917(PF01769) TP0387(PF01098)-TP0917(PF01769)
PF00460	Flg_bb_rod	PF02875	Mur_ligase_C	2	3.03	TP0961(PF00460)-TP0341(PF02875) TP0903(PF02875)-TP0396(PF00460)
PF00460	Flg_bb_rod	PF08245	Mur_ligase_M	2	3.03	TP0961(PF00460)-TP0341(PF08245) TP0903(PF08245)-TP0396(PF00460)
PF01476	LysM	PF03448	MgtE_N	2	3.02	TP0042(PF01476)-TP0917(PF03448) TP0155(PF01476)-TP0917(PF03448)
PF00571	CBS	PF01476	LysM	2	3.02	TP0042(PF01476)-TP0917(PF00571) TP0155(PF01476)-TP0917(PF00571)

PF01476	LysM	PF01769	MgtE	2	3.02	TP0042(PF01476)-TP0917(PF01769) TP0155(PF01476)-TP0917(PF01769)
PF00515	TPR_1	PF01515	PTA_PTB	2	3.01	TP0094(PF01515)-TP0067(PF00515) TP0094(PF01515)-TP0920(PF00515)
PF01515	PTA_PTB	PF07719	TPR_2	2	2.90	TP0094(PF01515)-TP0067(PF07719) TP0094(PF01515)-TP0920(PF07719)
PF01751	Toprim	PF07719	TPR_2	3	2.89	TP0492(PF01751)-TP0648(PF07719) TP0492(PF01751)-TP0095(PF07719) TP0496(PF07719)-TP0492(PF01751)
PF02254	TrkA_N	PF06429	DUF1078	2	2.89	TP0660(PF06429)-TP0024(PF02254) TP0961(PF06429)-TP0024(PF02254)
PF02080	TrkA_C	PF06429	DUF1078	2	2.89	TP0660(PF06429)-TP0024(PF02080) TP0961(PF06429)-TP0024(PF02080)
PF00515	TPR_1	PF01799	Fer2_2	2	2.80	TP0820(PF00515)-TP0080(PF01799) TP0080(PF01799)-TP0920(PF00515)
PF04509	CheC	PF06429	DUF1078	2	2.75	TP0720(PF04509)-TP0660(PF06429) TP0720(PF04509)-TP0397(PF06429)
PF00669	Flagellin_N	PF03129	HGTP_anticodon	2	2.71	TP0792(PF00669)-TP0160(PF03129) TP0659(PF00669)-TP0160(PF03129)
PF00587	tRNA-synt_2b	PF00669	Flagellin_N	2	2.71	TP0792(PF00669)-TP0160(PF00587) TP0659(PF00669)-TP0160(PF00587)
PF01966	HD	PF06429	DUF1078	2	2.68	TP0651(PF01966)-TP0397(PF06429) TP0961(PF06429)-TP0877(PF01966)
PF00004	AAA	PF02687	FtsX	2	2.63	TP0582(PF02687)-TP1005(PF00004) TP0582(PF02687)-TP0765(PF00004)
PF00004	AAA	PF00004	AAA	2	2.60	TP0330(PF00004)-TP0330(PF00004) TP1005(PF00004)-TP1005(PF00004)
PF02775	TPP_enzyme_C	PF07719	TPR_2	2	2.59	TP0421(PF07719)-TP0939(PF02775) TP0648(PF07719)-TP0939(PF02775)
PF01855	POR_N	PF07719	TPR_2	2	2.59	TP0421(PF07719)-TP0939(PF01855) TP0648(PF07719)-TP0939(PF01855)
PF01558	POR	PF07719	TPR_2	2	2.59	TP0421(PF07719)-TP0939(PF01558) TP0648(PF07719)-TP0939(PF01558)
PF00037	Fer4	PF07719	TPR_2	2	2.59	TP0421(PF07719)-TP0939(PF00037) TP0648(PF07719)-TP0939(PF00037)
PF00515	TPR_1	PF00753	Lactamase_B	2	2.58	TP0819(PF00753)-TP0095(PF00515) TP0819(PF00753)-TP0920(PF00515)
PF00753	Lactamase_B	PF07719	TPR_2	2	2.51	TP0819(PF00753)-TP0095(PF07719) TP0819(PF00753)-TP0920(PF07719)
PF01052	SpoA	PF06429	DUF1078	2	2.39	TP0720(PF01052)-TP0660(PF06429) TP0720(PF01052)-TP0397(PF06429)
PF07719	TPR_2	PF07719	TPR_2	4	2.37	TP0421(PF07719)-TP0095(PF07719) TP0471(PF07719)-TP0421(PF07719) TP0067(PF07719)-TP0095(PF07719) TP0648(PF07719)-TP0095(PF07719)
PF00133	tRNA-synt_1	PF00515	TPR_1	2	2.37	TP0067(PF00515)-TP0586(PF00133) TP0648(PF00515)-TP0586(PF00133)
PF00515	TPR_1	PF08264	Anticodon_1	2	2.37	TP0067(PF00515)-TP0586(PF08264) TP0648(PF00515)-TP0586(PF08264)
PF04851	ResIII	PF07719	TPR_2	2	2.28	TP0380(PF04851)-TP0421(PF07719) TP0380(PF04851)-TP0095(PF07719)
PF00133	tRNA-synt_1	PF07719	TPR_2	2	2.27	TP0067(PF07719)-TP0586(PF00133) TP0648(PF07719)-TP0586(PF00133)
PF07719	TPR_2	PF08264	Anticodon_1	2	2.27	TP0067(PF07719)-TP0586(PF08264) TP0648(PF07719)-TP0586(PF08264)

PF00271	Helicase_C	PF07719	TPR_2	3	2.21	TP0380(PF00271)-TP0421(PF07719) TP0380(PF00271)-TP0095(PF07719) TP0526(PF00271)-TP0067(PF07719)
PF00515	TPR_1	PF02080	TrkA_C	2	2.15	TP0648(PF00515)-TP0513(PF02080) TP0648(PF00515)-TP0024(PF02080)
PF00515	TPR_1	PF02254	TrkA_N	2	2.15	TP0648(PF00515)-TP0513(PF02254) TP0648(PF00515)-TP0024(PF02254)
PF02254	TrkA_N	PF07719	TPR_2	2	2.13	TP0648(PF07719)-TP0513(PF02254) TP0648(PF07719)-TP0024(PF02254)
PF02080	TrkA_C	PF07719	TPR_2	2	2.13	TP0648(PF07719)-TP0513(PF02080) TP0648(PF07719)-TP0024(PF02080)

Supplementary Table 16 Selected (highly reliable) interactions of four conservation classes

	COG1	COG2	TPA1	TPA2	Description 1	Description 2
Conservation Class 1	COG1026	COG2269	TP0025	TP1040	conserved hypothetical protein {Borrelia burgdorferi}	lysyl-tRNA synthetase (lysS) {Escherichia coli}
	COG1419	NOG46983	TP0713	TP0711	flagellar-associated GTP-binding protein (flhF) {Treponema pallidum}	conserved hypothetical protein {Borrelia burgdorferi}
	COG1344	COG1699	TP0870	TP0658	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	transmembrane protein, putative {Bacillus subtilis}
	COG1582	COG1843	TP0726	TP0728	flagellar protein (flbD) {Treponema pallidum}	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}
	COG1582	COG4786	TP0726	TP0961	flagellar protein (flbD) {Treponema pallidum}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}
	COG1077	COG1426	TP0497	TP0334	rod shape-determining protein (mreB) {Borrelia burgdorferi}	conserved hypothetical protein {Bacillus subtilis}
	COG1595	COG2199	TP0092	TP0981	RNA polymerase sigma factor E (rpoE) {Mycobacterium leprae}	sensory transduction histidine kinase, putative {Synechocystis PCC6803}
	COG1352	COG2206	TP0630	TP0877	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}	conserved hypothetical protein {Borrelia burgdorferi}
	COG2199	COG2206	TP0981	TP0877	sensory transduction histidine kinase, putative {Synechocystis PCC6803}	conserved hypothetical protein {Borrelia burgdorferi}
	COG2204	COG2204	TP0519	TP0519	response regulatory protein (atoC) {Borrelia burgdorferi}	response regulatory protein (atoC) {Borrelia burgdorferi}
	COG0280	COG2204	TP0094	TP0519	phosphate acetyltransferase (pta) {Methanosarcina thermophila}	response regulatory protein (atoC) {Borrelia burgdorferi}
	COG1014	COG1815	TP0939	TP0396	pyruvate oxidoreductase {Synechocystis PCC6803}	flagellar basal-body rod protein (flgB) {Treponema denticola}
	COG1344	COG2199	TP0870	TP0981	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	sensory transduction histidine kinase, putative {Synechocystis PCC6803}
	COG0739	COG1344	TP0702	TP0870	conserved hypothetical protein {Borrelia burgdorferi}	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}
	COG0840	COG1344	TP0640	TP0870	methyl-accepting chemotaxis protein (mcp2) {Treponema pallidum}	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}
	COG0840	COG1157	TP0640	TP0402	methyl-accepting chemotaxis protein (mcp2) {Treponema pallidum}	flagellum-specific ATP synthase (fliI) {Treponema denticola}
	COG1317	COG1536	TP0401	TP0026	flagellar assembly protein (fliH) {Treponema	flagellar motor switch protein (fliG)

				denticola}	{Treponema denticola}
COG1256	COG1886	TP0660	TP0720	flagellar hook-associated protein 1 (flgK) {Borrelia burgdorferi}	flagellar motor switch protein (fliY) {Treponema pallidum}
COG1558	COG1886	TP0397	TP0720	flagellar basal-body rod protein (flgC) {Treponema denticola}	flagellar motor switch protein (fliY) {Treponema pallidum}
COG1536	COG1886	TP0026	TP0720	flagellar motor switch protein (fliG) {Treponema denticola}	flagellar motor switch protein (fliY) {Treponema pallidum}
COG1536	COG1766	TP0400	TP0399	flagellar motor switch protein (fliG) {Treponema denticola}	flagellar basal-body M ring protein (fliF) {Treponema denticola}
COG1536	COG1868	TP0026	TP0721	flagellar motor switch protein (fliG) {Treponema denticola}	flagellar motor switch protein (fliM) {Treponema pallidum}
COG1536	COG1677	TP0026	TP0398	flagellar motor switch protein (fliG) {Treponema denticola}	flagellar hook-basal body co mplex protein (fliE) {Treponema denticola}
COG1536	COG4786	TP0026	TP0961	flagellar motor switch protein (fliG) {Treponema denticola}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}
COG1352	COG1536	TP0630	TP0026	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}	flagellar motor switch protein (fliG) {Treponema denticola}
COG1352	COG1815	TP0630	TP0396	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}	flagellar basal-body rod protein (flgB) {Treponema denticola}
COG1344	COG1352	TP0870	TP0630	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	chemotaxis protein methyltransferase (cheR) {Borrelia burgdorferi}
COG1344	COG2882	TP0868	TP0403	flagellar filament 34.5 kDa core protein (flaB1) {Treponema pallidum}	flagellar protein, putative {Treponema denticola}
COG1256	COG1516	TP0660	TP0943	flagellar hook-associated protein 1 (flgK) {Borrelia burgdorferi}	flagellar protein (fliS) {Bacillus subtilis}
COG1344	COG1516	TP0870	TP0943	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	flagellar protein (fliS) {Bacillus subtilis}
COG1749	COG1843	TP0727	TP0728	flagellar hook protein (flgE) {Treponema pallidum}	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}
COG1677	COG1815	TP0398	TP0396	flagellar hook-basal body co mplex protein (fliE) {Treponema denticola}	flagellar basal-body rod protein (flgB) {Treponema denticola}
COG1558	COG4786	TP0397	TP0961	flagellar basal-body rod protein (flgC) {Treponema denticola}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}
COG1815	COG1843	TP0396	TP0728	flagellar basal-body rod protein (flgB) {Treponema denticola}	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}
COG1344	COG1815	TP0870	TP0396	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}	flagellar basal-body rod protein (flgB) {Treponema denticola}
COG1291	COG1684	TP0725	TP0716	flagellar motor rotation protein (motA) {Treponema pallidum}	flagellar biosynthetic protein (fliR) {Treponema pallidum}

Conservation Class 2	COG0445	COG0561	TP0044	TP0290	glucose inhibited division protein A (gidA) {Borrelia burgdorferi}	conserved hypothetical protein {Lactobacillus sake}
	COG0093	COG0799	TP0199	TP0738	ribosomal protein L14 (rplN) {Borrelia burgdorferi}	conserved hypothetical protein {Bacillus subtilis}
	COG0526	COG0771	TP0100	TP0903	thioredoxin, putative {Bradyrhizobium japonicum}	UDP-N-acetylmuramoylalanine--D-glutamate ligase (murD) {Borrelia burgdorferi}
	COG0357	COG0459	TP0946	TP0030	glucose-inhibited division protein B (gidB) {Escherichia coli}	heat shock protein (groEL) {Treponema pallidum}
	COG0228	COG0250	TP0905	TP0236	ribosomal protein S16 (rpsP) {Bacillus subtilis}	transcription antitermination protein (nusG) {Borrelia burgdorferi}
	COG0442	COG0459	TP0160	TP0030	prolyl-tRNA synthetase (proS) {Escherichia coli}	heat shock protein (groEL) {Treponema pallidum}
	COG0124	COG0124	TP0641	TP0641	histidyl-tRNA synthetase (hisS) {Borrelia burgdorferi}	histidyl-tRNA synthetase (hisS) {Borrelia burgdorferi}
	COG0477	COG2812	TP0840	TP1005	conserved hypothetical integral membrane protein {Archaeoglobus fulgidus}	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}
	COG0090	COG0223	TP0192	TP0756	ribosomal protein L2 (rplB) {Borrelia burgdorferi}	methionyl-tRNA formyltransferase (fmt) {Haemophilus influenzae}
	COG0012	COG0188	TP0124	TP0005	conserved hypothetical GTP-binding protein {Borrelia burgdorferi}	DNA gyrase, subunit A (gyrA) {Bacillus subtilis}
	COG0188	COG0526	TP0005	TP0100	DNA gyrase, subunit A (gyrA) {Bacillus subtilis}	thioredoxin, putative {Bradyrhizobium japonicum}
	COG0173	COG0493	TP0985	TP0735	aspartyl-tRNA synthetase (aspS) {Borrelia burgdorferi}	glutamate synthase (gltA) {Pyrococcus sp.}
	COG0546	COG0739	TP0554	TP0782	phosphoglycolate phosphatase (gph) {Haemophilus influenzae}	hypothetical protein
	COG0188	COG2199	TP0005	TP0981	DNA gyrase, subunit A (gyrA) {Bacillus subtilis}	sensory transduction histidine kinase, putative {Synechocystis PCC6803}
	COG0305	COG1595	TP0058	TP0092	replicative DNA helicase (dnaB) {Bacillus subtilis}	RNA polymerase sigma factor E (rpoE) {Mycobacterium leprae}
	COG0820	COG2812	TP0068	TP1005	conserved hypothetical protein {Synechocystis PCC6803}	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}
	COG0178	COG1197	TP0514	TP0344	excinuclease ABC, subunit A (uvrA) {Bacillus subtilis}	transcription-repair coupling factor (trcF) {Borrelia burgdorferi}
	COG0632	COG2255	TP0543	TP0162	Holliday junction DNA helicase (ruvA) {Haemophilus influenzae}	Holliday junction DNA helicase (ruvB) {Haemophilus influenzae}

	COG0222	COG0802	TP0240	TP0875	ribosomal protein L7/L12 (rplL) {Haemophilus influenzae}	conserved hypothetical protein {Synechocystis PCC6803}
	COG0227	COG0740	TP0362	TP0507	ribosomal protein L28 (rpmB) {Treponema pallidum}	ATP-dependent Clp protease proteolytic component (clpP) {Haemophilus influenzae}
	COG0305	COG0593	TP0058	TP0001	replicative DNA helicase (dnaB) {Bacillus subtilis}	chromosomal replication initiator protein (dnaA) {Borrelia burgdorferi}
	COG2812	COG2812	TP1005	TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}
	COG0305	COG2812	TP0058	TP1005	replicative DNA helicase (dnaB) {Bacillus subtilis}	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}
	COG0223	COG0242	TP0756	TP0757	methionyl-tRNA formyltransferase (fmt) {Haemophilus influenzae}	polypeptide deformylase (def) {Synechocystis PCC6803}
	COG0188	COG0305	TP0005	TP0058	DNA gyrase, subunit A (gyrA) {Bacillus subtilis}	replicative DNA helicase (dnaB) {Bacillus subtilis}
	COG0465	COG0465	TP0330	TP0330	cell division protein (ftsH) {Mycoplasma genitalium}	cell division protein (ftsH) {Mycoplasma genitalium}
Conservation Class 3	COG0322	COG1432	TP0472	TP0894	excinuclease ABC, subunit C (uvrC) {Methanobacterium thermoautotrophicum}	conserved hypothetical protein {Synechocystic PCC6803}
	COG0457	COG1432	TP0648	TP0894	conserved hypothetical protein {Borrelia burgdorferi}	conserved hypothetical protein {Synechocystic PCC6803}
	COG0457	COG1643	TP0067	TP0526	conserved hypothetical protein {Borrelia burgdorferi}	ATP-dependent helicase (hrpA) {Borrelia burgdorferi}
	COG0195	COG1643	TP0892	TP0526	N utilization substance protein A (nusA) {Borrelia burgdorferi}	ATP-dependent helicase (hrpA) {Borrelia burgdorferi}
	COG0090	COG1643	TP0192	TP0526	ribosomal protein L2 (rplB) {Borrelia burgdorferi}	ATP-dependent helicase (hrpA) {Borrelia burgdorferi}
	COG0208	COG1344	TP0053	TP0870	ribonucleoside-diphosphate reductase, subunit beta (nrdB) {Helicobacter pylori}	flagellar filament 31 kDa core protein (flaB3) {Treponema pallidum}
	COG0265	COG4786	TP0773	TP0961	periplasmic serine protease DO (htrA) {Haemophilus influenzae}	flagellar basal-body rod protein (flgG) {Borrelia burgdorferi}
	COG0526	COG1843	TP0100	TP0728	thioredoxin, putative {Bradyrhizobium japonicum}	flagellar hook assembly scaffolding protein (flgD) {Treponema pallidum}
	COG0442	COG1344	TP0160	TP0792	prolyl-tRNA synthetase (proS) {Escherichia coli}	flagellar filament 33 kDa core protein (flaB2) {Treponema pallidum}
	COG0608	COG0817	TP0704	TP0517	single-stranded-DNA-specific exonuclease (recJ)	Holliday junction nuclease (ruvC)

