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The prospect of approved and commercially available phage therapeutics

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ABSTRACT

As antibiotic resistance of bacterial pathogens spreads, interest in bacteriophage (phage) therapy has soared again in many countries. Currently, there is no phage therapeutic with marketing approval and phage treatments are relegated to few patients, mostly under compassionate use schemes when approved drugs failed or are unavailable. Commercially manufactured and approved phage preparations could both expand the availability of therapeutic phages for existing, exemptional treatment schemes and result in more broadly usable phage therapeutics with marketing authorization. The lack of clinical evidence from modern clinical trials and issues with the patenting of phages are often seen as important challenges toward commercially produced and approved therapeutic phages. Here, an analysis of available data suggests that while a surge in patent filings and new clinical trials by biotech companies has begun and these challenges may be surmountable, the long-term success of commercial phage therapeutics will hinge on policy solutions that address post-approval regulatory and economic barriers.

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1. Introduction

About 1·14 million people died from infections by bacteria resistant to antimicrobials globally in 2021 [1]. This number almost equals global deaths from HIV and malaria combined [2], and is expected to rise to more than 1·9 million in 2050 if remediation measures cannot be established [1]. At the same time, the development of new antimicrobials to address the mounting threat of antibiotic resistance and combat critical multiresistant bacterial pathogens is inadequate [3].

The pandemic spread of antibiotic resistance [1,4] has sparked new interest in the use of bacteriophages (phages) to fight bacterial pathogens [5–8]. Phages are viruses that specifically infect and can destroy bacteria. Phage therapy was largely abandoned in most countries following the availability of first antibiotics after World War II [5,8]. However, apart from some former Soviet republics (especially Georgia and Russia), where phages existed as approved drugs [9,10], phage therapy is relegated to a few individual patients under various regulatory conditions for compassionate use cases, i.e. when approved drugs are unavailable or failed [5,6,11,12]. Countries where phages are used in this way include Australia, China, various European Union (EU) member states (e.g., France, Germany, Poland), the United Kingdom and the USA [11]. Regulatory exemptions for such a use include expanded access programs in the USA or named patient-based schemes in countries of the European Union [12]. In addition, phages can be used under regulatory exemptions for individually prescribed medicines prepared in pharmacies, e.g., in the EU as “magistral formula” [13]. Belgium uses a national scheme based on this exemption for treating individual patients with personalized phage products [13,14]. Such a magistral solution for phage therapy in hospitals has very recently been also approved in Portugal [15].

There are several issues for making phage treatments an easy to implement and generally applicable standard therapy. To start with, in contrast to many antibiotics that affect a broad spectrum of bacteria, most studied phages have a narrow host range. While this feature can allow to avoid “collateral damage” to the microbiome, it poses challenges when it comes to effectively combat multiple bacterial species or variable strains underlying an infection, as well as to cope with the possible development of bacterial phage resistance [5,6]. Two phage therapy concepts have been developed to address these challenges. First, the use of predefined, or “fixed” (“off-the-shelf”), phage cocktails (Fig. 1, *left panel*) that are intended to target the bacterial strains most commonly associated with a specific type of infection. Ideally, these phage mixtures contain phages with different host ranges and multiple phage strains per targeted bacterial species. Such cocktails can become

