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

Diversification of DNA-encoded libraries by photoredox catalysed sp^3-coupling

Newcastle University, Cancer Research UK Newcastle Drug Discovery Unit
Partners: Durham University, AstraZeneca

Supervisory Team	• **Mike Waring (Newcastle) - Lead supervisor** • **Akane Kawamura (Newcastle)** • **Nidhal Selmi (AstraZeneca)**

Project overview/context

The project will develop new methods for making DNA-encoded libraries using photoredox catalysis, a new method in organic synthesis for coupling of sp^3 carbon centres. The project will develop photoredox coupling reactions to on-DNA substrates and use the methods prepare novel lead-like libraries. The project is co-sponsored by AstraZeneca, a world leading pharmaceutical company and the work will be carried out in close collaboration with them. The project will be ideal for students with ambitions for a career in organic and medicinal chemistry research.

Research Project

DNA-encoded libraries provide an exciting new technology for finding startpoints for new drug discovery. They consist of a collection of small molecules, which are covalently attached to a unique DNA-tag that is unique to each compound. This allows the library to be screened against protein targets very efficiently.

Despite the current promise offered by DNA-encoded libraries, further DNA-compatible chemistry to synthesise more chemically diverse libraries is highly desirable. In particular the coupling of sp^3 carbon centres to produce compounds of greater 3-dimensionality would be very beneficial. Photoredox chemistry, an area of cutting edge synthetic chemistry, offers a number of versatile methods to install a variety of sp^3-rich moeities. However, the application of photoredox chemistry to on-DNA synthesis is currently limited.

The project will start with development of the reactions using photoredox coupling using model DNA-tagged substrates. We will explore a small set of reactions that allow the coupling of various reagents, particularly those with sp^3 carbon centres This will establish the optimum conditions for carrying out the reaction. It will commence with screening of conditions followed by reaction optimisation exploring multiple factors such as substrate concetrations and catalyst loading to establish the best conditions that are applicable across a broad substrate scope.

With reaction conditions established, a series of libraries will be synthesised that exploit the methodology. These libraries will be screened against proteins of interest to establish their utility.

Once the screening is complete, hits will be resynthesised without their DNA tags to validate their activity and a small SAR study will be carried out around the hits to demonstrate their optimisatbility.

Training & Skills

The project will provide invaluable training in the fields of organic synthesis, chemical biology and molecular design, which will be highly desirable for a future career in medicinal chemistry or related areas. The work will provide a particular focus on the growing fields of DNA-encoded library synthesis and follow up medicinal chemistry.

Reaction optimisation will be carried out using statistical techniques such as factorial experimental design and

hence will also provide ideal training for organic reaction development.
Through the Centre for Doctoral Training, you will also access a bespoke training programme of transferrable skils focussed on science, innovation and business skills.
You will join an vibrant and thriving research group centred on the application of chemistry to biological and medical problems. This will provide an inspiring and supportive environment for your PhD studies.

Further Information

Enquiries should be sent to Prof. Mike Waring, mike.waring@ncl.ac.uk, Tel. 0191 208 8591

How to Apply

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

When applying to Newcastle University please select the Course Code **8207F (PhD in Molecular Sciences)**
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. 22_01)** that you are applying for in the studentship/partnership reference field when prompted (all codes are outlined in the individual project adverts and can be 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 state 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

The project will involve close collabration with the industrial partner, AstraZeneca. An AstraZeneca scientist working in the DNA encoded librariy field will provide additional supervision and the project will involve a placement period in AstraZeneca's laboratories.

Should you have any queries regarding the application process to Newcastle University please contact Selina McCarthy, MoSMed CDT Manager: Selina.McCarthy@newcastle.ac.uk or email mosmed.cdt@newcastle.ac.uk

Within the MoSMedCDT 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.

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