					{Borrelia burgdorferi}	{Escherichia coli}
	COG0802	COG0860	TP0875	TP0247	conserved hypothetical protein {Synechocystis PCC6803}	N-acetylmuramoyl-L-alanine amidase (amiA) {Escherichia coli}
	COG0457	COG2199	TP0648	TP0981	conserved hypothetical protein {Borrelia burgdorferi}	sensory transduction histidine kinase, putative {Synechocystis PCC6803}
	COG0457	COG1396	TP0648	TP0461	conserved hypothetical protein {Borrelia burgdorferi}	hypothetical protein
	COG0457	COG0845	TP0648	TP0965	conserved hypothetical protein {Borrelia burgdorferi}	membrane fusion protein, putative {Haemophilus influenzae}
	COG0577	COG0845	TP0963	TP0965	conserved hypothetical integral membrane protein {Bacillus subtilis} _	membrane fusion protein, putative {Haemophilus influenzae}
	COG0280	COG0457	TP0094	TP0920	phosphate acetyltransferase (pta) {Methanosarcina thermophila}	hypothetical protein
	COG0173	COG0845	TP0985	TP0965	aspartyl-tRNA synthetase (aspS) {Borrelia burgdorferi}	membrane fusion protein, putative {Haemophilus influenzae}
	COG0477	COG0845	TP0840	TP0965	conserved hypothetical integral membrane protein {Archaeoglobus fulgidus}	membrane fusion protein, putative {Haemophilus influenzae}
	COG0457	COG1061	TP0095	TP0380	hypothetical protein	DNA repair helicase, putative {Saccharomyces cerevisiae}
	COG0552	COG1061	TP0578	TP0380	cell division protein (ftsY) {Bacillus subtilis}	DNA repair helicase, putative {Saccharomyces cerevisiae}
	COG0457	COG1516	TP0648	TP0943	conserved hypothetical protein {Borrelia burgdorferi}	flagellar protein (fliS) {Bacillus subtilis}
	COG0457	COG3391	TP0471	TP0421	hypothetical protein	conserved hypothetical protein {Borrelia burgdorferi}
	COG0457	COG1194	TP0470	TP0343	conserved hypothetical protein {Synechocystis PCC6803}	A/G-specific adenine glycosylase, putative {Helicobacter pylori}
	COG0249	COG0457	TP0328	TP0095	DNA mismatch repair protein (mutS) {Borrelia burgdorferi}	hypothetical protein
	COG0457	COG0558	TP0067	TP0730	conserved hypothetical protein {Borrelia burgdorferi}	conserved hypothetical protein {Caenorhabditis elegans}
Conservation Class 4	COG0125	COG0457	TP0354	TP0648	thymidylate kinase (tmk) {Methanococcus jannaschii}	conserved hypothetical protein {Borrelia burgdorferi}
	COG0012	COG0457	TP0124	TP0067	conserved hypothetical GTP-binding protein {Borrelia burgdorferi}	conserved hypothetical protein {Borrelia burgdorferi}
	COG0124	COG0457	TP0641	TP0622	histidyl-tRNA synthetase (hisS) {Borrelia	hypothetical protein

				burgdorferi}	
	COG0445	COG0457	TP0044	TP0954	glucose inhibited division protein A (gidA) {Borrelia burgdorferi}	conserved hypothetical protein {Methanobacterium thermoautotrophicum}
	COG0242	COG0457	TP0757	TP0468	polypeptide deformylase (def) {Synechocystis PCC6803}	conserved hypothetical protein {Bacillus subtilis}
	COG0457	COG2812	TP0648	TP1005	conserved hypothetical protein {Borrelia burgdorferi}	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}
	COG0335	COG0457	TP0909	TP0496	ribosomal protein L19 (rplS) {Borrelia burgdorferi}	conserved hypothetical protein {Borrelia burgdorferi}
	COG0457	COG0566	TP0095	TP0054	hypothetical protein	conserved hypothetical protein {Escherichia coli}

Supplementary Table 17 Predicted essenential genes for *T. pallidum*. Predictions are based on data for *E. coli*, *B. subtilis*, and M. genitalium employing orthology relationships from the MBGD database.

		essential in …		
Gene	**Description**	***E. coli***	***B. subtilis***	**M. genitalium**
TP0001	chromosomal replication initiator protein (dnaA) {Borrelia burgdorferi}	+	+	+
TP0002	DNA polymerase III, subunit beta (dnaN) {Pseudomonas putida}	+	+	+
TP0005	DNA gyrase, subunit A (gyrA) {Bacillus subtilis}	+	+	+
TP0015	phenylalanyl-tRNA synthetase beta subunit (pheT) {Borrelia burgdorferi}	+	+	+
TP0019	transcription elongation factor (greA) {Borrelia burgdorferi}			+
TP0024	conserved hypothetical protein {Bacillus subtilis}			+
TP0029	UDP-N-acetylglucosamine 1-carboxyvinyltransferase (murA) {Borrelia burgdorferi}	+	+	
TP0030	heat shock protein (groEL) {Treponema pallidum}		+	+
TP0044	glucose inhibited division protein A (gidA) {Borrelia burgdorferi}			+
TP0051	peptide chain release factor 1 (prfA) {Borrelia burgdorferi}	+		+
TP0052	protoporphyrinogen oxidase (hemK) {Haemophilus influenzae}	+		+
TP0053	ribonucleoside-diphosphate reductase, subunit beta (nrdB) {Helicobacter pylori}	+	+	+
TP0056	oxaloacetate decarboxylase (oadA) {Klebsiella pneumoniae}	+	+	
TP0058	replicative DNA helicase (dnaB) {Bacillus subtilis}	+	+	+
TP0060	ribosomal protein L9 (rplI) {Bacillus subtilis}		+	+
TP0061	ribosomal protein S18 (rpsR) {Bacillus stearothermophilus}	+	+	+
TP0062	single-strand DNA binding protein (ssb) {Borrelia burgdorferi}	+		
TP0063	ribosomal protein S6 (rpsF) {Borrelia burgdorferi}		+	
TP0075	sugar ABC transporter, permease protein {Rhizobium sp.}			+
TP0076	sugar ABC transporter, permease protein {Rhizobium sp.}			+
TP0077	capsular polysaccharide biosynthesis protein (cap5D) {Staphylococcus aureus}			+
TP0090	UDP-N-acetylmuramate dehydrogenase (murB) {Borrelia burgdorferi}	+	+	
TP0091	cysteinyl-tRNA synthetase (cysS) {Borrelia burgdorferi}	+	+	+
TP0092	RNA polymerase sigma factor E (rpoE) {Mycobacterium leprae}	+		
TP0094	phosphate acetyltransferase (pta) {Methanosarcina thermophila}			+
TP0097	translation initiation factor 1 (infA) {Borrelia burgdorferi}	+	+	+
TP0098	heat-shock protein, putative {Legionella pneumophila}			+
TP0100	thioredoxin, putative {Bradyrhizobium japonicum}		+	
TP0102	rep helicase, single-stranded DNA-dependent ATPase (rep) {Borrelia burgdorferi}		+	
TP0105	DNA polymerase I (polA) {Treponema pallidum}			+
TP0107	licC protein (licC) {Haemophilus influenzae}			+
TP0108	pyrophosphate--fructose 6-phosphate 1-phosphotransferase (pfk) {Borrelia burgdorferi}		+	+

TP0116	excinuclease ABC, subunit B (uvrB) {Methanobacterium thermoautotrophicum}			+
TP0139	conserved hypothetical protein {Bacillus subtilis}			+
TP0140	K+ transport protein (ntpJ) {Bacillus subtilis}			+
TP0160	prolyl-tRNA synthetase (proS) {Escherichia coli}	+	+	
TP0182	conserved hypothetical protein {Mycobacterium tuberculosis}	+	+	
TP0184	small protein (smpB) {Synechocystis PCC6803}			+
TP0185	signal peptidase I (sip) {Bacillus subtilis}	+		
TP0187	translation elongation factor TU (tuf) {Escherichia coli}		+	+
TP0188	ribosomal protein S10 (rpsJ) {Borrelia burgdorferi}	+	+	+
TP0189	ribosomal protein L3 (rplC) {Borrelia burgdorferi}	+	+	+
TP0190		+	+	+
TP0191	ribosomal protein L23 (rplW) {Thermotoga maritima}	+	+	+
TP0192	ribosomal protein L2 (rplB) {Borrelia burgdorferi}	+	+	+
TP0193	ribosomal protein S19 (rpsS) {Borrelia burgdorferi}	+	+	+
TP0194	ribosomal protein L22 (rplV) {Borrelia burgdorferi}	+	+	+
TP0195	ribosomal protein S3 (rpsC) {Bacillus subtilis}	+	+	+
TP0196	ribosomal protein L16 (rplP) {Synechocystis PCC6803}	+	+	+
TP0198	ribosomal protein S17 (rpsQ) {Bacillus stearothermophilus}	+	+	+
TP0199	ribosomal protein L14 (rplN) {Borrelia burgdorferi}	+	+	+
TP0200	ribosomal protein L24 (rplX) {Bacillus subtilis}	+	+	+
TP0201	ribosomal protein L5 (rplE) {Borrelia burgdorferi}	+	+	+
TP0202	ribosomal protein S14 (rpsN) {Borrelia burgdorferi}	+	+	+
TP0203	ribosomal protein S8 (rpsH) {Borrelia burgdorferi}	+	+	+
TP0204	ribosomal protein L6 (rplF) {Borrelia burgdorferi}	+	+	+
TP0205	ribosomal protein L18 (rplR) {Bacillus stearothermophilus}	+	+	+
TP0206	ribosomal protein S5 (rpsE) {Borrelia burgdorferi}	+	+	+
TP0207	ribosomal protein L15 (rplO) {Borrelia burgdorferi}	+	+	+
TP0208	preprotein translocase subunit (secY) {Borrelia burgdorferi}	+	+	+
TP0209	ribosomal protein L36 (rpmJ) {Chlorella vulgaris}		+	+
TP0210	ribosomal protein S13 (rpsM) {Borrelia burgdorferi}	+	+	+
TP0211	ribosomal protein S11 (rpsK) {Borrelia burgdorferi}	+	+	+
TP0212	DNA-directed RNA polymerase, alpha subunit (rpoA) {Borrelia burgdorferi}	+	+	+
TP0213	ribosomal protein L17 (rplQ) {Borrelia burgdorferi}	+	+	+
TP0215	grpE protein (grpE) {Borrelia burgdorferi}	+		+
TP0216	heat shock protein 70 (dnaK) {Borrelia burgdorferi}			+
TP0227	cobalt ABC transporter, ATP-binding protein {Methanococcus jannaschii}			+
TP0230	primosomal protein N (priA) {Borrelia burgdorferi}		+	
TP0234	ribosomal protein L33 (rpmG) {Thermus aquaticus}		+	+
TP0235	preprotein translocase subunit (secE) {Thermotoga maritima}	+		
TP0236	transcription antitermination protein (nusG) {Borrelia burgdorferi}	+		+
TP0237	ribosomal protein L11 (rplK) {Thermotoga maritima}			+
TP0238	ribosomal protein L1 (rplA) {Borrelia burgdorferi}		+	+
TP0239	ribosomal protein L10 (rplJ) {Streptomyces antibioticus}	+	+	+
TP0240	ribosomal protein L7/L12 (rplL) {Haemophilus influenzae}	+	+	+
TP0241	DNA-directed RNA polymerase, beta subunit (rpoB)	+	+	+

	{Borrelia burgdorferi}			
TP0242	DNA-directed RNA polymerase, beta' subunit (rpoC) {Escherichia coli}	+	+	+
TP0243	ribosomal protein S12 (rpsL) {Leptospira biflexa}	+	+	+
TP0244	ribosomal protein S7 {Borrelia burgdorferi}	+	+	+
TP0251	DNA-binding protein II {Bacillus subtilis}		+	
TP0252	apolipoprotein N-acyltransferase, putative {Haemophilus influenzae}	+		
TP0255	ribosomal protein L31 (rpmE) {Haemophilus influenzae}		+	+
TP0256	CDP-diacylglycerol--glycerol-3-phosphate 3-phosphatidyltransferase (pgsA) {Bacillus subtilis}	+		
TP0264	deoxyribose-phosphate aldolase (deoC) {Bacillus subtilis}			+
TP0270	polynucleotide adenylyltransferase (pcnA) {Borrelia burgdorferi}		+	
TP0272	SpoOJ regulator (soj) {Bacillus subtilis}			+
TP0275	UDP-N-acetyl-D-mannosamine transferase, putative {Streptococcus pneumoniae}		+	
TP0279	ribosomal protein S1 (rpsA) {Escherichia coli}	+	+	+
TP0283	lipopolysaccharide core biosynthesis protein (kdtB) {Escherichia coli}	+		
TP0288	spore coat polysaccharide biosynthesis protein (spsF) {Bacillus subtilis}	+		
TP0290	conserved hypothetical protein {Lactobacillus sake}			+
TP0294	phosphoribosyl pyrophosphate synthetase (prs) {Borrelia burgdorferi}	+	+	+
TP0295	xylulokinase (xylB) {Borrelia burgdorferi}			+
TP0296	conserved hypothetical protein {Pseudomonas putida}		+	
TP0305	CTP synthase (pyrG) {Synechocystis PCC6803}	+	+	
TP0306	ribosomal protein S4 {Borrelia burgdorferi}	+	+	+
TP0307	conserved hypothetical protein {Borrelia burgdorferi}			+
TP0321	ribose/galactose ABC transporter, ATP-binding protein (rbsA) {Borrelia burgdorferi}			+
TP0322	ribose/galactose ABC transporter, permease protein (rbsC) {Borrelia burgdorferi}			+
TP0326	outer membrane protein {Helicobacter pylori}	+		
TP0329	serine hydroxymethyltransferase (glyA) {Bacillus subtilis}		+	+
TP0340	folylpolyglutamate synthetase (folC) {Bacillus subtilis}	+		
TP0341	UDP-N-acetylmuramate--alanine ligase (murC) {Borrelia burgdorferi}	+	+	
TP0345	phospho-N-acetylmuramoyl-pentapeptide-transferase (mraY) {Helicobacter pylori}	+	+	
TP0354	thymidylate kinase (tmk) {Methanococcus jannaschii}	+	+	+
TP0357	biotin--acetyl-CoA-carboxylase ligase (birA) {Mycobacterium tuberculosis}	+	+	
TP0361	lysophosphatidic acid acyltransferase, putative {Homo sapiens}	+		+
TP0362	ribosomal protein L28 (rpmB) {Treponema pallidum}	+	+	+
TP0367	chromosome segregation SMC protein homolog {Bacillus subtilis}		+	
TP0371	conserved hypothetical protein {Bacillus subtilis}	+	+	
TP0373	conserved hypothetical protein {Bacillus subtilis}	+	+	+
TP0379	preprotein translocase subunit (secA) {Borrelia burgdorferi}	+	+	+
TP0383	conserved hypothetical protein {Enterococcus hirae}			+
TP0384	conserved hypothetical protein {Borrelia burgdorferi}			+

TP0386	UDP-N-acetylmuramoylalanyl-D-glutamyl-2,6-diaminopimelate--D-alanyl-D-alanine ligase (murF) {Synechocystis PCC6803}	+	+	
TP0387	cell division protein (ftsW) {Borrelia burgdorferi}	+		
TP0389	cell division protein (ftsA) {Borrelia burgdorferi}	+	+	
TP0390	cell division protein (ftsZ) {Borrelia burgdorferi}	+	+	+
TP0394	DNA topoisomerase I (topA) {Bacillus subtilis}	+	+	+
TP0406	glutamate racemase (murI) {Escherichia coli}	+	+	
TP0408	hypothetical protein	+		+
TP0410	protein-export membrane protein (secD) {Borrelia burgdorferi}	+		+
TP0411	protein-export membrane protein (secF) {Bacillus subtilis}	+		
TP0416	signal recognition particle protein (ffh) {Borrelia burgdorferi}	+	+	+
TP0417	apolipoprotein N-acyltransferase (cutE) {Escherichia coli}	+		
TP0436	conserved hypothetical protein {Borrelia burgdorferi}			+
TP0441	conserved hypothetical protein {Escherichia coli}	+	+	+
TP0446	gcpE protein (gcpE) {Bacillus subtilis}	+	+	
TP0448	uracil phosphoribosyltransferase, putative {Bacillus subtilis}			+
TP0452	isoleucyl-tRNA synthetase (ileS) {Borrelia burgdorferi}		+	+
TP0458	conserved hypothetical protein {Mycoplasma genitalium}		+	
TP0464	conserved hypothetical protein {Haemophilus influenzae}			+
TP0472	excinuclease ABC, subunit C (uvrC) {Methanobacterium thermoautotrophicum}			+
TP0474	conserved hypothetical protein {Borrelia burgdorferi}			+
TP0475	glucose-6-phosphate isomerase (gpi) {Borrelia burgdorferi}			+
TP0476	acetate kinase (ack) {Methanosarcina thermophila}			+
TP0492	DNA primase (dnaE) {Clostridium acetobutylicum}		+	+
TP0493	RNA polymerase sigma-70 factor (rpoD) {Borrelia burgdorferi}		+	+
TP0497	rod shape-determining protein (mreB) {Borrelia burgdorferi}	+	+	
TP0498	rod shape-determining protein (mreC) {Borrelia burgdorferi}	+	+	
TP0500	penicillin-binding protein (pbp) {Borrelia burgdorferi}	+		
TP0501	rod shape-determining protein (rodA) {Borrelia burgdorferi}	+		
TP0512	conserved hypothetical protein {Rhodobacter capsulatus}	+		
TP0514	excinuclease ABC, subunit A (uvrA) {Bacillus subtilis}			+
TP0516	virulence factor (mviN) {Haemophilus influenzae}	+		
TP0523	UDP-N-acetylglucosamine--N-acetylmuramyl-(pentapeptide) pyrophosphoryl-undecaprenol N-acetylglucosamine transferase (murG) {Borrelia burgdorferi}	+	+	
TP0524	ATP-dependent protease LA (lon) {Borrelia burgdorferi}			+
TP0525	translation elongation factor P (efp) {Borrelia burgdorferi}			+
TP0537	triosephosphate isomerase (tpi) {Borrelia burgdorferi}		+	+
TP0538	phosphoglycerate kinase (pgk) {Borrelia burgdorferi}	+	+	+
TP0541	GTP-binding protein (era) {Borrelia burgdorferi}	+	+	+

TP0542	pyrophosphate--fructose 6-phosphate 1-phosphotransferase, beta subunit {Borrelia burgdorferi}		+	+
TP0547	penicillin tolerance protein (lytB) {Helicobacter pylori}	+	+	
TP0550	thiophene and furan oxidation protein (thdF) {Borrelia burgdorferi}			+
TP0559	conserved hypothetical protein {Archaeoglobus fulgidus}			+
TP0560	transketolase (tktA) {Bacillus subtilis}		+	
TP0576	peptide chain release factor 2 (prfB) {Borrelia burgdorferi}		+	
TP0578	cell division protein (ftsY) {Bacillus subtilis}	+	+	+
TP0580	conserved hypothetical integral membrane protein {Borrelia burgdorferi}	+		
TP0581	ABC transporter, ATP-binding protein {Borrelia burgdorferi}	+		+
TP0582	conserved hypothetical integral membrane protein {Borrelia burgdorferi}	+		
TP0586	leucyl-tRNA synthetase (leuS) {Borrelia burgdorferi}	+	+	+
TP0589	phosphocarrier protein HPr (ptsH) {Bacillus subtilis}			+
TP0591	HPr kinase (ptsK) {Bacillus subtilis}			+
TP0595	adenylate kinase (adk) {Bacillus subtilis}	+	+	+
TP0596	polynucleotide adenylyltransferase (pcnB) {Escherichia coli}		+	
TP0600	zinc protease, putative {Haemophilus influenzae}	+		
TP0601	conserved hypothetical protein {Synechocystis PCC6803}	+	+	
TP0602	phosphatidate cytidylyltransferase (cdsA) {Borrelia burgdorferi}	+	+	
TP0603	conserved hypothetical protein {Borrelia burgdorferi}	+		
TP0604	ribosome recycling factor {Bacillus subtilis}	+	+	+
TP0605	translation elongation factor TS (tsf) {Spirulina platensis}	+	+	+
TP0606	ribosomal protein S2 (rpsB) {Borrelia burgdorferi}	+	+	+
TP0609	asparaginyl-tRNA synthetase (asnS) {Synechocystis PCC6803}	+	+	+
TP0611	ABC transporter, ATP-binding protein {Synechocystis PCC6803}		+	
TP0612	conserved hypothetical protein {Bacillus subtilis}		+	
TP0614	nitrogen fixation protein (nifS) {Bacillus subtilis}		+	+
TP0615	nitrogen fixation protein (nifU) {Mycobacterium leprae}		+	+
TP0627	exonuclease (sbcC) {Escherichia coli}			+
TP0628	conserved hypothetical protein {Borrelia burgdorferi}		+	
TP0632	tryptophanyl-tRNA synthetase (trsA) {Borrelia burgdorferi}	+	+	+
TP0633	protein-methionine-S-oxide reductase (msrA) {Methanobacterium thermoautotrophicum}			+
TP0634	DNA ligase (lig) {Thermus aquaticus}	+	+	+
TP0641	histidyl-tRNA synthetase (hisS) {Borrelia burgdorferi}	+	+	+
TP0642	phosphomannomutase (manB) {Bacillus subtilis}			+
TP0643	DNA polymerase III, subunit epsilon (dnaQ) {Escherichia coli}		+	+
TP0647	seryl-tRNA synthetase (serS) {Borrelia burgdorferi}	+	+	+
TP0649	hemolysin (tlyC) {Borrelia burgdorferi}			+
TP0653	spermidine/putrescine ABC transporter, permease protein (potB) {Archaeoglobus fulgidus}			+

