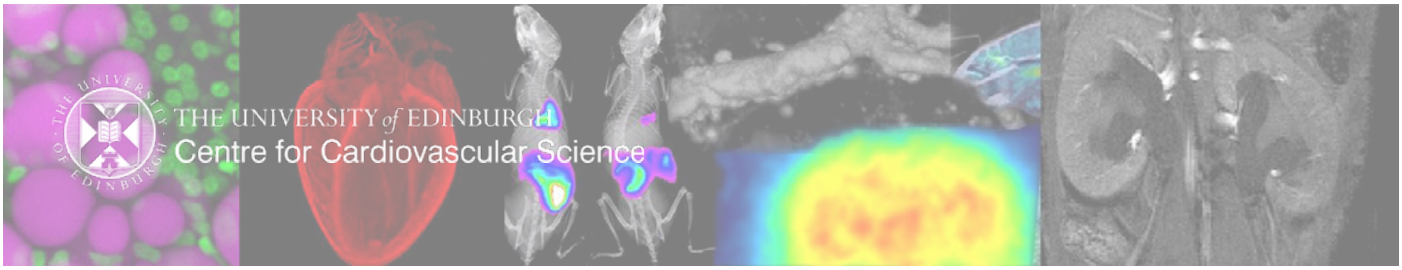
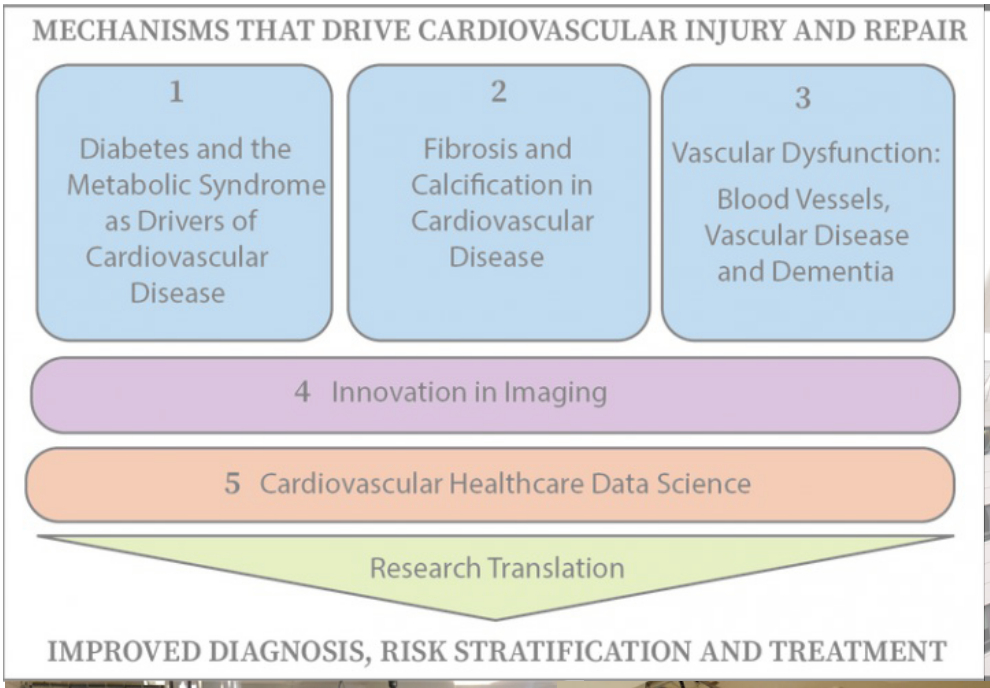
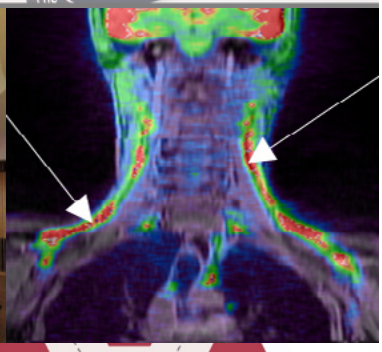
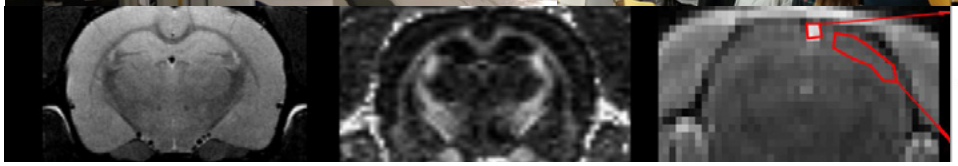


