Reflection article

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. The only current downside of established model systems is their inability to infect pathogenic bacteria. However, evolutionary experiments have shown that it is possible to extend the host range of phages to infect previously resistant bacteria. The same experiments could be used in the future to breed model phages to infect pathogens and hence could provide a new avenue to develop phage therapeutic agents.

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, 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).

The rise and fall of phages as therapeutic agents

Independently discovered by Frederick Twort in 1915 (Twort 1915) and Félix d'Hérelle in 1917 (d'Hérelle 1917), bacteriophages (translating to "bacteria-eater") are viruses that prey upon bacteria. Phages are simple entities. Their genomes, either RNA or DNA, single- or double-stranded, are protected by capsids that can take various shapes and sizes (Ackermann 2007). They are the most numerous biological entities on Earth (Brüssow and Hendrix 2002; Angly et al. 2009) and are ubiquitous in every natural, human-altered, and artificial biome (*e.g.,* wastewater treatment reservoirs, industries) (Batinovic et al. 2019).

In the early 1900s, phages had already been considered as treatments for bacterial infections in animals and humans (d'Hérelle 1918; d'Hérelle 1919; d'Hérelle 1925). However, the lack of understanding of phage biology divided the scientific community and slowly undermined clinical applications. On one side of the debate, Felix d'Hérelle recognised phages as viruses and their antimicrobial action *in vitro* and *in vivo*. On the other side, Jules Bordet (Nobelist and director of the Pasteur Institute in Brussels at the time) contested Felix d'Hérelle's work, attributing the observed bacterial lysis to the action of a "self-perpetuating lytic enzyme" (Summers 2012; Summers 2017). Furthermore, phages lacked standardised production and controls, and their host spectra were considered too narrow to effectively treat bacterial infections (Summers 2012). The association of phage therapy with German and Japanese medicine during the Second World War and with communism post-war put an end to any further applications in the West (Summers 2012). Phages were ultimately rejected in favour of newly discovered antibiotics (Nicolaou and Rigol 2018).

Phage comeback: an old solution for a modern problem

The overuse and misuse of antibiotics have slowly driven the emergence and spread of multidrug-resistant bacteria, creating an urgent need for alternative or complementary solutions to classic antibiotic treatments. One of these solutions is phage therapy. Phage therapy is the administration of one or more virulent (strictly lytic) phages to a patient suffering from a bacterial infection. Eastern countries such as Poland, Georgia, and Russia never ceased to use phage therapy (Villarroel et al. 2017; Międzybrodzki et al. 2018). In Western countries, however, phage therapy experienced a renaissance only relatively recently between the 1980s and 2000s (Carlton 1999; Summers 2001; Wittebole et al. 2014; Barron 2022) through the re-discovery of phage antimicrobial effectiveness in mice and farm animals (Smith and Huggins 1982; Smith and Huggins 1983; Barrow and Soothill 1997). Especially in the past two decades, phage therapy has garnered more and more attention, with recent studies focusing on phages to treat foodborne pathogens and 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 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). In the targeted approach, phages are isolated from environments where bacteria are abundant (e.g., sewage or wastewater treatment plants) and tested against the target bacterium. Phages that successfully lyse the target bacterium are purified and administered to the patient (Zhvania et al. 2017; Chan et al. 2018; Ferry et al. 2018; Cano et al. 2020; Dedrick et al. 2021; Dedrick et al. 2023).

A generic phage cocktail with a broad host spectrum is part of traditional over-the-counter medicine used in Georgia, Poland and Russia. Vials containing different phage cocktails are sold without a prescription to patients seeking treatment for proinflammatory or enteric diseases (Kutter et al. 2010). The EU and 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 environmental phages

Eligible phages for compassionate use primarily come from 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 et al. 2020), and their clinical efficacy has been successfully demonstrated in many case studies (McCallin et al. 2019; Abedon et al. 2021). However, isolating phages and generating high-density virus stocks against *Enterococcus faecium* and *faecalis* or *Staphylococcus aureus* strains have been challenging despite the enormous variety of phages present in environmental reservoirs (Mattila et al. 2015).

However, the characterisation of new phages from the environment is time-consuming, mainly because of safety assessments. Even if rare, some phages can carry genes encoding dangerous toxins and other metabolites that could be harmful if they were to be expressed (Krüger and Lucchesi 2015; Jamet et al. 2017; Dragoš et al. 2021). Moreover, phages can also spread antibiotic-resistance genes *via* transduction (Colavecchio et al. 2017).

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, frequency of emergence of phage-resistant bacteria), the potential optimisation of its host range (titration), and its storage conditions (temperature, 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).

Good Manufacturing Practices 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 environmental 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 uncharacterized environmental phage isolates.