TP0654	spermidine/putrescine ABC transporter, permease protein (potC) {Haemophilus influenzae}			+
TP0657	carbon storage regulator (csrA) {Bacillus subtilis}	+		
TP0662	fructose-bisphosphate aldolase (cbbA) {Alcaligenes eutrophus}	+	+	+
TP0667	uridine kinase (udk) {Borrelia burgdorferi}			+
TP0669	DNA polymerase III, subunit alpha (dnaE) {Bacillus subtilis}	+		+
TP0670	D-alanine--D-alanine ligase (ddlA) {Salmonella choleraesuis}		+	
TP0672	glycyl-tRNA synthetase (glyS) {Borrelia burgdorferi}			+
TP0673	glutamyl-tRNA synthetase (gltX) {Borrelia burgdorferi}	+	+	+
TP0680	o-sialoglycoprotein endopeptidase (gcp) {Borrelia burgdorferi}	+	+	+
TP0681	alanine racemase (alr) {Treponema pallidum}		+	
TP0683	octaprenyl-diphosphate synthase {Treponema pallidum}	+	+	
TP0689	GTP-binding protein {Treponema pallidum}	+	+	+
TP0694	5,10-methenyltetrahydrofolate synthetase, putative {Homo sapiens}			+
TP0712	ATP-binding protein (ylxH) {Treponema pallidum}	+		
TP0732	methylenetetrahydrofolate dehydrogenase (folD) {Bacillus subtilis}	+	+	+
TP0734	purine nucleoside phosphorylase (deoD) {Bacillus stearothermophilus}			+
TP0740	conserved hypothetical protein {Bacillus subtilis}			+
TP0741	conserved hypothetical protein {Borrelia burgdorferi}	+		
TP0742	GTP-binding protein (obg) {Borrelia burgdorferi}	+	+	+
TP0743	ribosomal protein L27 (rpl27) {Synechocystis PCC6803}	+	+	+
TP0745	ribosomal protein L21 (rplU) {Bacillus subtilis}	+	+	+
TP0746	pyruvate, phosphate dikinase {Eleocharis vivipara}			+
TP0756	methionyl-tRNA formyltransferase (fmt) {Haemophilus influenzae}	+	+	+
TP0757	polypeptide deformylase (def) {Synechocystis PCC6803}	+		+
TP0758	ribosomal protein S21 (rpsU) {Myxococcus xanthus}		+	
TP0760	penicillin-binding protein (pbp) {Borrelia burgdorferi}	+	+	
TP0765	cell division protein (ftsH) {Helicobacter pylori}	+		+
TP0767	translation elongation factor G (fusA) {Borrelia burgdorferi}	+	+	+
TP0770	ATP-dependent RNA helicase {Archaeoglobus fulgidus}			+
TP0773	periplasmic serine protease DO (htrA) {Haemophilus influenzae}	+		
TP0780	NH(3)-dependent NAD(+) synthetase (nadE) {Rhodobacter capsulatus}	+	+	+
TP0794	S-adenosylmethionine synthetase (metK) {Escherichia coli}	+	+	+
TP0798	methionyl-tRNA synthetase (metG) {Borrelia burgdorferi}	+	+	+
TP0803	hypothetical protein			+
TP0805	exoribonuclease II (rnb) {Synechocystis PCC6803}			+
TP0807	ribosomal protein L32 (rpmF) {Borrelia burgdorferi}		+	+
TP0808	acyl carrier protein (acpP) {Borrelia burgdorferi}	+	+	
TP0809	ribonuclease III (rnc) {Borrelia burgdorferi}	+	+	
TP0814	thioredoxin reductase (trxB) {Bacillus subtilis}		+	+
TP0817	enolase (eno) {Treponema pallidum}	+	+	+

TP0819	conserved hypothetical protein {Borrelia burgdorferi}		+	
TP0824	transketolase B (tktB) {Haemophilus influenzae}	+	+	+
TP0826	conserved hypothetical protein {Borrelia burgdorferi}			+
TP0828	holo-acyl-carrier protein synthase (acpS) {Borrelia burgdorferi}	+	+	+
TP0830	pseudouridylate synthase (hisT) {Borrelia burgdorferi}			+
TP0831	arginyl-tRNA synthetase (argS) {Borrelia burgdorferi}}	+	+	+
TP0834	tyrosyl-tRNA synthetase (tyrS) {Borrelia burgdorferi}	+	+	+
TP0837	threonyl-tRNA synthetase (thrS) {Haemophilus influenzae}	+		+
TP0841	periplasmic serine protease DO (htrA) {Borrelia burgdorferi}	+		
TP0842	methionine aminopeptidase (map) {Bacillus subtilis}	+	+	+
TP0844	glyceraldehyde 3-phosphate dehydrogenase (gap) {Trypanoplasma borreli}	+		+
TP0848	ribosomal protein L20 (rplT) {Borrelia burgdorferi}	+	+	+
TP0849	ribosomal protein L35 (rpmI) {Borrelia burgdorferi}		+	+
TP0850	translation initiation factor 3 (infC) {Borrelia burgdorferi}	+	+	+
TP0852	prolipoprotein diacylglyceryl transferase (lgt) {Haemophilus influenzae}	+		+
TP0861	glucosamine-fructose-6-phosphate aminotransferase (glmS) {Haemophilus influenzae}	+	+	
TP0863	nitrogen fixation protein (nifS) {Rhodobacter sphaeroides}		+	
TP0875	conserved hypothetical protein {Synechocystis PCC6803}	+	+	
TP0876	conserved hypothetical protein {Escherichia coli}	+	+	
TP0885	deoxyuridine 5'-triphosphate nucleotidohydrolase (dut) {Helicobacter pylori}	+		
TP0887	ribosomal protein S15 (rpsO) {Borrelia burgdorferi}		+	+
TP0888	riboflavin kinase/FMN adenylyltransferase (ribF) {Escherichia coli}	+		+
TP0890	ribosome-binding factor A (rbfA) {Bacillus subtilis}			+
TP0891	translation initiation factor 2 (infB) {Borrelia burgdorferi}	+	+	+
TP0892	N utilization substance protein A (nusA) {Borrelia burgdorferi}	+	+	+
TP0901	conserved hypothetical integral membrane protein {Borrelia burgdorferi}			+
TP0903	UDP-N-acetylmuramoylalanine--D-glutamate ligase (murD) {Borrelia burgdorferi}	+	+	
TP0905	ribosomal protein S16 (rpsP) {Bacillus subtilis}	+	+	+
TP0908	tRNA (guanine-N1)-methyltransferase (trmD) {Borrelia burgdorferi}	+	+	+
TP0909	ribosomal protein L19 (rplS) {Borrelia burgdorferi}	+	+	+
TP0917	Mg2+ transport protein (mgtE) {Borrelia burgdorferi}		+	
TP0919	thioredoxin (trx) {Bacillus subtilis}		+	+
TP0921	NADH oxidase {Streptococcus mutans}			+
TP0925	flavodoxin {Clostridium beijerinckii}	+		
TP0926	signal peptidase I, putative {Bacillus licheniformis}	+		
TP0933	UDP-N-acetylmuramoylalanyl-D-glutamate--2,6-diaminopimelate ligase (murE) {Borrelia burgdorferi}	+	+	
TP0949	membrane protein {Borrelia burgdorferi}	+		+
TP0951	ribosomal protein L34 (rpmH) {Borrelia burgdorferi}	+	+	+
TP0964	ABC transporter, ATP-binding protein {Bacillus subtilis}	+		+

TP0973	phenylalanyl-tRNA synthetase alpha subunit (pheS) {Borrelia burgdorferi}	+	+	+
TP0975	conserved hypothetical protein {Borrelia burgdorferi}	+		
TP0978	signal peptidase II (lsp) {Borrelia burgdorferi}	+		
TP0985	aspartyl-tRNA synthetase (aspS) {Borrelia burgdorferi}	+	+	+
TP0999	cell division protein, putative {Borrelia burgdorferi}	+		
TP1005	DNA polymerase III, subunits gamma and tau (dnaH) {Borrelia burgdorferi}	+	+	
TP1006	DNA gyrase, subunit B (gyrB) {Treponema pallidum}	+	+	+
TP1008	ribonucleoside-diphosphate reductase, subunit alpha (nrdA) {Helicobacter pylori}	+	+	+
TP1009	glycerol-3-phosphate dehydrogenase (gpsA) {Bacillus subtilis}	+	+	
TP1011	peptidyl-tRNA hydrolase (pth) {Haemophilus influenzae}	+	+	+
TP1013	chaperonin (groES) {Bacillus stearothermophilus}	+	+	+
TP1016	basic membrane protein (tpn39b) {Treponema pallidum}		+	
TP1017	alanyl-tRNA synthetase (alaS) {Borrelia burgdorferi}		+	+
TP1018	conserved hypothetical protein {Borrelia burgdorferi}		+	+
TP1020	glu-tRNA amidotransferase, subunit A (gatA) {Archaeoglobus fulgidus}		+	+
TP1021	glu-tRNA amidotransferase, subunit B (gatB) {Borrelia burgdorferi}		+	+
TP1024	ribosomal protein S9 (rpsI) {Bacillus stearothermophilus}	+	+	+
TP1025	ribosomal protein L13 (rplM) {Borrelia burgdorferi}	+	+	+
TP1028	DNA helicase II (uvrD) {Thermus thermophilus}		+	
TP1035	valyl-tRNA synthetase (valS) {Borrelia burgdorferi}}	+	+	+
TP1039	adenine phosphoribosyltransferase (apt) {Haemophilus influenzae}			+
TP1040	lysyl-tRNA synthetase (lysS) {Escherichia coli}		+	+

Supplementary Table 18 Interactions of possible virulence genes (Weinstock et al. 1998).

Gene	Description	Interactions		
		all	**as bait**	**as prey**
Hemolysins				
TP0027	hemolysin, putative {Borrelia burgdorferi}	1	1	
TP0028	hemolysin, putative {Synechocystis PCC6803}	0		
TP0649	hemolysin (tlyC) {Borrelia burgdorferi}	0		
TP0936	hemolysin, putative {Synechocystis PCC6803}	0		
TP1037	hemolysin III (hlyIII) {Bacillus cereus}	1		1
Miscellaneous functions				
TP0502	hypothetical protein	0		
TP0580	conserved hypothetical integral membrane protein {Borrelia burgdorferi}	1	1	
TP0680	o-sialoglycoprotein endopeptidase (gcp) {Borrelia burgdorferi}	0		
TP0835	ankyrin, putative {Homo sapiens}	0		
Polysaccharide biosynthesis				
TP0077	capsular polysaccharide biosynthesis protein (cap5D) {Staphylococcus aureus}	1		1
TP0078	spore coat polysaccharide biosynthesis protein (spsC) {Bacillus subtilis}	2		2
TP0107	licC protein (licC) {Haemophilus influenzae}	0		
TP0283	lipopolysaccharide core biosynthesis protein (kdtB) {Escherichia coli}	0		
TP0288	spore coat polysaccharide biosynthesis protein (spsF) {Bacillus subtilis}	0		
TP0440	spore coat polysaccharide biosynthesis protein, putative {Synechocystis PCC6803}	0		
TP0562	spore coat polysaccharide biosynthesis protein (spsE) {Bacillus subtilis}	0		
Regulators				
TP0038	regulatory protein (pfoS/R) {Treponema pallidum}	4	4	
TP0454	hypothetical protein	0		
TP0516	virulence factor (mviN) {Haemophilus influenzae}	2	2	
TP0519	response regulatory protein (atoC) {Borrelia burgdorferi}	31	2	30
TP0520	sensory transduction histidine kinase (authentic frameshift)	0		
TP0877	conserved hypothetical protein {Borrelia burgdorferi}	5	1	4
TP0980	histidine phosphokinase/phophatase (ntrB) {Mycobacterium leprae}	0		
TP0981	sensory transduction histidine kinase, putative {Synechocystis PCC6803}	18	13	5
Potential membrane or surface-exposed proteins				
TP0006	Tp75 protein {Treponema pallidum}	6	6	
TP0020	76K protein {Treponema pallidum}	0		
TP0034	ABC transporter, periplasmic binding protein {Streptococcus pneumoniae}	3	2	1
TP0163	ABC transporter, periplasmic binding protein (troA) {Treponema pallidum}	5	5	
TP0171	lipoprotein, 15 kDa (tpp15) {Treponema pallidum}	17		17
TP0225	leucine-rich repeat protein TpLRR {Treponema pallidum}	1		1
TP0292	outer membrane protein (tpn50) {Treponema pallidum}	1		1
TP0298	exported protein (tpn38b) {Treponema pallidum}	2	2	
TP0319	membrane lipoprotein (tmpC) {Treponema pallidum}	0		
TP0326	outer membrane protein {Helicobacter pylori}	0		
TP0327	cationic outer membrane protein (ompH) {Yersinia enterocolitica}	0		
TP0435	lipoprotein, 17 kDa (tpp17) {Treponema pallidum}	11	11	
TP0470	conserved hypothetical protein {Synechocystis PCC6803}	1		1
TP0486	antigen, p83/100 {Borrelia burgdorferi}	0		
TP0567	conserved hypothetical protein {Borrelia burgdorferi}	5	5	
TP0571	Tp70 protein {Treponema pallidum}	2	2	
TP0574	carboxypeptidase, 47 kDa {Treponema pallidum}	0		
TP0624	conserved hypothetical protein {Borrelia burgdorferi}	0		
TP0702	conserved hypothetical protein {Borrelia burgdorferi}	3	1	2

TP0729	treponemal aqueous protein (tap1) {Treponema pallidum}	0		
TP0768	membrane protein (tmpA) {Treponema pallidum}	1		1
TP0769	outer membrane protein (tmpB) {Treponema pallidum}	0		
TP0796	conserved hypothetical protein {Haemophilus influenzae}	0		
TP0819	conserved hypothetical protein {Borrelia burgdorferi}	13	13	
TP0821	lipoprotein (tpn32) {Treponema pallidum}	0		
TP0957	Tp33 protein {Treponema pallidum}	0		
TP0971	membrane antigen, pathogen-specific (tpd) {Treponema pallidum}	1	1	
TP0989	P26 {Borrelia burgdorferi}	0		
TP0993	rare lipoprotein A, putative {Borrelia burgdorferi}	0		
TP1016	basic membrane protein (tpn39b) {Treponema pallidum}	1		1
TP1038	bacterioferrin (TpF1) {Treponema pallidum}	3	3	
Tpr proteins				
TP0009	tpr protein A (tprA) (authentic frameshift)	0		
TP0011	tpr protein B (tprB) {Treponema pallidum}	0		
TP0117	tpr protein C (tprC) {Treponema pallidum}	1	1	
TP0131	tpr protein D (tprD) {Treponema pallidum}	1	1	
TP0313	tpr protein E (tprE) {Treponema pallidum}	0		
TP0316	tpr protein F (tprF) (authentic frameshift)	0		
TP0317	tpr protein G (tprG) {Treponema pallidum}	0		
TP0610	tpr protein H (tprH) {Treponema pallidum}	2	1	1
TP0620	tpr protein I (tprI) {Treponema pallidum}	1		1
TP0621	tpr protein J (tprJ) {Treponema pallidum}	0		
TP0897	tpr protein K (tprK) {Treponema pallidum}	1		1
TP1031	tpr protein L (tprL), authentic frameshift {Treponema pallidum}	0		

Supplementary Table 19 Functional associations of pathogenicity related and essential genes.

GO1	GO2	Z-Value	# Y2H interactions
secondary metabolism (GO:0019748)	PATH_SURFACE	4.64	2
ribosome (GO:0005840)	PATH_TPR_PROTEINS	4.09	2
ribonucleoprotein complex (GO:0030529)	PATH_TPR_PROTEINS	4.02	2
intracellular (GO:0005622)	PATH_TPR_PROTEINS	3.26	2
cellular process (GO:0009987)	TOP50_EXPRESSION	3.04	2
intracellular (GO:0005622)	PATH_POOLED	2.95	15
secondary metabolism (GO:0019748)	PATH_POOLED	2.88	2
lipid metabolism (GO:0006629)	PATH_SURFACE	2.83	2
macromolecule catabolism (GO:0009057)	PATH_SURFACE	2.75	3
PATH_SURFACE	TOP50_EXPRESSION	2.75	7
structural molecule activity (GO:0005198)	PATH_TPR_PROTEINS	2.67	2
phosphotransferase activity, alcohol group as acceptor (GO:0016773)	TOP50_EXPRESSION	2.63	2
intracellular (GO:0005622)	PATH_REGULATORS	2.62	7
nucleobase, nucleoside, nucleotide and nucleic acid metabolism (GO:0006139)	TOP50_EXPRESSION	2.60	7
ion transport (GO:0006811)	LOWEST50_EXPRESSION	2.57	9
biosynthesis (GO:0009058)	PATH_SURFACE	2.54	4
protein catabolism (GO:0030163)	essential	2.48	2
ion transporter activity (GO:0015075)	LOWEST50_EXPRESSION	2.48	8
electron carrier activity (GO:0009055)	essential	2.46	18
electron carrier activity (GO:0009055)	essential in all	2.41	7
transferase activity (GO:0016740)	TOP50_EXPRESSION	2.38	14
response to stress (GO:0006950)	PATH_SURFACE	2.33	6
cellular metabolism (GO:0044237)	PATH_SURFACE	2.32	4
cellular metabolism (GO:0044237)	essential	2.32	26
translation factor activity, nucleic acid binding (GO:0008135)	TOP50_EXPRESSION	2.30	4
nucleotide binding (GO:0000166)	PATH_SURFACE	2.29	17
cellular metabolism (GO:0044237)	TOP50_EXPRESSION	2.28	6
carbohydrate metabolism (GO:0005975)	PATH_SURFACE	2.26	6
transporter activity (GO:0005215)	PATH_SURFACE	2.24	2
protein biosynthesis (GO:0006412)	PATH_TPR_PROTEINS	2.24	2
nucleobase, nucleoside, nucleotide and nucleic acid metabolism (GO:0006139)	TOP 20 EXPRESSION	2.22	4
TOP 10 EXPRESSION	isomerase activity (GO:0016853)	2.22	3
(GO:0003723)	PATH_POOLED	2.18	9
PATH_REGULATORS	PATH_REGULATORS	2.16	2
catabolism (GO:0009056)	LOWEST50_EXPRESSION	2.15	2
ribosome (GO:0005840)	PATH_REGULATORS	2.14	5
lipid metabolism (GO:0006629)	essential	2.14	10
antioxidant activity (GO:0016209)	essential	2.12	3
TOP 10 EXPRESSION	PATH_SURFACE	2.12	3
cell motility (GO:0006928)	TPA_DB_HYPOTHETICAL	2.12	61
DNA binding (GO:0003677)	PATH_POOLED	2.07	12
helicase activity (GO:0004386)	essential in all	2.07	7
transporter activity (GO:0005215)	TOP50_EXPRESSION	2.07	3
structural molecule activity (GO:0005198)	PATH_REGULATORS	2.02	8

transferase activity (GO:0016740)	TOP 20 EXPRESSION	2.01	7

Supplementary Table 20 Functional associations of pathogenicity related and essential genes (TIGR subrole).

Subrole 1	Subrole 2	Z-Value	# Y2H interactions
PATH_SURFACE	Pathogenesis	8.69	2
Pathogenesis	TOP50_EXPRESSION	6.16	2
PATH_POOLED	Pathogenesis	4.96	2
PATH_TPR_PROTEINS	Ribosomal proteins: synthesis and modification	4.14	2
Cations and iron carrying compounds	LOWEST50_EXPRESSION	3.39	8
2'-Deoxyribonucleotide metabolism	TOP50_EXPRESSION	3.28	2
PATH_SURFACE	TOP50_EXPRESSION	2.75	7
PATH_REGULATORS	Ribosomal proteins: synthesis and modification	2.22	5
PATH_REGULATORS	PATH_REGULATORS	2.16	2
Carbohydrates, organic alcohols, and acids	TOP50_EXPRESSION	2.16	3
TOP 10 EXPRESSION	PATH_SURFACE	2.12	3
TOP50_EXPRESSION	Translation factors	2.11	4
Biosynthesis	essential	2.08	3
Conserved	essential	2.07	230
LOWEST50_EXPRESSION	Unknown substrate	2.06	2
Protein and peptide secretion and trafficking	essential	2.05	11
2'-Deoxyribonucleotide metabolism	essential in all	2.05	2
Protein modification and repair	essential in all	2.03	6

Supplementary Table 21 *E. coli* gene mutants screened for 5-FdU sensitivity.