REA3 BIMONTHLY NEWSLETTER

February 2021

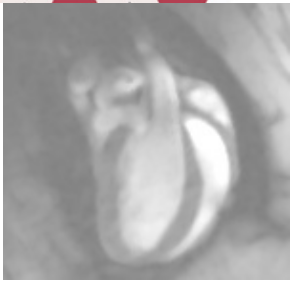


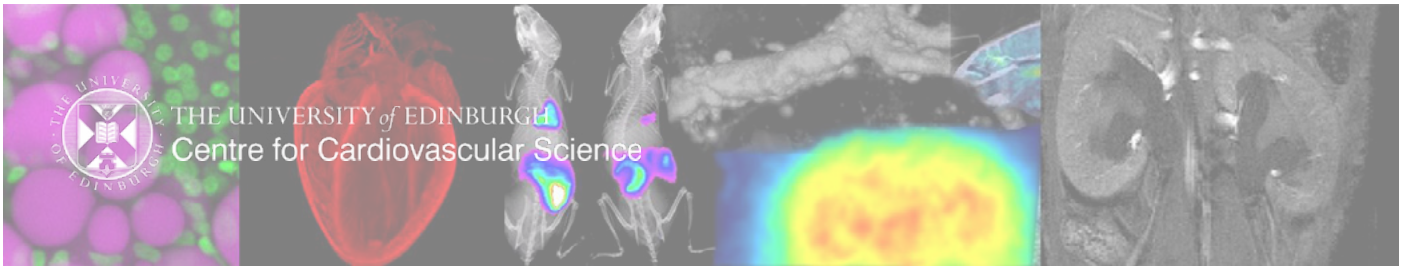




THE UNIVERSITY of EDINBURGH

BHF Research Excellence Award University of Edinburgh





INTRODUCTION

Welcome to our first edition for 2021 of the REA3 newsletter. A slightly later issue than normal but then these are not "normal" times. We will be back to our usual timetable from March.

In the November 2020 newsletter, we were hoping to start 2021 with renewed optimism for a return to pre-Covid life. Unfortunately, it has been a bumpier journey than envisaged with schools being closed again, working from home being extended and continued for many, and the sadness plus tragedy of lives lost across the UK.

Science has remained at the forefront during this pandemic. The important work that is taking place within our institutions has been highlighted and continues to be developed. This includes futher vaccines that have been designed and approved for full use. And the roll out of the vaccines has gathered pace, which allows for the optimism to return, though perhaps with more caution.

Dr Vicky Macrae

We have two contributors from our Spring 2020 Pump Priming Round within these pages. Dr Vicky Macrae who received translational funding for, "*Profiling of selective Autotaxin inhibitors in calcific aortic disease*" and also from Dr Mihaela Crisan, one of our Early Career Researchers, and her project, "*CD248, a novel pericyte-expressed regulator of cardiac vascular remodelling and fibrosis post-injury?*"