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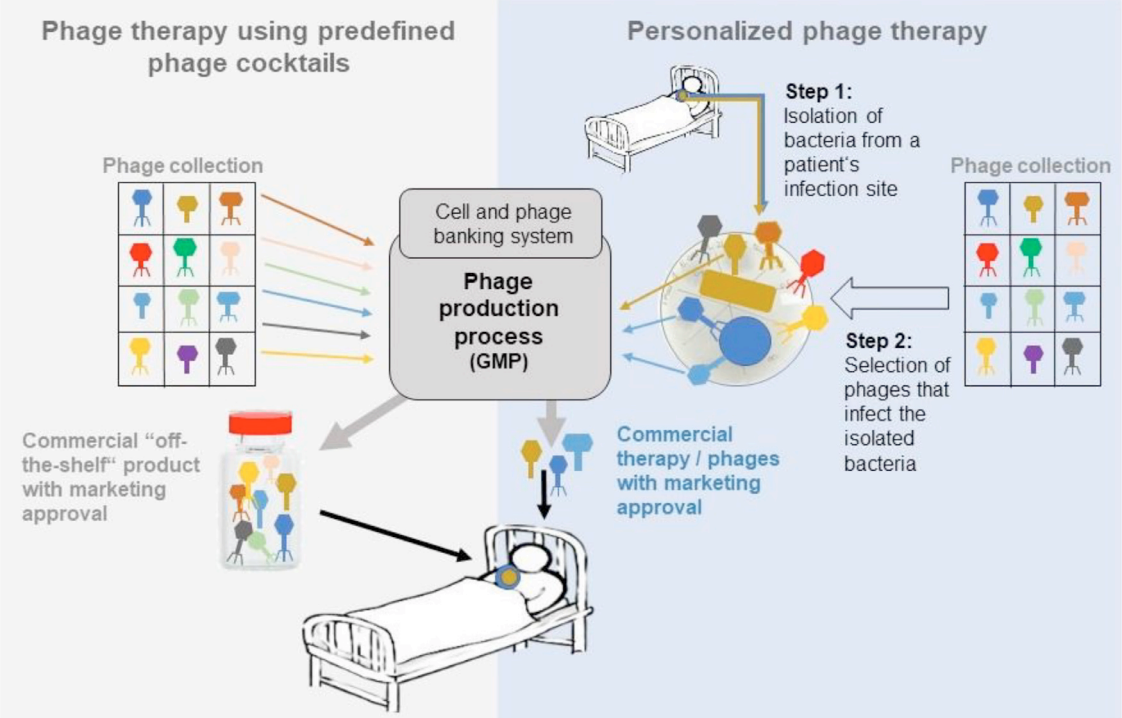

Fig. 1. Phage therapy concepts and production of therapeutic phages. *Left panel.* Phage therapy approach using pre-defined ("off-the-shelf") phage preparations. These preparations usually contain mixtures (cocktails) of phages that should target the most common bacterial strains associated with a specific type of infection. *Right panel.* Personalized phage therapy. This therapy concept first requires the isolation of pathogens from a patient's infection site, in order to identify, in a second step, phages that can infect the isolated pathogens. If necessary, phages can be adapted ("trained") to the pathogen strains from patients to overcome phage selectivity and resistance issues. In both phage therapy concepts, phages are typically selected from existing phage collections. The production of therapeutic phages is an elaborate process that must comply with Good Manufacturing Practices (GMP) standards if the phages are to be used in clinical trials and marketing authorization is intended. This process includes bacterial cell and phage banking systems with well-characterized and controlled master and working stocks of the phages to be produced and the bacterial strains used for their propagation, in order to secure and scale up manufacturing.

highly complex and difficult to produce when infections involve multiple species or strains of pathogens. Similarly, they are often not feasible or successful for fighting important pathogen species with mainly narrow-range phages (eg., *Acinetobacter baumannii, Mycobacterium abscessus)* [5–7]. The second concept is personalized phage therapy. It is based on phages, or cocktails of phages, that are selected in laboratory assays for their ability to infect the bacteria present at and first isolated from a particular patient's infection site (Fig. 1, *right panel*). This requires to screen a panel of phages on each clinical isolate, which can be logistically challenging. Additionally, phages can be adapted ("trained") by the in vitro selection of phage mutants to overcome phage selectivity and resistance issues [6,16]. In both phage therapy concepts, phages are typically derived from existing phage collections [17].

Furthermore, as phages need host cells for their reproduction and are evolving entities, production of therapeutic phages requires elaborate processes to ensure phage identity and purity (including absence of virulence factors or bacterial toxins), potency, and stability. Phages intended for use in clinical trials and for obtaining marketing approval must be produced under Good Manufacturing Practices (GMP) standards. This entails a production process (Fig. 1) that, in order to secure and scale up manufacturing with fermentation and purification steps, requires strictly controlled bacterial cell and phage banking systems for the phages to be produced and the bacterial strains utilized for their production [18–20]. However, since such manufacturing is infrastructure- and time-intensive, it appears uncertain whether personalized phage preparations could be produced flexibly and timely enough according to GMP standards [16,20,21].