Model phages are easily obtainable, manipulatable, trackable, and producible at high concentrations (Skaradzińska et al. 2020). The deep knowledge of these model systems acquired over the last ~ 100 years makes them relatively predictable and safe therapeutic agents (Bruttin and Brüssow 2005; Wichman et al. 2005; Bull and Molineux 2008; Budynek et al. 2010; Wichman and Brown 2010; Azam and Tanji 2019).

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). Phages are engineered to deliver a large variety of molecules, ranging from degrading-biofilm enzymes (Lu and Collins 2007) to *in situ* CRISPR-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 agents has, to our knowledge, not been investigated (Gildea et al. 2022). Model phages prey on *E. coli*, *Salmonella*, and *Streptococcus* species. While some of the most notorious pathogens belong to these species, model phages only infect harmless relatives of dangerous pathogenic strains. However, we believe that current model phages could potentially be bred to (*i*) extend their host range to directly infect pathogenic strains belonging to *E. coli*, *Salmonella*, and

Streptococcus species and (*ii*) reduce the evolution of phage resistance through evolution experiments (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 ssDNA genome that contains only 11 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 in O-antigen) LPS molecules (Feige and Stirm 1976).

The biology of ΦX174 is extremely well known. ΦX174 can easily be fully synthesised (Smith et al. 2003) and manipulated in the laboratory (Christakos et al. 2016) and is highly host-specific. In a study of 783 different *E. coli* isolates, only six (0.8 %) 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).

Apart from its high host specificity, there are other reasons for why ΦX174 treatment likely causes little side effects. 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 et al. 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 et al. 1971; Fogelman et al. 2000). ΦX174 has even been approved for human

applications by the U.S. Food and Drug Administration (FDA) as a marker of patients' immune responses (Rubinstein et al. 2000; Bearden et al. 2005).

Another characteristic that makes ΦX174 a potentially safe therapeutic is the fact that it carries a very small genome that contains only 11 genes. The function of every single gene is known and has been studied (Sun et al. 2017; Logel and Jaschke 2020; Breitbart and Fane 2021). It does not carry virulence genes and cannot pick up cargo genes since additional genes do not fit into the very small capsid (Russell and Müller 1984; Aoyama and Hayashi 1985).

Despite ΦX174's high host specificity, the mechanism by which ΦX174 lyses and kills the host is extremely conserved and can kill a wide range of bacteria. 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 to a very conserved and essential protein called MraY (Bernhardt et al. 2000). In biotechnology, the expression of only 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*, *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 enter the cell.

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 (such as effector genes (Du et al. 2023)) 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 et al. 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 *Acinetobacter baumannii*, *Enterococcus faecium*, and *Staphylococcus aureus* (Mattila et al. 2015).

Evolving phages to infect bacterial pathogens

To develop ΦX174 (and other model phages) into a therapeutic agent to infect pathogens, existing experimental evolution protocols can be adapted (Bono et al. 2013; Burrowes et al. 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 **1B**). 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 et al. 2019). This experimental evolution protocol is highly effective at increasing phage host ranges by maximizing 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 minimize the chance of phage resistance evolution. Phage resistance evolution can be minimized by phage 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 and Duerkop 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).

The evolution of phage resistance can also be reduced through co-evolution experiments called phage training (Borin et al. 2021) (**Fig. 1E**). Instead of co-evolutionary phage training, a targeted approach can also be applied. For this purpose, 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 can then be 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 et al. 2017; Burrowes et al. 2019; Borin et al. 2021; Srikant et al. 2022; Romeyer Dherbey et al. 2023). This approach is likely more laborious than the co-evolutionary 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.