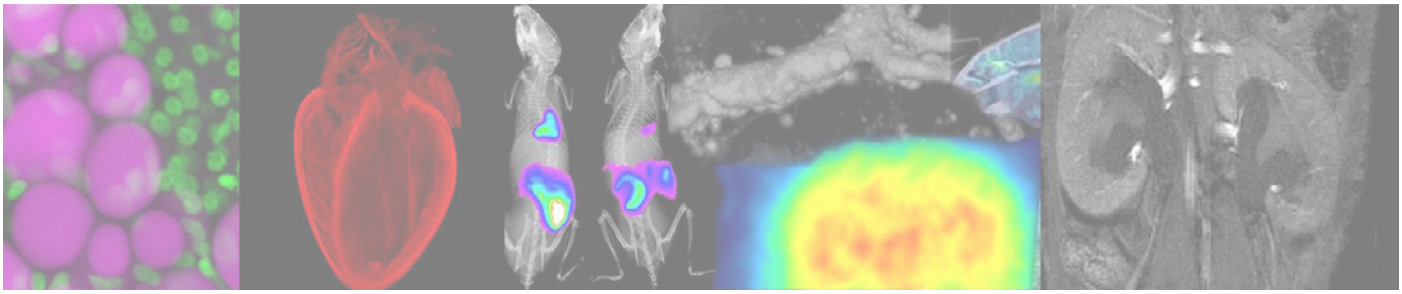
Dr Mihaela Crisan

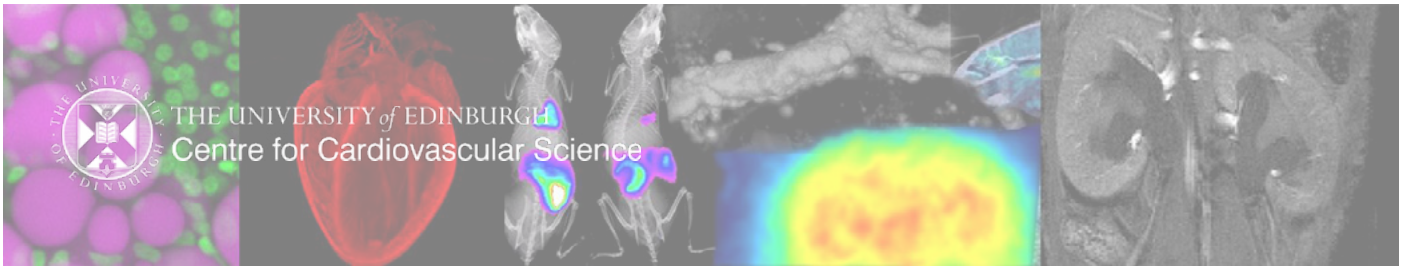
Professor Carmel Moran has provided an overview of gender and inclusion data for REA3 that was presented at the External Advisory Board in November 2020. Further reporting and recording will continue until the end of the funding in 2023. We are happy with the progress made so far but there is always room for improvement.

Any new articles or ideas can still be sent to Gillian Joyce to be included for future mailings:
Gillian.Joyce@ed.ac.uk

We extend our thanks to everyone in the REA3 sphere and beyond and look forward to giving our next update in Spring 2021.

Professor Andrew H Baker, Director REA3
Professor David Newby, Deputy Director REA3





Dr Vicky Macrae - Profiling of selective Autotaxin inhibitors in calcific aortic disease

Amount awarded: £27,671

Co-applicants: Dr Patrick Hadoke & Professor Scott Webster

Calcific aortic stenosis (CAS) is the leading cause of valve disease in the developed world. Left untreated symptomatic severe CAS is universally fatal, yet we lack any effective pharmacotherapies capable of slowing disease progression. The lack of drug therapy for CAS therefore represents a major unmet clinical need. Interestingly, the risk factors for CAS are similar to those for atherosclerosis; though the factors driving these diseases are distinct.

This REA3-funded project will establish proof of concept that pharmacological inhibition of Autotaxin (ATX) will provide therapeutic benefit in CAS and atherosclerosis. ATX is a ubiquitous enzyme which mediates production of lysophosphatidic acid (LPA), which is implicated in a range of pathophysiological events, including inflammation, fibrosis and the transition of cells to a bone-like (osteogenic) phenotype. Through an active collaboration with the University of Strathclyde, we have recently profiled novel and selective ATX inhibitors, which potently inhibit ATX and demonstrate anti-fibrotic activity in vitro and in vivo

We have previously shown that mice deficient in ApoE show atherosclerotic plaque calcification, and also serve as a model of CAS (Figure 1). We will therefore use these mice to address our hypothesis that ATX inhibition will reduce calcification in advanced atherosclerosis and CAS. This proposal will employ innovative methodologies involving the application of novel 18F-NaF PET CT imaging techniques, developed by our laboratories in collaboration with Adriana Tavares, to detect and quantify micro and macro soft tissue calcification in mice in vivo. This uses the same advanced imaging techniques developed for human (PET/CT), which demonstrated that animals exhibited macro-calcification, visible on CT, and active microcalcification, indicated by specific Na18F uptake.