Ultimately, a key challenge for clinical use is determining the optimal indications and developing the regimen for the clinical use of phage treatments. So far, positive results on efficacy and safety of phage therapy have come almost exclusively from case studies and series of case studies, respectively, most of which have used personalized phage preparations in combination with antibiotics [16,22]. Certain phage strains can act synergistically with antibiotics (e.g., strains that target drug efflux pumps), and emerging bacterial resistance against such strains can resensitize bacteria to antibiotics [5,6,16]. A recent publication of 100 consecutive cases suggests that the probability of eradicating targeted bacteria was 70% lower when antibiotics were not used concomitantly [16]. With the exception of one study on the treatment of antibiotic-resistant chronic otitis [23], the few randomized controlled trials (RCTs) – the kind of rigorous clinical studies typically required for marketing approval of drugs – failed to prove efficacy. All of these trials involved predefined cocktails of natural phages [7,8].

The case study findings [16,22] suggest that phage therapy can benefit patient populations with various difficult-to-treat (acute and chronic) infections. These include important groups of infections such as bone infections (osteomyelitis), infections of cardiac devices or orthopedic implants (e.g., prosthetic joints), respiratory infections (e.g., in cystic fibrosis patients), urinary tract infections, hard-to-treat skin or wound infections, and cases of severe sepsis [16,22]. Most of the difficult-to-treat infections in the studies were caused by multidrug-resistant bacterial strains [22], but such infections can also be recalcitrant to antibiotic treatment due to other factors, particularly biofilm formation [24,25].

Ultimately, conducting more clinical studies to determine which infections and patient populations can be successfully and reliably treated in clinics with a specific phage therapy approach will be crucial to developing phage treatments as a standard of care and

making them available to more patients. Additionally, enhancing the availability of suitable phages will be important.

Approved and commercially produced phages should be an important step toward making phage therapies available on a larger scale. In addition to "off-the-shelf" phage products and phages as active substances for commercial personalized phage therapies, they could also improve phage supply for the increasing number of publicly funded national initiatives that strive to allow the treatment of larger numbers of patients [14], including magistral schemes for personalized phage therapies as in Belgium and Portugal. Realizing the goal of commercial phage therapeutics with marketing approval will primarily depend on costly and high-risk research and development (R&D) processes, including multi-phase clinical trials for marketing authorization. The so far missing clinical evidence on efficacy from RCTs, regulatory issues related to approval processes primarily designed for invariable chemical drugs, as well as questions on the patenting of phages and their implications for economic prospects, are considered as major hurdles for investing in and developing such phage therapeutics [5,9].

2. The question of phage patents

Patents are considered a major incentive for innovation in developing new drugs because R&D is lengthy, expensive and risky compared to launching generic medicines. Various studies suggest that, compared to other forms of intellectual property protection (such as trade secrets, trademarks or copyrights), patents are more important for R&D in the biopharmaceutical industry than in other industries [26]. In addition, patents are considered relevant for start-up biotechnology companies to attract investors and raise venture capital [27–29].

Naturally occurring phages are considered difficult to patent or, at least, it appears uncertain how strong patent protection can be [30,31]. There are several reasons for this. Thus, the therapeutic use as well as methods for isolating natural phages have been known since the first publications in the 1920s and 1930s, and are so within the public domain. Moreover, similar phages with the same effect could be isolated from the environment relatively easily. Finally, natural products may not be considered inventions and patentable, or only under special conditions. For instance, though naturally occurring genes or organisms are not a priori excluded from patentability in the EU, the Biopatent Directive (Directive 98/44 EC) allows the patenting of "biological material" (i.e., "material containing genetic information and capable of reproducing itself or being reproduced in a biological system") only if it is "isolated or produced from its natural environment by means of a technical process" [32]. In the USA, mainly a 2013 decision of the US Supreme Court (regarding the case Association for Molecular Pathology v. Myriad Genetics) relating to isolated genomic DNA, and the interpretation of this decision by the US Patent and Trademark Office (USPTO) in particular, entailed that all "products of nature" are unpatentable. This is the case even when these are isolated and purified from nature [33]. It is very unlikely thereafter that naturally occurring phages as such (at least as individual phages) are patentable in the USA, regardless of how they have been isolated or purified.

Yet even in the USA – also after the Supreme Court's decision on the "Myriad case" in 2013 – various patents have been granted for mixtures of natural phages, as well as for preparations or treatments based on combinations of phages and antibiotics (Table 1). These mixtures or combinations have to show activity beyond that of the natural product, i.e. the individual phages [30]. Such patents have also been granted in Australia, Canada, China, Europe or Japan (Table 1). Though it remains to be seen how strong these patents can actually be, these cases indicate that patents for cocktails of natural phages or for natural phages combined with antibiotics can be obtained.