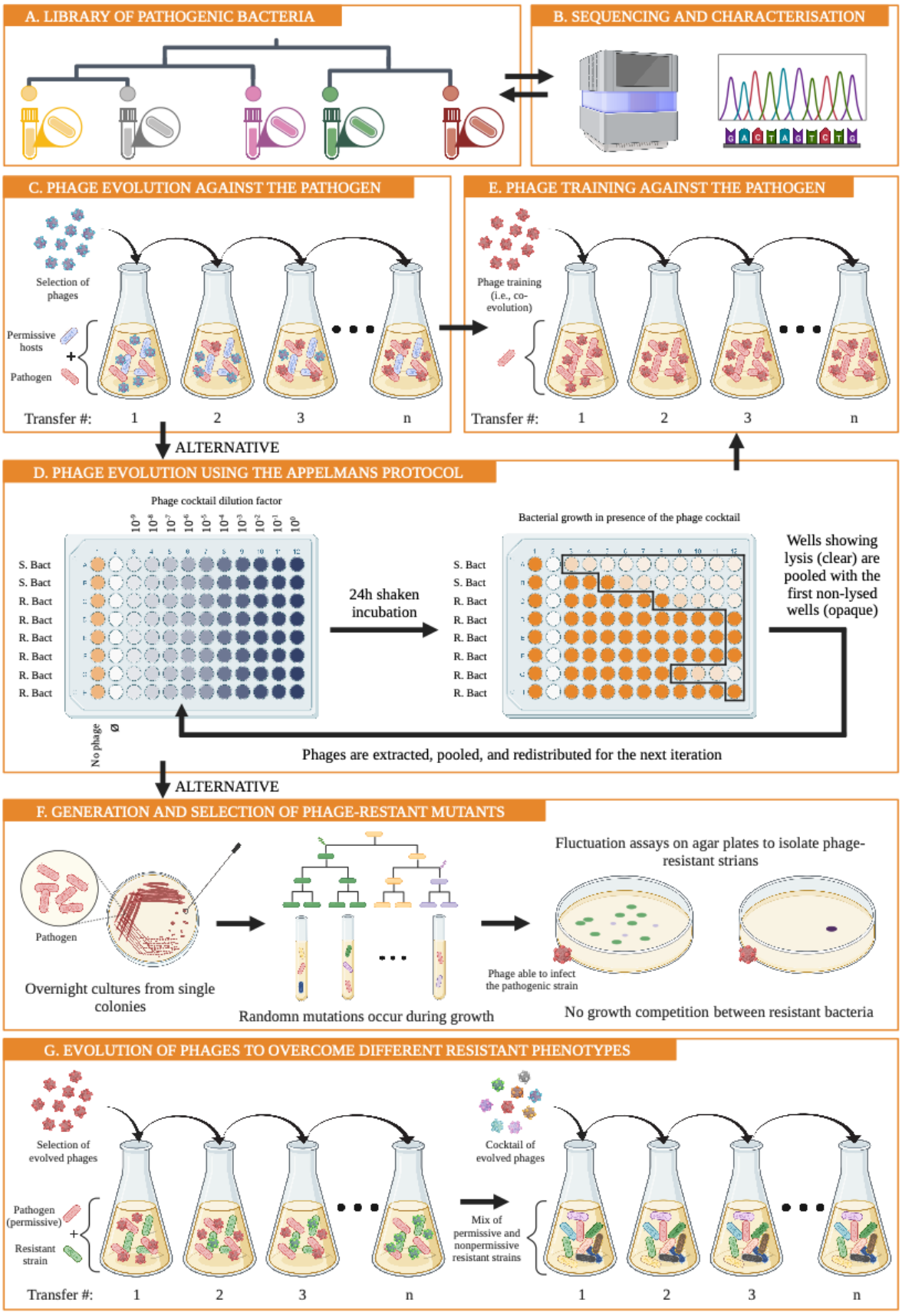
A. LIBRARY OF PATHOGENIC BACTERIA
B. SEQUENCING AND CHARACTERISATION
C. PHAGE EVOLUTION AGAINST THE PATHOGEN
Selection of phages
Permissive hosts
Pathogen
Transfer #: 1 2 3 n
E. PHAGE TRAINING AGAINST THE PATHOGEN
Phage training (i.e., co-evolution)
Transfer #: 1 2 3 n
ALTERNATIVE
D. PHAGE EVOLUTION USING THE APPELMANS PROTOCOL
Phage cocktail dilution factor
S. Bact
S. Bact
R. Bact
R. Bact
R. Bact
R. Bact
R. Bact
R. Bact
No phage
24h shaken incubation
Bacterial growth in presence of the phage cocktail
Wells showing lysis (clear) are pooled with the first non-lysed wells (opaque)
Phages are extracted, pooled, and redistributed for the next iteration
ALTERNATIVE
F. GENERATION AND SELECTION OF PHAGE-RESTANT MUTANTS
Pathogen
Overnight cultures from single colonies
Randomn mutations occur during growth
Fluctuation assays on agar plates to isolate phage-resistant strians
Phage able to infect the pathogenic strain
No growth competition between resistant bacteria
G. EVOLUTION OF PHAGES TO OVERCOME DIFFERENT RESISTANT PHENOTYPES
Selection of evolved phages
Pathogen (permissive)
Resistant strain
Transfer #: 1 2 3 n
Cocktail of evolved phages
Mix of permissive and nonpermissive resistant strains
1 2 3 n

Fig. 1. 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 et al. 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).

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 et al. 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 mRNA 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, 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 capitalize on our profound insight into their biology and evolution (Luciano et al. 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 programs) 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,

370 has first to be conducted to demonstrate the efficacy of phage model systems to treat infection
371 caused by pathogenic bacteria. Hence, in parallel with the ongoing search for novel environmental
372 phages, we advocate investing resources into developing phage model systems for phage therapies.
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