

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



Structure-guided approach to assay development for inhibiting Dengue virus replication

Department of Biosciences, Durham University

Supervisory Team

- Lead Supervisor: Dr Liz Morris, Assistant Professor (Biochemistry), Department of Biosciences, Durham University
- Co-Supervisor: Dr Jon Marles-Wright, Senior Lecturer, School of Biology, Newcastle University

Project overview/context

Dengue virus, transmitted by mosquitos in Africa, Asia and central America, infects hundreds of millions of people and causes around 20,000 deaths, primarily in children, each year. With no licensed drugs and a vaccine recommended to people only after a previous Dengue infection, new anti-viral therapeutic strategies are needed.

Previous research has revealed the structures of Dengue virus proteins and RNA. However, it remains unknown how these molecules assemble. Here, we will determine how proteins interact in the “Dengue virus replication complex” and design high-throughput assays for drug discovery against Dengue and related viruses such as Zika.

Research Project

About the Project:

We are seeking an enthusiastic and motivated PhD candidate to study how the Dengue virus enzymes NS3 and NS5 assemble for viral replication and develop high-throughput assays for small molecule screening.

Dengue virus infects ~390 million people and kills ~20,00 people, including children, annually, mostly in tropical climates. Few drugs are licensed for RNA viruses in general and none for Dengue or other flaviviruses.

A structure-guided approach accelerates drug discovery but requires information about the structure and organization of protein targets. The Dengue virus replication complex is an assembly of 7 non-structural proteins that replicates the short RNA genome of the virus. Equivalent complexes are targeted in other anti-viral treatments, such as against Hepatitis C (a close relative of Dengue), HIV, SARS-CoV-2 and the Herpes Simplex type 1 virus. However, the assembly of the Dengue virus replication complex remains poorly characterised.

Here, you will use structural biology and biophysics methods to determine how the two Dengue enzymes, NS3 and NS5, interact at the heart of this complex. You will collect electron microscopy and small angle X-ray scattering (SAXS) data and build a model of the NS3-NS5 complex using previous X-ray structures of the individual proteins. Subsequently, you will develop high-throughput assays to screen small molecules that inhibit the assembly and enzyme activities of this complex. This will enable future *in vitro* and *in silico* drug discovery efforts.

You will gain training in the following techniques:

- Single particle electron microscopy
- SAXS
- X-ray crystallography
- Protein structure prediction, such as AlphaFold
- Developing high-throughput enzymological assays to screen small molecules
- Förster resonance energy transfer (FRET) assay development
- Recombinant protein expression and purification



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About You:

You must possess or expect to obtain at least an upper second class Master's or a first class Bachelor's degree in Biochemistry, Biology, Chemistry or a related discipline. This project will suit someone with a keen interest in the structures of proteins and a curiosity in structure-guided drug discovery. Prior experience in structural biology, biophysics or enzymology is not required.

About Us:

This project is hosted by Dr Liz Morris, Assistant Professor (Biochemistry) within the Durham University Biosciences Department. Here, you will join a team of Bioscientists working alongside Chemists studying biomolecular interactions. We have state-of-the-art facilities for protein production, protein biophysics, high-throughput assay development and X-ray crystallography. In addition, you will get training in electron microscopy in Dr Jon Marles-Wright's lab, Senior Lecturer in Newcastle University's School of Biology.

Durham University, where you will primarily be based, is an outstanding centre of research and teaching excellence. Here you will join one of the University's seventeen colleges through which you can access student-led activities, such as sports, theatre, music or volunteering, as well as welfare support.

The student will benefit from a multidisciplinary training approach at the interface between the biological and physical sciences. They will learn a broad range of biological and biophysical techniques, gain experience in developing high-throughput assays for drug discovery and develop a deep understanding of protein structure solving and prediction methods.

In Dr Morris's lab at Durham, the student will gain experimental expertise in molecular biology, bacteriology, recombinant protein production, protein biophysics, enzymology, assay development and structural biology methods including small angle X-ray scattering and X-ray crystallography. This will be complemented by computational approaches including molecular docking and protein structure prediction using machine-learning, such as AlphaFold. In Dr Marles-Wright's lab at Newcastle, training in electron microscopy will be provided in the second year of the project, including grid preparation and data analysis. Experience in electron microscopy, in particular, is highly sought after in academia and industry.

Outside of the lab, the student will be encouraged to attend workshops and courses to complement their learning and develop a further network of peers. In addition, the student will develop transferrable skills such as presentation and writing skills through presenting their work at national and international conferences.

Training & Skills

Further Information

You are encouraged to send informal enquiries (with CV attached and scientific interests detailed) to liz.morris@durham.ac.uk so that we can support your application to the program.

How to Apply

To apply for this project please visit the Durham University application portal to be found at: [Home · Application Portal \(microsoftcrmpportals.com\)](https://microsoftcrmpportals.com)

Please select the course 'PhD in Molecular Sciences for Medicine (EPSRC CDT)', which is registered in the Chemistry Department and indicate the reference **mos23_09** in the 'Field of Study' section of the application form. Please note that there is no need to submit a Research Proposal with your application,

however we do require a Covering Letter, CV, academic transcripts, the contact details of two referees and proof of English language proficiency if relevant.

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 application process at Durham University please contact the Durham MoSMed CDT Manager, Emma Worden at: emma.worden@durham.ac.uk



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