Decoding Heart Failure: Integrating Single-Cell Data for Precision Medicine and Therapeutic Discovery

Principal supervisor: Dr Calum McMullen (LHCS)

Co-supervisors: Dr Wendi Bacon (LHCS), Dr Katja Rietdorf (STEM)

Location: The Open University, Milton Keynes, United Kingdom

Full-time study only.

Duration & Funding: 3 year 3 month studentship; Stipend £18,622 per annum; Training grant £1,100 per annum

Application due date: 4pm, 2nd February 2024

Notification of shortlisting: 5th February 2024

Interview: 12-16th February 2024 via Microsoft Teams

Final Funding Decision: March 2024. This is part of a pooled School process, so the selected applicant will be put forward to a reviewing panel in March for final decisions. Applicants will be notified if they are selected and will be informed of the panel decision afterwards.

Start date: October 2024

Science-related enquiries: calum.mcmullen@open.ac.uk

Process-related enquiries: STEM-LHCS-PHD@open.ac.uk

Research area/keywords: Bioinformatics, Cardiovascular Medicine, Heart Failure
Project background and description

Heart failure (HF) is a leading cause of death worldwide and is an end-stage pathophysiologic state in a number of cardiovascular disorders. HF is mediated by molecular mechanisms that lead to the dysfunction, and eventual loss, of cardiac cells. Though these mechanisms are complex, progress is being made in understanding the dynamic interplay between them and the pathological consequences that ultimately cause the heart to fail.

To better understand this, the Heart Cell Atlas has recently published a nearly 1 million cell databank of single cell and single nuclei data from 25 donors (https://www.heartcellatlas.org). Recent integration of this reference with smaller datasets across multiple cardiovascular diseases has yielded a wealth of cellular subtype and transcriptional signatures (Marisa Loach – OU PhD student, Manuscript in Preparation). In this project, the student will take this data from exploration to clinical application, to identify cellular network interactions in failing hearts that could serve both as a diagnostic marker and as a pharmacological target to ameliorate HF.

This project will use a combination of bioinformatics and wet-lab experiments to identify transcriptional networks in healthy and failing hearts, predict drug targeting of specific cell subtypes and test these in the lab. The computational pipeline will use such drug discovery inference algorithms as Drug2Cell (https://www.sanger.ac.uk/technology/drug2cell/) to predict cellular targets, interactions, and treatment efficacy. The efficacy of promising pharmacological interventions will then be assessed via wet-lab experiments using human iPSC-derived cardiac cells (in collaboration with our industrial partner, Cytochroma Ltd.) in both single cell and co-cultured cardiovascular models. We will examine the effect of these interventions on known HF pathophysiological changes including Ca²⁺ dysregulation, mitochondrial dysfunction, and inflammatory signalling.

Together, this combined ‘wet’ and ‘dry’ lab approach will be used to assess the accuracy of computational modelling in predicting drug targets and determine the efficacy of treatments to alleviate HF pathophysiology.

References

Eligibility

1. Applicants will have a First Class or Upper Second undergraduate degree or Masters degree (or equivalent experience) in Pharmacology, Biomedical Science, Biochemistry, Bioinformatics, Computer Science or a related area
2. The student would be required to live in the UK and within commuting distance to The Open University in Milton Keynes
3. Both UK and overseas students may apply for this project. The registration for non-UK students will be covered by this project, but not visa or NHS costs
4. This project is a combination of bioinformatics and cardiovascular biology and will involve both lab experiments and computational work. Please only apply if you are willing to do both aspects

Desirable Criteria

Though previous experience in the following is not essential (all of the techniques required for this project can be learned), this project would be well-suited to candidates who:

1. Are experienced in mammalian cell culture.
2. Have experience in cell imaging/microscopy (wide-field or confocal fluorescence microscopy) and/or molecular biology techniques (electrophoresis, Western blotting, IHC/IF, flow cytometry etc).
3. Have excellent communication skills, the ability to conduct scientific literature searches independently, and data analysis experience with proficiency in statistical software.
4. Are interested in or have experience with bioinformatics analysis.
5. Are interested in or have experience with Galaxy (a run through this tutorial would suffice as a minimum: [https://training.galaxyproject.org/training-material/topics/introduction/tutorials/galaxy-intro-short/tutorial.html](https://training.galaxyproject.org/training-material/topics/introduction/tutorials/galaxy-intro-short/tutorial.html))

Most importantly, applicants should have a passion for cardiovascular biology/bioinformatics and a willingness to learn.

We are committed to widening participation and awarding PhD studentships to a diverse community of applicants. We particularly welcome applications from under-represented groups. Equal Opportunity is University policy.
How to apply

Please check this page for application entry requirements: https://www.open.ac.uk/postgraduate/research-degrees/degrees-we-offer/doctor-of-philosophy-phd

Please submit to STEM-LHCS-PHD@open.ac.uk an:

- application form and
- 2-page (A4) personal statement outlining your suitability for the studentship, what you hope to achieve from the PhD and your research experience to date

You do not need to submit a research proposal.

Information and the application form is found here: https://www.open.ac.uk/postgraduate/research-degrees/how-to-apply/mphil-and-phd-application-process. Note that as part of the application form, you will be asked to submit further documents (CV, degree transcripts, etc.)