Written evidence submitted by Dr Clare Trippett on behalf of CPI (INS0047)

Science and Technology Committee Inquiry: The Antimicrobial Potential of Bacteriophages

Executive summary

- Due to CPI's extensive experience in the translation of new biopharmaceutical products to market we wish to submit written evidence on the process development and manufacturing infrastructure needed in the UK to enable the progression and deployment of phage therapies.
- The lack of manufacturing capacity for phage is recognised as one of the major barriers to progressing phage therapy in the UK, therefore CPI's evidence will focus on the process development, manufacturing and analytical characterisation requirements needed to enable the successful translation of therapeutic phage candidates into the clinic.
- The UK does not currently possess the infrastructure to enable progression of phage therapies into clinical trials. Lack of infrastructure to support manufacturing process development, analytical development, scale up and GMP manufacture is currently a barrier to translating new therapeutic phage candidates into clinical trials and the commercial market.
- As with phage therapy translational challenges due to a lack of manufacturing capacity exist for other classes of microbiome therapeutics, meaning innovative companies and academics developing new treatments are forced to go outside of the UK for product manufacture to go into clinical trials. This represents a lost financial opportunity for the UK and may have long term impact as once companies have secured manufacturing sources from outside the UK it may be difficult to recoup them.
- Investment into process development and manufacturing facilities for phage may benefit from being included as part of a broader microbiome remit. A flexible facility to address the translational gap for phage and other microbiome therapeutic modalities would help to mitigate the potential risk associated with the financial viability of manufacturing phage therapies alone.
- The UK has an opportunity to take an early lead in supporting the sector and to invest in the required infrastructure and capabilities to support phage and microbiome process development, scale up and GMP manufacture. Creating an onshore supply of phage will help to tackle AMR and increase the UK's resilience, providing capability that could be pivoted for use in a future health emergency and creating economic impact in terms of new jobs and industrial development. There is also opportunity for international impact through export opportunities associated with supplying UK manufactured phage globally.

1.0 Introduction

CPI is a leading independent technology innovation centre and a founding member of the UK's High Value Manufacturing Catapult, acting as a catalyst to bring together industry, academia, government and investors to translate bright ideas and research into the marketplace. CPI has extensive experience and expertise in pharmaceutical innovation, developing novel manufacturing solutions and scaling up the production of new and novel therapeutics and vaccines. As experts in the

translation of new biopharmaceutical products to market CPI wish to submit written evidence on the process development and manufacturing infrastructure needed in the UK to enable the progression and deployment of phage therapies.

Bacterial antimicrobial resistance (AMR) has emerged as a serious global burden and threat to public health. It is estimated that there were 4.95 million deaths associated with bacterial AMR in 2019, including 1.27 million deaths directly attributed to bacterial AMR (1). The six leading pathogens for deaths associated with antimicrobial resistance have been identified as *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii* and *Pseudomonas aeruginosa*, which have been identified as priority pathogens by WHO (2). Despite the urgency associated with the death toll and negative economic impact of AMR, investment into new antimicrobials has been relatively small compared to other public health issues that have similar or smaller impact (3).

The AMR crisis is driving the search for new antimicrobials, with bacteriophage (phage) therapy showing encouraging potential as one option to provide an alternative or supplementary approach for tackling resistant infections or providing treatment to patients where antibiotic therapy may not be an option. Phages are the most abundant life form on earth, and their ability to target a specific species of bacterial pathogen and evolve in response to resistance makes them a valuable natural resource to exploit for improving the health of humans, animals and plants.

The lack of manufacturing capacity for phage is recognised as one of the barriers to the deployment of phage therapies in the UK, therefore CPI's evidence will focus on the process development, manufacturing and analytical characterisation requirements needed to enable the successful translation of therapeutic phage candidates into the clinic.

2.0 The translational gap for phage therapies: manufacturing process development, scale up and GMP production

There are currently two main formats for phage therapy:

- pre-formulated, defined phage cocktails (an 'off the shelf' approach)
- personalised phage treatment provided for a named patient that is informed by screening a pathogen against a phage library

The two formats require different development approaches. The evidence provided here is of particular relevance to the production of pre-formulated, commercial phage cocktails, although production of personalised phage treatments for compassionate use will also be discussed.

The UK does not currently possess the infrastructure to enable progression of phage therapies into clinical trials. Lack of infrastructure to support manufacturing process development, scale up and production to Good Manufacturing Practice (GMP) is currently a barrier to translating new therapeutic phage candidates into clinical trials and the commercial market. This is slowing development of the clinical evidence base for phage based treatment approaches.

There is very limited global capacity for GMP phage manufacture. To CPI's knowledge there are currently four countries that possess the capabilities for GMP phage production; Slovenia, Portugal, Norway and the United States. No GMP manufacturing capacity for phage exists in the UK. The lack of UK manufacturing infrastructure for phage was highlighted in the recently published Innovate UK-KTN report 'Human Intestinal Microbiome Therapies and Diagnostics' (4) where a key recommendation was to create a flexible microbiome and phage bioprocessing facility to accommodate phage process development and manufacture and support the development of new therapies and growth of the sector in the UK, as well as attracting international clients working in this field.