We anticipate that the data generated from this study will support a follow-on translational funding application to investigate targeting ATX as a novel therapy for calcific disease.

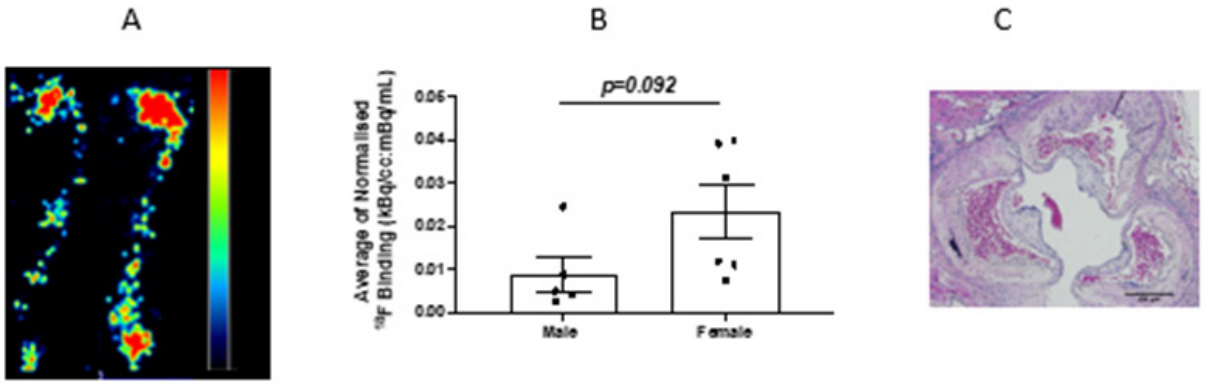
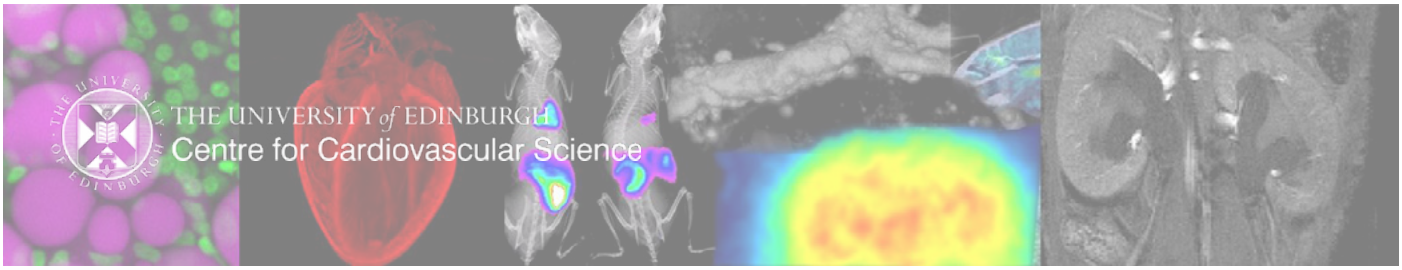


Figure 1. (A) PET/CT analysis of calcification in aortas from Male (left) and Female(right) ApoE-/- mice, (B) quantified to assess differences between male and female and (C) H&E staining of lesions in the aortic valve.



Dr Mihaela Crisan - CD248, a novel pericyte-expressed regulator of cardiac vascular remodelling and fibrosis post-injury?

Amount awarded: £31,500

Co-applicants: Dr Bruno Péault, Dr Adriana Tavares, Prof Carmel Moran, Prof Clare Isacke, Prof David Newby, David Craig, Dr Gillian Gray & Dr Mairi Brittan

I would like to thank the REA3 panel for this highly competitive award and the opportunity I am given to assess the feasibility of a larger project and to engage into new collaborations with experts in the field. Importantly, this will also help to establish new research directions in my laboratory that can be funded from other sources at later stages.

Last month, the BHF declared that more than a quarter of all deaths in the UK are caused by heart and circulation diseases; that is more than 160,000 deaths every year – or one death every three minutes. As an expert in pericytes and tissue regeneration, I took advantage of this REA3 award to bring together experts from both vasculature and heart fields, basic scientists and clinicians, to fight these diseases.

