

## **Written Evidence Submitted by CF Syndicate in AMR (PHA0030)**

### **What is the CF Syndicate in AMR?**

People with cystic fibrosis (pwCF) are susceptible to developing recurrent respiratory infections which over time become difficult to treat due to the development of resistance, leading to a progressive decline in lung function. There have been no new class of antibiotics for 30 years, therefore there is an urgent and unmet need for new classes of antimicrobials to treat respiratory infections in CF. To that end, in 2019 Medicines Discovery Catapult joined forces with the Cystic Fibrosis Trust to form the CF antimicrobial resistance (AMR) Syndicate. The aim of the Syndicate is to accelerate the translation of novel CF antimicrobials to the clinic, bringing new and effective treatments to pwCF faster. Recently, LifeArc joined the Syndicate as a managing partner to further strengthen antimicrobial discovery efforts. The Syndicate's agenda has been informed by extensive efforts to understand the research landscape and the needs of the CF infection research community. This agenda has been developed through a cross-sector collaborative approach, which has involved close working with pwCF together with leading experts across industry, academia and the NHS.

### **1. How well established is the evidence base for phages as an antimicrobial for humans? What are the strengths and weaknesses?**

There is strong evidence for the use of phages. Phages were first identified over 100 years ago. Before the widespread use of antibiotics, phage preps were manufactured for use in people. In some parts of the world (largely Russia and Georgia) phages have been used throughout this period. A centre for phage treatment and expertise has been established in Tbilisi, Georgia since 1923.

It is important to understand the strengths and weaknesses of using phages as a therapeutic option in humans. Firstly, they are self-replicating and self-limiting. This means that they will only increase in number when the infection is present. Once the infection is cleared, they will not replicate and will dissipate. Secondly, they are very specific and can target a pathogen without destroying healthy microbiomes. No other treatment has these features. Phage cocktails (a mixture of different phages) can be tailored to make it difficult for bacteria to evolve resistance, or to direct the evolution of pathogenic bacteria to make them less harmful for humans. Furthermore, altering these cocktails would allow a personalised medicine approach. Phages are easy to isolate and therefore it may be possible to isolate new phages against resistant bacteria. Phages are also relatively easy to engineer. A further positive is that the fundamental biology of phages means that they are able to evolve and overcome bacterial resistance.

The challenges are that, in order to use phages effectively, the pathogen must be known. Therefore powerful diagnostics need to go hand-in-hand with this therapy. There is a lack of knowledge about how phages interact with antibiotics, and how these may be used in combination. More research is needed to clarify this. Furthermore, it is not clear how phages are distributed to different organs when inside the human body. Organs respond in different ways making it difficult to determine clinical dosages and penetration into the site of an infection in tissues may also be different between individual phage. Finally, phages often carry a number of genes with unknown function.

In the literature, there are many examples of individuals being treated with phage therapy outside of the clinical trial setting. There have also been two larger clinical trials that have shown that phage therapy is a safe form of treatment<sup>1</sup>. These two trials had well-reported issues with design and application and therefore the results from these were disappointing. There has been a rapid increase in the number of phage-related clinical trials (>25 since 2020). These include trials by Biom-X in the

US, using engineered phage targeted at lung infections in people with CF<sup>2</sup>. A recent clinical trial has also demonstrated efficacy of phage therapy in treating diabetic foot ulcers<sup>3</sup>.

There have been several promising case studies of the use of phage in pwCF<sup>4,5</sup>. One of these highlighted eradication of a severe chronic lung infection with non-tuberculous Mycobacteria<sup>5</sup>. This treatment then enabled the individual to undergo a life-saving lung transplant. There is also an example of use in a pwCF at Great Ormond Street Hospital in the UK<sup>6</sup>. Combined, these case studies highlight the potential for phage therapy in pwCF.

