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

Generation of DNA aptamers to detect and differentiate between latent and active tuberculosis

Newcastle University, Translational and Clinical Research Institute (NUTCRI)

Newcastle University, Biosciences Institute (NUBI)
Durham University, Department of Chemistry

Supervisory Team	• **Principal Investigator: Dr Neil Keegan, NUTCRI** • **Co-Investigator: Dr Alistair Brown, NUBI** • **Co-Investigator: Dr Clare Mahon, Durham University**

Project overview

Tuberculosis (TB) is the leading cause of mortality from an infectious disease worldwide, with one third of humans already infected with *Mycobacterium tuberculosis* (*Mtb*), either in the active or latent form, representing a huge reservoir of disease. The current landscape of TB is characterised by; a lack of efficient diagnostic methods at the Point-of-Need, increasing appearance of multidrug resistant strains, ineffective therapeutic coverage and the lack of a universal vaccine. This project will improve diagnostic provision by developing novel recognition molecules – DNA-aptamers - that bind to unique biomarkers in the *Mtb* membrane, differentiating between active and latent TB infections.

Research Project

Are you interested in tackling the re-emerging problem of infectious diseases and antimicrobial resistance? The WHO estimate there are 1.6 million TB related deaths annually, which equates to a global health issue worthy of our attention. The aim of this research project is to develop agile and globally impactful Point-of-Need diagnostics for TB.

Despite the WHO led “End TB Strategy” and the advances in diagnosis and treatment, it is estimated that 37% of annual TB cases are unreported. These “hidden” 3.6 million TB cases are the main factor associated with TB transmission, including multidrug resistant (MDR)-TB. Additionally, post-primary re-activation of TB in latently infected individuals is also a source of new TB cases. Significantly, developing countries with endemic TB have limited access to diagnostic technologies and treatment. These countries can only diagnose and treat latent and MDR-TB at well-equipped specialized medical centres. The lack of decentralized access to TB diagnostic tests makes early detection, treatment and follow-up difficult. This project will enable the development of new diagnostic solutions by generating reagents that can differentiate between latent and active TB.

The project follows a transdisciplinary approach to science allowing the student to work across traditional scientific boundaries. In the initial phase, we will focus on molecular microbiology and *Mtb* growth to obtain stocks of the latent and active TB biomarkers. In the second phase, we will use an *in vitro* selection approach based on combinatorial chemistry and molecular biology - systematic evolution of ligands by exponential enrichment (SELEX) - to find DNA aptamers that bind our target biomarkers with high specificity. Extensive biophysical characterisation studies will be undertaken after the selection process. In addition, the aptamers will allow the team to investigate TB persistence from a molecular microbiology standpoint. In the final phase, we will move towards translational work. Aptamers that

identify/differentiate between latent-TB and active-TB could greatly improve on traditional laboratory tests. In addition, the aptamers will be used for next generation Point-of-Need test development. Dr Keegan is a key academic within the Interdisciplinary Research Collaboration (IRC) i-sense, a national research effort focussing on decentralized diagnostics. Therefore, i-sense Point-of-Need solutions – https://www.i-sense.org.uk/ - will be available to use with the aptamers developed in this project.

In short, the project provides an exciting opportunity to carry out TB research and translate the results into diagnostic applications.

Training & Skills

Dr Keegan will supervise the combinatorial chemistry / molecular biology approach – SELEX. He will also supervise the development of translational assays suitable for deployment at the Point-of-Need. The training will cross the boundaries of biochemistry / biomedical sciences /biotechnology. Dr Brown will focus on molecular microbiology providing the student with a wealth of *Mtb* knowledge and supervise experiments that increase our understanding of *Mtb* persistence. Dr Mahon will supervise the biophysical characterisation studies providing training in structural analysis and molecular interactions. The transdisciplinary training model described will produce a well-rounded scientist, with many desirable skills and a wide career path.

Through the Centre for Doctoral Training, you will also access a bespoke training programme of transferrable skills focussed on science, innovation and business skills. Dr Keegan will also signpost translational training available via i-sense https://www.i-sense.org.uk/research-and-training/education-alliance

Further Information

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How to Apply

You must apply through the University's online postgraduate application system

You will need to:

- Insert the **programme code 8207F** in the programme of study section
- Select '**PhD in Molecular Sciences'** as the programme of study
- Input (only) the **studentship reference code (e.g. 21_07)** that you are applying for in the studentship/partnership reference field when prompted (all codes are outlined in the individual project adverts found on the MoSMed website: https://research.ncl.ac.uk/mosmed/phdstudentships/).
- Attach all documents that are requested including a CV and cover letter. The cover letter must **clearly** state the project reference code, the full title of the studentship and set out how your interests and experience relate to the project
- Attach degree transcripts and certificates and, if English is not your first language, a copy of your English language qualifications
- Email: mosmed.cdt@ncl.ac.uk once you have submitted your application to confirm the project you have applied for. Please include the studentship reference code and full project title.

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