ORF	CLONE #	DEFINITION	ROW	COL
B0058	1	orf, hypothetical protein	1	1
B0479	1	fosmidomycin resistance prote	1	19
B0568	1	bacteriophage N4 receptor, ou membrane protein	1	21
B0659	1	orf, hypothetical protein	1	23
B0081	1	orf, hypothetical protein	1	3
B0082	1	putative apolipoprotein	1	5
B0099	1	7,8-dihydro-8-oxoguanine-triphosphatase, prefers dGTP, causes AT-GC transversions	1	7
B0103	1	putative DNA repair protein	1	9
B0285	1	orf, hypothetical protein	1	11
B0343	1	galactoside permease (M prote	1	13
B0433	1	regulates beta-lactamase synth	1	15
B0443	1	orf, hypothetical protein	1	17
B0661	1	orf, hypothetical protein	3	1
B0931	1	nicotinate phosphoribosyltransferase	3	19
B1053	1	putative transport protein	3	21
B1097	1	putative thymidylate kinase (E 2.7.4.9)	3	23
B0710	1	orf, hypothetical protein	3	3
B0736	1	orf, hypothetical protein	3	5
B0741	1	peptidoglycan-associated lipoprotein	3	7
B0766	1	putative phosphatase	3	9
B0822	1	orf, hypothetical protein	3	11
B0835	1	orf, hypothetical protein	3	13
B0845	1	putative DEOR-type transcriptional regulator	3	15
B0898	1	putative transport	3	17
B1100	1	orf, hypothetical protein	5	1
B1534	1	putative transport protein	5	19
B1543	1	putative transport protein	5	21
B1601	1	putative transport protein	5	23
B1134	1	putative phosphohydrolase	5	3
B1135	1	orf, hypothetical protein	5	5
B1197	1	trehalase, periplasmic	5	7
B1203	1	putative GTP-binding protein	5	9
B1330	1	orf, hypothetical protein	5	11
B1344	1	orf, hypothetical protein	5	13
B1452	1	putative receptor	5	15
B1529	1	orf, hypothetical protein	5	17
B1630	1	orf, hypothetical protein	7	1
B1959	1	putative transmembrane subu	7	19
B1962	1	orf, hypothetical protein	7	21
B1981	1	putative transport protein, shikimate	7	23
B1681	1	orf, hypothetical protein	7	3
B1688	1	orf, hypothetical protein	7	5
B1758	1	putative cytochrome oxidase	7	7
B1759	1	orf, hypothetical protein	7	9
B1769	1	putative transport protein	7	11
B1813	1	orf, hypothetical protein	7	13
B1864	1	orf, hypothetical protein	7	15
B1865	1	dATP pyrophosphohydrolase	7	17
B1983	1	orf, hypothetical protein	9	1
B2367	1	multidrug resistance protein Y	9	19
B2406	1	xanthosine permease	9	21
B2467	1	orf, hypothetical protein	9	23
B1985	1	orf, hypothetical protein	9	3
B2077	1	putative transport protein	9	5
B2098	1	putative nucleoside permease protein	9	7
B2106	1	orf, hypothetical protein	9	9
B2183	1	16S pseudouridylate 516 synth	9	11
B2251	1	orf, hypothetical protein	9	13
B2299	1	putative regulator	9	15
B2322	1	putative transport protein	9	17
B2493	1	putative permease	11	1
B2791	1	orf, hypothetical protein	11	19
B2830	1	putative invasion protein	11	21
B2841	1	low-affinity L-arabinose transp system proton symport protei	11	23
B2516	1	putative membrane protein	11	3
B2517	1	orf, hypothetical protein	11	5
B2565	1	protein interacts with RecR an possibly RecF proteins	11	7
B2581	1	orf, hypothetical protein	11	9
B2587	1	alpha-ketoglutarate permease	11	11
B2686	1	multidrug resistance; probably membrane translocase	11	13
B2775	1	putative transport protein	11	15
B2789	1	putative transport protein	11	17
B2880	1	orf, hypothetical protein	13	1
B3196	1	orf, hypothetical protein	13	19
B3519	1	cytoplasmic trehalase	13	21
B3523	1	putative transport protein	13	23
B2881	1	putative dehydrogenase	13	3
B2943	1	galactose-proton symport of transport system	13	5
B2952	1	putative resistance protein	13	7
B2960	1	orf, hypothetical protein	13	9
B3034	1	orf, hypothetical protein	13	11
B3093	1	transport of hexuronates	13	13
B3148	1	orf, hypothetical protein	13	15

B3184	1	orf, hypothetical protein	13	17
B3651	1	putative RNA methylase	15	1
B3473	1	putative transport	15	19
B3413	1	orf, hypothetical protein	15	21
B2771	1	putative transport protein	15	23
B3660	1	putative permease transporter	15	3
B0353	1	putative transport protein	15	5
B1683	1	orf, hypothetical protein	15	7
B1775	1	putative transport protein	15	9
B2051	1	GDP-mannose mannosyl hydrolase	15	11
B2182	1	bicyclomycin resistance protei transmembrane protein	15	13
B2214	1	orf, hypothetical protein	15	15
B2866	1	orf, hypothetical protein	15	17
B0058	2	orf, hypothetical protein	1	2
B0577	2	putative transport	1	20
B0659	2	orf, hypothetical protein	1	22
B0661	2	orf, hypothetical protein	1	24
B0081	2	orf, hypothetical protein	1	4
B0082	2	putative apolipoprotein	1	6
B0103	2	putative DNA repair protein	1	8
B0284	2	orf, hypothetical protein	1	10
B0285	2	orf, hypothetical protein	1	12
B0443	2	orf, hypothetical protein	1	14
B0479	2	fosmidomycin resistance prote	1	16
B0568	2	bacteriophage N4 receptor, ou membrane protein	1	18
B0710	2	orf, hypothetical protein	3	2
B0931	2	nicotinate phosphoribosyltransferase	3	20
B1053	2	putative transport protein	3	22
B1086	2	orf, hypothetical protein	3	24
B0736	2	orf, hypothetical protein	3	4
B0741	2	peptidoglycan-associated lipoprotein	3	6
B0766	2	putative phosphatase	3	8
B0822	2	orf, hypothetical protein	3	10
B0835	2	orf, hypothetical protein	3	12
B0842	2	proton motive force efflux pu	3	14
B0845	2	putative DEOR-type transcriptional regulator	3	16
B0898	2	putative transport	3	18
B1097	2	putative thymidylate kinase (E 2.7.4.9)	5	2
B1452	2	putative receptor	5	20
B1529	2	orf, hypothetical protein	5	22
B1534	2	putative transport protein	5	24
B1100	2	orf, hypothetical protein	5	4
B1134	2	putative phosphohydrolase	5	6
B1135	2	orf, hypothetical protein	5	8
B1197	2	trehalase, periplasmic	5	10
B1203	2	putative GTP-binding protein	5	12
B1234	2	orf, hypothetical protein	5	14
B1330	2	orf, hypothetical protein	5	16
B1344	2	orf, hypothetical protein	5	18
B1596	2	putative transport protein	7	2
B1813	2	orf, hypothetical protein	7	20
B1864	2	orf, hypothetical protein	7	22
B1865	2	dATP pyrophosphohydrolase	7	24
B1601	2	putative transport protein	7	4
B1630	2	orf, hypothetical protein	7	6
B1681	2	orf, hypothetical protein	7	8
B1688	2	orf, hypothetical protein	7	10
B1690	2	putative transport system permease protein	7	12
B1758	2	putative cytochrome oxidase	7	14
B1759	2	orf, hypothetical protein	7	16
B1769	2	putative transport protein	7	18
B1959	2	putative transmembrane subu	9	2
B2299	2	putative regulator	9	20
B2322	2	putative transport protein	9	22
B2367	2	multidrug resistance protein Y	9	24
B1962	2	orf, hypothetical protein	9	4
B1981	2	putative transport protein, shikimate	9	6
B1983	2	orf, hypothetical protein	9	8
B1985	2	orf, hypothetical protein	9	10
B2077	2	putative transport protein	9	12
B2098	2	putative nucleoside permease protein	9	14
B2183	2	16S pseudouridylate 516 synth	9	16
B2251	2	orf, hypothetical protein	9	18
B2406	2	xanthosine permease	11	2
B2742	2	lipoprotein	11	20
B2775	2	putative transport protein	11	22
B2789	2	putative transport protein	11	24
B2467	2	orf, hypothetical protein	11	4
B2493	2	putative permease	11	6
B2516	2	putative membrane protein	11	8
B2517	2	orf, hypothetical protein	11	10
B2565	2	protein interacts with RecR an possibly RecF proteins	11	12
B2587	2	alpha-ketoglutarate permease	11	14
B2605	2	putative outer membrane prot	11	16
B2686	2	multidrug resistance; probably membrane translocase	11	18
B3697	1	orf, hypothetical protein	13	2
B4111	1	low-affinity transport system; proline permease II	13	20
B4180	1	orf, hypothetical protein	13	22
B4210	1	putative transmembrane subu	13	24
B3710	1	putative transport protein	13	4
B3827	1	orf, hypothetical protein	13	6
B3874	1	putative resistance protein (transport)	13	8
B4020	1	putative alpha helix protein	13	10
B4022	1	orf, hypothetical protein	13	12
B4031	1	xylose-proton symport	13	14
B4044	1	DNA-damage-inducible prote	13	16
B4092	1	phosphonate metabolism	13	18
B4332	1	putative transport protein	15	2

B2214	2	orf, hypothetical protein	15	20
B3673	1	2-module integral membrane pump; multidrug resistance	15	22
B2771	2	putative transport protein	15	24
B4337	1	putative transport protein	15	4
B4356	1	putative transport protein, cry orf, joins former yjiZ and yjjL	15	6
B0353	2	putative transport protein	15	8
B1683	2	orf, hypothetical protein	15	10
B1775	2	putative transport protein	15	12
B1856	2	orf, hypothetical protein	15	14
B2051	2	GDP-mannose mannosyl hydrolase	15	16
B2182	2	bicyclomycin resistance protei transmembrane protein	15	18
B0045	3	putative transport protein	2	1
B0842	3	proton motive force efflux pu	2	19
B0957	5	outer membrane protein 3a (II*;G;d)	2	21
B1086	5	orf, hypothetical protein	2	23
B0045	4	putative transport protein	2	3
B0099	3	7,8-dihydro-8-oxoguanine-triphosphatase, prefers dGTP, causes AT-GC transversions	2	5
B0284	3	orf, hypothetical protein	2	7
B0343	3	galactoside permease (M prote	2	9
B0433	3	regulates beta-lactamase synth	2	11
B0446	3	orf, hypothetical protein	2	13
B0446	4	orf, hypothetical protein	2	15
B0577	3	putative transport	2	17
B1234	3	orf, hypothetical protein	4	1
B2536	5	MFS (major facilitator superfamily) transporter	4	19
B2581	4	orf, hypothetical protein	4	21
B2594	3	suppressor of ftsH mutation	4	23
B1242	3	putative channel protein	4	3
B1242	5	putative channel protein	4	5
B1269	3	orf, hypothetical protein	4	7
B1269	4	orf, hypothetical protein	4	9
B1543	3	putative transport protein	4	11
B1596	4	putative transport protein	4	13
B1690	3	putative transport system permease protein	4	15
B2106	3	orf, hypothetical protein	4	17
B2594	4	suppressor of ftsH mutation	6	1
B2867	2	putative dehydrogenase	6	19
B2867	4	putative dehydrogenase	6	21
B2880	2	orf, hypothetical protein	6	23
B2605	3	putative outer membrane prot	6	3
B2742	3	lipoprotein	6	5
B2791	2	orf, hypothetical protein	6	7
B2830	2	putative invasion protein	6	9
B2835	2	putative resistance proteins	6	11
B2835	3	putative resistance proteins	6	13
B2841	2	low-affinity L-arabinose transp system proton symport protei	6	15
B2851	5	orf, hypothetical protein	6	17
B2881	2	putative dehydrogenase	8	1
B3093	2	transport of hexuronates	8	19
B3127	3	putative transport protein	8	21
B3127	4	putative transport protein	8	23
B2924	2	putative transport protein	8	3
B2924	5	putative transport protein	8	5
B2943	2	galactose-proton symport of transport system	8	7
B2952	2	putative resistance protein	8	9
B2954	2	putative ribosomal protein	8	11
B2954	3	putative ribosomal protein	8	13
B2960	2	orf, hypothetical protein	8	15
B3034	2	orf, hypothetical protein	8	17
B3148	2	orf, hypothetical protein	10	1
B3465	4	orf, hypothetical protein	10	19
B3519	2	cytoplasmic trehalase	10	21
B3523	2	putative transport protein	10	23
B3184	3	orf, hypothetical protein	10	3
B3196	2	orf, hypothetical protein	10	5
B3290	2	transport of potassium	10	7
B3290	3	transport of potassium	10	9
B3364	4	putative transport	10	11
B3397	5	orf, hypothetical protein	10	13
B3434	2	orf, hypothetical protein	10	15
B3434	3	orf, hypothetical protein	10	17
B3547	3	putative resistance protein	12	1
B3754	4	putative transport protein	12	19
B3812	2	putative phosphatase	12	21
B3812	3	putative phosphatase	12	23
B3547	5	putative resistance protein	12	3
B3651	2	putative RNA methylase	12	5
B3659	3	two-module transport protein	12	7
B3659	4	two-module transport protein	12	9
B3660	2	putative permease transporter	12	11
B3697	2	orf, hypothetical protein	12	13
B3710	3	putative transport protein	12	15
B3754	2	putative transport protein	12	17
B3827	2	orf, hypothetical protein	14	1
B4111	2	low-affinity transport system; proline permease II	14	19
B4146	2	orf, hypothetical protein	14	21
B4146	3	orf, hypothetical protein	14	23
B3874	3	putative resistance protein (transport)	14	3
B3907	2	rhamnose transport	14	5
B3907	3	rhamnose transport	14	7
B4020	2	putative alpha helix protein	14	9
B4022	2	orf, hypothetical protein	14	11
B4031	2	xylose-proton symport	14	13
B4044	3	DNA-damage-inducible prote	14	15
B4092	2	phosphonate metabolism	14	17
B4180	2	orf, hypothetical protein	16	1
B3673	2	2-module integral membrane pump; multidrug resistance	16	19
B3473	2	putative transport	16	21

B3413	2	orf, hypothetical protein	16	23
B4210	2	putative transmembrane subu	16	3
B4332	2	putative transport protein	16	5
B4337	2	putative transport protein	16	7
B4356	2	putative transport protein, cry orf, joins former yjiZ and yjjL	16	9
B4374	2	putative phosphatase	16	11
B4374	5	putative phosphatase	16	13
B1856	3	orf, hypothetical protein	16	15
B2866	2	orf, hypothetical protein	16	17
B0957	6	outer membrane protein 3a (II*;G;d)	2	2
B0243	3	gamma-glutamylphosphate reductase	2	20
B0386	1	pyrroline-5-carboxylate reduct	2	22
B0386	2	pyrroline-5-carboxylate reduct	2	24
B2170	6	putative transport	2	4
B2170	7	putative transport	2	6
B2536	6	MFS (major facilitator superfamily) transporter	2	8
B2851	6	orf, hypothetical protein	2	10
B3364	6	putative transport	2	12
B3397	7	orf, hypothetical protein	2	14
B3465	7	orf, hypothetical protein	2	16
B0243	2	gamma-glutamylphosphate reductase	2	18
B0436	1	trigger factor; a molecular chaperone involved in cell div	4	2
B1859	2	orf, hypothetical protein	4	20
B1863	1	Holliday junction nuclease; resolution of structures; repair	4	22
B1863	2	Holliday junction nuclease; resolution of structures; repair	4	24
B0436	2	trigger factor; a molecular chaperone involved in cell div	4	4
B0472	2	recombination and repair	4	6
B0472	3	recombination and repair	4	8
B0489	1	putative protease	4	10
B0489	2	putative protease	4	12
B1363	1	trk system potassium uptake; p of Rac prophage	4	14
B1363	2	trk system potassium uptake; p of Rac prophage	4	16
B1859	1	orf, hypothetical protein	4	18
B2048	1	phosphomannomutase	6	2
B2892	2	ssDNA exonuclease, 5 --> 3 specific	6	20
B3019	1	DNA topoisomerase IV subu A	6	22
B3019	3	DNA topoisomerase IV subu A	6	24
B2048	2	phosphomannomutase	6	4
B2220	2	response regulator of ato, ornithine decarboxylase antizy (sensor ATOS)	6	6
B2220	3	response regulator of ato, ornithine decarboxylase antizy (sensor ATOS)	6	8
B2554	1	putative 2-component transcriptional regulator	6	10
B2554	2	putative 2-component transcriptional regulator	6	12
B2569	2	GTP-binding elongation facto may be inner membrane prote	6	14
B2569	5	GTP-binding elongation facto may be inner membrane prote	6	16
B2892	1	ssDNA exonuclease, 5 --> 3 specific	6	18
B3176	1	similar to phosphoglucomutas and phosphomannomutases	8	2
B3741	2	glucose-inhibited division; chromosome replication?	8	20
B3868	2	response regulator for gln (ser glnL) (nitrogen regulator I, NI	8	22
B3868	4	response regulator for gln (ser glnL) (nitrogen regulator I, NI	8	24
B3176	2	similar to phosphoglucomutas and phosphomannomutases	8	4
B3299	1	50S ribosomal subunit protein L36	8	6
B3299	2	50S ribosomal subunit protein L36	8	8
B3425	1	protein of glp regulon	8	10
B3425	2	protein of glp regulon	8	12
B3652	1	DNA helicase, resolution of Holliday junctions, branch migration	8	14
B3652	2	DNA helicase, resolution of Holliday junctions, branch migration	8	16
B3741	1	glucose-inhibited division; chromosome replication?	8	18
B4004	1	response regulator of hydroge 3 activity (sensor HydH)	10	2
B1214	2	orf, hypothetical protein	10	20
b3409	dfe	ferrous iron transport protein	10	22
b1203	dyc	putative GTP-binding protein	10	24
B4004	3	response regulator of hydroge 3 activity (sensor HydH)	10	4
B4174	1	protease specific for phage lambda cII repressor	10	6
B4174	2	protease specific for phage lambda cII repressor	10	8
B4175	1	protease specific for phage lambda cII repressor	10	10
B4175	2	protease specific for phage lambda cII repressor	10	12
B3508	1	putative transport ATPase	10	14
B3508	2	putative transport ATPase	10	16
B1214	1	orf, hypothetical protein	10	18
b4146	dyg	orf, hypothetical protein	12	2
B2698	1	regulator, OraA protein	12	20

B2698	2	regulator, OraA protein	12	22
b1100	dyc	orf, hypothetical protein	12	4
b1864	dyel	orf, hypothetical protein	12	6
b1983	dye	orf, hypothetical protein	12	8
b2517	dyf	orf, hypothetical protein	12	10
B2699	1	DNA strand exchange and renaturation, DNA-dependen ATPase, DNA- and ATP-dependent coprotease	12	12
B2699	2	DNA strand exchange and renaturation, DNA-dependen ATPase, DNA- and ATP-dependent coprotease	12	14
B2733	1	methyl-directed mismatch rep	12	16
B2733	2	methyl-directed mismatch rep	12	18
yebCyeeN	1	dyebC/dyeeN RP427	14	20
yebCyeeN	2	dyebC/dyeeN RP427	14	22
wtRP437	1	RP437	14	4
wtRP437	2	RP437	14	6
BW25113	1	WI	14	8
BW25113	2	WI	14	10
BW25113	3	WT	14	12
BW25113	4	WT	14	18
BW25113	5	WI	16	20
wtRP437	6	RP437	16	22
wtRP437	7	RP437	16	24
BW25113	8	WT	16	14
BW25113	9	WT	16	16
BW25113	10	WT	16	18

Supplementary Table 22 *E. coli* gene-deletion mutants with reduced motility. All mutant strain from a systematic gene-deletion library for *E. coli* (Baba et al. 2006)were tested for reduced motility using an automated robotic procedure.

