VIRUS EVOLUTION

Virus Evolution, 2024, **10(1)**, 1–9
DOI: https://doi.org/10.1093/ve/veae007
Advance Access Publication 13 January 2024
Reflections

The untapped potential of phage model systems as therapeutic agents

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Abstract

With the emergence of widespread antibiotic resistance, phages are an appealing alternative to antibiotics in the fight against multidrug-resistant bacteria. Over the past few years, many phages have been isolated from various environments to treat bacterial pathogens. While isolating novel phages for treatment has had some success for compassionate use, developing novel phages into a general therapeutic will require considerable time and financial resource investments. These investments may be less significant for well-established phage model systems. The knowledge acquired from decades of research on their structure, life cycle, and evolution ensures safe application and efficient handling. However, one major downside of the established phage model systems is their inability to infect pathogenic bacteria. This problem is not insurmountable; phage host range can be extended through genetic engineering or evolution experiments. In the future, breeding model phages to infect pathogens could provide a new avenue to develop phage therapeutic agents.

Keywords: phage therapy; antibiotic resistance; phage model systems; experimental evolution; ΦX174.

Infections caused by multidrug-resistant bacterial strains are one of the most pressing issues in medicine, a situation that is only expected to worsen in the coming decades (WHO 2021; Murray et al. 2022). ESKAPEE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp., and *Escherichia coli*) are the principal targets for the development of novel antimicrobial strategies (Mulani et al. 2019). Among alternative treatment approaches currently under investigation (e.g. pre- and probiotics, antimicrobial peptides, antibodies, and oligonucleotides for silencing resistance genes), bacteriophages (phages) are one of the most promising alternatives to treat bacterial infections (Rios et al. 2016; Ghosh et al. 2019; Łojewska and Sakowicz 2021; Streicher 2021). Treating bacterial infections with phages is also called phage therapy.

Especially in the past two decades, phage therapy has increasingly been used to treat bacterial infections in humans and animals (Adhya et al. 2005; Maimaiti et al. 2023). Two distinct strategies are commonly followed in phage therapy: a broad and a targeted approach (Gordillo Altamirano and Barr 2019; Froissart and Brives 2021). The broad approach involves assembling a predetermined phage cocktail composed of genetically diverse phages (∼10–40) with a wide host spectrum, emulating the antibiotics' much broader killing spectrum (Villarroel et al. 2017; McCallin et al. 2018). The targeted approach relies on the use of phages that can specifically infect the bacterial pathogen. These phages are often identified among collections of pre-characterised phages or can be freshly isolated from environmental sources. Phages that demonstrate the best efficiency at infecting and killing the targeting bacterium are administered to the patient (Zhvania et al. 2017; Chan et al. 2018; Ferry et al. 2018; Cano et al. 2020; Dedrick et al. 2021, 2023).

A generic phage cocktail with a broad host spectrum is part of a traditional over-the-counter medicine used in Georgia, Poland, and Russia (McCallin et al. 2018; Międzybrodzki et al. 2018). Vials containing different phage cocktails are sold without a prescription to patients seeking treatment for proinflammatory or enteric diseases (Kutter et al. 2010). The European Union (EU) and United States of America (USA), however, have preferentially developed personalised-medicine approaches that specifically target the pathogen responsible for the bacterial infection (Froissart and Brives 2021). Nonetheless, phage therapy is currently considered highly experimental and can only be used in rare cases as a last resort or compassionate treatment (EMA 2018a; McCallin et al. 2019; FDA 2022; Hitchcock et al. 2023). Compassionate use, also called expanded access, is a treatment option that allows the use of an unauthorised medical product outside clinical trials for the treatment of a patient with a serious or immediately life-threatening disease for which all alternative therapeutic options have been exhausted (EMA 2018a; FDA 2022).

Advantages and disadvantages of newly isolated phages

Eligible phages for compassionate use come mostly from recent environmental samples. Since the environment is the predominant source of all types of phages, it offers an undeniable advantage to find phages 'on-demand' with desired traits for therapeutic purposes (Weber-Dąbrowska et al. 2016; Schooley et al. 2017; Zhvania et al. 2017; Chan et al. 2018; Ferry et al. 2018). Sewage from the immediate vicinity of hospitals is almost guaranteed to contain phages active against human pathogens (Latz et al. 2016). These phages can be easily detected and isolated from environmental samples (Clokie and Kropinski 2009; Ács, Gambino, and Brøndsted 2020), and there is evidence of their efficacy from case studies (McCallin et al. 2019; Abedon, Danis-Wlodarczyk, and Alves 2021). However, isolating phages and generating high-density virus stocks against two of the ESKAPEE species, *E. faecium* and *faecalis* and *S. aureus* strains, have been challenging despite the enormous variety of phages present in environmental reservoirs (Mattila, Ruotsalainen, and Jalasvuori 2015).