Table 1
Key subject matters and examples of patents granted related to phage therapy.

	International publication no.	Description	Assignee	Jurisdiction, grant date (year)
Compositions based on natural phages	WO2013164640	Design and composition of panels of bacteriophages for the prevention or treatment of bacterial infections	Armata Pharmaceuticals	CA 2013, 2020, 2023; AU, JP 2017; US 2018; EP 2019
	WO2015059298	Novel bacteriophages against *P. aeruginosa* strains, and their manufacture and formulation	Phaxiam (formerly Pherecydes Pharma)	AU 2018; US 2018, 2019; EP, 2020; JP 2020, 2023; CN 2022
	WO2019048930	Bacteriophage compositions and therapeutic uses thereof, including to modulate inflammatory bowel disease	Biomx Ltd, Yeda Res. and Dev. Co Ltd, Keio University	EP 2022
	WO2018106135	Bacteriophage compositions comprising respiratory antibacterial phages, used either alone or in further combination with antibiotics	Technophage SA	AU, EP, JP 2022; US 2023
GM phages (including nonreplicative phage particles)	WO2017174809	Generation of recombinant phages bearing hybrid host range determinant sequences, and sequences encoding proteins toxic to bacteria	Phico Therapeutics Ltd	US 2020; AU, JP 2022
	WO2014124226	Reducing the number of pathogenic bacteria in a mixed bacteria population, involving a carrier and CRISPR systems	Rockefeller University	US 2020, 2022
	WO2016177682	Methods, uses, engineered sequences and vectors (incl. phages) involving CRISPR systems to target specific bacteria in a mixed population	Snipr Technologies Ltd	US 2017, 2020, 2021, 2022, 2023; AU 2019, 2023; EP 2021
Novel processes or technologies	WO2017223101	Methods for, i.a., identifying bacterial strains from patients, isolating phages from the environment and generating phage libraries	US Department of Navy	US 2019
	WO2012057643	Method of producing and purifying phage preparations by affinity chromatography	Hirszfeld Institute of Immunology and Experimental Therapy	EP 2017; US 2018
	WO2008110840	Use of phages to induce sensitivity to antibiotics	Bio-Control Ltd/ Ampliphi Biosciences	AU, US 2013; EP, JP 2016; CA 2017

AU, Australia; CA, Canada; CN, China; EP, Europe (European Patent); JP, Japan; US, United States. Sources: Google Patents, Lens.org.

