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

Natural Products, Synthetic Biology and the Formulation of Novel Antimicrobials

Durham University, Department of Biosciences and Newcastle University, Biosciences Institute

Supervisory Team	• **Prof. Paul Denny, Dept. of Biosciences, Durham University (Lead Supervisor)** • **Prof. Jan Quinn, Biosciences Institute, Newcastle University (co-supervisor)**

Project overview/context

Leishmaniasis and serious fungal disease, both caused by complex eukaryotic pathogens, are global problems for which we are only equipped with a limited array of drugs which are threatened by increasing resistance. With the failure of conventional small molecule drug screening and rational drug design to reveal new antileishmanials and antifungals, attention has turned once again to the natural world – the original source of most antimicrobials. In a collaborative project, involving partners from academia and industry, we will identify and evaluate the efficacy, mode of action and clinical potential of modified natural product antimicrobials against *Leishmania* species and *Candida albicans*.

Research Project

Natural products are a mainstay of treatments for leishmaniasis and fungal disease. Amphotericin B (AmB), a polyene natural product from *Streptomyces nodosus,* is licensed to treat life-threatening fungal infections and is deployed in the Asian leishmaniasis elimination programme. In both cases AmB is extremely potent with broad-ranging activity. However, issues with toxicity can lead to discontinuation. In addition, poor solubility makes administration problematic.

AmB functions by binding ergosterol, the primary sterol in the plasma membrane of fungi and *Leishmania* species. In recent work we have identified a potent antileishmanial triterpenoid saponin where selectivity was also postulated to depend upon ergosterol.

Natural products are challenging and non-cost effective for chemical synthesis. AmB is no exception and in this project we are collaborating with Prof Jason Micklefield (University of Manchester) who is bioengineering *S. nodosus* to deliver AmB derivatives to reduce toxicity and improve bioavailability. The successful candidate will spend time in Manchester working with the Micklefield group to select and purify derivatives for further evaluation. These and the antileishmanial saponin (provided by our industrial partner Naturiol Ltd) will then be screened for their ability to kill the fungal pathogen *Candida albicans* (Newcastle) and *Leishmania* (Durham) in established assays.

Subsequently, the selected active compounds will be screened against defined AmB resistant *Leishmania* and an inhouse library of parasites with mutations in genes involved in the synthesis of the sterols associated with drug sensitivity (Durham). This will directly inform us of the genes associated with *Leishmania* polyene resistance and subsequently, equivalent mutants in orthologous genes in *C. albicans* will be obtained/created and evaluated for polyene and saponin resistance (Newcastle). Together these two data sets will clarify the mode of action of these compounds.

The ambition is to identify active, soluble and bioavailable polyenes which can be developed for oral therapies. However, many natural products require formulation to facilitate activity, the saponin being one. Integrating with a collaborative project with Dr Justin Tian (Queens Belfast) insoluble compounds will be formulated into liposomes. The activity of these will then

be analysed against *C. albicans* and *L. mexicana* infected macrophages (Durham and Newcastle), with hits entering preclinical studies.

Training & Skills

To ensure the polyene compound triage is successful the appointed candidate will undertake a 6-8 week placement in Manchester to gain familiarity with synthetic biology platforms and practical experience of compound purification and QC. Subsequently, *Leishmania* and *Candida* work at Durham and Newcastle respectively will facilitate the successful candidate to gain expertise in category 2 pathogen manipulation, assay development and industrial standard compound screening. During this time, liaison with Naturiol Ltd to discuss results will also be undertaken, facilitating an understanding of the potential of university spin-outs. Hit compounds will then be subject to mode-of-action analyses in both the fungal and protozoan pathogens faciliatating skills development in modern molecular genetic technology as applied to human pathogens. In the final phase, the appointed candidate will gain experience of advanced drug formulation in a 6-8 week placement in Belfast before further compound evaluation and assessment of the potential to enter preclinical studies.

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 **MoSMed22_10** in 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

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