## **2. What regulatory approaches have been used by other countries for the use of phages and what lessons can the UK learn?**

There are many countries that are ahead of the UK for phage regulation and administration. Belgium has been at the forefront of the recent phage movement. They have the Magistral protocol, which was approved by the Belgian health authority and is the most advanced phage regulatory framework in the EU<sup>7</sup>. Pharmacists can access these phage suspensions to make specific magistral phage preparations. The EU are currently considering adopting this approach. In Poland, phage therapy is available yet classed as an experimental treatment regime. Phage therapy is permitted under certain conditions when no proven treatment is available. This has been available since 2005 and supports a personalised medicine approach.

Australia has formalised their approach more recently with a clear, national effort. The STAMP (Standardised Treatment and Monitoring of Phage therapy) protocol has been released that regulates the process of phage therapy rather than a specific phage product<sup>8</sup>. It does not require phages to be made under GMP (Good Manufacturing Practice) protocol for their use in clinical trials. This is the biggest limitation to their use in the UK where everything needs to be made under GMP (if manufactured in the UK). While there is a pre-production site for phages based at Loughborough University, there are no GMP facilities for phage production in the UK. The manufacturer JAFRAL in Lithuania produces GMP phages, but the estimated cost for 4 phages is £1 million in 9 months. While other countries use much cheaper approaches, this cost seems unattainable for use in the NHS.

In both Georgia and Russia phages are widely accepted, used without a prescription and can be bought off the shelf. There is an opportunity to learn from their manufacturing experience, However, UK regulation would likely require more clarity and control.

In the US, single-patient early access emergency use of an investigational drug (eIND) can be submitted to the FDA on an individual patient basis. Some clinical trials have now also begun in the US.

In the UK, it may be possible to use phage therapy in last resort cases, provided it is unsolicited by the patient, the liability is on the clinician/Trust, and the phages have to be manufactured to GMP standard if produced in the UK. Thus, this approach has been used by a very small number of individuals.

## **3. What opportunities does the UK have for regulatory divergence from the EU on phages, and what would the implications be?**

Phage therapy is classed as an 'unlicensed special' as defined in the MHRA Guidance Note 14 (2014). There is currently no clear regulatory framework in place. There have been early indications that the Innovative Licensing and Access Pathway (<https://www.gov.uk/guidance/innovative-licensing-and-access-pathway#products-in-scope-of-the-ilap>) might be an appropriate route for phage therapy as a

biological medicine, but additional discussions and likely a designated product will be required to map out this pathway in more detail.

The EU is considering adopting the Belgian approach, the Magistral protocol. The current EU framework requires each phage/phage cocktail to be defined following authorisation and marketing. This is counterintuitive with a key feature of phages, namely their ability to evolve. Divergence from this in the UK would make modifying phage cocktails quicker and easier. This would support a personalised medicine approach that can rapidly respond to bacterial resistance.

Furthermore, genetically modified (GM) products are not currently accepted in the EU. Phages are readily modified and some of the clinical cases and trials have utilised GM phage. If the UK were to accept GM products, this would make available the use of synthetic/modified phages.

The requirement for GMP phage if manufactured in the UK (but not if sourced outside the UK) is clearly a major barrier. In the short term, an approach could be removing or altering this requirement resulting in cheaper and easier access. This is the approach taken for Phase I clinical trials in the US. Requirements are then more stringent for Phase II/III trials. However, in the longer term, the UK needs to invest in GMP infrastructure for this purpose. Clear regulatory guidance from MHRA is needed.

#### **4. What are the major barriers and opportunities relating to the development and deployment of phages in the UK?**

In terms of direct clinical applications, the opportunities are that phages could be used to improve the health and clinical outcomes of a potentially large number of individuals. This would also decrease our reliance on antibiotics. This could have a major impact, particularly conditions that require long term antibiotic usage such as lung infections in pwCF. Long term, this could alleviate some pressure/costs for the NHS. Furthermore, removing antibiotic pressure could simultaneously reduce overall resistance and ensure the safeguarding of some antibiotics for last resort use.

The major barriers are a lack of clarity regarding routes to patient use. For some patient groups, public opinion could be a potential barrier. However for PwCF, reducing the negative effects of antibiotics has been identified in the top 5 priority research questions identified by patients, families and clinicians<sup>9</sup>. Phage therapy was also identified as a key area of interest therefore this is likely not a major barrier in this group. A further consideration is the narrow host range of phages which will potentially require powerful, strain-level bacterial diagnostics. However, this is again less of an issue for those with chronic infections where it may be easier to isolate the infecting bacteria and directly test phage efficacy against it before use in the patient.

