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

New methods for scaled synthesis of nucleoside 5'-triphosphates and their application in gene synthesis

Durham University, Department of Chemistry, Evonetix Ltd, Cambridge UK and Centre for Life, Newcastle.

Supervisory Team	• **Dr. David R. W. Hodgson, Dept of Chemistry, Durham University (Lead Supervisor)** • **Dr. Guy Kiddle, Evonetix, (co-supervisor)** • **Dr. Michael Hodskinson, Evonetix, (co-supervisor)** • **Prof. Majlinda Lako, Faculty of Medical Sciences, Newcastle University (co-supervisor)**

Project overview/context

Despite their ubiquity across medical and biological sciences, robust, routes towards the efficient delivery of large quantities of deoxynucleoside 5'-triphodphates (dNTPs) are still not routinely available. The need for dNTPs has increased with the advent of synthetic biology and nucleic acids-based therapies, specifically in the guise of delivering high quality, low cost nucleic acid products. Evonetix Ltd is developing disruptive technologies that require novel dNTPs, on scale, to bring their enzymatic gene synthesis technology to market. This project will develop new, scalable approaches towards the preparation and purification of dNTPs using batch and flow chemistries and new chromatographic strategies.

Research Project

We aim to deliver affordable synthetic routes for modified dNTPs for synthetic gene production that will underpin biotechnology and biomedical sciences. Our findings will also be applicable across NTP and dNTP systems that are widely used in academic and industrial research settings.

Background
Since the advent of the phosphoramidite approach and the availability of 'gene machines' nucleic acid tools have powered several revolutions within the biosciences, medicine and industry, including the Next Generation Sequencing and Synthetic Genes 'booms'. Currently, the lack of rapid access to large arrays of high fidelity, synthetic DNAs is a limitation to exploring varied gene products efficiently, in parallel. The Evonetix technology platforms, including the novel, complementary pairing of an engineered enzyme with designed dNTPs developed between Durham and Evonetix, promises to remove these bottlenecks.

Research Plan
Preliminary findings from Durham will be developed through this programme to provide a platform for dNTP production. Specifically, the student will work on:

1. Delivery of improved synthesis technologies for dNTPs

The student will explore the reactivities of phosphorylating and phosphitylating reagents and apply these findings in flow. Flow Chemistry offers controlled, repeatable mixing procedures that are readily scalable.

2. Delivery of improved purifications of dNTPs

The student will explore the use of off-the-shelf pre-packed cartridge-based chromatography media for efficient purifications of dNTPs. These will be further explored alongside controlled precipitation strategies.

3. Use of dNTPs in enzymatic technology platform at Evonetix

The student will gain 'hands-on' biological experience of using their dNTP products at Evonetix, in enzyme assay

development and applying these tools to on-chip DNA synthesis. Their time in Evonetix will also allow them to gain invaluable experience of a start-up alongside exposure to engineering, product development, automation, in-silico synthesis, the QC validation process and many other aspects of a truly interdisciplinary commercialization strategy.

Training & Skills

The student's primary area of training and skills development will be in the field of nucleotide synthesis.

The student will be involved in regular meetings with the interdisciplinary team at Evonetix to discuss progress across chemistry, protein engineering, assay development, surface chemistry, device engineering and product testing pillars of the project.
The student will spend time working on-site at Evonetix at a later stage of the programme to transfer knowledge and capability. They will gain experience of working in a vibrant, growing start-up company and an appreciation of the broader programme in its commercial context

Further Information

Please contact David Hodgson (d.r.w.hodgson@durham.ac.uk) if you require further details.

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_11** 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

Newcastle University Durham University UKRI Engineering and Physical Sciences Research Council