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

Expanding the Build-Couple-Transform paradigm to develop highly diverse screening libraries for drug discovery Newcastle University (Chemistry), Durham University

Supervisory Team	• **Prof. Mike Waring (Newcastle), Dr. Hannah Stewart (Newcastle), Dr. Natalie Ellison (Newcastle), Dr. Allegra Franchino (Durham)**

Project overview/context

Compound libraries provide ideal hits for drug discovery, but their construction usually relies on a common starting material, meaning the libraries lack scaffold diversity. Our Build-Couple-Transform paradigm addresses this, using multiple diversification reactions on a central template to produce an array of scaffolds. This project will develop new organic chemistry to build libraries, with a focus on saturated heterocycles. The libraries will be tested to identify hits against novel protein targets. The project will provide ideal training in organic synthesis and medicinal chemistry design and will be ideally suited for a student wishing to explore a career in drug discovery.

Research Project

Introduction

We have developed a new paradigm for the generation of lead-like libraries with scaffold diversity: Build-Couple-Transform (BCT, J Med Chem 2022, 65, 11322). Nineteen transformations of a reactive central template were developed and applied to pools of 4 or 5 compounds. Screening of these pools delivered hits for a number of proteins (e.g. CDK2).

In this project, we will expand the BCT paradigm to new templates and transformations, ultimately resulting in new pooled libraries to be screened against proteins with potential applications to cancer. The project will expand the BCT paradigm, validating its utility within drug discovery. Its power will then be exemplified through screening, validation and optimisation of resulting hits against important targets within oncology.

Workplan

1. **Original Transformations**

Expansion of the published transformations to related central templates will change both the nature of the resulting scaffolds and the substituent vectors: affording new libraries with further diversity.

2. **Novel Templates and Transformations**

A novel core template, offers the opportunity to develop an entirely new set of transformations, giving rise to a lead-like library covering a new area of chemical space and therefore offering potential hits against different protein targets. A limiting factor in existing lead-like screening libraries is the prevalence of “flat” aromatic scaffolds, therefore, the focus for this new set of transformations will be saturated heterocycles derived from substituted imines, which can undergo a range of 1,2 and 1,3 cycloadditions, giving access to 4-, 5- and 6-membered saturated heterocycles, aromatic heterocycles and more.

3. **Pooled Libraries**

The optimised transformations will be applied to pools of 4-5 compounds, efficiently demonstrating the scope of the transformations with regard to the substituents whilst much more rapidly and efficiently synthesising screening libraries.

4. **Biological Screening and Lead optimization**

The resulting libraries will be screened against novel protein targets through an initial screening triage by SPR. Potential hits will then be soaked with protein crystals to identify which of the pooled compounds has

hit. The efficient 3-step route enables rapid follow-up synthesis of the individual component of the pool to validate the hit.

Training & Skills

The project will provide essential training to the student in:

- Organic synthesis as applied to medicinal chemistry
- Medicinal chemistry design principles, with particular emphasis on structural diversity and physicochemical properties in screening libraries
- Synthesis and application of diversity oriented screening libraries
- Broad knowledge of the science of medicinal chemistry and structural biology
- Transferrable skills in scientific methods, management and leadership through the CDT training programme.

Together, this will provide a skillset that is the ideal basis for a career in medicinal chemistry or chemical biology.

Further Information

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

How to Apply

If applying to a **Newcastle project**, you must apply through the University's **Apply to Newcastle Portal**. Once registered select **'Create a Postgraduate Application'.**

Please note, at this time we can only accept applications from students who qualify for UK/home fees for this project. Please see the URKI website for more details.

Use 'Course Search' to identify your programme of study:

- search for the 'Course Title' using the programme code: **8207F**
- select '**PhD Molecular Sciences for Medicine (SNES)'** as the programme of study

You will then need to provide the following information in the 'Further Questions' section:

- a 'Personal Statement' (this is a mandatory field) - upload a document or write a statement directly into the application form. Please include the full title of the studentship, the studentship code, and how your interests and experience relate to the project.
- the relevant studentship code **(mos23_13)** in the 'Studentship/Partnership Reference' field. If you wish to apply for additional studentships, please make sure to add the relevant studentship reference each time, before submitting each separate application. For example, you may wish to apply for mos23_13 AND mos23_14. **You must include the relevant code for your application to be considered.**
- when prompted for how you are providing your research proposal - select 'Write Proposal'. You should then type in the title of the relevant research project. You do not need to upload a research proposal.
- An up to date CV.
- Please upload all documents in PDF format.

Equality, Diversity and Inclusion (EDI)
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 MoSMed application process to Newcastle University please contact Craig Hinds, the MoSMed CDT Manager: **mosmed.cdt@newcastle.ac.uk.**

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