**University of Leicester**

**BBSRC MIBTP Studentship Project 2025-6 entry.**

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Name of non-academic partner organisation: Carus Animal Health, Surrey, UK

**Section 2 – *Project Information***

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| **Project Title** | iCase: Structural and Molecular Characterisation of Jumbo Phage SPFM10 for the Development of Phage Therapy Against Non-Typhoidal Salmonella |
| **Project Summary**  |
| Foodborne infections caused by Non-typhoidal *Salmonella* (NTS) due to consumption of contaminated meat and poultry is a significant public health concern. The challenge of treating these infections is compounded by the increasing prevalence of multidrug-resistant (MDR) strains of NTS, with approximately 10–30% of isolates demonstrating resistance to multiple antibiotic classes. As conventional antibiotic treatments lose efficacy against MDR *Salmonella*, alternative therapeutic approaches such as bacteriophage therapy offer significant potential. Phage therapy utilises bacteriophages to target bacterial pathogens. Our collaborators have made notable advancements in employing lytic jumbo phages as a novel strategy for addressing NTS infections1,2,3,4. One of the most promising phages identified for this purpose is SPFM10, a jumbo phage characterised for its high lytic efficiency against NTS2,4 and its ability to withstand harsh industrial processes necessary for administration through animal feed3,4.The overarching goal of this project is to characterise the SPFM10 jumbo phage, with a focus on understanding its structural and molecular mechanisms of bacterial recognition, binding, and infection. These insights will be essential for developing a phage therapy strategy that can be used to combat foodborne NTS infections, particularly those involving MDR strains. The specific aims of this project are as follows:1. **Structural Characterisation of SPFM10**

We plan to elucidate the structural of SPFM10 using cryo-EM. Preliminary NSEM, cryo-EM grid preparation, and test data collection have already been completed at our in-house facility yielding medium-resolution maps. The PhD student will optimise sample preparation and data collection to achieve high-resolution structures of these components and integrate that with genomic and proteomic data.1. **Elucidating Phage-Bacterial Binding Mechanisms**

Here, we will investigate the molecular interactions between SPFM10 and its bacterial host. This will be accomplished through cryo-electron tomography (cryo-ET) to visualise the binding of SPFM10 to *Salmonella* cell surfaces. SPFP10 infecting *Salmonella* minicells will be used to undertake cryo-ET and sub-tomogram averaging will then be employed to reconstruct high-resolution models of the phage-host interface, revealing the molecular basis of phage recognition and initial infection.1. **Phage Therapy Development**

Leveraging the insights from the structural studies, strategies to improve SPFM10’s effectiveness against *Salmonella* will be developed. Mutant phages with optimized binding domains or tail fibres will be engineered to enhance specificity and infection efficiency. These modified phages will be tested in *in-vitro* assays using *Salmonella* cultures, followed by *in-vivo* testing in animal models with our industrial partner to evaluate their efficacy in neutralizing NTS strains.  |
| **References** |
| 1. Thanki AM, Brown N, Millard AD, Clokie MRJ. Genomic Characterization of Jumbo *Salmonella* Phages That Effectively Target United Kingdom Pig-Associated *Salmonella* Serotypes. *Front Microbiol*. 2019, 10:1491.
2. Thanki AM, Clavijo V, Healy K, Wilkinson RC, Sicheritz-Pontén T, Millard AD, Clokie MRJ. Development of a Phage Cocktail to Target *Salmonella* Strains Associated with Swine. *Pharmaceuticals (Basel)*. 2022, 15:58.
3. Thanki AM, Mignard G, Atterbury RJ, Barrow P, Millard AD, Clokie MRJ. Prophylactic Delivery of a Bacteriophage Cocktail in Feed Significantly Reduces Salmonella Colonization in Pigs. *Microbiol Spectr*. 2022, 10:e0042222.
4. Thanki AM, Hooton S, Whenham N, Salter MG, Bedford MR, O'Neill HVM, Clokie MRJ. A bacteriophage cocktail delivered in feed significantly reduced *Salmonella* colonization in challenged broiler chickens. *Emerg Microbes Infect.* 2023, 12:2217947.
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