OFFICE OF TECHNOLOGY ASSESSMENT
AT THE GERMAN BUNDESTAG

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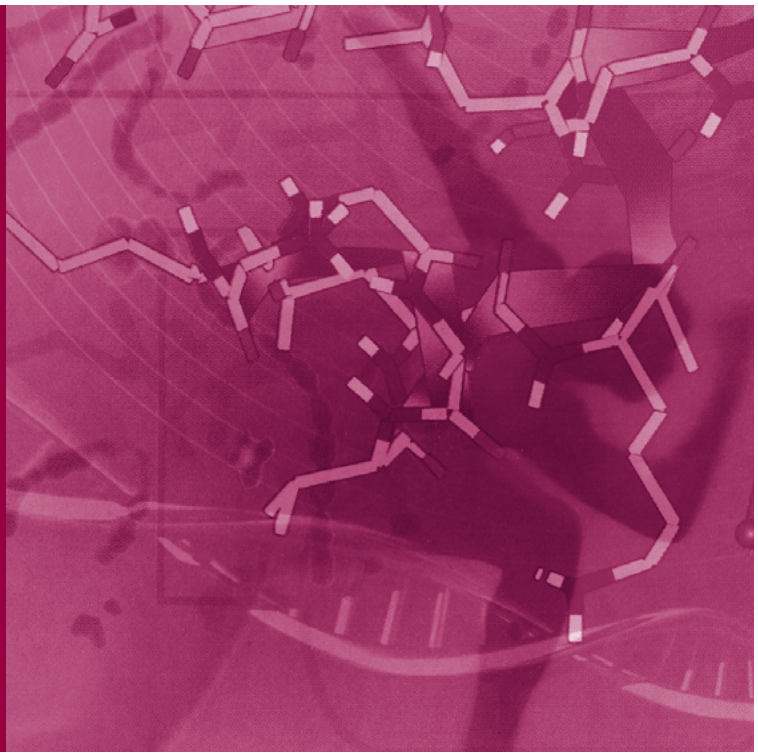
Gene doping

Summary



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SUMMARY

It is highly likely that a qualitatively new form of doping will emerge in the coming years and pose new challenges in the fight against doping, namely the widespread use of a number of very modern substances and procedures aimed specifically at influencing gene activity. These may be, on the one hand, methods of gene and cell therapy, and on the other hand methods of targeted manipulation of gene expression using highly specific agents (collectively termed »gene doping« in the broadest sense). It is, by contrast, improbable in the foreseeable future that strategies will be used for making permanent changes to the genetic make-up of athletes.

The following key questions are the cornerstones of the TAB report. Which scientific results could cater to the needs of potential gene doping? Where are the future gateways in top-level and popular sport? And how can prohibitions and monitoring be used in responding to this? To complement these thematic perspectives, gene doping will also be put into the context of social trends and structures. Questioned will be which behavioural patterns and attitudes play a role at the level of individual athletes and how gene doping as a form of deviant behaviour is influenced by different social contexts and actors.

The present final report constitutes the conclusion of the TAB project »Gene Doping«. It was commissioned on the recommendation of the Sports Committee of the German Parliament by the Committee for Education, Research, and Technology Assessment.

THE TERM GENE DOPING – IN THE NARROW AND BROAD SENSES

The term »gene doping« is often construed very narrowly, namely as the abuse of methods in gene and cell therapy, whereby in concrete terms genetic material in the form of DNA or RNA is introduced into a cell, an organ, or an organism. The TAB analysis is based on the broader perspective of the World Anti-Doping Agency (WADA), which – in line with its list of prohibitions under gene doping – explicitly also includes the use of other methods to influence gene activity: »the non-therapeutic use of cells, genes, genetic elements or the modulation of gene expression, having the capacity to improve athletic performance«.