SCREEN_RESULT: result for both independent strains of respective mutant in whole genome screen
SWARMING_DIAMETER[%]: Percentage of swarming diameter found in retest
STRONGLY REDUCED: Mutants with a swarming diameter reduced to
20% or more are classified to have strongly reduced motility
LB_22h: OD600 measured after 22h incubation at 37°C in LB medium (taken from Baba et al. 2006)

BNAME	NAME	SCREEN_RESULT	SWARMING DIAMETER[%]	STRONGLY REDUCED	LB_22h
B0014	dnaK	strongly reduced/strongly reduced	16	yes	0.465
B0015	dnaJ	strongly reduced/strongly reduced	32	no	0.506
B0051	ksgA	reduced/reduced	38	no	0.764
B0116	lpdA	strongly reduced/strongly reduced	32	no	0.337
B0119	yacL	reduced/strongly reduced	40	no	0.718
B0161	degP	reduced/reduced	24	no	0.357
B0222	lpcA	strongly reduced/strongly reduced	35	no	0.437
B0253	ykfA	reduced/reduced	45	no	0.695
B0405	queA	reduced/strongly reduced	45	no	0.834
B0406	tgt	reduced/reduced	46	no	0.765
B0418	pgpA	strongly reduced/strongly reduced	38	no	0.655
B0556	rzpD	reduced/reduced	47	no	0.817
B0628	lipA	strongly reduced/strongly reduced	23	no	0.296
B0631	ybeD	reduced/strongly reduced	35	no	0.341
B0637	ybeB	reduced/strongly reduced	42	no	0.69
B0659	ybeY	strongly reduced/strongly reduced	3	yes	0.467
B0662	ubiF	strongly reduced/strongly reduced	5	yes	0.308
B0688	pgm	reduced/strongly reduced	29	no	0.363
B0695	kdpD	reduced/reduced	46	no	0.44
B0721	sdhC	reduced/strongly reduced	36	no	0.42
B0734	cydB	reduced/strongly reduced	43	no	0.525
B0738	tolR	strongly reduced/strongly reduced	41	no	0.478
B0739	tolA	reduced/strongly reduced	43	no	0.461
B0910	cmk	strongly reduced/strongly reduced	28	no	0.388
B0913	ycaI	reduced/reduced	28	no	0.753
B0969	yccK	strongly reduced/strongly reduced	18	yes	0.72
B1049	mdoH	strongly reduced/strongly reduced	34	no	0.524
B1070	flgN	strongly reduced/strongly reduced	28	no	0.467
B1071	flgM	reduced/reduced	47	no	0.676
B1072	flgA	strongly reduced/strongly reduced	45	no	0.463
B1073	flgB	strongly reduced/strongly reduced	3	yes	0.478
B1074	flgC	strongly reduced/strongly reduced	3	yes	0.5
B1075	flgD	strongly reduced/strongly reduced	3	yes	0.441
B1076	flgE	strongly reduced/strongly reduced	3	yes	0.466
B1077	flgF	strongly reduced/strongly reduced	10	yes	0.513
B1078	flgG	strongly reduced/strongly reduced	0	yes	0.467
B1080	flgI	strongly reduced/strongly reduced	18	yes	0.417
B1081	flgJ	strongly reduced/strongly reduced	19	yes	0.419
B1082	flgK	strongly reduced/strongly reduced	3	yes	0.501
B1083	flgL	strongly reduced/strongly reduced	35	no	0.507
B1089	rpmF	strongly reduced/strongly reduced	39	no	0.421
B1105	ycfM	reduced/strongly reduced	0	yes	0.592

B1133	trmU	reduced/strongly reduced	36	no	0.687
B1166	ymgB	strongly reduced/strongly reduced	42	no	0.67
B1187	fadR	reduced/reduced	49	no	0.916
B1192	ldcA	reduced/strongly reduced	41	no	0.637
B1203	ychF	reduced/strongly reduced	43	no	0.692
B1226	narJ	reduced/strongly reduced	41	no	0.591
B1236	galU	strongly reduced/strongly reduced	24	no	0.476
B1237	hns	strongly reduced/strongly reduced	30	no	0.507
B1280	yciM	reduced/strongly reduced	34	no	0.418
B1289	ycjD	reduced/reduced	50	no	0.68
B1357	ydaS	strongly reduced/strongly reduced	43	no	0.45
B1428	ydcK	strongly reduced/strongly reduced	43	no	0.596
B1445	ydcX	reduced/strongly reduced	50	no	0.692
B1534	ydeE	reduced/strongly reduced	34	no	0.619
B1643	ydhI	reduced/strongly reduced	45	no	0.582
B1659	ydhB	reduced/strongly reduced	46	no	0.754
B1693	aroD	reduced/reduced	35	no	0.607
B1717	rpmI	reduced/reduced	45	no	0.658
B1755	ynjC	reduced/reduced	45	no	0.79
B1878	flhE	reduced/strongly reduced	27	no	0.557
B1879	flhA	reduced/strongly reduced	29	no	0.426
B1880	flhB	strongly reduced/strongly reduced	3	yes	0.448
B1881	cheZ	strongly reduced/strongly reduced	39	no	0.554
B1882	cheY	strongly reduced/strongly reduced	3	yes	0.655
B1883	cheB	strongly reduced/strongly reduced	14	yes	0.771
B1884	cheR	strongly reduced/strongly reduced	38	no	0.707
B1885	tap	strongly reduced/strongly reduced	7	yes	0.875
B1887	cheW	strongly reduced/strongly reduced	3	yes	0.492
B1888	cheA	reduced/strongly reduced	3	yes	0.919
B1889	motB	strongly reduced/strongly reduced	34	no	0.502
B1890	motA	strongly reduced/strongly reduced	3	yes	0.494
B1891	flhC	strongly reduced/strongly reduced	26	no	0.417
B1892	flhD	strongly reduced/strongly reduced	46	no	0.468
B1922	fliA	strongly reduced/strongly reduced	3	yes	0.605
B1923	fliC	strongly reduced/strongly reduced	4	yes	0.348
B1924	fliD	strongly reduced/strongly reduced	4	yes	0.411
B1925	fliS	strongly reduced/strongly reduced	4	yes	0.414
B1933	(yedN)	reduced/strongly reduced	45	no	0.503
B1938	fliF	strongly reduced/strongly reduced	3	yes	0.442
B1939	fliG	strongly reduced/strongly reduced	3	yes	0.492
B1940	fliH	strongly reduced/strongly reduced	29	no	0.511
B1941	fliI	strongly reduced/strongly reduced	3	yes	0.519
B1942	fliJ	strongly reduced/strongly reduced	21	no	0.556
B1943	fliK	strongly reduced/strongly reduced	45	no	0.397
B1945	fliM	strongly reduced/strongly reduced	3	yes	0.596
B1946	fliN	strongly reduced/strongly reduced	12	yes	0.531
B1948	fliP	strongly reduced/strongly reduced	3	yes	0.559
B1949	fliQ	strongly reduced/strongly reduced	10	yes	0.484
B1950	fliR	strongly reduced/strongly reduced	3	yes	0.496
B2218	(rcsC)	strongly reduced/strongly reduced	35	no	0.472
B2261	menC	reduced/strongly reduced	35	no	0.449
B2296	ackA	reduced/reduced	17	yes	0.816
B2329	aroC	reduced/reduced	35	no	0.621
B2435	amiA	reduced/reduced	46	no	0.823
B2501	ppk	reduced/reduced	47	no	0.757

B2507	guaA	strongly reduced/strongly reduced	6	yes	0.19
B2512	yfgL	strongly reduced/strongly reduced	7	yes	0.369
B2516	yfgA	strongly reduced/strongly reduced	2	yes	0.293
B2525	fdx	strongly reduced/strongly reduced	23	no	0.379
B2527	hscB	reduced/strongly reduced	30	no	0.332
B2551	glyA	reduced/strongly reduced	30	no	0.668
B2594	rluD	strongly reduced/strongly reduced	18	yes	0.346
B2603	yfiR	strongly reduced/strongly reduced	7	yes	0.716
B2620	smpB	reduced/strongly reduced	15	yes	0.734
B2699	recA	reduced/reduced	47	no	0.245
B2754	ygbF	strongly reduced/strongly reduced	15	yes	0.502
B2848	yqeJ	reduced/strongly reduced	46	no	0.593
B2894	xerD	reduced/reduced	47	no	0.638
B2898	ygfZ	reduced/strongly reduced	44	no	0.385
B2907	ubiH	strongly reduced/strongly reduced	25	no	0.559
B3058	folB	reduced/strongly reduced	0	yes	0.488
B3104	yhaI	reduced/strongly reduced	27	no	0.747
B3138	agaB	reduced/reduced	0	yes	0.712
B3162	deaD	reduced/reduced	26	no	0.765
B3164	pnp	strongly reduced/strongly reduced	49	no	0.615
B3179	rrmJ	strongly reduced/strongly reduced	48	no	0.52
B3180	yhbY	reduced/strongly reduced	44	no	0.698
B3202	rpoN	reduced/reduced	22	no	0.555
B3261	fis	strongly reduced/strongly reduced	18	yes	0.524
B3268	yhdW	reduced/strongly reduced	33	no	0.776
B3299	rpmJ	reduced/reduced	14	yes	0.26
B3343	yheL	reduced/strongly reduced	18	yes	0.67
B3344	yheM	reduced/strongly reduced	27	no	0.664
B3386	rpe	strongly reduced/strongly reduced	21	no	0.602
B3387	dam	reduced/strongly reduced	48	no	0.416
B3507	yhiF	reduced/reduced	35	no	0.524
B3525	yhjH	strongly reduced/strongly reduced	34	no	0.775
B3619	rfaD	strongly reduced/strongly reduced	33	no	0.325
B3620	rfaF	reduced/strongly reduced	45	no	0.365
B3728	pstS	reduced/reduced	33	no	0.636
B3732	atpD	reduced/strongly reduced	33	no	0.237
B3735	atpH	strongly reduced/strongly reduced	28	no	0.315
B3736	atpF	strongly reduced/strongly reduced	29	no	0.259
B3791	rffA	reduced/reduced	50	no	0.531
B3792	wzxE	reduced/reduced	23	no	0.713
B3838	tatB	reduced/strongly reduced	37	no	0.655
B3842	rfaH	strongly reduced/strongly reduced	49	no	0.26
B3870	glnA	strongly reduced/strongly reduced	35	no	0.387
B3911	cpxA	strongly reduced/strongly reduced	12	yes	0.413
B3936	rpmE	strongly reduced/strongly reduced	0	yes	0.338
B3966	btuB	reduced/strongly reduced	41	no	0.613
B3984	rplA	strongly reduced/strongly reduced	24	no	0.539
B3997	hemE	strongly reduced/strongly reduced	14	yes	0.579
B4141	yjeH	reduced/strongly reduced	16	yes	0.45
B4145	yjeJ	reduced/reduced	20	yes	0.815
B4161	yjeQ	strongly reduced/strongly reduced	46	no	0.637
B4172	hfq	strongly reduced/strongly reduced	32	no	0.286
B4225	chpB	reduced/reduced	38	no	0.618
B4232	fbp	reduced/strongly reduced	35	no	0.313
B4275	yjgX	reduced/reduced	49	no	0.732

B4313	fimE	reduced/reduced	44	no	0.89
B4355	tsr	reduced/reduced	32	no	0.811
B4362	dnaT	strongly reduced/strongly reduced	7	yes	0.179
B4363	yjjB	reduced/reduced	40	no	0.745
B4390	nadR	reduced/reduced	31	no	0.723
B4401	arcA	reduced/reduced	30	no	0.741
B4402	yjjY	reduced/reduced	25	no	0.781

Supplementary Table 23 Functional associations in motility set. *T. pallidum* (TPA), yeast-two-hybrid protein interactions

	Funclass	count	percent (of ints)	counttotal	percent (of genome)	Z-value	RANKING POS
1	**motility**	**33**	**18.8**	**52**	**5.0**	**10.4**	**1000**
2	**tRNA aminoacylation**	**11**	**6.3**	**25**	**2.4**	**2.6**	**992**
3	Hypothetical proteins	44	25.0	174	16.7	1.7	925
4	Conserved	44	25.0	174	16.7	1.7	925
5	DNA-dependent RNA polymerase	4	2.3	8	0.8	1.9	919
6	Pyrimidine ribonucleotide biosynthesis	1	0.6	1	0.1	2.0	833
7	Electron transport	3	1.7	7	0.7	1.2	810
8	Protein modification and repair	1	0.6	2	0.2	1.0	681
9	Biosynthesis and degradation of polysaccharides	1	0.6	2	0.2	0.9	650
10	Transcription	5	2.8	24	2.3	0.1	491
11	DNA replication, recombination, and repair	10	5.7	49	4.7	0.0	454
12	2'-Deoxyribonucleotide metabolism	1	0.6	4	0.4	0.2	444
13	DNA metabolism	10	5.7	51	4.9	-0.1	406
14	Protein synthesis	19	10.8	99	9.5	-0.2	378
15	Degradation	1	0.6	5	0.5	0.0	375

Supplementary Table 24 Functional associations in motility set. C. jejuni (CJE) – all yeast-two-hybrid protein interactions.

	Funclass	count	percent (of ints)	counttotal	percent (of genome)	Z-value	RANKING POS
1	**Cell envelope**	**182**	**26.4**	**339**	**20.5**	**3.3**	**998**
2	**Glycolysis/gluconeogenesis**	**17**	**2.5**	**19**	**1.1**	**3.2**	**997**
3	**Protein folding and stabilization**	**16**	**2.3**	**19**	**1.1**	**2.7**	**990**
4	**Protein fate**	**40**	**5.8**	**65**	**3.9**	**2.2**	**976**
5	**Molybdopterin**	**8**	**1.2**	**9**	**0.5**	**2.2**	**968**
6	Unknown substrate	2	0.3	1	0.1	2.7	949
7	Degradation of DNA	5	0.7	5	0.3	1.9	935
8	Amino acid biosynthesis	36	5.2	66	4.0	1.4	910
9	Aspartate family	11	1.6	16	1.0	1.5	900
10	Aromatic amino acid family	10	1.4	15	0.9	1.5	892
11	Biosynthesis and degradation of murein sacculus and peptidoglycan	11	1.6	17	1.0	1.4	891
12	Purines, pyrimidines, nucleosides, and nucleotides	23	3.3	41	2.5	1.2	866
13	Amino acids, peptides and amines	15	2.2	26	1.6	1.1	841
14	Unclassified	22	3.2	42	2.5	1.0	806
15	Role category not yet assigned	22	3.2	42	2.5	1.0	806

Supplementary Table 25 Functional associations in motility set. C. jejuni (CJE HCF) – yeast-two-hybrid protein high confidence interactions.

	Funclass	count	percent (of ints)	counttotal	percent (of genome)	Z-value	RANKING POS
1	**motility**	**12**	**8.6**	**47**	**2.8**	**3.9**	**999**
2	**Glycolysis/gluconeogenesis**	**6**	**4.3**	**19**	**1.1**	**3.1**	**988**
3	**Energy metabolism**	**22**	**15.7**	**155**	**9.4**	**2.0**	**959**
4	Cell envelope	40	28.6	339	20.5	1.8	943
5	Unknown substrate	1	0.7	1	0.1	3.2	927
6	Carbohydrates, organic alcohols, and acids	3	2.1	12	0.7	1.9	915
7	Protein folding and stabilization	4	2.9	19	1.1	1.7	904
8	Electron transport	13	9.3	98	5.9	1.3	865
9	Protein fate	9	6.4	65	3.9	1.2	850
10	Protein and peptide secretion and trafficking	3	2.1	16	1.0	1.3	814
11	Biosynthesis and degradation of murein sacculus and peptidoglycan	3	2.1	17	1.0	1.2	794
12	Amino acids, peptides and amines	4	2.9	26	1.6	1.0	789
13	Role category not yet assigned	5	3.6	42	2.5	0.6	646
14	Degradation of DNA	1	0.7	5	0.3	0.8	637
15	Toxin production and resistance	2	1.4	16	1.0	0.4	573

Supplementary Table 26 Functional associations in motility set. H. pylori (HPY) – yeast-two-hybrid protein interactions.

	Funclass	count	percent (of ints)	counttotal	percent (of genome)	Z-value	RANKING POS
1	**motility**	**12**	**8.6**	**53**	**3.3**	**4.5**	**1000**
2	**2'-Deoxyribonucleotide metabolism**	**3**	**2.2**	**6**	**0.4**	**3.1**	**974**
3	DNA-dependent RNA polymerase	1	0.7	2	0.1	1.9	819
4	DNA replication, recombination, and repair	7	5.0	48	3.0	1.2	818
5	Degradation	1	0.7	2	0.1	1.8	812
6	Adaptations to atypical conditions	2	1.4	9	0.6	1.4	810
7	Amino acids and amines	2	1.4	8	0.5	1.3	803
8	Menaquinone and ubiquinone	1	0.7	3	0.2	1.4	736
9	Protein and peptide secretion and trafficking	2	1.4	11	0.7	0.9	700
10	TCA cycle	1	0.7	5	0.3	0.8	632
11	Fermentation	1	0.7	5	0.3	0.7	567
12	Fatty acid and phospholipid metabolism	3	2.2	25	1.6	0.3	540
13	Detoxification	1	0.7	7	0.4	0.4	490
14	Purines, pyrimidines, nucleosides, and nucleotides	4	2.9	39	2.5	0.1	487
15	Toxin production and resistance	1	0.7	8	0.5	0.3	468

Supplementary Table 27 Functional associations in motility set. *E. coli* (ECO SAI) – socio-affinity score filtered MS-generated protein interactions.

	Funclass	count	percent (of ints)	counttotal	percent (of genome)	Z-value	RANKING POS
1	**Transcription**	**10**	**2.5**	**38**	**0.9**	**3.3**	**998**
2	**Cell division**	**7**	**1.7**	**20**	**0.5**	**3.6**	**994**
3	**DNA metabolism**	**18**	**4.4**	**103**	**2.4**	**2.5**	**991**
4	**Transcription factors**	**6**	**1.5**	**19**	**0.4**	**3.0**	**988**
5	**Purine ribonucleotide biosynthesis**	**5**	**1.2**	**17**	**0.4**	**2.7**	**979**
6	**Nucleotide and nucleoside interconversions**	**4**	**1.0**	**10**	**0.2**	**3.0**	**975**
7	**Chromosome-associated proteins**	**2**	**0.5**	**2**	**0.0**	**3.8**	**961**
8	**Purines, pyrimidines, nucleosides, and nucleotides**	**13**	**3.2**	**77**	**1.8**	**1.9**	**953**
9	**Protein modification and repair**	**4**	**1.0**	**15**	**0.3**	**2.2**	**953**
10	Degradation of RNA	3	0.7	8	0.2	2.4	943
11	DNA replication, recombination, and repair	14	3.4	90	2.1	1.8	939
12	Protein synthesis	17	4.2	120	2.8	1.6	922
13	Ribosomal proteins: synthesis and modification	9	2.2	56	1.3	1.6	912
14	2'-Deoxyribonucleotide metabolism	3	0.7	11	0.3	1.9	909
15	Pyridoxine	2	0.5	5	0.1	2.0	897

Supplementary Table 28 Functional associations in motility set. *E. coli* (ECO SPOKE) – Spoke model MS-generated protein interactions.