The characterisation of new phages from the environment is time-consuming, mainly because of safety and efficacy assessments. Before being considered for clinical applications, a phage's critical quality attributes (CQAs) must be fully known (Yu et al. 2014; Pirnay et al. 2015; Mutti and Corsini 2019). These include its identity (origin, family and subfamily, morphology, and biology), the presence or absence of potentially damaging genetic determinants (conferring toxicity, virulence, lysogeny, or antibiotic resistance), the phage's *in vivo* efficacy (host range, stability of lysis, efficiency of plating, and frequency of emergence of phage-resistant bacteria), the potential optimisation of its host range (titration), and its storage conditions (temperature and cryopreservation). Because health agencies require phages to be fully characterised (CQAs) and produced for clinical trials under good manufacturing practices (GMPs), there is currently no broadly available phage treatment in Western countries (Rohde et al. 2018).

GMPs represent the quality, safety, and traceability standards a medicinal product or drug must meet before being authorised for clinical trials and markets (EMA 2018b; Bretaudeau et al. 2020). Phages are categorised as such in the EU and the USA. One exception is Belgium, where phages are produced following a standardised recipe called a monograph (Pirnay et al. 2018). However, the standardisation of phage production requires considerable investment of time and money (Bretaudeau et al. 2020), is difficult to adhere to because of high phage mutation rates (Pirnay et al. 2018), and might be technologically impossible if phages have to be trained to enhance their lytic ability or when phage cocktails are needed to make the treatment resilient against evolution of phage resistances (Yang et al. 2020; Borin et al. 2021; Science, Innovation, and Technology Committee 2023).

Phage model systems can become promising therapeutic agents

Alongside the use of newly discovered phages for therapy, well-studied phage model systems should also be considered. Model phages such as Dp-1, T4, T7, MS2, or ΦX174 have significant benefits over newly isolated phages.

The main difference between newly isolated phages and model phages is the knowledge available on their biology. The deep knowledge accumulated for model phages should make them predictable and safe therapeutic agents (Bruttin and Brüssow 2005; Wichman, Millstein, and Bull 2005; Bull and Molineux 2008; Budynek et al. 2010; Wichman and Brown 2010; Azam and Tanji 2019). Model phages are easily obtainable, manipulatable, trackable, and producible at high concentrations (Skaradzińska et al. 2020).

Although model phages have not been used in phage therapy yet, they have been used for different clinical applications. For example, model phages have been used as gene delivery vehicles for *in vivo* treatments (Ghaemi et al. 2010; Bakhshinejad and Sadeghizadeh 2014; Fu and Li 2016; Hosseinidoust 2017). The deliveries range from biofilm-degrading enzymes (Lu and Collins 2007) to *in situ* Clustered Regularly Interspaced Short Palindromic Repeats-Cas chromosomal targeted systems (Dong et al. 2021; Huan et al. 2023). These delivery systems have been used for gene therapy and to treat tumours (Ghaemi et al. 2010; Rao and Zhu 2022; Zhu et al. 2023).

While phage vectors could also be created to release antimicrobial compounds *in situ* to treat pathogenic bacterial strains (Du et al. 2023), the possibility of directly turning model phages into the primary therapeutic agent has, to our knowledge, not been investigated (Gildea et al. 2022). Probably because model phages only infect harmless relatives of dangerous pathogenic strains such as *E. coli*, *Salmonella*, and *Streptococcus* species.

First steps towards extending the host range of model species have been done in the past. For example, Phage T2 has been engineered to infect pathogenic *E. coli* O157:H7 by exchanging phage coat proteins g37 and g38 with those of a newly isolated phage PP01 (Yoichi et al. 2005). In the model Phage T3, host range mutants have been constructed through site-directed mutagenesis that reduced the evolution of phage resistance (Yehl et al. 2019). In microviruses, exchanging coat proteins through genetic engineering successfully extended the host range of Phages ST-1 and α3 (Roznowski et al. 2019).