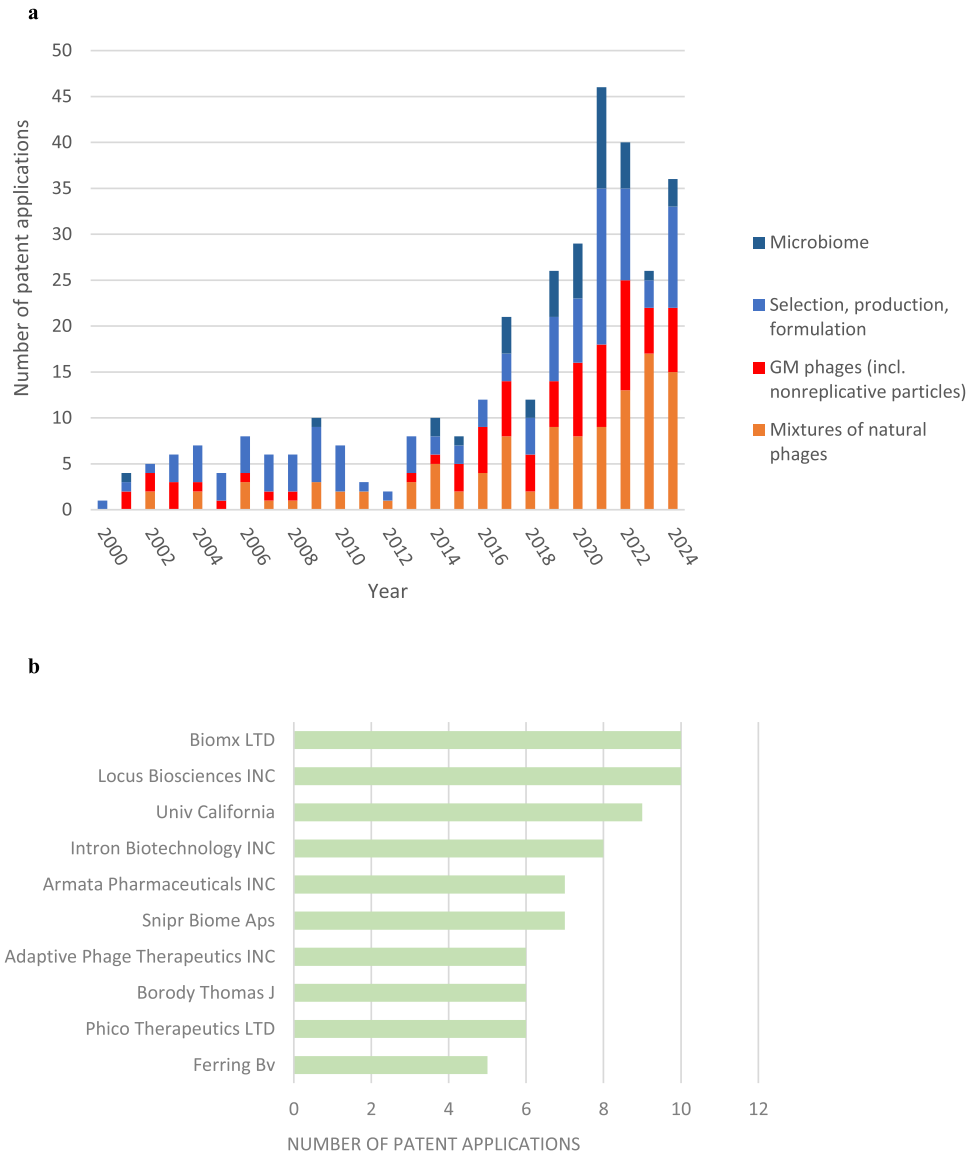

Fig. 2. A rise in patent applications related to phage therapy since the mid-2010s. a, Number of published transnational patent applications per year since the year 2000. Transnational patent applications [34] were identified in The Lens patent database (https://www.lens.org/). The Boolean search term "bacteriophage OR phage" was used to search applications' titles, abstracts and claims and narrowed down to class A61 (medicine or veterinary medicine; hygiene) of the Cooperative Patent Classification. All patent applications unrelated to human phage therapy (e.g., on phage display technology, phage-derived vectors for other therapies, veterinary use only) were manually eliminated (for the so curated list of patent applications, see Supplementary Data 2), and the remaining applications were analyzed for the indicated categories (see also text). b, Top-10 patent applicants

Genetically modified (GM) phages, on the other hand, are generally patentable, in both the EU and the USA (for examples, see Table 1) [30,31]. Furthermore, it is possible to patent new processes and technologies for phage therapy [30], including methods for the isolation, activity testing and purification of phages, or the generation of phage libraries (Table 1).

3. A recent rise in patent applications related to phage therapy

Despite the limitations and uncertainties related to patenting, particularly of natural phages, the number of transnational patent applications (i.e., patent applications for several countries) [34] related to phage therapy has increased substantially since the mid-2010s (Fig. 2a), with eight commercial biotech or biopharmaceutical companies among the top-10 applicants (Fig. 2b). About 33% of applications published since this time claim mixtures of natural phages, 32% techniques to select, manufacture or formulate phage compositions, and 23% GM phages or nonreplicative phage particles. Applications related to altering microbiome composition have grown to 12% (Fig. 2a).

The overall number of patent applications is still relatively small, though; e.g., when compared to corresponding figures for chimeric antigen receptor (CAR) T-cell cancer therapies (counting more than 3000 transnational applications until 2019) [35]. Similar to the most promising phage therapy approaches to combat important multidrug-resistant bacterial pathogens [6,7,16], these treatments are limited to rather small groups of patients (see below).

4. Young biotech companies strive for patents and drive new clinical trials

Since the early 2000s, various companies have emerged with the aim of developing phage therapies. Since then, a number of them have undergone mergers and acquisitions, and not all

have survived. These companies are mainly based in the EU (e.g., Eligo Bioscience, Phaxiam Therapeutics [formerly Pherecydes Pharma, announced judicial liquidation in June 2025], SNIPR Biome, TechnoPhage), Israel (BiomX), the UK (e.g., NexaBiome [formerly Fixed Phage], Phico Therapeutics [declared bankruptcy in May 2024]), and the USA (e.g., Adaptive Phage Therapeutics [acquired by BiomX in March 2024], Armata Pharmaceuticals, Locus Biosciences). In addition, there are several companies that aim to develop phages for different application areas, including human medicine (like Intralytix in the USA, iNtRON Biotechnology in South Korea, or Phagelux in China and the USA).

