THE UNIVERSITY of EDINBURGH
School of Chemistry

EastBio DTP – Integrating Chemical Cross-Linking and Molecular Dynamics to Map Glycoprotein Interactomes

Enveloped viruses are commonly coated with highly glycosylated glycoproteins termed ‘spikes’, that offer a degree of multivalency through trimeric organisation. Similarly, the cell surface, as well as organelle membranes, are enriched in glycoproteins, importantly being the first site of contact for an invading virus. Glycans play a critical role not only in mediating virus-host interactions but also in immune recognition, where dense ‘glycan shields’ mask epitopes to evade detection. This project aims to interpret chemical cross-linking data using computational modelling to understand how glycan specificity governs protein interactions.

Chemical cross-linking mass spectrometry (XL-MS) is a powerful technique for probing intra- and inter-molecular interactions. By forming stable covalent linkages, XL-MS provides spatial information on which protein regions are in close proximity, acting as a molecular ‘ruler’ Although XL-MS has been widely applied to map protein-protein interactions in isolated organelles, intact virions, and cells, its potential for studying glycoprotein interactomes is mostly unexplored. Collaborators at the University of Oxford have recently made progress in this direction by incorporating metabolic glycoprotein engineering and bioorthogonal click chemistry, enabling the selective cross-linking of glycans or glycoproteins with their interaction partners. However, interpreting the resulting structural data is challenging due to the intrinsic flexibility of proteins and glycan molecules. Glycans, being long and branched, can link to multiple distant binding sites, while proteins occupy a dynamic conformational space.

The student will leverage molecular dynamics simulations to characterize the flexibility of proteins and glycans, and develop models to estimate which binding sites a glycan could reach. By estimating the spatial reach of glycans, the student will develop detailed models of glycosylated protein-protein interactions that better reflect in vivo biology. Initial studies will focus on the SARS-CoV-2 spike protein and its interaction with the ACE2 receptor, before progressing to more complex cellular systems. The student will be embedded into the vibrant community of computational research groups within the School of Chemistry of the University of Edinburgh, and will have the opportunity of visiting our collaborator at the University of Oxford, Dr Sean Burnap, to gain insight on how experimental data is gathered and processed.

Funding Notes

This opportunity is open to UK and international students and provides funding covering stipend and UK level tuition fees. The University of Edinburgh covers the difference between home and international fees meaning that the EastBio DTP offers fully-funded studentships to all appointees. There is a cap on the number of international students the DTP recruits. It is therefore important for us to know from the outset which fees status category applicants will fall under when applying to the University.

Please refer to UKRI website for full eligibility criteria: ‘Get a studentship to fund your doctorate – UKRI’

https://www.ukri.org/apply-for-funding/studentships-and-doctoral-training/get-a-studentship-to-fund-your-doctorate/

How to Apply

Closing date is Friday 17 January 2025, 11.59 pm GMT.

This 4-year PhD project is part of a competition funded by EastBio BBSRC Doctoral Training Partnership (DTP). For detailed guidance on the application process and the EastBio Application and Reference Forms, please see:

https://biology.ed.ac.uk/eastbio/how-to-apply

Please send your completed EastBio Application Form and a copy of your academic transcripts in pdf format to the Chemistry Graduate School, email: chemistry.gradschool@ed.ac.uk

Please also contact your referees and ask them to submit their references on the EastBio reference form template to Chemistry Graduate School, email: chemistry.gradschool@ed.ac.uk by the application deadline of 17 January 2025.

Equality and Diversity

The School of Chemistry holds a Silver Athena SWAN award in recognition of our commitment to advance gender equality in higher education. The University is a member of the Race Equality Charter and is a Stonewall Scotland Diversity Champion, actively promoting LGBT equality.

The University has a range of initiatives to support a family friendly working environment.

For further information, please see our University Initiatives website:

https://equality-diversity.ed.ac.uk/inclusion/family-and-carer