Genetic engineering has been shown to successfully extend host ranges of model and non-model phages. However, extending the host range via genetic engineering usually involves the transmission of the coat protein of a phage that can infect a target bacterium to another phage of interest (Yoichi et al. 2005; Roznowski et al. 2019). In the absence of phages that can infect a bacterium of interest, evolution experiments are an efficient approach to extend host ranges. Model phages, in particular, could be bred to extend their host range to directly infect pathogenic strains belonging to *E. coli*, *Salmonella*, and *Streptococcus* species and reduce the evolution of phage resistance (Bull et al. 2003; Meyer et al. 2012; Borin et al. 2021; Romeyer Dherbey et al. 2023). In our opinion, ΦX174 is a particularly interesting model system. We will highlight specific advantages and features of this phage model in the following paragraphs.

ΦX174 may be a suitable candidate for phage therapy

ΦX174 is one of the oldest phage model systems (Sertic and Bulgakov 1935; Wichman and Brown 2010; Lacković and Toljan 2020) that has been used for almost 90 years to study phage, molecular, synthetic, and evolutionary biology (Sanger et al. 1978; Smith et al. 2003; Jaschke et al. 2012; Mukherjee et al. 2015; Breitbart and Fane 2021). ΦX174 is a small (~30 nm) tailless coliphage belonging to the *Microviridae* family. It carries a 5,386 nucleotide long single-stranded DNA (ssDNA) genome that contains only eleven genes (Sinsheimer 1959; Sanger et al. 1978). ΦX174 is a virulent phage that relies on attaching to the core oligosaccharide of the host's lipopolysaccharide (LPS) for infection. In the laboratory, ΦX174 infects—and hence is usually grown on—*E. coli* C, which

produces rough type (i.e. lacking the O-antigen) LPS molecules (Feige and Stirm 1976).

The knowledge accumulated on ΦX174 may also be useful to turn ΦX174 into a therapeutic agent. ΦX174 can easily be fully synthesised (Smith et al. 2003) and manipulated in the laboratory (Christakos et al. 2016), making genetic engineering extremely easy. The effect of a large number of mutations and the function of protein domains in the viral life cycle have been studied extensively (Breitbart and Fane 2021). Deep knowledge on the effect of individual mutations may be useful because it could help identify the cause for viral evolution during therapy. Insight into causes for viral evolution will help understand why clinical trials fail to be sufficiently efficacious, the main cause for clinical trial failure at the moment (Hitchcock et al. 2023). Identifying and understanding the cause for treatment failure will make it easier to design efficacious therapeutic agents.

Therapeutic agents have to be both efficacious and safe. Phages are generally considered safe for human application (Liu et al. 2021). Similarly, ΦX174 should be a very safe therapeutic agent. ΦX174 is highly host specific. In a study of 783 different *E. coli* isolates, only six (0.8 per cent) isolates could be infected by ΦX174 (Michel et al. 2010). This high degree of specificity means that ΦX174, like other phages, will likely be harmless to the patient's microbiota in contrast to antibiotics (Denou et al. 2009; Galtier et al. 2016; Ramirez et al. 2020; Mu et al. 2021). Moreover, relatives of ΦX174, the *Microviridae* phages, can be isolated from gut samples and are considered part of the healthy human gut microbiome (Lim et al. 2015; Manrique et al. 2016; Shkoporov et al. 2019; Sausset et al. 2020). As such, *Microviridae* phages from the gut are probably tolerated by the human immune system and will be less prone to be recognised and degraded prior to successful infection (Hodyra-Stefaniak et al. 2015; Bull, Levin, and Molineux 2019). Evidence for the tolerance of ΦX174 by the immune system without excessive inflammatory response comes from *in vivo* experiments. For those experiments, high doses of ΦX174 were given to patients intravenously to measure differences between healthy individuals and patients with compromised immunity (Ochs, Davis, and Wedgwood 1971; Fogelman et al. 2000). ΦX174 has even been approved for human applications by the U.S. Food and Drug Administration as a marker of patients' immune responses (Rubinstein et al. 2000; Bearden et al. 2005). While treatment safety is not a major concern for compassionate use cases and phage treatment is generally considered safe, rare side effects could become more of an issue when phages are applied to large parts of the population and over long periods of time.

