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

Proteomics-based assessment of drug performance *in vivo* by establishing target engagement methods and characterizing new disease models

Newcastle University (Biosciences Institute)
Durham University
Boehringer Ingelheim (BI), Biberach, Germany

Supervisory Team	• **Prof Matthias Trost, Newcastle University (Lead)** • **Dr Maria Dueñas, Newcastle University** • **Dr Tom Bretschneider, BI** • **Prof Ehmke Pohl, Durham University**

Project overview/context

Precise predictions of the performance of drug candidates in patients from pre-clinical systems is key for a successful drug development. These predictions require an in-depth understanding about the interaction of a drug with its biological target and the testing of these in translatable disease models.
The quantitative assessment of the binding of a drug candidate with its target especially within *in vivo* experiments provides essential information to improve the prediction of the drug efficacy.
Moreover, selecting the right animal model to test the drug performance is crucial in this context.
In this work, state-of-the-art proteomics methods will be established to assess the *in vivo* target engagement of drugs and new animal models will be characterized to improve their predictiveness.

Research Project

Modern drug discovery is based on new therapeutic concepts (NTCs), which are largely unexplored. The ambition is to develop innovative treatments for patients with unmet medical need.
Challenges within the work on these NTCs are, to build an understanding of the target biology, target-to-disease link and to translate pre-clinical to clinical information.
Studying the interaction of a new drug candidate with its target biology is of utmost importance for a successful drug development. In particular, two major information are of relevance in that regard.
Firstly, demonstrating engagement of chemical matter with the biological target is of relevance for the assessment of the selectivity and efficacy of the drug candidate. Especially understanding the quantitative relationship of the pharmacokinetics and target-engagement of is key for predicting the performance of a drug candidate in human. Various biophysical, structural, and biochemical approaches are available. However, their applicability to samples from *in vivo* experiments is limited. Proteomics-based approaches made good progress in the past years to gather target engagement information. In this PhD project, we will develop methods for the quantitative determination of target engagement of drug candidates from *in vivo* samples (e.g. tissue, plasma) via Thermal Proteome Profiling within which the Trost group has substantial expertise (Miettinen et al, EMBO J, 2018; Marin-Rubio et al, J Med Chem, 2022).
Secondly, animal models play a crucial role in the pre-clinical assessment of drug candidates. The selection of the right model for the right purpose is detrimental to generate predictive outcomes for the human situation. The selection of such models is depending on their mechanistic biological understanding and overlap to available human data. For both, a molecular characterization especially of newly established models is the basis for decisions. In this PhD project, we will characterize new disease models towards the proteomic signature and provide hypothesis for their molecular mode-of-action.

Both projects will utilise heavily state-of-the-art proteomics methods and data analysis for the improved

characterization of drug candidates to provide innovative medicines to patients in future.

Training & Skills

The student will receive training in a wide range of techniques, including mass spectrometry, proteomics, data analysis using R, biochemistry, and medicinal chemistry.
Within the CDT, the student will have a number of programmes available to learn new "soft" skills, including a taught training programme and the opportunity to complete a "mini-MBA".

Further Information

Please contact Prof Matthias Trost for details: matthias.trost@ncl.ac.uk

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_11)** 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_11 AND mos23_12. **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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