

Application of micellar catalysis to forbidden on-DNA reactions

Newcastle University, Cancer Research UK Newcastle Drug Discovery Unit

Partners: Durham University, Exscientia

Supervisory Team

- **Mike Waring (Newcastle) – Lead supervisor**
- **Akane Kawamura (Newcastle)**
- **Garry Pairaudeau (Exscientia)**

Project overview/context

The project will develop new methods for making DNA-encoded libraries using our recently developed micellar catalysis methods. The project will extend the range of DNA-compatible chemistry to explore the potential for micellar approaches to facilitate traditionally DNA-incompatible reactions. The methods developed will then be used to prepare novel lead-like libraries. The project is co-sponsored by Exscientia, one of the world's fastest growing pharmaceutical companies 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. Many traditional methods of organic synthesis are not compatible with DNA-tagged substrates. For example acidic and oxidising conditions cause DNA damage and dehydration reactions are disfavoured because of the need to carry out reactions in water. Our recently developed micellar methodology

has the scope to enable these traditionally forbidden reactions by localising the organic reactants to the substrate portion of the molecule and protecting the DNA-tag from the reaction conditions.

In this project we will explore the feasibility of this concept using a range of acid catalysed reactions. The project will commence with a screen of reagents and conditions and the most promising conditions will then be optimised to establish the best conditions across a range of substrates.

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 optimisability.

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

skills 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_02)** 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/>)

The project will involve close collaboration with the industrial partner, Exscientia. An Exscientia scientist working in the DNA encoded library field will provide additional supervision.

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- 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

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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