	Funclass	count	percent (of ints)	counttotal	percent (of genome)	Z-value	RANKING POS
1	**Protein folding and stabilization**	**26**	**4.6**	**34**	**0.8**	**16.1**	**1000**
2	**Biosynthesis of cofactors, prosthetic groups, and carriers**	**19**	**3.4**	**100**	**2.3**	**4.9**	**1000**
3	**Pyridine nucleotides**	**14**	**2.5**	**2**	**0.0**	**35.7**	**1000**
4	**Protein synthesis**	**32**	**5.7**	**120**	**2.8**	**9.0**	**1000**
5	**Protein fate**	**38**	**6.7**	**114**	**2.7**	**11.7**	**1000**
6	**Ribosomal proteins: synthesis and modification**	**25**	**4.4**	**56**	**1.3**	**11.4**	**1000**
7	**Degradation of proteins, peptides, and glycopeptides**	**8**	**1.4**	**34**	**0.8**	**4.0**	**999**
8	**DNA-dependent RNA polymerase**	**3**	**0.5**	**6**	**0.1**	**4.2**	**994**
9	**Cell division**	**5**	**0.9**	**20**	**0.5**	**3.1**	**992**
10	**Biosynthesis and degradation of polysaccharides**	**5**	**0.9**	**26**	**0.6**	**2.7**	**980**
11	**DNA metabolism**	**12**	**2.1**	**103**	**2.4**	**2.0**	**951**
12	Molybdopterin	2	0.4	7	0.2	2.4	930
13	Transcription	5	0.9	38	0.9	1.7	909
14	ATP-proton motive force interconversion	2	0.4	9	0.2	1.9	882
15	Purine ribonucleotide biosynthesis	3	0.5	17	0.4	1.7	877

Supplementary Table 29 Functional associations in motility set. *E. coli* (ECO MOTILITY) – mutants showing reduced motility

	Funclass	count	percent (of set)	counttotal	percent (of genome)	Z-value	p-value
1	**motility**	**43**	**27.0**	**68**	**1.6**	**26.3**	**9.22E-47**
2	**ATP-proton motive force interconversion**	**3**	**1.9**	**9**	**0.2**	**4.9**	**3.37E-03**
3	**Menaquinone and ubiquinone**	**3**	**1.9**	**15**	**0.3**	**3.5**	**1.46E-02**
4	**Transcription factors**	**3**	**1.9**	**19**	**0.4**	**2.9**	**2.68E-02**
5	**tRNA and rRNA base modification**	**3**	**1.9**	**19**	**0.4**	**2.8**	**2.68E-02**
6	**Lipoate**	**1**	**0.6**	**1**	**0.0**	**5.1**	**3.71E-02**
7	**Biosynthesis and degradation of surface polysaccharides and lipopolysaccharides**	**4**	**2.5**	**38**	**0.9**	**2.3**	**3.82E-02**
8	**Transcription**	**4**	**2.5**	**38**	**0.9**	**2.2**	**3.82E-02**
9	Chromosome-associated proteins	1	0.6	2	0.0	3.7	7.14E-02
10	Protein synthesis	7	4.4	120	2.8	1.2	8.02E-02
11	Biosynthesis of cofactors, prosthetic groups, and carriers	6	3.8	100	2.3	1.3	8.90E-02
12	DNA metabolism	6	3.8	103	2.4	1.2	9.54E-02
13	DNA replication, recombination, and repair	5	3.1	90	2.1	1.0	1.25E-01
14	Prophage functions	1	0.6	4	0.1	2.4	1.33E-01
15	Aromatic amino acid family	2	1.3	21	0.5	1.3	1.41E-01

Supplementary Table 30 Functional associations in motility set. *B. subtilis* (BSU MOTILITY) – mutants showing reduced motility.

	Funclass	count	percent (of set)	counttotal	percent (of genome)	Z-value	p-value
1	**motility**	**45**	**30.8**	**51**	**1.2**	**31.5**	**6.54E-62**
2	**Chemotaxis and motility**	**3**	**2.1**	**7**	**0.2**	**5.4**	**1.34E-03**
3	**Molybdopterin**	**2**	**1.4**	**8**	**0.2**	**3.3**	**2.85E-02**
4	**Biosynthesis and degradation of surface polysaccharides and lipopolysaccharides**	**4**	**2.7**	**44**	**1.1**	**2.0**	**5.08E-02**
5	Cell envelope	9	6.2	168	4.1	1.4	6.80E-02
6	Biosynthesis and degradation of murein sacculus and peptidoglycan	5	3.4	73	1.8	1.5	7.28E-02
7	Degradation	1	0.7	9	0.2	1.2	2.40E-01
8	Degradation of proteins, peptides, and glycopeptides	2	1.4	47	1.1	0.3	2.70E-01
9	Pyruvate family	1	0.7	11	0.3	0.9	2.73E-01
10	Detoxification	2	1.4	53	1.3	0.1	2.77E-01
11	Sugars	2	1.4	53	1.3	0.1	2.77E-01
12	Pentose phosphate pathway	1	0.7	13	0.3	0.7	3.00E-01
13	Aerobic	1	0.7	16	0.4	0.5	3.32E-01
14	Biosynthesis and degradation of polysaccharides	1	0.7	22	0.5	0.2	3.67E-01
15	Carbohydrates, organic alcohols, and acids	1	0.7	24	0.6	0.2	3.72E-01

Supplementary Table 31 Functional associations in motility set. *E. coli* (FLHD) – genes regulated by FlhD.

	Funclass	count	percent (of set)	counttotal	percent (of genome)	Z-value	p-value
1	**motility**	**43**	**26.2**	**68**	**1.6**	**25.5**	**4.18E-46**
2	**TCA cycle**	**6**	**3.7**	**20**	**0.5**	**6.2**	**6.55E-05**
3	**Nitrogen metabolism**	**3**	**1.8**	**7**	**0.2**	**5.6**	**1.65E-03**
4	**Fermentation**	**4**	**2.4**	**25**	**0.6**	**3.1**	**1.17E-02**
5	**Central intermediary metabolism**	**7**	**4.3**	**70**	**1.6**	**2.8**	**1.18E-02**
6	**Energy metabolism**	**20**	**12.2**	**366**	**8.5**	**1.7**	**2.62E-02**
7	Aspartate family	3	1.8	25	0.6	2.1	5.43E-02
8	Pyrimidine ribonucleotide biosynthesis	2	1.2	12	0.3	2.3	6.53E-02
9	Carbohydrates, organic alcohols, and acids	7	4.3	109	2.5	1.5	6.65E-02
10	Transport and binding proteins	15	9.1	313	7.3	0.9	7.37E-02
11	Amino acid biosynthesis	7	4.3	113	2.6	1.4	7.39E-02
12	Glutamate family	3	1.8	29	0.7	1.8	7.40E-02
13	Entner-Doudoroff	1	0.6	4	0.1	2.1	1.36E-01
14	Amino acids, peptides and amines	5	3.0	93	2.2	0.8	1.39E-01
15	Aerobic	2	1.2	21	0.5	1.3	1.47E-01

Supplementary Table 32 Transmembrane protein fragments. These fragments were selected for cloning and testing for protein interactions. The "fragment id" encodes the full-length protein and gives the start and end amino-acid positions, e.g. TP0020-494_707 indicates the segment between amino-acid 494 and 707 of protein TP0020. The location shows the predicted localisation to the cytoplasmic (i) or periplasmic (o) face of the membrane. The TM count shows the number of transmembrane segments of the full-length protein. The defline is taken from the SwissProt database.

Fragment ID	location	TM count	defline
TP0020-494_707	i	2	76K protein.
TP0023-64_98	i	11	Sodium-and chloride-dependent transporter.
TP0042-1_153	i	1	Hypothetical protein.
TP0070-54_107	i	3	Hypothetical protein TP0070.
TP0090-1_94	i	1	UDP-N-acetylenolpyruvoylglucosamine reductase (EC 1.1.1.158) (UDP-N- acetylmuramate dehydrogenase).
TP0106-160_193	i	12	Carnitine transporter, putative.
TP0106-419_455	i	12	Carnitine transporter, putative.
TP0126-1_73	i	2	Hypothetical protein TP0126.
TP0126-211_291	i	2	Hypothetical protein TP0126.
TP0138-84_245	i	2	Hypothetical protein TP0138.
TP0140-444_480	i	15	K+ transport protein (NtpJ).
TP0143-1_40	i	12	Thiamine ABC transporter, permease protein, putative.
TP0143-216_257	i	12	Thiamine ABC transporter, permease protein, putative.
TP0143-485_519	i	12	Thiamine ABC transporter, permease protein, putative.
TP0151-104_219	i	7	Conserved hypothetical integral membrane protein.
TP0173-178_227	i	2	Hypothetical protein TP0173.
TP0181-27_122	i	2	Hypothetical protein TP0181.
TP0208-232_265	i	10	Preprotein translocase subunit (SecY).
TP0208-409_450	i	10	Preprotein translocase subunit (SecY).
TP0208-85_118	i	10	Preprotein translocase subunit (SecY).
TP0219-280_572	i	10	Sigma factor SigG regulation protein, putative.
TP0219-596_715	o	10	Sigma factor SigG regulation protein, putative.
TP0220-67_108	i	2	Anti-sigma F factor antagonist (SpoIIAA-1).
TP0222-1_124	i	1	Hypothetical protein TP0222 precursor.
TP0273-209_263	i	4	Hypothetical protein TP0273.
TP0273-71_126	i	4	Hypothetical protein TP0273.
TP0301-335_377	i	10	Conserved hypothetical integral membrane protein.
TP0322-1_42	i	8	Ribose/galactose ABC transporter, permease protein (RbsC-1).
TP0335-1_36	i	2	Hypothetical protein TP0335.
TP0336-1_42	i	10	ComE protein, putative.
TP0336-141_309	o	10	ComE protein, putative.
TP0338-128_162	i	2	Hypothetical protein TP0338 precursor.
TP0347-1_45	i	4	Hypothetical protein.
TP0347-241_276	i	4	Hypothetical protein.
TP0357-1_77	i	1	Biotin--acetyl-CoA-carboxylase ligase (BirA).
TP0387-105_148	o	8	Cell division protein (FtsW).
TP0387-198_281	o	8	Cell division protein (FtsW).
TP0392-94_319	i	2	Hypothetical protein.
TP0399-494_567	i	2	Flagellar M-ring protein.
TP0405-38_149	i	1	McbG protein, putative.
TP0414-266_309	i	11	D-alanine glycine permease (DagA).
TP0429-583_622	i	7	V-type ATP synthase subunit I 1 (EC 3.6.3.14) (V-type ATPase subunit I 1).
TP0433-112_256	i	2	Hypothetical protein.
TP0444-1_45	i	1	Hypothetical protein.
TP0471-38_469	i	1	Hypothetical protein.

TP0479-1_40	i	3	Hypothetical protein.
TP0481-1_106	i	1	Hypothetical protein TP0481.
TP0485-121_284	i	3	Adenylate cyclase.
TP0485-308_614	o	3	Adenylate cyclase.
TP0515-24_196	i	2	Hypothetical protein.
TP0516-1_57	i	12	Virulence factor mviN homolog.
TP0516-414_450	i	12	Virulence factor mviN homolog.
TP0533-372_425	i	4	V-type ATP synthase subunit I 2 (EC 3.6.3.14) (V-type ATPase subunit I 2).
TP0536-76_133	i	2	Probable protein-export membrane protein secG.
TP0555-360_396	i	10	Glutamate/ aspartate transporter, putative.
TP0561-1_212	i	1	Hypothetical protein.
TP0577-1_493	i	2	Hypothetical protein TP0577.
TP0577-575_614	i	2	Hypothetical protein TP0577.
TP0582-1_64	i	4	Conserved hypothetical integral membrane protein.
TP0593-1_79	i	3	Hypothetical protein TP0593.
TP0600-125_383	i	4	Hypothetical zinc metalloprotease TP0600 (EC 3.4.24.-).
TP0602-243_287	i	8	Phosphatidate cytidylyltransferase (CdsA).
TP0651-35_364	i	7	Conserved hypothetical integral membrane protein.
TP0651-546_803	i	7	Conserved hypothetical integral membrane protein.
TP0653-181_212	i	6	Spermidine/putrescine ABC transporter, permease protein (PotB).
TP0671-1_39	i	5	Sn-1,2-diacylglycerol cholinephosphotransferase, putative.
TP0671-91_135	i	5	Sn-1,2-diacylglycerol cholinephosphotransferase, putative.
TP0686-1_192	i	8	Galactoside transport system permease protein mglC homolog.
TP0697-162_202	i	2	Hypothetical protein.
TP0707-1_58	i	2	Hypothetical protein TP0707.
TP0707-114_159	i	2	Hypothetical protein TP0707.
TP0708-73_171	i	2	Hypothetical protein TP0708.
TP0719-1_113	i	1	ORF-3 (Hypothetical protein).
TP0722-58_182	i	1	Flagellar fliL protein.
TP0725-201_259	i	4	Chemotaxis protein motA (Motility protein A).
TP0725-59_143	i	4	Chemotaxis protein motA (Motility protein A).
TP0730-1_86	i	6	Hypothetical protein.
TP0730-142_198	i	6	Hypothetical protein.
TP0753-62_94	i	2	Hypothetical protein TP0753.
TP0760-1_40	i	1	Penicillin-binding protein (Pbp-3).
TP0763-1_41	i	2	Hypothetical protein TP0763.
TP0763-97_313	i	2	Hypothetical protein TP0763.
TP0765-1_83	i	1	Cell division protein ftsH homolog (EC 3.4.24.-).
TP0765-107_609	o	1	Cell division protein ftsH homolog (EC 3.4.24.-).
TP0771-1_33	i	9	Conserved hypothetical integral membrane protein.
TP0779-79_139	i	4	DedA protein (DedA).
TP0780-628_679	i	1	Probable glutamine-dependent NAD(+) synthetase (EC 6.3.5.1) (NAD(+) synthase [glutamine-hydrolyzing]).
TP0790-394_430	i	12	Antibiotic transport protein, putative.
TP0832-46_271	i	1	Hypothetical protein.
TP0902-74_125	i	3	Carboxylesterase (Est).
TP0918-168_257	i	3	Conserved hypothetical integral membrane protein.
TP0958-406_444	i	17	Dicarboxylate transporter (DctM).
TP0963-304_335	i	4	Conserved hypothetical integral membrane protein.
TP0972-1_221	i	6	Conserved hypothetical integral membrane protein.
TP0976-1_52	i	2	Hypothetical protein TP0976.
TP0976-134_459	i	2	Hypothetical protein TP0976.
TP0978-104_153	i	3	Lipoprotein signal peptidase (EC 3.4.23.36) (Prolipoprotein signal peptidase) (Signal peptidase II) (SPase II).

TP0986-138_177	i	6	Conserved hypothetical integral membrane protein.
TP1036-1_102	i	8	Cation-transporting ATPase, P-type.
TP1036-235_389	i	8	Cation-transporting ATPase, P-type.
TP1036-445_734	i	8	Cation-transporting ATPase, P-type.
TP1037-1_36	i	7	Hypothetical UPF0073 protein TP1037.

Supplementary Table 33 Filtered subset of transmembrane protein fragment (TMPF) interactions. The interacting baits and preys with their description, predicted location (i=intracellular, o=extracellular), and the total number of transmembrane segments of the respective protein (#) are given.

bait	description	loc	#	prey	description	loc	#
TP0126-1_73	hypothetical protein	i	2	TP0485-308_614	adenylate cyclase	o	3
TP0126-1_73	hypothetical protein	i	2	TP0519	response regulatory protein (atoC)		
TP0126-1_73	hypothetical protein	i	2	TP0664	flagellar filament outer layer protein (flaA)		
TP0126-1_73	hypothetical protein	i	2	TP0684	methylgalactoside ABC transporter, periplasmic galactose-binding protein (mglB)		
TP0126-1_73	hypothetical protein	i	2	TP0757	polypeptide deformylase (def)		
TP0138-84_245	hypothetical protein	i	2	TP0463	hypothetical protein		
TP0138-84_245	hypothetical protein	i	2	TP0519	response regulatory protein (atoC)		
TP0138-84_245	hypothetical protein	i	2	TP0554	phosphoglycolate phosphatase (gph)		
TP0151-104_219	conserved hypothetical integral membrane protein	i	7	TP0519	response regulatory protein (atoC)		
TP0151-104_219	conserved hypothetical integral membrane protein	i	7	TP0561	conserved hypothetical protein		
TP0151-104_219	conserved hypothetical integral membrane protein	i	7	TP0917	Mg2+ transport protein (mgtE)		
TP0181_27-122	hypothetical protein	i	2	TP0463	hypothetical protein		
TP0181_27-122	hypothetical protein	i	2	TP0618	hypothetical protein		
TP0181_27-122	hypothetical protein	i	2	TP0664	flagellar filament outer layer protein (flaA)		
TP0181_27-122	hypothetical protein	i	2	TP0684	methylgalactoside ABC transporter, periplasmic galactose-binding protein (mglB)		
TP0181_27-122	hypothetical protein	i	2	TP0757	polypeptide deformylase (def)		
TP0181_27-122	hypothetical protein	i	2	TP0832-46_271	hypothetical protein	i	1
TP0181_27-122	hypothetical protein	i	2	TP1013	chaperonin (groES)		
TP0208-85_118	preprotein translocase subunit (secY)	i	10	TP0287	conserved hypothetical protein		
TP0208-85_118	preprotein translocase subunit (secY)	i	10	TP0519	response regulatory protein (atoC)		
TP0208-85_118	preprotein translocase subunit (secY)	i	10	TP0618	hypothetical protein		
TP0220_67-108	anti-sigma F factor antagonist (spoIIAA)	i	2	TP0995	cyclic nucleotide binding protein		
TP0220-67_108	anti-sigma F factor antagonist (spoIIAA)	i	2	TP0684	methylgalactoside ABC transporter, periplasmic galactose-binding protein (mglB)		
TP0273-71_126	hypothetical protein	i	4	TP0485-308_614	adenylate cyclase	o	3
TP0273-71_126	hypothetical protein	i	4	TP0651	conserved hypothetical integral membrane protein		
TP0273-71_126	hypothetical protein	i	4	TP0779-79_139	dedA protein (dedA)	i	4
TP0322_1-42	ribose/galactose ABC transporter, permease protein (rbsC)	i	8	TP0917	Mg2+ transport protein (mgtE)		
TP0336-141_309	comE protein, putative	o	10	TP0287	conserved hypothetical protein		
TP0336-141_309	comE protein, putative	o	10	TP1013	chaperonin (groES)		
TP0338_128-162	hypothetical protein	i	2	TP0463	hypothetical protein		
TP0338_128-162	hypothetical protein	i	2	TP0757	polypeptide deformylase (def)		
TP0338_128-162	hypothetical protein	i	2	TP0974	hypothetical protein		
TP0338_128-162	hypothetical protein	i	2	TP1013	chaperonin (groES)		
TP0347-1_45	hypothetical protein	i	4	TP1013	chaperonin (groES)		
TP0387-105_148	cell division protein (ftsW)	o	8	TP0561	conserved hypothetical protein		
TP0387-105_148	cell division protein (ftsW)	o	8	TP0917	Mg2+ transport protein (mgtE)		
TP0392_94-319	conserved hypothetical protein	i	2	TP0095	hypothetical protein		
TP0392_94-319	conserved hypothetical protein	i	2	TP0287	conserved hypothetical protein		
TP0392_94-319	conserved hypothetical protein	i	2	TP0445	4-methyl-5(b-hydroxyethyl)-thiazole monophosphate biosynthesis enzyme (thiJ)		
TP0392_94-319	conserved hypothetical protein	i	2	TP0463	hypothetical protein		
TP0392_94-319	conserved hypothetical protein	i	2	TP0554	phosphoglycolate phosphatase (gph)		
TP0392_94-319	conserved hypothetical protein	i	2	TP0618	hypothetical protein		

