EPSRC Centre for Doctoral Training (CDT) in Molecular Sciences for Medicine (MoSMed)

Differential diagnostics for leishmaniasis - bench to field

Supervisory Team	• Lead Supervisor: Prof Paul Denny, Department of Biosciences, Durham University • Co-Supervisor: Dr Marloes Peeters (Chemical Engineering), Department of Engineering Newcastle University

Project overview/context

Cutaneous leishmaniasis (CL), caused by insect vector borne *Leishmania* species protozoa, is a global problem endemic across four continents. In recent years cases have increased dramatically due to migration and climate change. Whilst mostly non-lethal, CL is associated with severe scaring on exposed skin (particularly the face), social stigma and mental health issues. In many regions, including Pakistan (>10% global burden), CL is mainly caused by *Leishmania major* and *L. tropica.* Whilst the former is often self-healing and responds well to the WHO recommended treatment, the latter is increasingly non-responsive and leads to chronic, disfiguring lesions. Therefore, rapid accurate diagnosis of *L. tropica* CL is essential to facilitate appropriate treatment using alternative medicants. Working with our partners in Pakistan, you will build upon our current work and develop a low-cost, simple molecular diagnostic device which will be ready for in field diagnostic trials.

Research Project

More than 85% of new CL cases occur in 10 countries including Pakistan (>10% global cases), where it is primarily caused by sandfly transmitted *Leishmania major* and *L. tropica*. This situation is similar in other WHO Eastern Mediterranean region endemic countries. In recent outbreaks, including Sindh province, *L. tropica* has become dominant - ~80% in a preliminary PCR-based study (ICCBS Karachi, personal communication). Due to treatment failure and chronicity, it is essential to rapidly diagnose *L. topica* infection. However, there is currently no simple, rapid diagnostic available – a deficit recognised by WHO and others.

To address this problem, in this project you will develop, validate and test a novel DNA LAMP (Loop mediation isothermal AMPlification) assay and format this into a prototype low-cost field-ready device. LAMP is a single tube technique for targeted thermal DNA amplification. In contrast to PCR, LAMP can be performed rapidly outside a laboratory at a single temperature (30 minutes, 60-65°C) giving a dectable fluorescent signal.

Firstly, you will develop a differential LAMP assay to distinguish between isolated DNA from *L. major* and *L. tropica* in the laboratory. Then, with the validated assay in hand and working with our colleagues at ICCBS Karachi, you will test this using field samples - both isolated DNA from cultured infecting parasites and 'real world' skin biopsies (Durham).

Subsequently, having established a specific and sensitive LAMP assay that can detect and distinguish *L. major* and *L. tropica* infections in skin biopsy material, you will design, develop and construct a portable prototype device combining the thermal amplification with a detector to accurately measure the fluorescent signal of the formatted samples (Newcastle). You will then validate this prototype under laboratory conditions before entering a field trial under the direction ICCBS (Karachi, Sindh).

Importantly, this molecular diagnostic will detect active infections and facilitate focused therapy, which is important given the expense and toxic nature of available drugs and the frequent lack of response in *L. tropica* CL. Further downstream development will take the prototype instrument into a field-ready, mass market device. This is the ultimate ambition of this project and as such your input could produce real world impact.

Training & Skills

This is a project that straddles parasitology, molecular biology, medical engineering and field studies. You will receive training in all elements, starting with parasitology and molecular biology at Durham, and then device engineering at Newcastle. Finally, depending upon success, field testing will be conducted in Pakistan.

In conducting the project and engaging in the training you will gain expertise in category 2 pathogen manipulation, diagnostic development and testing, medical engineering and field trial design. This will involve multi-centre, multi-national management during which you will gain the skills necessary to work across both disciplinary and national boundaries. In the final phase you may be key in the commercial development of the device, facilitating an understanding of the potential of university spin-outs.

Further Information

Please contact Prof Paul Denny for further information: **p.w.denny@durham.ac.uk**

How to Apply

To apply for this project please visit the Durham University application portal to be found at: Home · Application Portal (microsoftcrmportals.com)

Please select the course 'PhD in Molecular Sciences for Medicine (EPSRC CDT)', which is registered in the Chemistry Department and indicate the reference **mos23_06 i**n the 'Field of Study' section of the application form. Please note that there is no need to submit a Research Proposal with your application, however we do require a Covering Letter, CV, academic transcripts, the contact details of two referees and proof of English language proficiency if relevant.

Within the MoSMed CDT we are committed to building a diverse community based on excellence and commitment. To that end in our recruitment of Doctoral Researchers we welcome applications from outstanding candidates of all backgrounds regardless of ethnicity, disability, gender identity, sexual orientation and will consider all applications equally based on merit.

Should you have any queries regarding the application process at Durham University please contact the Durham MoSMed CDT Manager, Emma Worden at: emma.worden@durham.ac.uk

Newcastle University Durham University UKRI Engineering and Physical Sciences Research Council