While ΦX174's high host specificity reduces potential side effects, it also severely limits ΦX174's application. However, ΦX174's limited ability to infect a host can potentially be remedied through evolution experiments. If ΦX174 can infect a host, then it is almost guaranteed to be able to kill it. ΦX174 expresses the E protein to lyse and kill the host by disrupting peptidoglycan synthesis (Orta et al. 2023). Peptidoglycan synthesis is disrupted through binding of the E protein to a very conserved and essential protein called MraY (Bernhardt, Roof, and Young 2000). In biotechnology, the expression of the E protein is used to make 'ghost cells' (empty bacterial cell envelopes) for vaccine production. This process works for a wide range of Gram-negative bacterial pathogens (e.g. *Salmonella enteritidis, Vibrio cholera*, and *Helicobacter pylori*) (Huter et al. 1999; Mayr et al. 2005; Ganeshpurkar et al. 2014). Hence, ΦX174 is predicted to be able to lyse any Gram-negative pathogen as long as it can recognise the host's LPS molecules.

Before a phage infects and kills a host bacterium, it needs to reach it. The smaller the phage, the easier it is for it to diffuse through the medium and reach the target bacterium. ΦX174 is extremely small, and its genome contains only eleven genes. The small size of ΦX174 (100 times smaller than T4, ∼2 million daltons vs 192 million daltons) allows for extremely fast diffusion through media (almost 10 times faster than T4) (Dubin et al. 1970; Bayer and DeBlois 1974). The small genome of ΦX174 also makes it one of the fastest growing phages, producing about 200 offspring per infected cell within 20 min (T4 produces about 80 progeny in 1 h) (Hutchison and Sinsheimer 1966; Eshelman et al. 2010). Both small size and fast replication probably make microviruses one of the most widespread and abundant phage families (Kirchberger and Ochman 2023).

Despite their abundance, no microviruses have so far been considered as the therapeutic agent (Kirchberger, Martinez, and Ochman 2022). One reason for the lack of consideration may be the lack of awareness of their biological importance. Biased isolation and sequencing methods, which failed to identify small ssDNA phages, have wrongly concluded that microviruses are almost non-existent in nature (Kirchberger and Ochman 2023). In contrast, recent research highlights their diversity and abundance in microbiomes (Creasy et al. 2018; Tisza et al. 2020; Zuo et al. 2020).

Current limitations of ΦX174

The most significant limitation to the current potential of model phages is their host specificity. ΦX174, in particular, is highly host specific (Michel et al. 2010). While this limits possible side effects, no study has yet demonstrated that ΦX174 can infect pathogens. To treat enterobacterial pathogens, novel ΦX174 strains must first be evolved. In previous experiments, we showed that ΦX174 can quickly evolve to infect spontaneously resistant *E. coli* C mutants (Romeyer Dherbey et al. 2023). Whether it is as easy to evolve ΦX174 to infect pathogenic strains remains to be tested.

While its small genome renders ΦX174 extremely tractable for genetic manipulation and analysis, as well as making it extremely unlikely to transport cargo genes, it also means that there is very limited space to easily add useful genes to the genome (Russell and Müller 1984; Aoyama and Hayashi 1985). Phage model systems with bigger genomes can more easily accommodate additional genes.

As with antibiotics, ΦX174 (and most other phages) can infect growing bacteria (Romeyer Dherbey et al. 2023) but cannot infect bacteria in stationary phase or dormancy (Bläsi, Henrich, and Lubitz 1985). Hence, ΦX174 may be more suited to treating acute rather than persistent infections. There are phage model systems that can infect bacteria in stationary phase that, in some situations, may be more appropriate therapeutic agents (Bryan et al. 2016; Tabib-Salazar et al. 2018; Kaldalu et al. 2020; La Rosa et al. 2021; Maffei et al. 2022).

For pathogens other than *E. coli* or *Salmonella*, ΦX174 may also not be the ideal model system. Beyond enterobacterial infections, novel phage model systems need to be established to treat other members of the ESKAPEE group, especially for *A. baumannii*, *E. faecium*, and *S. aureus* (Mattila, Ruotsalainen, and Jalasvuori 2015).