3.0 UK infrastructure required for translation of phage therapies into the clinic

The development of phage medicinal products includes preclinical and Phase I, II and III clinical trials. Appropriately manufactured phage must be available at each stage. Although phage is a new modality much can be learned from existing manufacturing approaches for biopharmaceuticals that have already progressed to market. The process development and manufacturing infrastructure needed to enable phage therapies to reach the clinic is discussed below.

3.1 Host cell and virus banks

The bacterial host strain used for phage production is a key component of the manufacturing process. Cell and virus banks that can be used consistently during process development and GMP manufacture are required. The cell and virus banks must be characterised according to regulatory guidance.

3.2 Development, optimisation and scale up of the manufacturing process

The manufacturing process refers to the sequence of steps that are necessary to produce the required amount of phage to a satisfactory quality level. Manufacturing process development for phage is critical as it results in an optimised production process with consistent yield and product quality that can be scaled to produce the required quantity of phages.

Process development is required to determine the optimal conditions to achieve a high titre of functional phage whilst also ensuring process impurities such as host cell debris are kept to an acceptable level. Development and optimisation is needed for the upstream cell culture process where the phage is propagated in its host cell, and the downstream process to purify replicative phages and remove unwanted material. Once the manufacturing process has been developed it is scaled to the volume required.

Alternative approaches to manufacturing phage for increased efficiency and shorter production times should also be considered, for example cell free production of phage that does not require culture of the host cell, and phage printing.

3.3 Analytical characterisation

As with other biopharmaceuticals such as vaccines, monoclonal antibodies and gene therapies the Critical Quality Attributes (CQAs) for phage must be defined and characterised to ensure the safety, quality and efficacy of the treatment. Development of suitable analytical methods for characterisation and a description of the acceptance criteria for the methods will both be required as part of phage characterisation. Having robust and reproducible analytical methods in place for phage characterisation will play a major role in regulatory approval and the launch of phage products.

3.4 Formulation and stability

Stability studies are required to understand the shelf life of phage preparations in a given formulation, with investigation into how the efficacy may change over a defined time period under defined environmental conditions such as temperature and humidity.

3.5 GMP manufacturing and quality control

The UK requires that phages are manufactured to GMP standards unless they have been imported into the UK. The aim of GMP is to ensure the safety and efficacy of manufactured medicines through rigorously controlled manufacturing processes and quality control (QC). Investment into a GMP grade production facility for phage would allow provision of phages for clinical trials and commercial supply of cost effective, pre formulated phage cocktails against some of the more common priority pathogens.

4.0 Personalised phage production

Phage therapy in the UK is available as an unlicensed special medicine on a named patient, compassionate use basis when licensed medicines have failed. Personalised phage preparations are based on matching phages from a biobank to the pathogen that is causing the patient's infection. The manufacture of personalised phage therapies in the UK is currently undefined as it is not directly compatible with the conventional approach to development and approval of medicinal products. There are significant challenges with the production of personalised phage in terms of how GMP grade manufacture can be achieved in the required timeframe, and in a cost-effective manner to respond to a small or single patient cohort. For unlicensed treatments one solution in the short term would be to permit less stringent requirements where the phage is produced to a GMP-like standard, with manufacturing performed to a high standard and the appropriate analytical testing in place to ensure product safety. This would shorten the lead time for the phage treatment to reach the patient. Production could be based on Quality by Design (QbD) approach that designs quality into the product and process.

It is worth noting that Phage Australia have developed the Standardised Treatment and Monitoring Protocol for Adults and Pediatric Patients (STAMP) to evaluate the clinical protocol for administering and monitoring phage therapy. To receive phage therapy a patient must be enrolled in the STAMP trial and have qualified to receive treatment under the special access scheme (compassionate access) where an infectious disease specialist has certified that all other treatment strategies have been attempted.

5.0 Microbiome therapeutics and phage

The human microbiome is the community of trillions of microorganisms that reside in the body. The microbiome plays a critical role in health and wellbeing and numerous studies have reported its link with diseases such as cancer, neurodegenerative disease and inflammatory bowel disease. Microbiome therapeutics have great potential to treat or prevent a wide range of health conditions and it is anticipated that in coming years the microbiome will emerge as an integral factor of personalised medicine, for example in cancer treatments (5). Microbiomes are also an important reservoir of novel antimicrobials for alternative or supplementary approaches to conventional antibiotics.

