Engineering *Clostridioides difficile* bacteriophages for therapeutic application

**Principal supervisor**
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**Co-supervisors**
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Prof. Ernesto Abel-Santos (University of Nevada, Las Vegas)

**Location** The Open University, Milton Keynes, United Kingdom

**Full-time only**

**Duration & Funding** 3 year 3 month studentship; Stipend £18,622 per annum; Training grant £4,500

**Application due date:** Jan 31, 2024

**Notification of shortlisting:** Feb 7, 2024

**Interview:** Feb 14, 2024 on Microsoft Teams (can be flexible on date if needed)

**Final Funding Decision:** March 2024. This is part of a pooled School process, so the selected applicant will be put forward to a reviewing panel in March for final decisions. Applicants will be notified if they are selected and will be informed of the panel decision afterwards.

**Start date:** October, 2024

**Science-related enquiries:** terry.bilverstone@open.ac.uk

**Process-related enquiries:** STEM-LHCS-PHD@open.ac.uk

**Research area/keywords:** *Clostridioides difficile*, bacteriophage, synthetic biology, medical microbiology

**Project Background**

*Clostridioides difficile* infection (CDI) is the leading cause of hospital-associated diarrhoea and is recalcitrant to conventional antibiotic therapy. Bacteriophage (phage) therapy represents an attractive alternative treatment strategy, although currently described *C. difficile* phages are temperate in nature and can integrate into the bacterial chromosome as a prophage, through the lysogenic cycle (Fig 1a). In this dormant state, prophages do not kill their bacterial host, which impairs the therapeutic suitability of temperate phages. We seek to remedy this, by engineering antibacterial effectors onto the chromosome of temperate *C. difficile* phages, to promote bacterial killing and prevent the initiation of lysogeny.
**Figure 1:** a) Lytic and lysogenic life cycles of temperature phages; b) *C. difficile* phage ϕCD1801 [1,5].

**Project Description**

This project will address the three limitations currently hampering the therapeutic potential of phages as an alternative treatment strategy for *C. difficile*.

i) **Few *C. difficile* phages have been described.**

Fewer than 50 phages infecting *C. difficile* have been described with publicly accessible genome sequences. The first aim of this project is therefore to use established methodologies to isolate novel phages infecting *C. difficile* from sewage and environmental samples [1].

ii) ***C. difficile* phages are temperate.**

We will endow a characterised temperate phage with a range of effectors anticipated to promote antibacterial activity and consequently prevent chromosomal integration. We will develop a novel *Drosophila* model of infection to test our therapeutically enhanced phage candidates [2-3], before progressing to a mouse model [4].

iii) ***C. difficile* phages have narrow subspecies host range.**

*C. difficile* phages have narrow subspecies host range. Recent advances in our understanding of phage-host interactions for *C. difficile* have elucidated the host receptor on the bacterial surface [1]. Armed with this information, we will isolate novel phages with broad host range activity against the prevalent strains in the UK, by virtue of their host receptor topology. Receptor binding determinants for host infection have recently been determined [5]. We will identify those determinants for the novel phages isolated here, applying this information to modify the host range of our therapeutically enhanced phages.

**References**


Eligibility

1. Applicants will ideally have a First Class or Upper Second undergraduate degree or Masters degree (or equivalent experience) in Microbiology, Biotechnology, Biomedical Science or similar subjects. Alternatively, a Bioinformatics graduate with wet-lab experience could be suitable.

2. The student would be required to live in the UK and within commuting distance to The Open University in Milton Keynes.

3. Applicants will need to satisfy eligibility criteria on written and spoken English skills.

Desirable Criteria

1. An interest in synthetic biology or medical microbiology subjects.

2. Demonstrable experience in microbiology or molecular biology laboratory techniques.

3. Experience of presenting research data including written reports and oral presentations.

4. Willingness to travel to the USA for a short research visit (~1 month) in the final year, subject to funding.

We are committed to widening participation and awarding PhD studentships to a diverse community of applicants. We particularly welcome applications from under-represented groups. Equal Opportunity is University policy.

How to apply

Please check this page for application entry requirements: https://www.open.ac.uk/postgraduate/research-degrees/degrees-we-offer/doctor-of-philosophy-phd

Please submit to STEM-LHCS-PHD@open.ac.uk an:

- Application form, and
- 2-page (A4) personal statement outlining your suitability for the studentship, what you hope to achieve from the PhD and your research experience to date

You do not need to submit a research proposal.

Information and the application form is found here: https://www.open.ac.uk/postgraduate/research-degrees/how-to-apply/mphil-and-phd-application-process, Note that as part of the application form, you will be asked to submit further documents (CV, degree transcripts, etc.)