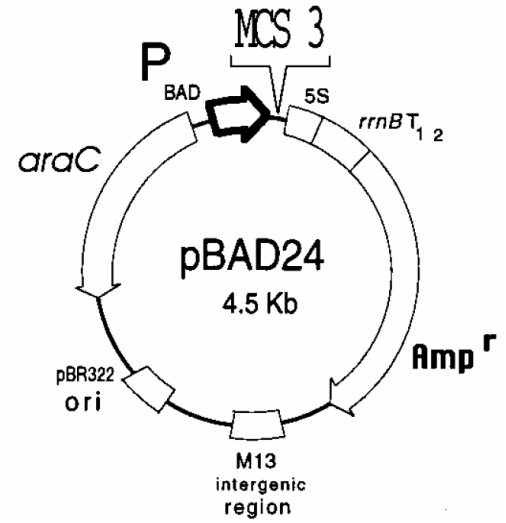
TP0392_94-319	conserved hypothetical protein	i	2	TP0917	Mg2+ transport protein (mgtE)		
TP0392_94-319	conserved hypothetical protein	i	2	TP0974	hypothetical protein		
TP0392_94-319	conserved hypothetical protein	i	2	TP0995	cyclic nucleotide binding protein		
TP0414-266_309	D-alanine glycine permease (dagA)	i	11	TP0405-38_149	mcbG protein, putative	i	1
TP0414-266_309	D-alanine glycine permease (dagA)	i	11	TP0485-308_614	adenylate cyclase	o	3
TP0414-266_309	D-alanine glycine permease (dagA)	i	11	TP0653-181_212	spermidine/putrescine ABC transporter, permease protein (potB)	i	6
TP0414-266_309	D-alanine glycine permease (dagA)	i	11	TP0790-394_430	antibiotic transport protein, putative	i	12
TP0433_112-256	hypothetical protein	i	2	TP0405-38_149	mcbG protein, putative	i	1
TP0433_112-256	hypothetical protein	i	2	TP0651-35_364	conserved hypothetical integral membrane protein	i	7
TP0433_112-256	hypothetical protein	i	2	TP0664	flagellar filament outer layer protein (flaA)		
TP0433_112-256	hypothetical protein	i	2	TP0684	methylgalactoside ABC transporter, periplasmic galactose-binding protein (mglB)		
TP0433_112-256	hypothetical protein	i	2	TP0711	conserved hypothetical protein		
TP0433_112-256	hypothetical protein	i	2	TP0712	ATP-binding protein (ylxH)		
TP0433_112-256	hypothetical protein	i	2	TP0757	polypeptide deformylase (def)		
TP0433_112-256	hypothetical protein	i	2	TP0832-46_271	hypothetical protein	i	1
TP0433_112-256	hypothetical protein	i	2	TP0974	hypothetical protein		
TP0433_112-256	hypothetical protein	i	2	TP1013	chaperonin (groES)		
TP0471-38_469	hypothetical protein	i	1	TP0095	hypothetical protein		
TP0471-38_469	hypothetical protein	i	1	TP0519	response regulatory protein (atoC)		
TP0471-38_469	hypothetical protein	i	1	TP0711	conserved hypothetical protein		
TP0479-1_40	hypothetical protein	i	3	TP1013	chaperonin (groES)		
TP0515-24_196	conserved hypothetical protein	i	2	TP0392-94_319	conserved hypothetical protein	i	2
TP0515-24_196	conserved hypothetical protein	i	2	TP0485-308_614	adenylate cyclase	o	3
TP0515-24_196	conserved hypothetical protein	i	2	TP0651-35_364	conserved hypothetical integral membrane protein	i	7
TP0515-24_196	conserved hypothetical protein	i	2	TP0730-142_198	conserved hypothetical protein	i	6
TP0533-372_425	V-type ATPase, subunit I (atpI)	i	4	TP0917	Mg2+ transport protein (mgtE)		
TP0593-1_79	hypothetical protein	i	3	TP0392-94_319	conserved hypothetical protein	i	2
TP0593-1_79	hypothetical protein	i	3	TP0399-494_567	flagellar basal-body M ring protein (fliF)	i	2
TP0593-1_79	hypothetical protein	i	3	TP0651-35_364	conserved hypothetical integral membrane protein	i	7
TP0593-1_79	hypothetical protein	i	3	TP0711	conserved hypothetical protein		
TP0593-1_79	hypothetical protein	i	3	TP0730-142_198	conserved hypothetical protein	i	6
TP0593-1_79	hypothetical protein	i	3	TP0780-628_679	NH(3)-dependent NAD(+) synthetase (nadE)	i	1
TP0593-1_79	hypothetical protein	i	3	TP0790-394_430	antibiotic transport protein, putative	i	12
TP0600-125_383	zinc protease, putative	i	4	TP0790-394_430	antibiotic transport protein, putative	i	12
TP0651-35_364	conserved hypothetical integral membrane protein	i	7	TP0463	hypothetical protein		
TP0651-35_364	conserved hypothetical integral membrane protein	i	7	TP0519	response regulatory protein (atoC)		
TP0651-35_364	conserved hypothetical integral membrane protein	i	7	TP0711	conserved hypothetical protein		
TP0651-546_803	conserved hypothetical integral membrane protein	i	7	TP0392-94_319	conserved hypothetical protein	i	2
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0287	conserved hypothetical protein		
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0392-94_319	conserved hypothetical protein	i	2
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0399-494_567	flagellar basal-body M ring protein (fliF)	i	2
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0405-38_149	mcbG protein, putative	i	1
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0651-35_364	conserved hypothetical integral membrane protein	i	7
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0653-181_212	spermidine/putrescine ABC transporter, permease protein (potB)	i	6

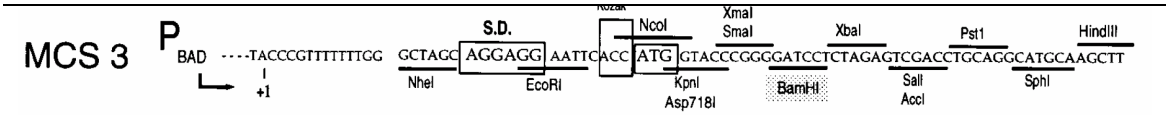
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0664	flagellar filament outer layer protein (flaA)		
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0712	ATP-binding protein (ylxH)		
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0730-1_86	conserved hypothetical protein	i	6
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0780-628_679	NH(3)-dependent NAD(+) synthetase (nadE)	i	1
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0790-394_430	antibiotic transport protein, putative	i	12
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0832-46_271	hypothetical protein	i	1
TP0671_91-135	sn-1,2-diacylglycerol cholinephosphotransferase, putative	i	5	TP0974	hypothetical protein		
TP0686-1_192	methylgalactoside ABC transporter, permease protein (mglC)	i	8	TP0519	response regulatory protein (atoC)		
TP0686-1_192	methylgalactoside ABC transporter, permease protein (mglC)	i	8	TP0561	conserved hypothetical protein		
TP0686-1_192	methylgalactoside ABC transporter, permease protein (mglC)	i	8	TP0917	Mg2+ transport protein (mgtE)		
TP0722_58-182	flagellar protein (fliL)	i	1	TP0722-58_182	flagellar protein (fliL)	i	1
TP0730-1_86	conserved hypothetical protein	i	6	TP0392-94_319	conserved hypothetical protein	i	2
TP0730-1_86	conserved hypothetical protein	i	6	TP0399-494_567	flagellar basal-body M ring protein (fliF)	i	2
TP0730-1_86	conserved hypothetical protein	i	6	TP0651-35_364	conserved hypothetical integral membrane protein	i	7
TP0730-1_86	conserved hypothetical protein	i	6	TP0653-181_212	spermidine/putrescine ABC transporter, permease protein (potB)	i	6
TP0730-1_86	conserved hypothetical protein	i	6	TP0664	flagellar filament outer layer protein (flaA)		
TP0730-1_86	conserved hypothetical protein	i	6	TP0697-162_202	hypothetical protein	i	2
TP0730-1_86	conserved hypothetical protein	i	6	TP0711	conserved hypothetical protein		
TP0730-1_86	conserved hypothetical protein	i	6	TP0730-1_86	conserved hypothetical protein	i	6
TP0730-1_86	conserved hypothetical protein	i	6	TP0730-142_198	conserved hypothetical protein	i	6
TP0730-1_86	conserved hypothetical protein	i	6	TP0780-628_679	NH(3)-dependent NAD(+) synthetase (nadE)	i	1
TP0730-1_86	conserved hypothetical protein	i	6	TP0790-394_430	antibiotic transport protein, putative	i	12
TP0753-62_94	hypothetical protein	i	2	TP0618	hypothetical protein		
TP0753-62_94	hypothetical protein	i	2	TP0684	methylgalactoside ABC transporter, periplasmic galactose-binding protein (mglB)		
TP0753-62_94	hypothetical protein	i	2	TP1013	chaperonin (groES)		
TP0765_1-83	cell division protein (ftsH)	i	1	TP0208-409_450	preprotein translocase subunit (secY)	i	10
TP0765_1-83	cell division protein (ftsH)	i	1	TP0399-494_567	flagellar basal-body M ring protein (fliF)	i	2
TP0765_1-83	cell division protein (ftsH)	i	1	TP0519	response regulatory protein (atoC)		
TP0765-1_83	cell division protein (ftsH)	i	1	TP0519	response regulatory protein (atoC)		
TP0765-1_83	cell division protein (ftsH)	i	1	TP0711	conserved hypothetical protein		
TP0765-1_83	cell division protein (ftsH)	i	1	TP0757	polypeptide deformylase (def)		
TP0765-1_83	cell division protein (ftsH)	i	1	TP0995	cyclic nucleotide binding protein		
TP0771-1_33	conserved hypothetical integral membrane protein _	i	9	TP0519	response regulatory protein (atoC)		
TP0771-1_33	conserved hypothetical integral membrane protein _	i	9	TP0554	phosphoglycolate phosphatase (gph)		
TP0771-1_33	conserved hypothetical integral membrane protein _	i	9	TP0618	hypothetical protein		
TP0771-1_33	conserved hypothetical integral membrane protein _	i	9	TP0664	flagellar filament outer layer protein (flaA)		
TP0771-1_33	conserved hypothetical integral membrane protein _	i	9	TP0757	polypeptide deformylase (def)		
TP0771-1_33	conserved hypothetical integral membrane protein _	i	9	TP0974	hypothetical protein		

TP0771-1_33	conserved hypothetical integral membrane protein _	i	9	TP0995	cyclic nucleotide binding protein		
TP0790-394_430	antibiotic transport protein, putative	i	12	TP0463	hypothetical protein		
TP0790-394_430	antibiotic transport protein, putative	i	12	TP0730-142_198	conserved hypothetical protein	i	6
TP0902-74_125	carboxylesterase (est)	i	3	TP0711	conserved hypothetical protein		
TP0918-168_257	conserved hypothetical integral membrane protein	i	3	TP0917	Mg2+ transport protein (mgtE)		
TP0972-1_221	conserved hypothetical integral membrane protein	i	6	TP0917	Mg2+ transport protein (mgtE)		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0059	hypothetical protein		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0286	conserved hypothetical protein		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0287	conserved hypothetical protein		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0341	UDP-N-acetylmuramate--alanine ligase (murC)		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0463	hypothetical protein		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0519	response regulatory protein (atoC)		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0554	phosphoglycolate phosphatase (gph)		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0618	hypothetical protein		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0664	flagellar filament outer layer protein (flaA)		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0684	methylgalactoside ABC transporter, periplasmic galactose-binding protein (mglB)		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0711	conserved hypothetical protein		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0773	periplasmic serine protease DO (htrA)		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0851	hypothetical protein		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0911	conserved hypothetical protein		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0945	ribulose-phosphate 3-epimerase (cfxE)		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0946	glucose-inhibited division protein B (gidB)		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0974	hypothetical protein		
TP1036-1_102	cation-transporting ATPase, P-type	i	8	TP0995	cyclic nucleotide binding protein		
TP1036-235_389	cation-transporting ATPase, P-type	i	8	TP0286	conserved hypothetical protein		
TP1036-235_389	cation-transporting ATPase, P-type	i	8	TP0974	hypothetical protein		
TP1036-235_389	cation-transporting ATPase, P-type	i	8	TP0995	cyclic nucleotide binding protein		
TP1036-235_389	cation-transporting ATPase, P-type	i	8	TP1013	chaperonin (groES)		

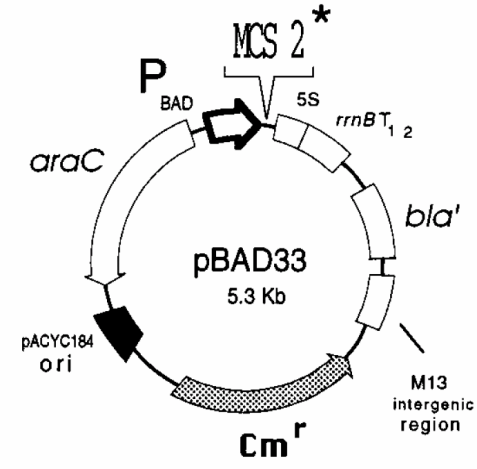
Supplementary Table 34 Vector maps

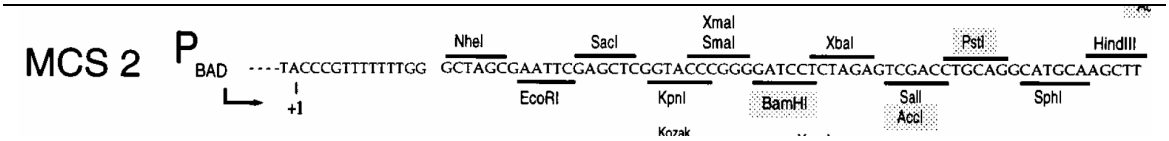
Name	Source	Comment
pBad24	Guzman *et al.*	pBad regulated expression in *E. coli*



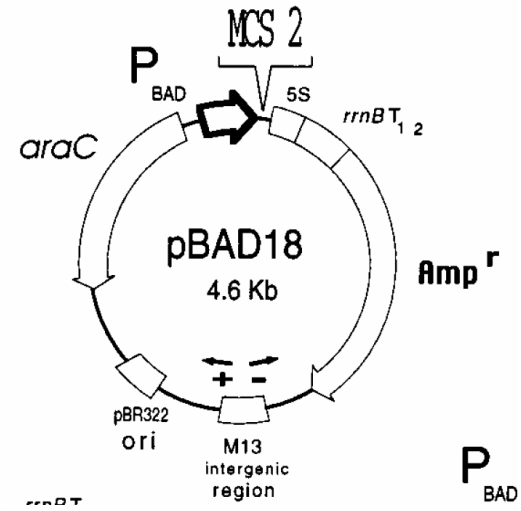


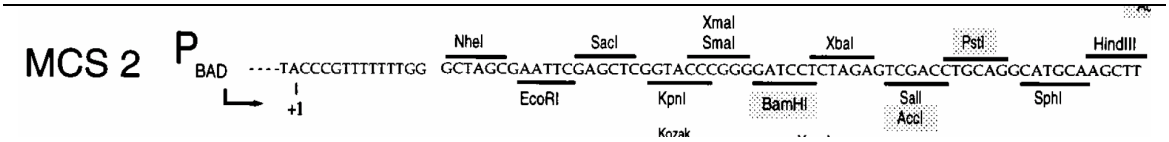
Name	Source	Comment
pBad33	Guzman *et al.*	pBad regulated expression in *E. coli*



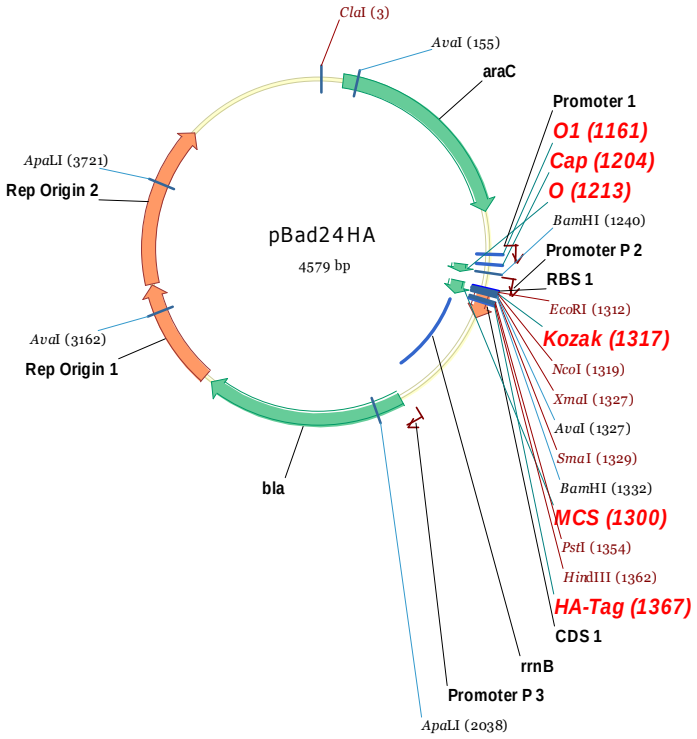


Name	Source	Comment
pBad18	Guzman *et al.*	pBad regulated expression in *E. coli*





Name	Source	Comment
pBad24HA	this work	pBad regulated expression in *E. coli* with HA tag

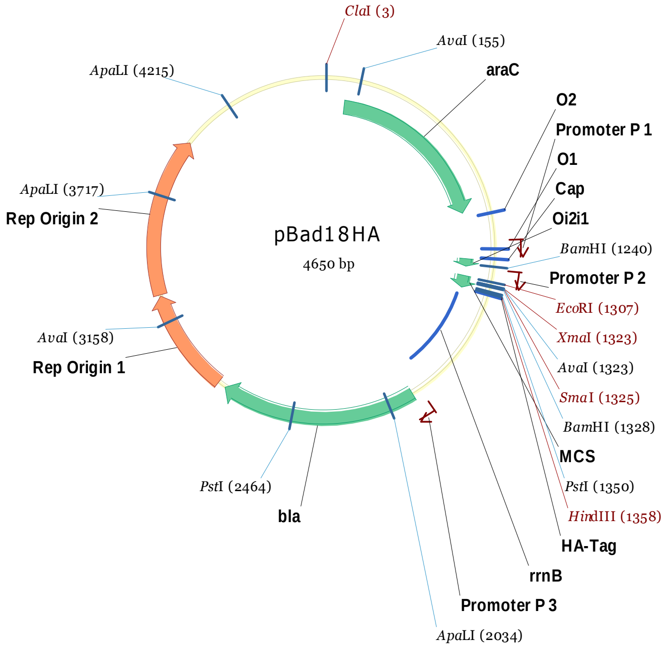


```
           S.D.      Kozak                                                    HA-Tag
         L  A  G  G  I  H  H  G  T  R  G  S  S  R  V  D  L  Q  A  C  K  L  Y  P  Y  D  V
1       CTAGCAGGAGGAATTCACCATGGTACCCGGGGATCCTCTAGAGTCGACCTGCAGGCATGCAAGCTTTACCCATACGACGT   80
1       GATCGTCCTCCTTAAGTGGTACCATGGGCCCCTAGGAGATCTCAGCTGGACGTCCGTACGTTCGAAATGGGTATGCTGCA   80
                   EcoRI   NcoI   RsaI    BamHI      HinfI        PstI   SphI
                           StyI      KpnI    DpnI      SalI                HindIII
                               BanI    SmaI      XbaI    AccI                AluI
                                   AvaI                 TaqI
                                    NciI                 HincII
                                    MspI
                                     NciI
                                        Sau3AI

          P  D  Y  A  G  *  A
81      CCCAGACTACGCTGGATGAGCT   102
81      GGGTCTGATGCGACCTACTCGA   102
        AatII
```

FEATURES:

- based on pBAD24 (addition of HA tag @ HindIII site)
- pBad promoter
- Amp^r
- pBR322 ori

Name	Source	Comment
pBad18HA	this work	pBad regulated expression in *E. coli* with HA tag

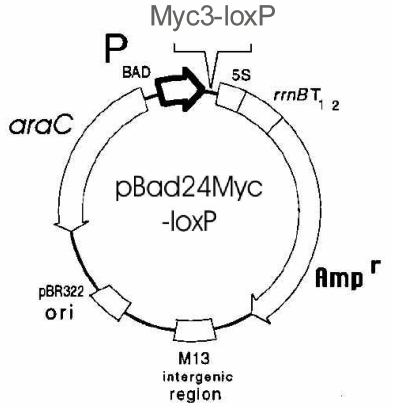


```
                                                                                HA-Tag
          A  S  E  F  E  L  G  T  R  G  S  S  R  V  D  L  Q  A  C  K  L  Y  P  Y  D  V  P
1         GCTAGCGAATTCGAGCTCGGTACCCGGGGATCCTCTAGAGTCGACCTGCAGGCATGCAAGCTTTACCCATACGACGTCCC   80
1         CGATCGCTTAAGCTCGAGCCATGGGCCCCTAGGAGATCTCAGCTGGACGTCCGTACGTTCGAAATGGGTATGCTGCAGGG   80
           NheI   EcoRI      BanII    SmaI      XbaI   SalI       PstI   SphI
                           Bsp1286I    BamHI         AccI             HindIII
                           SacI   KpnI               HincII
                             BanI
                                 AvaI


            D  Y  A  G  *  A
81        AGACTACGCTGGATGAGCT   99
81        TCTGATGCGACCTACTCGA   99
```

