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

The design, synthesis and application of covalent fragment libraries

Newcastle University, Cancer Research UK Newcastle Drug Discovery Unit

Partner: Astex Pharmaceuticals

Supervisory Team	• **Mike Waring (Newcastle) - (Lead)** • **Martin Noble (Newcastle)** • **Ehmke Pohl (Durham)** • **Chris Johnson (Astex)**

Project overview/context

Covalent drugs have undergone a renaissance recently, partly due to the success of cancer treatments such as ibrutinib and osimertinib. Covalent inhibitors can have improved efficacy and specificity. However, new methods for their discovery are highly desirable.
Fragments are an effective approach to new candidate drugs and are of great interest in covalent drug discovery.
The project will explore new fragment-based approaches to covalent inhibitors by synthesising probe compounds to define the ideal properties of covalent fragment leads, build a covalent library and incorporate these fragments into a larger DNA-encoded library.
The compounds will be tested in representative protein targets.

Research Project

Typically, covalent drugs have been discovered by introduction of a covalent “warhead” onto an existing potent reversible inhibitor. This is only applicable in cases for which a ligand already exists and therefore can not be used for novel proteins.
Alternatively, there have been recent attempts to develop libraries of lead-like and fragment-based covalent compounds to allow direct identification of covalent compounds through screening. Bespoke lead-like libraries are hard to design due to the size of chemical space. Covalent fragments, reduce the magnitude of this problem by being inherently smaller and simpler. However, their activity usually dominated by their reactivity, leading to a lack of specificity and making the optimization difficult. Hence, it is critical that a covalent fragment library consists of compounds capable of making productive non-covalent interactions. We will establish the principles of an optimal library, produce a prototype library and screen against exemplar proteins. We will also apply this learning to larger libraries with DNA-encoding.

Workplan

1. Establishing properties for a covalent fragment
We will design, synthesise and screen a series of probe molecules against a set of covalent protein targets to establish the guidelines for the design of covalent fragments.

2. Design a covalent fragment library
We will use the information from Part 1, combined with our existing knowledge of non-covalent fragments to design and synthesis new covalent fragments that will form a screening library for application to novel proteins.

3. Design and screening of covalent DELs
DNA-encoded libraries (DELs) offer a complementary approach to fragment-based lead generation, as they allow the screening of large numbers of more complex compounds. The development of covalent DELs has challenges related to the compatibility of reactive compounds. We will use kowledge from the early part

of the project to incorproate covalent groups into DELs and explore approaches to screening them against protein targets.

Together this project will give new insights into methods for identifying covalent inhibitors. The project will establish new methodology and lead to new chemical hits for established non-proprietary proteins as well as providing a resource for the future discovery of novel compounds applicable to a range of target classes.

Training & Skills

The project will provide essential training to the student in:

- Medicinal chemistry design principles, with particular emphasis on fragments
- Organic synthesis as applied to medicinal chemistry
- Principles of biocompatible covalent reactivity
- Biophysical techniques and structural biology for characterisation of protein ligand complexes
- Broad knowledge of the science of medicinal chemistry and structural biology
- Tranferrable 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

For further information contact the lead supervisor Prof. Michael Waring: mike.waring@ncl.ac.uk
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How to Apply

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

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. 21_05)** that you are applying for in the studentship/partnership reference field when prompted (all codes are outlined in the individual project adverts 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 set out 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
- Email: mosmed.cdt@ncl.ac.uk once you have submitted your application to confirm the project you have applied for. Please include the studentship reference code and full project title.

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