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

Lead optimization by DNA-encoding

Newcastle University (Chemistry), Durham University, Evariste Technologies

Supervisory Team	• **Prof. Mike Waring, Newcastle University (Lead)** • **Dr. Mat Martin, Newcastle University** • **Prof. Ehmke Pohl, Durham University** • **Dr. Alfie Brennan, Evariste**

Project overview/context

The project will explore new methods for medicinal chemistry optimisation for drug discovery using DNA-encoding. DNA-encoded approaches are established in the early (hit discovery) stage of drug discovery but their use in later stage optimisation is relatively unexplored. We will develop new approaches for using DNA-encoded methods to explore optimisation of potency and ADME properties. In collaboration with Evariste Technologies (a cutting-edge AI-based drug discovery company), the project will involve oragnic synthesis as applied to medicinal chemistry and will provide ideal training for a student wishing to pursue a career in medicinal chemistry or chemical biology.

Research Project

Within the group, we have developed new methodology for the synthesis of DNA-encoded compounds with, in some cases, unparalleled efficiency. This has been applied to the synthesis of screening libraries. In this project we will expand on these preliminary results and apply the approach to optimization of compounds for exemplar proteins with potential application in cancer.

The project will develop a new method for carrying out the early stages of compound optimization, harnessing the advantages of DNA-encoded synthesis, such as the vastly increased compound throughput and reduced synthesis time.

Workplan

1. Compound synthesis

We will develop new approaches to synthesise set of DNA-tagged compounds that are targeted to the proteins of interest and designed to explore structure-activity relationships. This will exploit the novel chemistry for synthesis of DNA-conjugates that has been established in the group and apply them to specifically designed inhibitors.

2. Potency Evaluation

All DNA-encoded libraries are thus far screened by affinity selection. Ironically, the quantitative link between ligand affinity and pull-down frequency has not been investigated. For hit finding, generally the output reveals a binary (binder / non-binder) result. Using the proteins and targeted libraries identified in stage 1, alongside a selected set of on- and off-DNA hits with a range of affinities, correlating them with Kd values determined by SPR.

3. ADME screening

In addition to potency data, determining ADME data is critical for compound optimization. A potential drawback of the use of DNA-encoded maturation is that such data can not easily be determined for on-DNA substrates. However, it is possible routine screens, such as microsomal stability and permeability could be carried out on DNA tagged substrates providing additional useful data for multi-parameter optimisation. We will assess these assays on model DNA-linked substrates and on pooled libraries and develop them further to generate comparable data to their off-DNA analogues.

4. Lead optimization

With these data in hand, a subsequent cycle (or more if time permits) of compound maturation using designed libraries based on the most promising hits will be carried out for a selected target to demonstrate practical applicability of the approach.

Training & Skills

The project will provide essential training to the student in:

- Medicinal chemistry design principles, with particular emphasis on potency and physicochemical property optimsation
- Organic synthesis as applied to medicinal chemistry
- Synthesis and application of DNA encoded 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'.**

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_12)** 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_12 AND mos23_13. **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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