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

A novel drug discovery workflow combining DNA-encoded library, AI machine learning, and cryo-electron microscopy

Newcastle University Biosciences Institute

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Project overview/context

Structural biology has become a *tour de force* enabling the discovery of small molecules for novel medicine. More recent technological advances give rise to innovative screening platforms by affinity selection (DNA-encoded library), computational algorithms to systematically analyse and predict hits (machine-learning), and alternative high-resolution structural techniques without crystallization (cryo-electron microscopy). Using as exemplar an emerging therapeutic target, the metabolic enzyme glycogen synthase, this project establishes a workflow for hit discovery and optimization that incorporates these cutting-edge technologies, and validates its utility for target proteins that are less well explored in drug discovery.

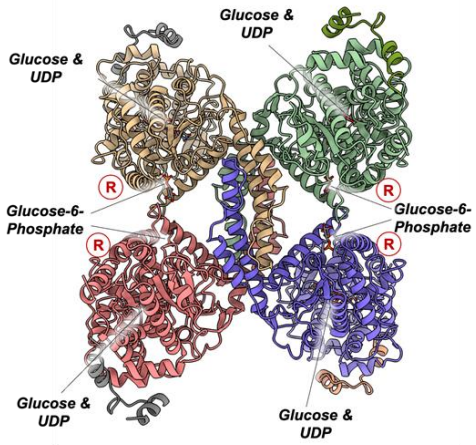
Research Project

The advance of high-throughput protein structures by x-ray crystallography has facilitated greatly hit discovery and optimisation for novel drug development. Nevertheless, many important therapeutic targets (*e.g.* protein complexes, membrane proteins) are recalcitrant to crystallisation, the pre-requisite for x-ray structure determination.

On another hand, the 'resolution revolution' of single-particle cryo-electron microscopy (cryo-EM) has elevated itself to be a worthy contender for application in structure-based drug design. Using human glycogen synthase (GYS1) as exemplar, this project aims to establish a novel unique workflow for structure-based drug discovery.

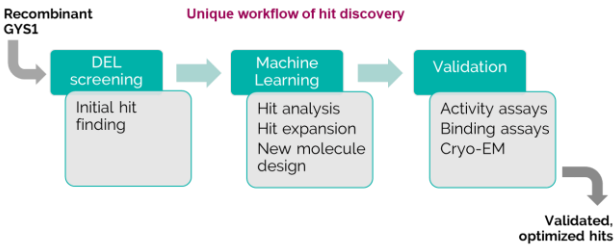
GYS1 is an emerging therapeutic target for Pompe and allied diseases in glycogen metabolism, although very few inhibitors are available, due in a large part to the lack of GYS1 3D structures and inherent difficulties in its crystallization. We have recently made breakthrough by determining the structure of human GYS1 for the first time using cryo-EM.

3.0 Å resolution cryo-EM structure of GYS1



This project exploits three innovative platform technologies, namely DNA-encoded library (DEL) screening, artificial intelligence (AI)-driven machine learning (ML), and cryo-EM structure determination, to identify, design and characterise small moleules that act on the GYS1 enzyme.

The student will be based in a structural biology lab, work closely with medicinal chemists and computational chemists, and interact with industrial AI specialists at Standigm Inc, in order to explore the uncharted small molecule chemical space for GYS1.



The impact of the project is two-fold: (1) novel chemical matters for GYS1 towards the goal of first-in-class small molecule therapy; (2) a generalisable drug discovery workflow, incorporating the three state-of-the-art technologies, for less explored target proteins.

Further reading:
https://doi.org/10.1016/j.bmc.2021.116273
https://www.nature.com/articles/d42473-020-00354-y
https://doi.org/10.1101/2021.11.12.468446

Further Information

Email wyatt.yue@newcastle.ac.uk
Visit https://www.staff.ncl.ac.uk/yuelab/
Follow on @TheYueLab

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_07)** 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/)
- 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

Training & Skills

The student will have a unique opportunity to work at the interface of academia (Newcastle, Durham) and industry (Standigm Inc) labs, towards early stage drug discovery. The supervisory team will provide multi-disciplinary training and access to facilities in the cutting-edge fields of structural biology, high-throughput screening, and computational biology. The student will be supported in writing manuscripts and presenting findings at international conferences. These training skills and experience will be highly valuable for career development in translational research and medicine discovery.

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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