Only by adopting this broader interpretation can as many relevant methods, procedures and agents as possible be included in the analysis. The scientific basis

of the new (gene) doping options consists in ever more advanced techniques of molecular biology and our increased knowledge of the molecular mechanisms of cell function. The explosive nature of the topic in both social and political terms results from the fact that these advances will result in an increased number of options for specific and subtle manipulation of gene activity, which will presumably be increasingly hard to detect. Differences in the methods used – whether the manipulation proceeds via transmission of genetic material such as DNA or RNA or in other pharmacological ways – should not constitute a reasonable exclusion criterion for an analysis of the consequences, particularly in view of future anti-doping measures.

NO »GENETICALLY IMPROVED« ATHLETES FORSEEABLE

One idea frequently encountered with regard to the aim of potential gene doping approaches is that of »improving« the genetic make-up of athletes through knowing which gene variants can bring about a particularly high level of performance, either by specifically manipulating the whole organism or by prenatal selection. A detailed investigation into the results of genome research, however, shows that molecular genetic knowledge of »high-performance gene variants« is so far extremely limited, fuzzy, and contradictory, so that any »promising« procedures for altering the genetic disposition in a targeted manner are foreseeably highly improbable. The TAB project thus found no evidence that strategies for human selection or breeding to induce increased performance levels in sport will be technically feasible in the foreseeable future. There is currently no scientific basis for such ideas and presentations regarding gene doping in the future.

THE AIM OF GENE DOPING: GENE REGULATION

The aim of gene doping is in fact to specifically influence (modify) endogenous gene activity, whether this be in the form of the activation, strengthening, weakening or blocking of so-called gene expression. The underlying biochemical and physiological processes are highly complex, both at the cellular level and at the level of overall regulation in the body (and thus will only be outlined in the report). The network of feedback controls of attributes relevant to physiological performance results in a multitude of targets for pharmacological and molecular biological modulation – for new therapeutic treatment strategies but also in turn for doping purposes. The possible consequences of such interventions are very hard to predict. This can still be seen when used in medical therapy to try to treat patients (in the form of adverse effects or a lack of efficacy of the agents). Where

such methods and procedures are abused in healthy or highly trained humans, who thus despite their high physiological performance are also particularly susceptible to disorders, it must also be expected that the consequences are hard to predict.

GENE THERAPY AND OTHER METHODS OF MODIFYING GENE ACTIVITY

Gene doping in the narrow sense abuses the techniques of gene and cell therapy for the purposes of increasing physical performance. Gene therapy is used to denote strategies in which genes or genetic elements are introduced into cells from outside, to remedy inherited or acquired genetic disorders. Genes are introduced into the cells – this is called »gene transfer« – by means of so-called vectors (or »carriers«, most of them so far have been specially adapted viruses). Gene therapies already tested on humans have been directed mainly at cancers, monogenic inherited diseases, infectious diseases (especially HIV), and cardiovascular disorders. In contrast to what is commonly presented, the objective here is often not any permanent change but rather transient measures which may have to be repeated.

Assessment of the previous results of gene therapy is important for evaluating its potential relevance for doping. Overall, gene therapy does not yet constitute established medical practice. It is, on the contrary, overwhelmingly still at the experimental stage, and evaluation of the previous therapeutic results is a matter of great controversy. Treatments continue to be frequently related to serious adverse side effects, even including death. The vectors are considered responsible for some of the side effects observed. The proportion of clinical experiments that forgo viral vectors, which are more efficient but also particularly risky, in favour of using so-called »naked« DNA has continued to increase in the past few years. This is significant for possible gene doping since the use of non-viral DNA is probably much simpler and indeed also less risky.

In addition to the methods clearly designated as gene therapy, many other modern pharmacological treatment strategies are also directed at targeted modification of endogenous gene activity for the purposes of medical therapy. The agents used here include both very diverse and in some cases very complex biomolecules, such as proteins and RNA, and simple compounds that are easy to produce chemically.

PHYSIOLOGICAL STARTING POINTS AND MOLECULAR OBJECTIVES – RESEARCH STRATEGIES AND DEVELOPMENT PROJECTS

The most likely targets for possible gene doping are identified in three physiological areas and their molecular regulation: the structure of the skeletal muscles, oxygen supply, and energy supply.

