EASTBIO-Peptide-based precision anti-infectives for prophylaxis and treatment of foodborne listeriosis

University of Edinburgh > College of Medicine and Veterinary Medicine

Prof J A Vazquez-Boland Friday, January 17, 2025

Competition Funded PhD Project (Students Worldwide)

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About the Project

Listeriosis is a life-threatening food-borne infection caused by the facultative intracellular pathogen Listeria monocytogenes. Clinical manifestations are severe and include meningoencephalitis, bacteremia, stillbirth and neonatal sepsis. Listeriosis targets vulnerable groups including >60-years-olds, pregnant women and their babies, and immunocompromised individuals. It is the primary cause of death associated with foodborne illness in Western countries and the third most common cause of bacterial brain infection. The current antimicrobial treatment is suboptimal, with 15-35% lethality and neurological sequelae in 14 to 40% of cases despite antimicrobial therapy (1). How to clinically handle at-risk individuals identified as exposed to Listeria contaminated food also represents a challenge due to the harmful effects of antibioprophylaxis on the resident microbiota and in terms of selection of resistance. Novel drugs are therefore needed to improve the clinical management of Listeria infection and, critically, to prevent the development of listeriosis in Listeria-exposed fragilized people and pregnant women.

Listeria infection depends on activation of the listerial virulence by PrfA, a transcription factor, on sensing the host. PrfA function is essential for Listeria pathogenesis; its inactivation renders the bacteria harmless. The project will seek to inhibit PrfA as an anti-Listeria therapeutic strategy. The approach is based on fundamental knowledge developed by the host group on the molecular mechanisms of PrfA regulation. The Vazquez-Boland group recently showed that PrfA's transcriptional activity is directly inhibited via promiscuous (sequence-independent) binding of environmental oligopeptides imported from the medium and which Listeria utilize as their main N source. The inhibitory peptides compete with the PrfA-activating co-factor glutathione (itself a tripeptide) for its binding site at PrfA (2). The Vazquez-Boland group have characterized the binding mechanism at atomic resolution by analysing the crystal structures of different PrfA-peptide complexes (3).

In this project, you will exploit the available structural biology data of the interaction between the peptides and PrfA to develop and test in in vitro, ex vivo and in vivo models peptide-based Listeria anti-infective drugs for the treatment and prophylaxis of listeriosis. You will also use the peptide-based drugs as chemical tools to better elucidate the mechanisms by which PrfA regulates Listeria pathogenesis. This is an exciting opportunity to work in an interdisciplinary team between the Edinburgh Medical School, the IRR biomedical research institute and EaStChem School of Chemistry, gaining a wide range of skills at the interface between infection biology, microbial pathogenesis, chemical biology and medicinal chemistry.

References:

1. Koopmans, M.M., Brouwer, M.C., Vazquez-Boland, J.A. & van de Beek, D. Human listeriosis. Clin Microbiol Rev, e0006019 (2022).

2. Krypotou, E. et al. Control of bacterial virulence through the peptide signature of the Habitat. Cell Rep 26, 1815-1827 e5 (2019).

3. Hainzl, T. et al. Structural basis of promiscuous inhibition of Listeria virulence activator PrfA by oligopeptides. bioRxiv, 2024-05 (2024).

Informal project enquiries are encouraged and can be made to: v.boland@ed.ac.uk

How to Apply:

This 4-year PhD project is part of a competition funded by EASTBIO BBSRC Doctoral Training Partnership (DTP). Detailed guidance on the application process, and the EASTBIO Application and Reference Forms can be found on the EASTBIO DTP Website.

Please send your completed EASTBIO Application Form along with a copy of your academic degree/transcripts to: CIR.Postgraduate@ed.ac.uk. Please remember to put the project title in the subject line and also fill this Online Application Form.

You should also ensure that two references have been sent to CIR.Postgraduate@ed.ac.uk using the EASTBIO Reference Form. Please remind your referees to put the project title and your name in the subject line by the application deadline of 17th January 2025.

The Vazquez-Boland group is located in University of Edinburgh's Institute for Regeneration and Repair (IRR). The IRR has a broad interest in inflammation, tissue repair and regeneration in a range of tissues and settings including the lungs, kidney, liver, pancreas, bowel, bone, joints, skin, heart and brain. The Institute is located at the Edinburgh BioQuarter, a site shared by the Royal Infirmary Hospital and the University's Clinical Research facilities, and a perfect location to translate basic science into clinical therapies.

Funding Notes

This opportunity is open to UK and international students and provides funding covering stipend and UK level tuition fees. The University of Edinburgh covers the difference between home and international fees meaning that the EASTBIO DTP offers fully-funded studentships to all appointees. There is a cap on the number of international students the DTP recruits. It is therefore important for us to know from the outset which fees status category applicants will fall under when applying to our University.

Please refer to the UKRI website for full eligibility criteria: Get a studentship to fund your doctorate – UKRI

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