

Development of a minimally invasive, ultrasound guided, rat myocardial infarction model

Applications are now welcome for a funded PhD at the University of Edinburgh focussed on the development of a minimally-invasive ultrasound guided rat myocardial infarction (MI) model. This project is jointly funded for 3 years by the National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs) and the British Heart Foundation (BHF). The ultimate aim of this project is to fundamentally shift the way in which preclinical myocardial infarction research is performed in rats, improving welfare outcomes and reducing the number of animals which are needed. This project will offer world class training in *in vivo* cardiovascular research and non-invasive imaging using ultrasound and positron emission tomography (PET), in addition to training developing the candidates scientific, personal and career development skills. This project will equip the candidate for a successful career in preclinical cardiovascular research with a strong grounding in the 3Rs principals.

The primary supervisor for this project is Dr Mark MacAskill, with secondary supervision provided by Prof Adriana Tavares. This project will be based in the Centre for Cardiovascular Science, which is part of the newly formed Institute for Neuroscience and Cardiovascular Research (INCR), situated within the Edinburgh BioQuarter campus. In the latter stages of the project there will be scope for international collaboration in order to disseminate the newly developed model across collaborator sites.

PhD Start:
May 2025

Project Background:

In the UK, 7.6 million people are living with heart and circulatory diseases which are subsequently responsible for 27% of deaths, with MI and heart failure a major factor (BHF Factsheet 2024). Rodent MI models using infarcts generated via invasive thoracotomy have been the cornerstone of cardiovascular research, allowing investigation of the pathological mechanisms driving adverse outcomes, identifying imaging/therapeutic targets and evaluating novel therapies.

In the last decade across the UK, thousands of rats have been used for myocardial infarction research utilising the gold standard invasive thoracotomy approach. This project aims to significantly reduce these numbers and refine the welfare outcomes in the rats through the development of an ultrasound guided minimally-invasive approach to MI generation in rats. We anticipate that our minimally-invasive model will result in a significantly higher recovery rate which will reduce the number of animals required, as well as reducing pain while shortening procedure and recovery times. Further to this, under ultrasound guidance, we propose that there will be greater control of infarct size, reducing the likelihood of unnecessarily large infarct sizes and missed occlusions. These expectations are based on an equivalent minimally-invasive model in mice using permanent occlusion to generate MI which has recently been developed and is now in use in our research centre (1,2).

Project Aims and Workplan:

1. Optimisation of the equipment through the development of a rat ultrasound phantom, which will then be used for procedure training and also aid future dissemination of the model at other sites. The student will use previously generated computer tomography data to create a 3D printed, anatomically correct, rat phantom with ultrasound compatible heart and lung compartments.
2. To establish the recovery, accuracy and actual severity of the proposed minimally-invasive rat model using permanent coronary artery occlusion injury. In addition to histological evaluation of the model, the new approach will also be validated using blood biomarker measurement, echocardiography and PET imaging of inflammation using a radiotracer targeting the TSPO protein (3). Comparison of the measured outcomes will be made against a detailed historical dataset produced by Dr MacAskill and Prof Tavares using the gold standard invasive thoracotomy approach in order to benchmark this new model.
3. Upon successful completion of aims 1 and 2, the student will go onto investigate ischemia-reperfusion myocardial injury using an adapted version of the minimally invasive approach. Like in Aim 2, this temporary injury model will also be validated using blood biomarker measurement, echocardiography and PET imaging of inflammation. Comparison of the outcomes will be made against our historical datasets.

Project-specific training/experience will be provided in:

- Preclinical *in vivo* skills in animal procedures, surgery, recovery and monitoring.
- 3Rs orientated skills via internal and external activities.
- Cutting edge non-invasive imaging using ultrasound and PET, including training in image analysis.
- Histological evaluation including image analysis.

What we are looking for:

Candidates should be enthusiastic individuals who are motivated to develop a career in cardiovascular science and eager to acquire new hands-on *in vivo* skills throughout the PhD duration. Applicants will have a BSc (Hons) degree (First or Upper Second class or equivalent) or a Masters qualification (Distinction or Merit) in the field of biomedical sciences. Previous research experience is desirable.

We encourage applications from non-traditional backgrounds and those from under-represented groups. The University of Edinburgh holds a Silver Athena SWAN award in recognition of our commitment to advance gender equality in higher education. We are members of the Race Equality Charter and we are also Stonewall Scotland Diversity Champions, actively promoting LGBT equality.

Funding Notes:

The student will receive a tax-free stipend at the UKRI rate (£19,237 pa in 2024/25), and student tuition fees will be supported in accordance with the T&Cs of the award. For further information on the provided studentship and award, please contact Dr Mark MacAskill (mark.macaskill@ed.ac.uk). Please note, International Students will need to apply for a visa within UK government guidelines and be able to cover National Health Service surcharges.

Enquiries:

Informal enquiries are welcome to Dr Mark MacAskill (mark.macaskill@ed.ac.uk).

Application:

Please include a one-page personal statement highlighting your motivation for applying for this project, and the skills and experience to date that make you well suited to it. Please also submit your CV and two academic references. All documents should be sent or emailed to:

Lynn Meikle
Centre for Cardiovascular Science
The Queen's Medical Research Institute
47 Little France Crescent,
Edinburgh, EH16 4TJ. Tel: +44(0) 131 242 6724

Email: Lynn.Meikle@ed.ac.uk

Closing date: 16th March 2025

Interview date: Interviews will be held before the end of March, with the aim of beginning the project on 1st May 2025.

References:

1. Berkeley B, Thomson A. Suture-to-scan: ultrasonography-guided induction of heart injury. *Nat Rev Cardiol.* June 2024;41569.
2. Sicklinger F, Zhang Y, Lavine KJ, et al. A Minimal-Invasive Approach for Standardized Induction of Myocardial Infarction in Mice. *Circ Res.* 2020;127:1214-1216.
3. MacAskill MG, Stadulyte A, Williams L, et al. Quantification of Macrophage-Driven Inflammation During Myocardial Infarction with 18 F-LW223, a Novel TSPO Radiotracer with Binding Independent of the rs6971 Human Polymorphism. *J Nucl Med.* 2021;62:536-544.