Investigating the Mechanistic Role of Extracellular Vesicles in Anti-cancer Drug Induced Cardiotoxicity

Principal supervisor: Dr Calum McMullen

Co-supervisors: Dr Katja Rietdorf and Dr Daniel Johnson

Location: The Open University, Milton Keynes, United Kingdom

Full-time study only.

Duration & Funding: 3-year and 3 months (39 months) studentship; Stipend £19,237 per annum; Training grant £1,100 per annum.

Application due date: Monday, **27th January 2025**.

Interview: Week commencing **24th February 2025** via Microsoft Teams

Final Funding Decision: Week commencing **10th March 2025**. This is part of a pooled School process, so the selected applicant will be put forward to a reviewing panel for final decision. Applicants will be notified if they are selected and will be informed of the panel decision afterwards.

Start date: 1st October 2025

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

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

Research area/keywords: Cardio-oncology, Cardiotoxicity, Pharmacology, Cell Signalling, Extracellular Vesicles, Heart Failure

Project background and description

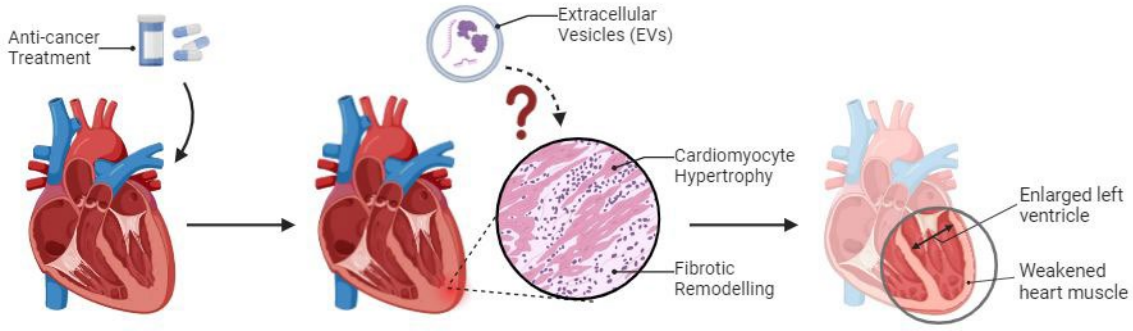

Figure 1. A schematic overview of this research project. Anti-cancer drugs are known to inadvertently disrupt cellular dynamics in the heart, leading to structural and functional changes that ultimately can cause the heart to fail if left unchecked. This project aims to determine what role, if any, EVs play in this process. Created with BioRender.com.

Research has shown that almost all cancer treatments inadvertently affect the heart and more than 10% of all cancer patients will die from heart disease, many of whom had normal heart function before receiving treatment. In some cancer groups, patients who have received cancer treatment are more likely to die from cardiovascular disease than the cancer itself (Patnaik et al., 2011). Despite the improvement in cancer treatment, there remains a large unmet medical need for treatments that do not have serious off-target effects.

Recent publications have suggested that extracellular vesicles (EVs) may play a role in this toxic mechanism (Figure 1). EVs carry cargo between cells and play a role in both physiological and pathological processes, such as cell communication and cancer progression. The literature shows that the effect of EVs released from cells treated with cancer drugs differs between cell types (Yarana et al., 2022). Preliminary data collected by this research group demonstrated that EVs isolated from endothelial cells treated with the anti-cancer drug sunitinib malate led to a decrease in cell viability when introduced to healthy, untreated endothelial cells.

In this project we plan to progress this work to better understand the role EVs play in this process. This research will be conducted using cardiac myocytes and cardiac fibroblasts, the two most prominent cell-types in the heart. We aim to (i) characterise the content of EVs isolated from cardiac cells treated with an anti-cancer drug; (ii) investigate the effect these EVs have on other cardiac cell types and elucidate the mechanism; and (iii) determine whether this cardiotoxic mechanism can be reduced/reversed by modulating EV uptake and/or content. The results of this project may lead to the identification of a novel component of the cardiotoxic mechanism that could serve as a target for pharmacological intervention to reduce/reverse this toxicity.

Student Experience

You will gain technical skills in cell culture (2D and 3D cell culture) and cell imaging (brightfield and fluorescent), and experience in a range of molecular biology techniques to look at changes in protein expression (Western blotting, gel electrophoresis, qPCR etc). You will also learn advanced techniques used in cardiovascular research to assess mitochondrial function and calcium mobility. You will also have opportunities to present your work at national and international conferences and publish your findings.

This project is part of a collaboration with an industry partner, Excellio Ltd. (Edinburgh, UK), and you will have the opportunity to complete a short placement (1 month) with Excellio to gain practical skills and industry experience.

References: McMullen et al. (2021) https://doi.org/10.3389/fcvm.2020.630480; Yarana et al. (2022) https://doi.org/10.3390/ijms232113465; Patnaik et al. (2011) https://doi.org/10.1186/bcr2901.

Eligibility

1. Applicants will have a First Class or Upper Second undergraduate degree or Masters degree (or equivalent experience) in Pharmacology, Biomedical Science, Biology, Biochemistry, 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. Overseas applicants: Applicants from overseas will also be asked to verify their visa status with original documentation if you have a current visa allowing entry to the UK.
5. Overseas applicants: If you are not from a majority English-speaking country, you will need to demonstrate your competence in the English Language in all four elements: reading writing, speaking and listening. The University requires an overall IELTS score of 6.5 with no less than 6.0 in any of the four categories. You will need to submit this with your application for consideration. Further details and a list of approved providers of accreditation can be found on the UK Visas and Immigration website.

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.

Most importantly, applicants should have a passion for science 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 send an email with your CV, a completed application form and a personal statement (maximum 2 pages, outlining your suitability for the studentship, what you hope to achieve from the PhD and your research experience to date) to STEM-LHCS-PHD@open.ac.uk

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 (degree transcripts, etc.)