Physiological starting points for gene doping strategies

> *Skeletal muscles:* Growth, structure, strength, stamina, regeneration (molecular targets: myostatin, HGH/IGF/MGF, Pax7, PPAR-delta)
> *Oxygen supply:* Haemoglobin concentration, vascular supply (molecular targets: EPO, HIF, VEGF)
> *Energy supply:* Fatty acid and glucose metabolism in liver and muscles (molecular targets: FATPs, GLUTs, PTP-1B)

Among the research strategies and development projects identified in the TAB project and described in detail in the report that have already reached the stage of clinical testing, there is only one that pursues an explicit gene therapy approach. The other techniques that are further developed are all pharmacological strategies for modifying gene activity. In preclinical research, i.e. in animal experiments, however, a large number of potential gene doping techniques have been successful, not only in the broad sense, but also in the narrow sense (e.g. the much-cited Repoxygen).

PARTICULAR HEALTH RISKS: AN EFFECTIVE OBSTACLE?

In principle, the underlying techniques or substances used in the practice of doping were developed for treating diseases. Their effectiveness in improving physical performance in healthy individuals has not been investigated. For this reason, the health risks involved in their abuse for doping purposes cannot be assessed as a matter of principle. Evidence is provided by the severe to catastrophic, in some cases even fatal, effects of doping on the health of athletes that have been seen in the past.

While from this perspective gene doping methods could hardly be more risky, it is possible to infer *specific risks* from the principles underlying the techniques used to specifically modify gene activity. Without any empirical evidence, however, these the merely the *scientifically plausible assumptions*. Here we can dis-

tinguish between the risks which arise when genetic material is channeled in (lack of tissue specificity in the vectors,. leading to an uncontrolled spread of the foreign gene in the organism and to mutations and immune reactions), and those which are the consequences of genetic overexpression (i.e. production in the body) of performance-relevant biomolecules (e.g. uncontrolled cell growth). In view of the complexity of regulating gene activity, it is highly probable that manipulating these mechanisms will cause a multitude of side effects – and thus potentially severe damage to health.

Taking the previous experience with conventional doping practices into consideration, the chances are low that these inestimable health risks alone will form an effective obstacle to the use of methods that are scientifically uncertain. The crucial factor in the use and dissemination of gene doping methods is probably – in addition to their basic availability – primarily their supposed effect, i.e. the potential improvement in physical performance, and their ability to go undetected (see below).

ACCESS PATHS

The main candidates for doping abuse are probably therapeutic procedures and pharmacological agents that are already licensed or are in use in clinical studies. To assess which gene doping strategies could become relevant within which time frame, it is important to continuously monitor current developments in research and development, particularly in pharmaceutical companies. One must assume, however, that by no means all projects that are relevant to gene doping will become known publicly (at least not at an early stage).

In addition to the abuse of licensed therapeutic agents or those in the process of being licensed, there are indications of a possibly even more disturbing approach, namely a kind of »individual« gene doping which circumvents all the test procedures involved in drug licensing procedures. As with designer steroids, which were explicitly manufactured by the BALCO company for doping purposes, genetic-pharmaceutical gene doping agents could also be produced that are specifically tailored to individuals or a small group of athletes. In some cases, the costs in terms of time and money would probably not be any higher than for non-designer agents. Comparatively simple methods are, for example, the construction of vectors on a viral basis, the production and administration of so-called naked DNA or the construction of gene vaccines to produce antibodies. These are routine tasks in molecular biology, and standard procedures, equipment and commercial kits already exist for many individual steps.

One frequent objection to gene doping scenarios is that the relevant methods are not failsafe and, above all, that possible performance enhancement has not been proven in healthy individuals or even highly trained athletes. The results of preventive research directed at doping practice show, however, that certain doping strategies are still used by athletes for doping purposes although the efficacy of these methods has been repeatedly rejected (e.g. in the case of the growth hormone).

GATEWAYS: TOP-LEVEL SPORT – BODYBUILDING – ANTI-AGING?

Procedures analogous to gene therapy (gene doping in the narrow sense) will probably present larger obstacles to abuse than the many methods or pharmaceutical developments for specifically manipulating gene activity. In view of the current status of the development of several projects in the biotechnological and pharmaceutical industry, one must assume that such methods can even now be used for doping if abusers gain access to clinical studies. Experience in the field of peptide hormones (EPO, growth hormone) has shown that this is possible.