Of note, five of the eight companies among the top-10 patent applicants (Fig. 2b) are rather young biotech companies: Adaptive Phage Therapeutics (acquired by BiomX), Armata Pharmaceuticals, BiomX, Locus Biosciences, and SNIPR Biome. They have been founded or created by merger and acquisition since 2015 and are focusing on "off-the-shelf" and/or personalized phage therapies for indications like bloodstream infections/sepsis, cystic fibrosis-associated respiratory infections, diabetic foot ulcers/osteomyelitis, prosthetic joint infections, or urinary tract infections. Together with the marked increase in patent applications, these young companies' high patenting activity suggests that interest in the development of commercial phage therapy has grown dynamically in the last decade, with a number of new biotech companies striving for patents to attract investment and protect their future products.

Further support for the importance upcoming players in phage therapy ascribe to patent protection comes from a first patent dispute in the US between Rockefeller University (which licensed the invention to its spin-off Eligo Bioscience) and SNIPR Biome. The patents in question claim the invention of using CRISPR systems in "vectors" or "carriers," including phage particles, for targeting certain bacteria (see also Table 1). Since Rockefeller University filed its patent application prior to the enactment of the 2013 America Invents Act (AIA) that introduced the "first-to-file" patent regime, it sought to use a pre-AIA interference proceeding (based on the then "first-to-invent" system) to challenge the validity of SNIPR Biome's patents. As a result, the USPTO invalidated several of SNIPR's US patents in November 2021 [36]. This decision was reversed by the US Court of Appeals for the Federal Circuit in July 2023, concluding that the initially invalidated patents (filed in 2016) are post-AIA patents and therefore cannot be subject to such a proceeding [37].

In keeping with the crucial role attributed to patents because of the need to conduct and recoup R&D costs for expensive clinical trials [26], the five young companies among the top-10 patent applicants have raised together about $740 million in funding (https://www.crunchbase.com/) and have been sponsoring a substantial part of the recent clinical trials (see next section). Nevertheless, companies face a chicken and egg situation, which is perhaps exacerbated by the lack of precedents for successful, full-scale RCTs: Successful clinical trials and thus the prospect of marketing authorization are a prerequisite for (further) investments, which are essential for conducting and improving clinical trials.

5. The quest for clinical truth and marketing approval

New clinical trials (registered at ClinicalTrials.gov) have been initiated in particular since the year 2020 with a sharp rise in the number of trials in the years 2020 to 2022, mainly due to a strong increase in the number of industry-sponsored trials (Fig. 3). This "new wave" of phage therapy trials includes both approaches using predefined phage cocktails and personalized phage mixtures. Furthermore, apart from natural phages also genetically engineered phages and non-replicative phage particles with recombinant DNA constructs are investigated (see also refs. [38,39]). The vast majority of these new clinical trials are designed as RCTs (see list of all clinical trials analyzed in the Supplementary Data 1). About two-thirds of these recent trials have been sponsored by industry and more than half of all the recent trials (for which the study locations were specified) are taking place in the US (Fig. 3; Supplementary Data 1).

Notably, the five young biotech companies among the top-10 patent applicants (see above) are responsible for over half of all the industry-sponsored clinical trials since the year 2020, and for all but one of all trials sponsored by the top-10 patent applicants (Fig. 3; Supplementary Data 1).

6. Future prospects – why marketing approval and patent protection may not be enough

The few previous, unsuccessful RCTs certainly suffered from conceptual or practical issues, such as failing to examine the actual causes of infection and/or the phage susceptibility of the pathogens, or difficulties in phage cocktail stability [7,8]. Despite some recent promising early-phase trial results for predefined phage cocktails [39–41] and personalized phages [42], it remains to be seen whether some of the new trials can finally prove efficacy as well as safety for certain indications and patient groups. Genetic engineering approaches [6,43] may help address the previously noted challenges, such as narrow host range and resistance development. Furthermore, advances in artificial intelligence models to predict phage-bacteria interactions [44] and cell-free production systems that may eventually include chemically synthesized phage genomes (e.g., ref. [45,46]), could provide new prospects for the rapid and highly flexible production of high-quality, personalized therapeutic phages [17,44,47].