For research, there are strong phage expertise in the UK but this has yet to be translated into more medical research and translation into patient therapies. The barrier to this is funding and research council priorities.

Regulatory barriers surround the need for GMP and purity of products in the UK. Phages are known to diversify (naturally evolve) and therefore this level of purity is challenging. Removing this requirement may stimulate further investment, particularly with “first in man” clinical trial facilities such as those available in Liverpool (see question 5).

In addition, there is uncertainty regarding the publication of data from patients treated on a named patient basis. These restrictions appear contrary to the guidance of the Declaration of Helsinki

Article 37 (of which the UK is a signatory), “Unproven Interventions can be used to evaluate its safety and efficacy and made publicly available. Clarity from MHRA is required here.

**5. How well developed is the UK’s phage research and clinical trial pipeline and how could it be improved?**

Currently there are many isolated groups within academia and medicine working on phages. A more collaborative effort between these groups is needed. This often occurs through funded, strategic consortia.

The CF Syndicate in AMR includes a number of researchers with an interest in phage therapy. We also recently published Target Product Profiles for new antimicrobial therapeutics in CF and these were designed to consider new approaches such as phage therapy <sup>10</sup>. The CF Trust and CF Foundation currently co-fund a strategic research centre, PIPE-CF, to define the preclinical pipeline for developing new therapeutics for lung infections in PwCF<sup>11</sup>. Phages are also being studied as part of this project and therefore these models could be used for preclinical experiments.

In general, there is a lack of knowledge among patients and clinicians of the phage treatments available and little understanding of what treatment entails and how to access it. On a broad scale, more engagement and education could address this. However there is some recognition of phage therapy as a potential option in pwCF. This was further highlighted in a recent documentary “Salt in my Soul”.

The UK has world class Clinical Research Facilities (CRFs) for Experimental Medicine. These are dedicated facilities, where specialist clinical and research and staff from UK universities and NHS Trusts work together on patient-orientated studies. The UKCRF Network supports CRFs by providing best practice guidance and tools to ensure each CRF delivers clinical trials of the highest standard. An example of this are the facilities in Liverpool.

The major opportunity is to run high quality clinical trials in the UK. The UK has excellent trial expertise and facilities. Such a trial could look towards personalised medicine approaches recently used in cancer therapeutic trials (such as CAR-T). There is the opportunity to be world leading in this approach but this would require flexibility in phage choice and preparation. Many clinicians view this as the primary method to see this therapy made available to patients. This would require significant funding.

**6. To what extent is the UK Government ensuring that phage research and development is adequately funded and supported?**

Phage therapy in the UK is currently poorly funded. The majority of research has been funded through internal grants and charities. There has been some funding through BBSRC to understand more about the evolutionary side of resistance to phage therapy, however, this is focused on the biology and not translation into a usable therapy.

There have been no phage-specific funding calls. This may have been hampered by the lack of a regulatory framework for phage therapy in the UK, as some funders may be less likely to fund bacteriophage therapy proposals due to this.

Furthermore, there are no funded phage biobanks. This would require a multi-centre approach. However, there is experience of coordinating these within the CF Syndicate in AMR as exemplified by the recently formed UK CF Infection Biorepository<sup>12</sup>.

An Innovate UK knowledge transfer network (KTN) to facilitate the use of phage across several sectors of the economy was set-up in 2022. The Phage-UK network has also recently formed (2021) and the CF Syndicate in AMR plans to work closely with them to understand future priorities.

Funding for novel therapeutics is very poor in general. Developing therapeutics is highly challenging and there have been examples of several companies facing bankruptcy despite promising results. Effective therapeutics are essential as a part of healthcare and therefore further funding in this area would stimulate advances in both science, industry and healthcare. Clarifying the regulatory pathway, addressing the need for GMP manufacture and “de-risking” aspects of the clinical development and trials approaches for phage therapy, would have a significant impact on translation and provide much-needed new therapies.

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