It is also worthy of consideration that, for instance, the abuse of myostatin inhibitors might well be promoted less in competitive sport than perhaps in recreational sport or specifically the world of bodybuilding (in internet fora, there has long been much discussion of and demand for these new drugs).

One possibly even much more significant route of access than via illegal appropriation of gene-modulating substances from clinical research (or the individual gene doping mentioned above) could open up in the long run in the borderline area of therapy for age-related limitations, e.g. the use of drugs that will be licensed by then to treat excessive muscle loss. The borders are fuzzy between this and the socially and politically highly relevant and cross-cutting topic of the non-therapeutic use of medication to improve everyday performance, which has been discussed increasingly for some time under the heading of »enhancement«.

DETECTABILITY AND TEST DEVELOPMENT

One crucial question in combating doping is whether and how gene doping can be detected. Past experience indicates that the development of detection tests in response to abuse is extremely insufficient for fighting doping effectively. WADA responded to this a few years ago by setting up an international programme to promote the detection of gene doping.

In gene therapy and gene modulation, attempts are made either to introduce a gene or a genetic element into particular body cells and to activate it there or to activate or inhibit a gene or genetic element that is already present. If the genetic or gene-regulating element that is introduced is chemically different from the endogenous substances, direct detection should be possible and qualitatively sufficient. The dynamics of rapid development coupled with great diversity and complexity in the area of gene modulation, however, have led most experts to suppose that methods of direct detection lose in significance because it would be far too costly to test for all possible manipulations.

In practice, there are several obstacles to detecting vectors (in gene therapeutic procedures) even though it is theoretically plausible, e.g. the difficulty of distinguishing them from naturally occurring viruses. The detection of non-viral vectors (naked DNA, siRNA) would probably be even more difficult due to the short half-life of nucleic acids. Entirely unclear is which form detection could take if cells are removed from the body, genetically changed outside the body and subsequently reintroduced into the body (known as ex-vivo procedures).

The vast majority of the 20 research projects currently sponsored by WADA are thus directed at identifying deviations from normal physiological conditions as indirect evidence of gene doping. This involves the determination of highly differentiated profiles for all sorts of molecules (DNA, RNA, proteins) in blood and tissue samples, so-called biomarkers or »molecular fingerprints«. The aim or strategy here is to develop an intelligent form of biomonitoring which provides unambiguous evidence of manipulated gene activity. This in itself might suffice as evidence. This method might, however, also only allow an initial suspicion to be substantiated, requiring additional specific evidence in order to prove with sufficient analytic certainty that anti-doping regulations have been violated. The question whether the biomonitoring strategy will be successful in the long run cannot be assessed at this time, since the relevant projects are at an early stage of development (for instance, the specific development of an implementable test – specifically to determine overall myostatin activity – is only mentioned as an aim in one single project). There is, however, currently no alternative in sight.

MONITORING AND SANCTIONS

Five years ago, as a precaution, WADA placed gene doping on the list of forbidden substances and methods (Prohibited List), which together with the World Anti Doping Code constitutes an important basis for measures employed by sport federations and national governments in their common fight against dop-