In addition to treating infection, phages also have potential for modulating a dysbiotic microbiome. Phage is considered to fall into a new class of medicines called 'microbiome therapeutics', which aim to modulate a person's microbiome to treat or prevent disease. Microbiome therapeutics are diverse and in addition to phage include modalities such as intestinal microbiota transfer (IMT), live biotherapeutic products (LBPs), functional fermentation compounds/metabolites from microbes (postbiotics), and targeted antimicrobials such as bacteriocins which are the antimicrobial peptides synthesised by bacteria to help them compete in the environment. The microbiome therapeutics market is developing rapidly and is expected to grow from USD 428 Million in 2021 to USD 3.5 Billion by 2030 (CAGR 28%) (6). A recent investigation into the microbiome drug landscape identified 524 microbiome therapeutics, the majority of which were in preclinical or clinical development, with 59

of these therapeutics based on phage (source: Beacon Microbiome by Hanson Wade, July 2022). A further report showed the UK was the second highest developer of live biotherapeutic products, with the highest being the United States (7). There have been three recent regulatory approvals in the field (8, 9, 10) with more anticipated in the near future.

As is the case with phage therapies there are similar translational challenges due to a lack of manufacturing capability for other types of microbiome therapeutics, meaning innovative companies and academics developing new treatments are forced to go outside of the UK for product manufacture to go into clinical trials. This represents a lost financial opportunity for the UK, and potential longer term impact as once companies have secured manufacturing sources from outside the UK it may be difficult to recoup them.

Despite the encouraging case studies showing successful treatment phage therapy is still at an early stage. Until the evidence base for the clinical efficacy of phage is further established investment into process development and manufacturing facilities for phage may benefit from being included as part of a broader microbiome remit. A flexible facility to address the translational gap for phage and other modalities of microbiome therapeutics would help to mitigate the potential risk associated with the financial viability of manufacturing phage therapies alone. The technical requirements for manufacturing phage and other modalities of microbiome therapeutic are similar, therefore from this perspective there is an opportunity for both to be made in the same facility. The facility could be designed to manufacture different products in parallel with appropriate levels of segregation. Switching between products could be achieved with validated change over and cleaning procedures.

In response to the recommendations made in the recent Innovate UK KTN report (4) CPI are aiming to establish a Microbiome and Phage Bioprocess Innovation Centre (MPBIC) and associated network of partners to provide the enabling infrastructure and capabilities to deliver end to end support for process development, scale up and clinical GMP grade production of new microbiome therapeutics and novel antimicrobials such as phage.

6.0 The UK phage opportunity

In line with the UK's ambition to be positioned as a global leader and superpower for science and technology there is an opportunity to take an early lead in supporting the sector and to invest in the required infrastructure and capabilities to support phage and microbiome production in the UK. This would facilitate process development, scale up and GMP manufacture that will enable the production of cost effective pre prepared phage cocktails for clinical trials. This will help to build the evidence base for phage and enable inward investment and commercial supply of approved therapies. Creating an onshore supply of phage will help to tackle AMR and increase the UK’s resilience, providing capability that could be pivoted for use in a future health emergency whilst also creating economic opportunity in terms of new jobs, industrial development and boosting the UK economy. Investment would also lead to opportunities for international impact through the export opportunities associated with supplying UK manufactured phage globally.

7.0 Recommendations

CPI would like to make the following recommendations to address the UK’s existing translational gap and support the development and deployment of phage therapies:

- Investment is needed to create the required infrastructure and capabilities to support process development and GMP manufacture for phage and other classes of microbiome therapy. Creation of this key infrastructure will support the development of new therapeutic candidates through clinical trials and commercialisation, helping to build the evidence base for phage and microbiome based treatments.

- A microbiome and phage bioprocess innovation centre should be created to act as a translational hub within the UK's current ecosystem. The centre should act as a central resource within a microbiome and phage innovation hub comprising of a network of UK companies and universities that possess relevant capabilities. The hub should provide end-to-end support for entrepreneurs and start-up companies working in the field and include financial guidance, regulatory advice, intellectual property support plus access to clinical trial facilities and manufacturing. A microbiome and phage skills and training network could be integrated into the hub, maximising the benefits of training support from both industry and academia.

9 May 2023

8.0 References

1. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Murray, Christopher J L et al. The Lancet, Volume 399, Issue 10325, 629 – 655
2. WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. 2017. https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1
3. WHO. 2019 antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline. World Health Organization, Geneva, 2019
4. https://iuk.ktn-uk.org/news/new-report-the-human-intestinal-microbiome-therapies-and-diagnostics-the-science-opportunities-and-challenges-published/
5. Behrouzi A, Nafari AH, Siadat SD. The significance of microbiome in personalized medicine. Clin Transl Med. 2019;8(1):16. Published 2019 May 13. doi:10.1186/s40169-019-0232-y
6. Young, Paul. Research to Impact: translating microbiome therapeutics research in the UK. s.l.: Durham University MBA Thesis, 2022.
7. https://beacon-intelligence.com/infographic/mmdd-2022-presentation/
8. https://www.fda.gov/news-events/press-announcements/fda-approves-first-fecal-microbiota-product
9. https://www.biomebank.com/news/biomebank-announces-world-first-regulatory-approval-for-donor-derived-microbiome-drug/
10. https://ir.serestherapeutics.com/news-releases/news-release-details/seres-therapeutics-and-nestle-health-science-announce-fda