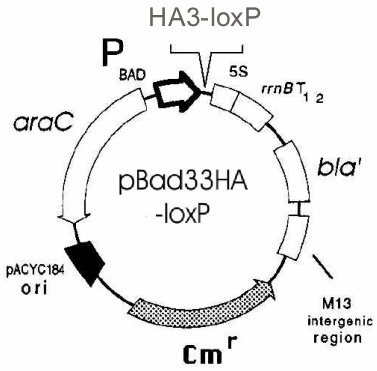
FEATURES:

- based on pBAD18 (addition of HA tag @ HindIII site)
- pBad promoter
- Amp^r
- pBR322 ori

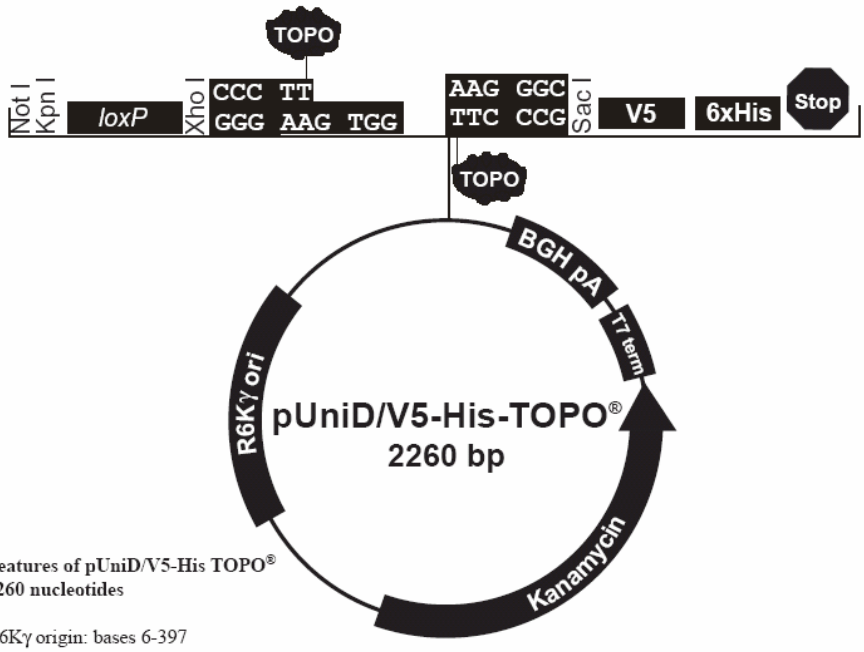
Name	Source	Comment
pBad24Myc-loxP	this work	pBad regulated expression in *E. coli* with Myc-Tag and loxP-site



Name	Source	Comment
pBad33HA-loxP	this work	pBad regulated expression in *E. coli* with HA-Tag and loxP-site

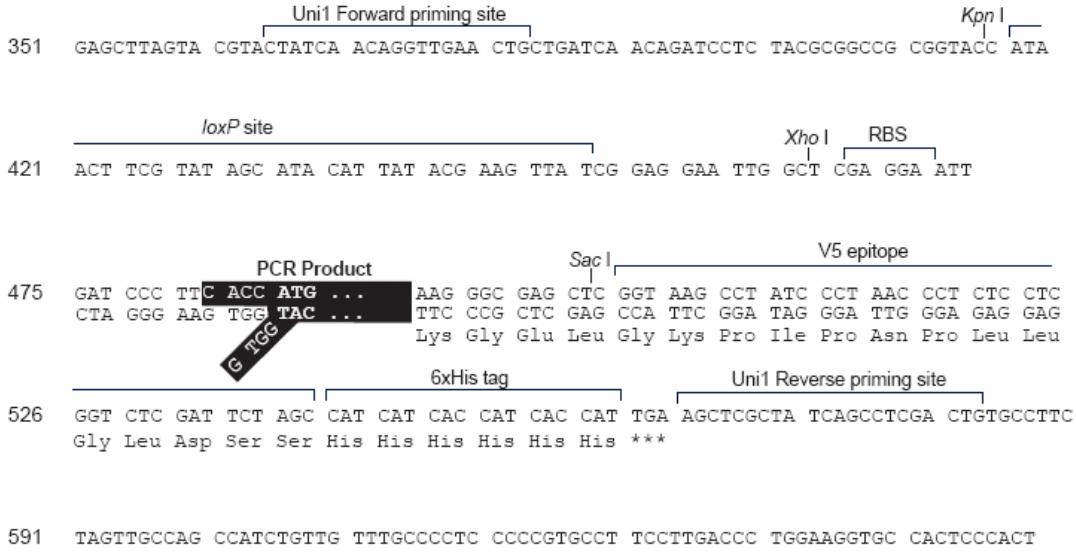


Name	Source	Comment
pUniD/V5-His-TOPO	Invitrogen	pUni Entry vector for UPS system

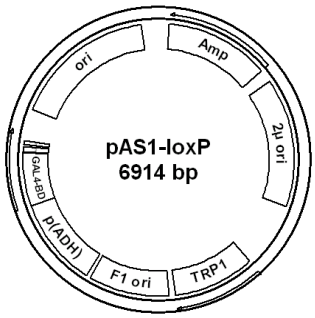


Features of pUniD/V5-His TOPO®
2260 nucleotides

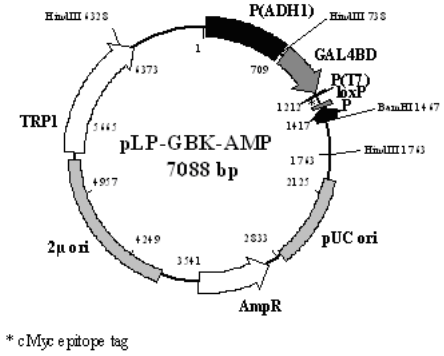
R6Kγ origin: bases 6-397
Uni1 Forward priming site: bases 365-383
loxP site: bases 418-451
Ribosome binding site: bases 467-471
TOPO® Recognition site I: 478-482
Overhang sequence: bases 483-486 (complementary strand)
TOPO® Recognition site II: bases 487-491
V5 epitope: bases 499-540
6xHis tag: bases: 541-558
Uni1 Reverse priming site: 562-583
BGH Polyadenylation sequence: bases 581-789
T7 transcription termination region: bases 804-932
Kanamycin resistance gene: bases 111-1905 (complementary strand)
Kan promoter: bases 1906-2043 (complementary strand)



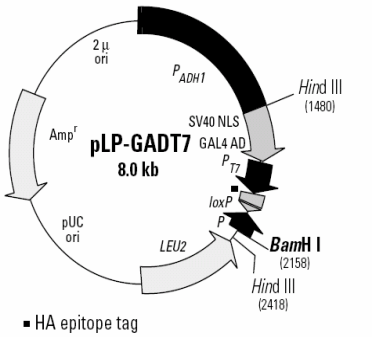
Name	Source	Comment
pAS1-loxP	McKevitt *et al.*	Y2H bait vector for UPS system



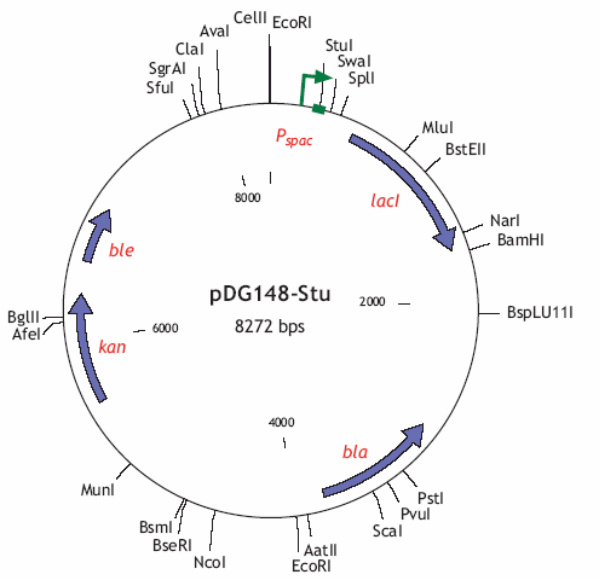
Name	Source	Comment
pLP-GBK-AMP	this study	Y2H bait vector for UPS system



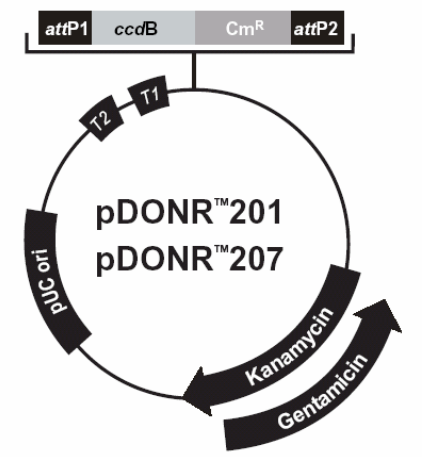
Name	Source	Comment
pLP-GADT7	Invitrogen	Y2H prey vector for UPS system

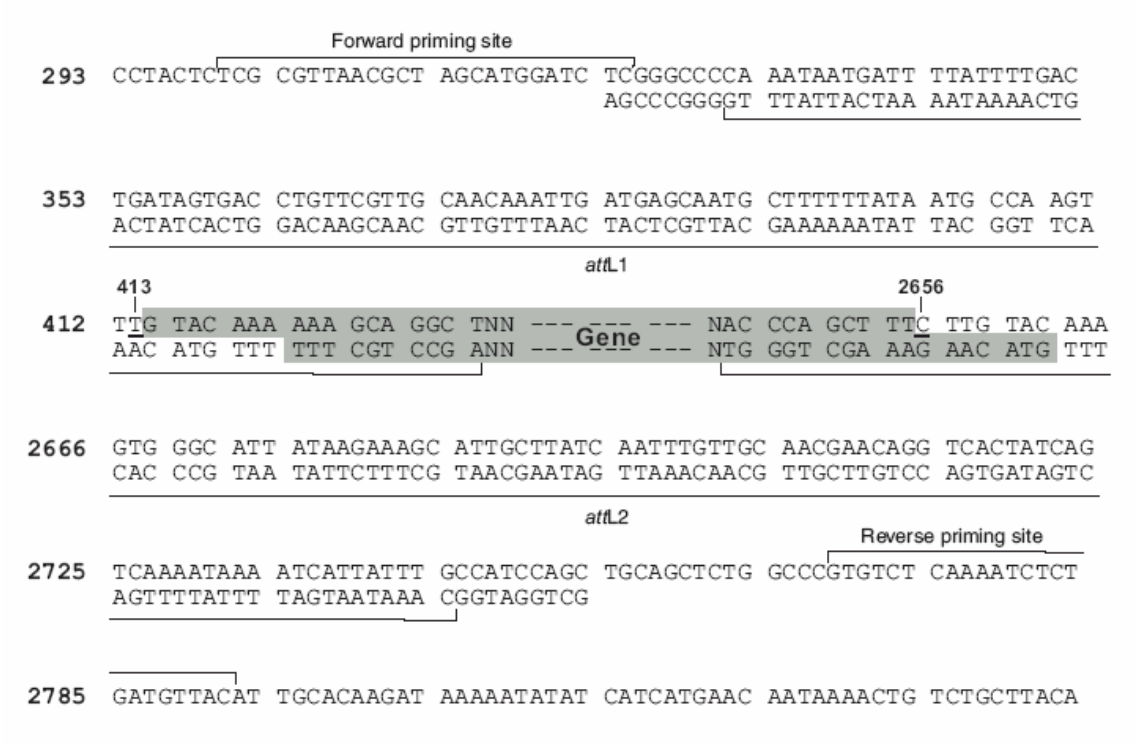


Name	Source	Comment
pDG148-Stu	Joseph *et al.*	Expression in *B. subtilis*

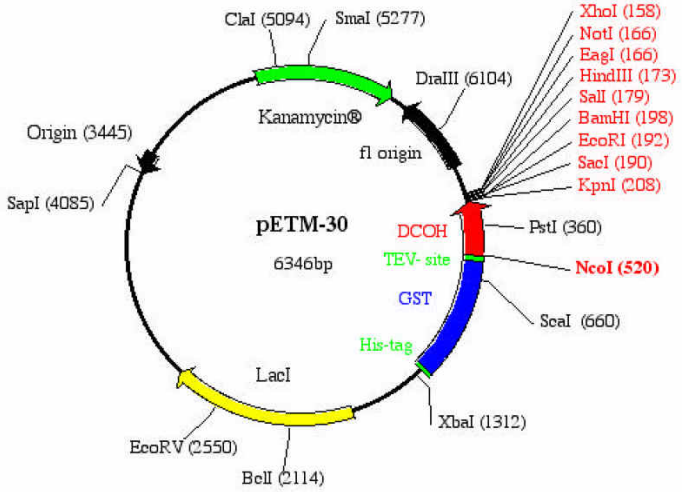


Name	Source	Comment
pDONR207	Invitrogen	Gateway System entry vector with gentamycin resistance



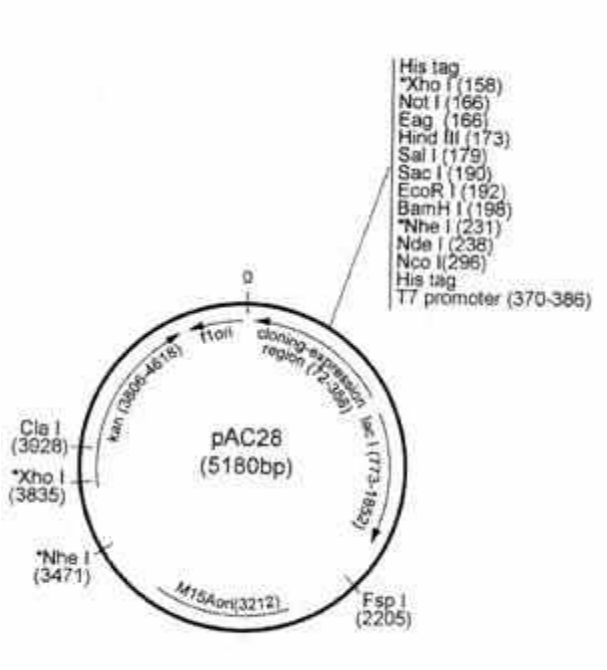


Name	Source	Comment
pETM-30	EMBL (Heidelberg)	Protein expression with GST and His tag

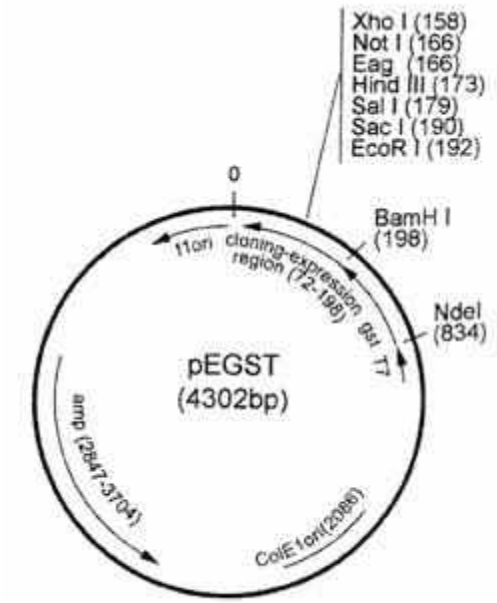


```
      T7 promoter  -->          Lac operator     XbaI
CGAAATTAATACGACTCACTATAGGGGAATTGTGAGCGGATAACAATTCCCCTCTAGAAATAATTT
GCTTTAATTATGCTGAGTGATATCCCCTTAACACTCGCCTATTGTTAAGGGGAGATCTTTATTAAA

                rbs                        His-tag
TGTTTAACTTTAAGAAGGAGATATACCATGAAACATCACCATCACCATCACAACACTAGTAGCAAT
ACAAATTGAAATTCTTCCTCTATATGGTACTTTGTAGTGGTAGTGGTAGTGTTGTGATCATCGTTA
                           METLysHisHisHisHisHisHisAsnThrSerSerAsn


TTCATGTCC..633bp..GACCATCCTCCAACTAGTGGATCTGGTGGTGGTGGCGGATGGATGAGC
AAGTACAGG...GST...CTGGTAGGAGGTTGATCACCTAGACCACCACCACCGCCTACCTACTCG
PheMetSer..211aa..AspHisProProThrSerGlySerGlyGlyGlyGlyGlyTrpMetSer

          TEV-site      NcoI
GAGAATCTTTATTTTCAG GGCGCCATGGCTGGCAAGCACACA..279bp..GCCGTGTCTATGACA
CTCTTAGAAATAAAAGTC CCGCGGTACCGACCGTTCGTGTGT...DCOH..CGGCACAGATACTGT
GluAsnLeuTyrPheGln|GlyAlaMETAlaGlyLysHisThr...93aa..AlaValSerMetThr

                                        NotI
         BamHI       SacI               EagI
   KpnI       EcoRI          SalI HindIII         XhoI   C-His-tag
TAGGTACCGGATCCGAATTCGAGCTCCGTCGACAAGCTTGCGGCCGCACTCGAGCACCACCACCAC
ATCCATGGCCTAGGCTTAAGCTCGAGGCAGCTGTTCGAACGCCGGCGTGAGCTCGTGGTGGTGGTG
***
```

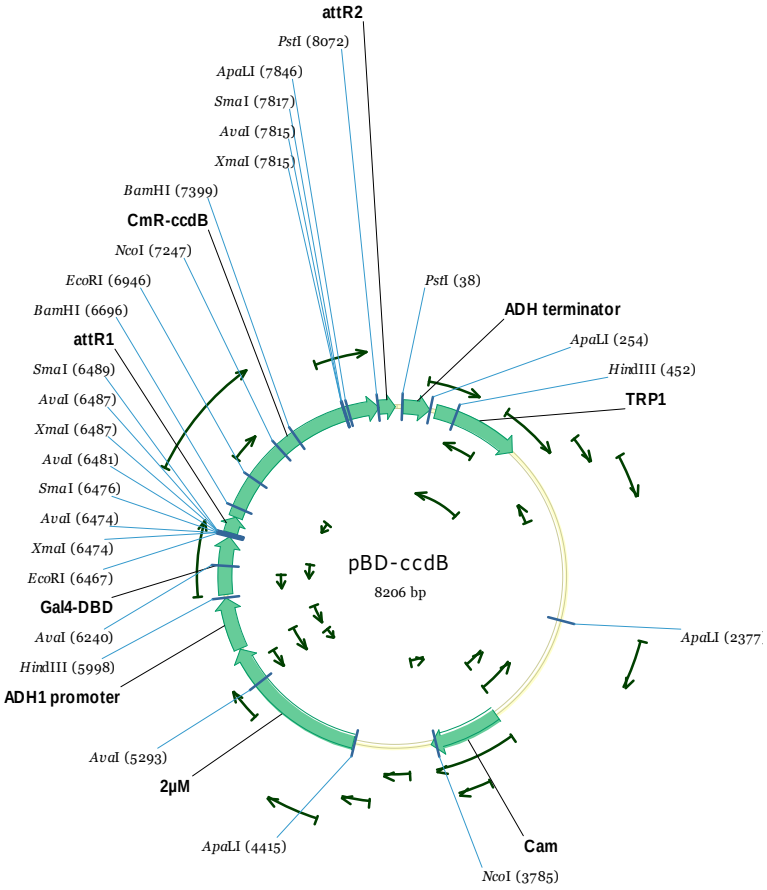
Name	Source	Comment
pAC28	Kholod *et al.*	Protein expression with His tag



Name	Source	Comment
pEGST	Kholod *et al.*	Protein expression with GST tag



Name	Source	Comment
pBD-ccdB	Satoko Yoshida	Bait vector for Gateway system



ADH terminator
Start: 45 End: 251

TRP1
Start: 294 End: 968

Cam
Start: 3271 End: 3822

2µM
Start: 4427 End: 5586

ADH1 promoter
Start: 5592 End: 5996

Gal4-DBD
Start: 6022 End: 6465

attR1
Start: 6499 End: 6623

CmR-ccdB
Start: 6624 End: 8078

attR2
Start: 8079 End: 8203

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8. Lebenslauf

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