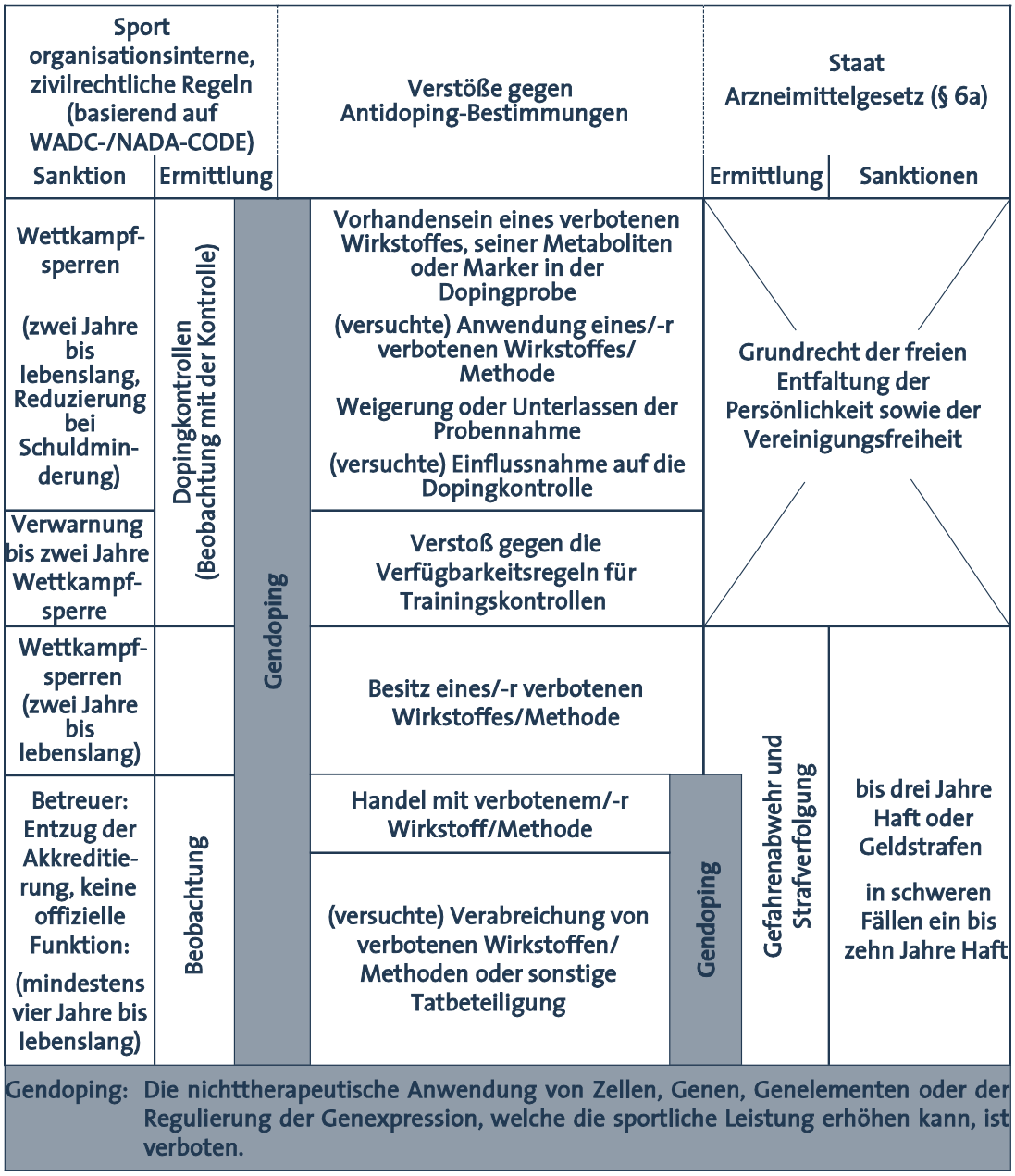
ing. All violations against the anti-doping regulations defined in the WADC include gene doping. According to this, personal use, refusal to comply with testing, possession, trafficking, administration to other persons, and other involvement in a violation are prohibited. Sports federations which have accepted the WADC, or the NADA Code specific to Germany, in the statutes of their own organizations, have formally prohibited their members from gene doping. This applies to large portions of competitive sport but not to individual sport as practised in fitness centres.

The Prohibited List has been incorporated into German law. The German Drug Law (*Arzneimittelgesetz*, AMG) forbids bringing substances on the Prohibited List into circulation, prescribing them or administering them to others for doping purposes in sport (including any attempt to do these things). The same applies to substances which are necessary for using the methods listed [including gene doping; Sect. 6 (3) AMG]. There is, however, no reference to Sect 4 (9) AMG which defines gene transfer agents as drugs.