Evolving phages to infect bacterial pathogens

To develop ΦX174 (and other model phages) into a therapeutic agent that infects pathogens, existing experimental evolution

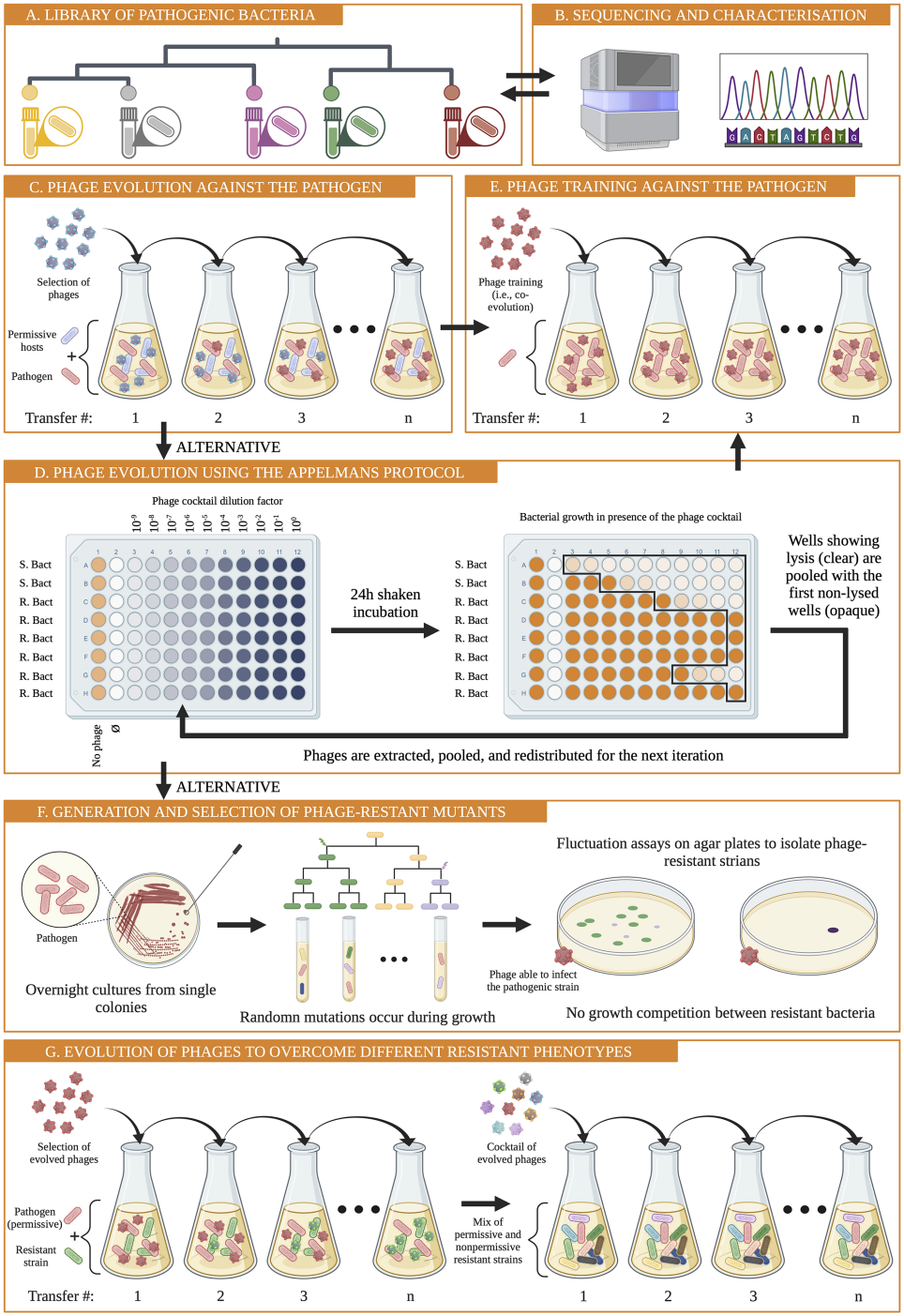

Figure 1. The proposed procedure to develop a phage model system into a therapeutic agent. (A) and (B) Bacterial pathogens are first sequenced and characterised. Phylogenetic trees can help to identify bacterial strains closely related to the target pathogen. Model phages are then adapted to the bacterial pathogens as well as closely related strains *in vitro*. (C) A selection of phages is pooled and serially transferred daily on a host culture containing a mixture of susceptible strains and the pathogenic strain of interest. Transfers continue until a phage is found to infect the pathogenic strain (Bono et al. 2013; Romeyer Dherbey et al. 2023). (D) Phage host range can also be increased using the Appelmans protocol. A selection of phages is pooled and iteratively grown on permissive and non-permissive bacterial strains. To maintain phage diversity from one iteration to another, the first rows contain permissive strains, followed by resistant pathogenic strains. Adapted from Burrowes, Molineux, and Fralick (2019). (E) Phages capable of infecting the pathogenic strains can be further trained to enhance their lytic ability against the pathogen, for example, by phage training in a coevolution experiment (Borin et al. 2021) or through a more targeted approach (F and G) (Romeyer Dherbey et al. 2023). (F) Emergence of phage resistance can be reduced by evolving a range of phage mutants that can infect spontaneously resistant bacteria. Spontaneous phage-resistant mutants can be generated on agar plates using a fluctuation assay (Luria and Delbrück 1943). (G) Left panel: similar to panel (C), phage strains are evolved to infect different phage-resistant variants without coevolution of the bacteria (Romeyer Dherbey et al. 2023). Right panel: for resistant strains that are difficult to infect, additional evolution experiments using a cocktail of phages adapted to easier resistant phenotypes (resistant phenotypes that phages evolved to infect quickly) may speed up evolution via recombination. Host diversity can help maintain phage diversity in the experiment (Romeyer Dherbey et al. 2023).

protocols can be adapted (Bono et al. 2013; Burrowes, Molineux, and Fralick 2019; Kok et al. 2023; Romeyer Dherbey et al. 2023) (Fig. 1). Firstly, the bacterial pathogen and several closely related strains need to be isolated and characterised (Fig. 1A and B). Then, a phage strain with the capacity to infect the pathogenic strain is evolved by serially transferring candidate phages in a mixture consisting of permissive hosts (necessary to propagate the phage) and the targeted pathogenic strain (Fig. 1C). Evolving phage populations are inoculated into fresh, exponentially growing host cultures at each transfer until one or more phages are found to infect the pathogenic strain.