However, even if clinical trials should be successful, and not only fixed phage cocktails but also personalized phage products could obtain marketing authorization and be produced commercially, the success of such phage therapies might ultimately depend on how they will navigate current critical regulatory and economic challenges after they enter the market.

7. Postapproval regulatory hurdles and financial woes

Thus, fixed ("off-the-shelf") phage cocktails need regular updates with new or adapted phages to compensate changes in the occurrence of bacterial strains or for potential bacterial phage resistance [48,49]. However, major post-approval changes such as in active ingredients would require lengthy approval processes, if not new applications for marketing authorizations (e.g., in the EU) [50,51]. It remains an open question whether schemes to flexibly compose phage products from a selection of phages in the approved dossier, as enabled by the guideline on phage therapy in the new European regulation on veterinary medicinal products [52], can solve this issue. Similarly, as no phage therapy product has obtained marketing approval yet, it is impossible to tell whether or to which extent uncertainties regarding the strength of patents for products involving natural phages or the exclusivity provided by patents (possibly together with other means, like trade secrets [31]), may actually affect or assure profitability upon commercialization of possible phage therapeutics.

8. Can phages escape the profitability quandary of new antibiotics?

There are reasons to suggest that the commercial viability of any potential phage therapeutic would need regulatory exclusivity in addition to patents, as well as other financial incentive schemes, after it enters the market. These reasons mainly relate to two economic challenges. First, phage products for more common infections or indications, which can frequently be also treated with

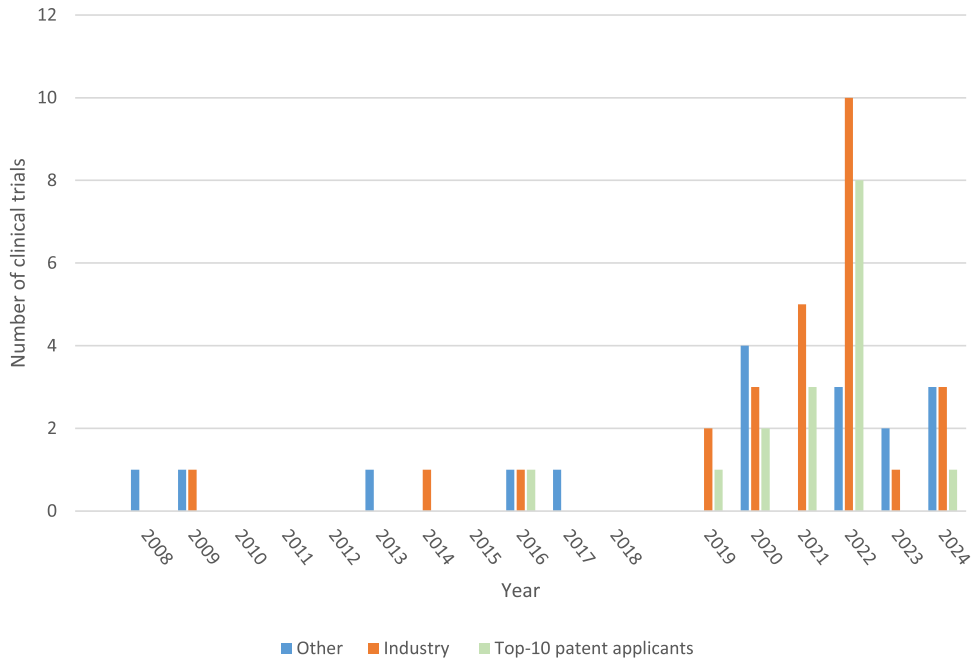

Fig. 3. The recent surge in clinical trials and their sponsorship. The ClinicalTrial.gov database (https://www.clinicaltrials.gov/) was searched by "bacteriophage OR phage" for "interventional studies (clinical trials)" registered until November 14, 2024. Search results were manually curated to remove studies unrelated to phage therapy (e.g., on diagnosis, immunization or phage-based vector constructs; the curated list of clinical trials is in the Supplementary Data 1) and analyzed for sponsorship by industry, other actors as well as sponsorship from the top-10 patent applicants (Fig. 2b).