In gene doping, the real problem lies less in prohibiting actions than in monitoring compliance with the ban and proving violations in a way that will stand up in court (problem of implementation). Sports federations can essentially check compliance with the prohibition by means of doping tests. Acceptable evidence for sports federations is primarily provided by body tissue or fluid samples which, by means of detection tests, allow the violation to be assumed with sufficient certainty. The state has broader powers of investigation. Since doping tests and criminal prosecution infringe the basic personal right of the athlete, the prohibited action must be formulated with sufficient precision (dictate of certainty). From a legal standpoint, there are doubts as to whether the current definition of gene doping will meet all the requirements.

It will probably even be harder to detect gene doping than current doping practices. The existing system of tests during competitions and training must be expanded. If it is necessary to take more blood samples or even tissue samples, the requirements on sampling increase considerably. Since they involve the personal rights of the athletes, the legality of the procedure must be well-founded as a matter of principle. This is probably only possible if a violation can be detected with sufficient certainty – i.e. if there is a test that stands up in court. Overall, it is to be expected that as a result of gene doping, the whole detection procedure will place even higher demands on sport jurisdiction than do current doping practices.

TABLE 1 DOPING VIOLATIONS AND THE REGIMEN OF SANCTIONS IN GERMANY



Source: WADA-/NADA Code, Arzneimittelgesetz, Prohibited List (Federal Law Gazette 2007, Part II, No. 18)

The state can provide support for sport in the prosecution of gene doping activities. The establishment of specialized police units and public prosecutors' offices for effective prosecution, the ongoing training of these individuals, clearly defined contact routes and contact persons and closer cooperation between prose-

cuting authorities and other bodies (science, sport, pharmaceutical manufacture) are already important now in the fight against conventional doping and will be mandatory for gene doping.

Since these repressive measures in the fight against gene doping will be very costly and bound up with a host of unresolved legal questions, it is unlikely that they will in themselves constitute an effective deterrent against gene doping. Concepts for preventing the occurrence of gene doping must also be introduced.

SOCIAL ASPECTS OF DOPING

Doping is an act of an individual in a social context. Like other rule-breaking behaviour, it is the result of individual developmental processes and conscious decisions. In view of the magnitude that doping has assumed in sport, however, it is not sufficient to point the finger at the deviant behaviour of individual athletes. On the contrary, to gain a comprehensive understanding of doping activity it is important for their social contexts to be observed. These include, for instance, the global commercialization of competitive and top-level sport. Sport itself has become a business, and for many athletes it has become a career. The media and the expectations of a worldwide public have created the necessary conditions for this and intensify the process of treating sporting performance as an economic entity. This makes winning »at all costs« even more important. The dominance of the performance imperative, together with the prospect of profits cause structures to evolve that are receptive to any means of improving performance.

In the system of sport, sports federations are the actors who seek to mediate between the demands for performance and success surrounding the athlete – politics, the media, sponsors, the public – and the athlete himself. They promote their athletes' readiness and capacity to perform, and they organize competitions to compare performance. Their position and their influence on the overall course of events depend on the successes achieved by their athletes. To this extent, they too are caught – just as the athlete is – in a kind of »doping trap«. They must satisfy the demands for »clean«, rule-abiding, competitive sport by taking up an active stance in the fight against doping. But by testing and sanctioning, they tend to jeopardize the athletes' success. Much of what the organizations do or do not do in terms of doping can be better explained by their involvement in the »system logic« of competitive sport.

The diagnosis of structural involvement in doping activity is, however, true not only for athletes, sports physicians and organizations, but also for government

actors. They promote sport because they want the successes, but they also support structures for detecting doping and sanctioning those involved, and establish prohibitions and statutory offences in legal codes. Success in anti-doping activity could, however, mean a lack of success for national athletes – one reason possibly being the fact that the doping practices of foreign competitors are not being combated equally stringently.

Overall, doping must be understood as an effect of specific social structures. By acting or neglecting to act, many actors have contributed to a system of organized irresponsibility. As a collectively produced problem, the widespread practice of doping can only be solved through common action at several levels. In view of the structures which have grown up over many years, it is not adequate to be optimistic here. The considerable problems of credibility in competitive sport could, however, indeed herald an effective curbing of doping practice. Gene doping could thus have the effect of a warning sign, further promote insights into the potential of doping to jeopardize sport, and assist in a process of redirection.