Alternatively, the host range of model phages can be extended using the Appelmans protocol (Burrowes, Molineux, and Fralick 2019). This experimental evolution protocol is highly effective at increasing phage host ranges by maximising the recombination opportunities between phage strains (Fig. 1D). It has also been used to enhance the infectivity of phages, thus making phages more effective therapeutic agents (Kok et al. 2023).

A successful therapeutic agent also needs to minimise the chance of phage resistance evolution. Phage resistance evolution can be minimised by combining phages with antibiotics or by combining different phages in cocktails. A phage cocktail aims to eliminate common bacterial resistance types and drive evolution toward bacterial mutants that are less fit and easier to eradicate (Yethon et al. 2000; Matsuura 2013; Pagnout et al. 2019; Simpson and Trent 2019; Burmeister et al. 2020; Mutalik et al. 2020). The immune system and/or specific antibiotics could then kill the remaining mutants (Roach et al. 2017; Burmeister et al. 2020; Mangalea, Duerkop, and Ottemann 2020). Phage resistance evolution can also be lowered by subinhibitory levels of antibiotics. In this case, the antibiotics prevent the emergence of a specific set of bacterial mutants (Parab et al. 2023).

Phage cocktails can consist of distantly related phages or of phages that are derived from a recent common ancestor. These recently diverged phages can be evolved through coevolution experiments, also called phage training (Borin et al. 2021) (Fig. 1E). Coevolution means that both phages and bacteria evolve at the same time and place. When cultures are transferred into fresh media, both evolved phages and evolved bacteria are transferred together. An alternative evolution experiment applies a more targeted approach, where bacteria and phages evolve sequentially. In the sequential evolution approach, phage-resistant mutants are first generated in fluctuation experiments (Luria and Delbrück 1943; Burmeister et al. 2020; Romeyer Dherbey et al. 2023) (Fig. 1F). New phage strains are then evolved to infect each resistant mutant (Fig. 1G). Finally, a selection of the evolved phages can be combined to create an effective phage cocktail (Yehl et al. 2019; Yang et al. 2020; Nale et al. 2021). Phages in these cocktails cannot only infect a diverse set of resistant bacterial strains but also recombine both *in vitro* and *in vivo* to generate phages that can infect bacteria with novel resistance phenotypes (De Sordi, Khanna, and Debarbieux 2017; Burrowes, Molineux, and Fralick 2019; Borin et al. 2021; Srikant, Guegler, and Laub 2022; Romeyer Dherbey et al. 2023).