existing antibiotics, would at least partially compete with relatively low-priced, often generic antibiotic drugs. Such competition is considered a major factor for the profitability issue of newly developed antibiotics [53,54]. Second, phage therapeutics that could have a particularly high or even unique benefit for patients and health systems by their ability to fight otherwise no longer treatable infections would be restricted to a rather limited number of cases. Even if such phage products might be used less restrictively than last-line antibiotics (as phages and phage mixtures can be adapted to emerging bacterial resistance [6,55]), such a broader use – i.e., beyond truly multidrug-resistant infections or cases of other difficult-to-treat infections for which all previous standard-of-care treatments (antibacterial, surgical, or both) were not successful – may then again face pricing pressure from inexpensive generic antibiotics.

Moreover, economies of scale and thus the cost at which GMP-grade phages can be offered, depend on the proportion of the phage batch that can actually be used for treatments [21]. Profitability could thus be even more problematic for phages that can be used less frequently, such as those to fight critical pathogens with high genetic diversity and narrow host-range phages (see above). These applications would mostly need personalized approaches [6,20], which are already subject to high costs linked to requirements for the testing of phage activity on patients' pathogen strains and would likely necessitate maintaining a diverse stock of GMP-grade phages.

9. In need of political investment

The need to recoup high costs through a low number of treatments is similar to the situation of orphan drugs for rare diseases, which in many countries or regions (e.g., Australia, China, EU, Japan, South Korea, USA) benefit from special incentives [56]. These frequently include tax credits for research expenses and/or prolonged market exclusivity [56,57]. Although first phage products under development have been granted orphan drug designation in the US [58–60], it is questionable whether orphan drug regulations or similar schemes will suffice to drive commercial development and enable the profitability of potential phage therapeutics for multidrug-resistant and other difficult-to-treat infections. This would likely require that these products achieve premium prices, similar to orphan cancer drugs or gene-based therapies. That seems most plausible for phage therapeutics against serious infections that can no longer be treated by most or all antibiotics. Based on experience with new antibiotics, it appears uncertain, however, whether antibacterial drugs – even when effective against critical multiresistant pathogens – could command premium prices and still be bought by a sufficiently large number of hospitals to be profitable. Various young companies that have developed such drugs went bankrupt or see their stock prices slide soon after the products entered the market [53,54,61].

Thus, additional solutions to provide financial incentives, that are ideally more specifically geared toward truly new kinds of antibacterials with a high or unique benefit for patients [62], will likely be needed to make phage therapies economically viable. Similar to, and potentially embeddable into, options discussed for novel antibiotics, such solutions may comprise separate payments for qualifying new antimicrobials in hospital reimbursement and advance procurement schemes that do not depend on the volume of sales [54,63]. Such schemes are, in particular, subscription-type models to pay upfront for access to certain antibiotic drugs, as tested in the UK or foreseen in the US PASTEUR Act [64,65]. Like for other new antibacterials, the combination of hospital reimbursement and advance procurement approaches will most likely be required [54] to ensure the economic viability of future phage medicines.

10. Conclusions

The severity of impacts that pandemics can have should offer a warning on the dangers of failing to make timely political investments in options that may help to combat the global spread of bacterial antimicrobial resistance. Current phage therapies lack marketing approval and are therefore relegated to regulatory ex-

emption schemes for the treatment of individual patients, and can be further limited by a shortage of suitable phages.

Available data on recent efforts suggests that major barriers to commercially producing therapeutic phages with marketing approval may be overcome. Thus, patent applications by companies focusing on phage therapy have soared and, in addition to patents on genetically modified phages, patents have also been obtained for cocktails of natural phages or for such phages combined with antibiotics. The latter could be especially important, since findings from case study series suggest that clinical success is considerably less probable without concomitant antibiotic use. Similarly, the number of successful clinical trials, which are the key prerequisite for marketing approval of phage therapeutics, has markedly increased, driven by a number of young biotech companies. This has led to promising initial results from RCTs using natural or genetically engineered phages.

However, we should not succumb to the false hope that once such phages or phage products have been shown to be safe and useful in clinical trials, they will become the long-awaited alternative or complement to antibiotics. In particular, future commercial phage therapeutics may face profitability issues similar to those of novel antibiotics - and their prospects may therefore depend on appropriate, much-needed policy solutions to these problems.

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Supplementary materials

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