NEED FOR INFORMATION AND ACTION

Gene doping means entering a political sphere characterized by incomplete and uncertain knowledge coupled with an urgent need for action. The following possible actions could represent the building blocks of a specific anti-gene doping strategy.

SCREENING OF BIOMEDICAL AND PHARMACEUTICAL DEVELOPMENT PROJECTS FOCUSSING ON THE RELEVANCE OF GENE DOPING

Gene doping abuses knowledge from basic and/or applied research in the life sciences that was intended to lead to new therapeutic strategies. Continuous predictive monitoring of biomedical and pharmaceutical development projects and of the potential demand side could provide strategically important information. This could become a kind of early warning system, providing guidance for those involved in the fight against doping and preventive doping research. The willingness to cooperate on the part of industry would be helpful here.

INVESTIGATE DETECTABILITY, DEVELOP TESTS, DESIGN »INTELLIGENT« MONITORING SYSTEMS

There is a great need for research and development into detecting gene doping as a key element in the system of monitoring and sanctions. A two-step approach currently seems the most promising. It covers »intelligent« monitoring and, where there are grounds for suspicion, specific tests for verification. This kind of monitoring requires both specialized (which orders of magnitude of measurements taken at which intervals provide evidence of physiological developments or conspicuous features induced by doping?) and legal clarification not only in terms of sanctioning but also with regard to data protection and personal protection.

CONCEPTS AND ACTIVITIES FOR PUBLIC INFORMATION CAMPAIGNS SPECIFIC TO GENE DOPING

Together with the further development of testing and sanctioning structures independent public information campaigns focussing on gene doping must be developed. For these to have a preventive effect, a broad design is necessary which covers the whole process of individual sporting development in which doping mentality and attitudes can gradually arise. Such an approach should take into consideration both the athlete's immediate surroundings (trainer, manager, physician) and the role of sponsors and the media.

ADAPT FUNDING POLICIES

In the context of the public funding of sport, those receiving financial support are now required to adhere to the rules set down by the WADA and NADA. To this extent, gene doping is covered. Repayment of financial support in the event of violations, however, requires proof that will stand up in court. Here too, detection proves to be the Achilles heel. Nevertheless, the demand for complying with anti-doping rules should be upheld at all events and, indeed, applied even more strictly to gene doping. To this extent, the state could serve as a role model for private sector sponsorship in its funding activities.

GERMAN DRUG LAW: CHECK ITS APPLICABILITY AND FURTHER STATUTORY OFFENCES

The German »*Gesetz zur Verbesserung der Bekämpfung des Dopings im Sport*« (»law to improve the fight against doping in sport«) has created better conditions for the prosecution of doping, particularly in the athletes' own milieu. The legislature must, however, investigate how these and other legal norms will have to be adapted to the dynamics of scientific and technical progress and doping practice. Gene doping must be more clearly defined as a prohibited activity in order to satisfy the principle of certainty. On the basis of the recent extension of the definition of doping to include substances that are intended for use in connection with prohibited methods, it should be possible to include the substances relevant for gene doping. To satisfy the principle of certainty, for instance, reference could be made in Section 6a, Paragraphs 2 und 2a AMG to Section 4, Paragraph 9a, AMG. In this way, the use of gene transfer agents for the purpose of gene doping could be prohibited. Furthermore, it should be considered whether the constituent element »*nicht geringe Menge*« (=»more than a small amount«) is even valid for gene doping or whether rather any non-medically indicated use of gene transfer agents in humans should be made a punishable offence.

PARLIAMENTARY TECHNOLOGY ASSESSMENT

The relevance of the subject of gene doping stems not only from its significance as a factor that will probably intensify the problem of doping in sport. The subject in fact indicates an overall social trend towards using pharmaceutical agents to manipulate physical and psychological performance. »Everyday doping« or »enhancement« is a currently relevant topic that points to the future for technology assessment and the committees of the German Bundestag.

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