The sequential evolution approach is likely more laborious than the coevolutionary approach since the bacterium can become phage resistant through many different pathways. However, knowledge about the identity and order of mutations makes it easier to understand how phage resistance works and how phages can overcome different types of resistance. A deeper understanding of phage resistance mechanisms will also make the application of synthetic approaches more effective.

The ability of phages to infect a host is critically dependent on the environment (Kim and Kathariou 2009; Koskella and Brockhurst 2014; Hernandez and Koskella 2019). Hence, once model phages have been evolved to infect pathogens *in vitro*, they may also have to be tested and potentially adapted to *in vivo* conditions before they can be used as therapeutic agents (De Sordi, Lourenço, and Debarbieux 2018; Hernandez and Koskella 2019; Hsu et al. 2019; Castledine et al. 2022). For example, bacteria susceptible to phages in solid media may be resistant to phage infection in liquid media (Romeyer Dherbey 2023). Again, experimental evolution may be the perfect tool to either adapt phages to the host environment or evolve phages that are robust to environmental change.

Raising phage therapy awareness with established phage model systems

Phage therapy has the potential to significantly improve treatment outcomes. However, one crucial aspect that hinges on its success is often overlooked: the perception of the general public. To engage people with phage therapy, we must ensure effective communication about phage research, its current limitations, and, most importantly, its potential to save lives (Gordillo Altamirano and Barr 2019; Ji and Cheng 2021; Niang et al. 2021).

Medical innovations are often met with great scepticism, especially by the general public (Johnson et al. 2020; Barrett et al. 2022). For example, the acceptance of the new messenger RNA Coronavirus Disease (COVID)-19 vaccine has been hampered by the spread of misleading or false information (Hussain et al. 2018; Burki 2020; Longhi 2022). As phages are also viruses, their acceptance and the willingness of people to rely on them as therapeutic agents could be impeded in similar ways. Moreover, phage therapy has already had to overcome the poor reputation obtained through its association with Axis powers during the Second World War and Cold War (Summers 2012). To prevent history from repeating itself, the narrative around phage therapy and its anthropological impact on modern society should be taken into consideration by scientists (biologists, anthropologists of sciences, and sociologists), media, and politics.

Fortunately, we still have time to effectively and transparently communicate about the advantages and limitations of phage therapy. Phage model systems represent a convenient tool for this endeavour as we can capitalise on our profound insight into their biology and evolution (Luciano, Young, and Patterson 2002; Hanauer et al. 2017). The knowledge acquired about model phage systems over the last 100 years will facilitate the communication of complex concepts about phages to the general public. For example, Phage T4 is already used in television reports and science cartoons (Kurzgesagt 2018) as the 'default phage', thanks to its striking morphology. Similarly, other phage model systems could be exploited to communicate information on phage biology and phage therapy. Finally, integrating phage biology and phage hunt classes (i.e. phage discovery programmes) may be a good way to construct collective knowledge and disseminate accurate information about phages (Elbers and Streefland 2000; Staub et al. 2016; Hanauer et al. 2017).

Conclusion

Established phage model systems are far from old fashioned. In addition to the purely economical, biological, and medicinal advantages, they may provide non-negligible sociological benefits.

These advantages could be decisive in establishing phage therapy as a common, safe, and inexpensive medical practice in the West once the technology is readily available. Extensive research, however, has first to be conducted to demonstrate the efficacy of phage model systems to treat infection caused by pathogenic bacteria. Hence, in parallel with the ongoing search for novel environmental phages, we advocate investing resources into developing phage model systems for phage therapies.

Acknowlegments

We would like to thank Dr Jeremy Barr for his insights on the field of phage therapy and Dr Jenna Gallie for her suggestions on the manuscript. We also thank the two anonymous reviewers for their comments on the manuscript.

Funding

The authors acknowledge generous funding from the Max Planck Society.

Conflict of interest: The authors declare no competing interests.

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Virus Evolution, 2024, **10(1)**, 1–9
DOI: https://doi.org/10.1093/ve/veae007
Advance Access Publication 13 January 2024
Reflections