Together with Adriana Tavares, Bruno Péault, Carmel Moran, Clare Isacke, David Craig, David Newby, Gillian Gray and Mairi Brittan, I aim to increase our understanding of the life-course mechanisms leading to cardiac microvascular rarefaction and fibrosis upon injury. We believe that blood vessel loss and fibrosis are linked. We propose that CD248, expressed on pericytes, is involved in cardiac remodelling and blood vessel rarefaction, and we introduce a new mouse model and a series of initial experiments to characterise the mechanism of action of CD248.

In mice, CD248 is expressed in developing blood vessels and is downregulated on resting adult blood vessels, including in the heart and kidney. However, recent reports showed that CD248 is upregulated after kidney injury. In addition, CD248 knockout mice (KO) were found to be protected against fibrosis and blood vessel loss. Whether these KO mice are also protected following heart injury is unknown.

We hypothesise that CD248-KO mice can be used to study the role of cardiac pericytes in vascular remodelling and fibrosis. However, we do not know if CD248 on pericytes is essential during homeostasis prior to injury. We will use the REA3 funds to import and establish the CD248-KO mouse colony in our Centre. We will then characterise CD248-KO mouse heart structure and function and vasculature in the absence of injury, using combinations of hematopoietic cell, pericyte and endothelial cell markers by immunohistochemistry (Figure, A), flow cytometry and high-resolution 3D echocardiography (Figure, B).

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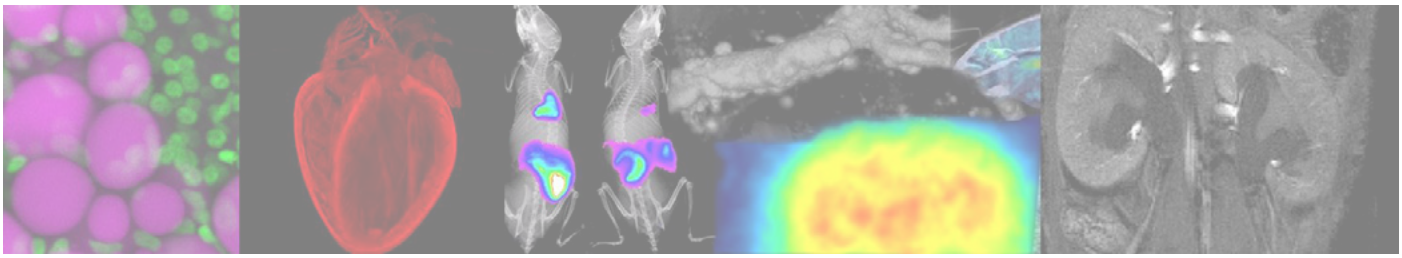

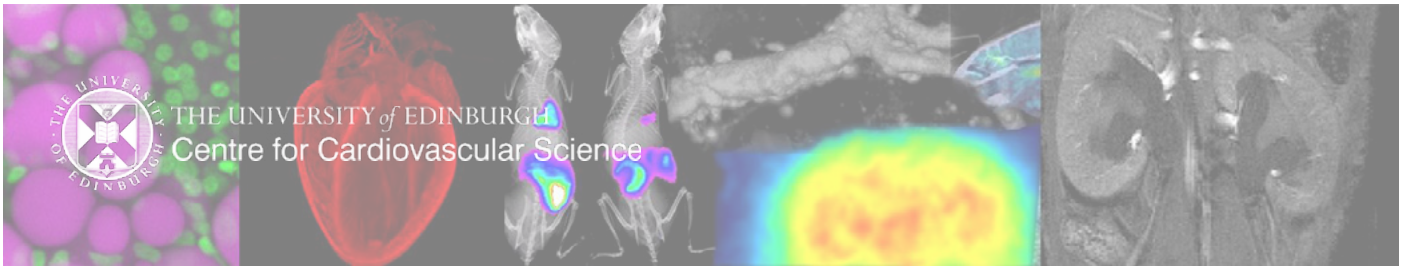

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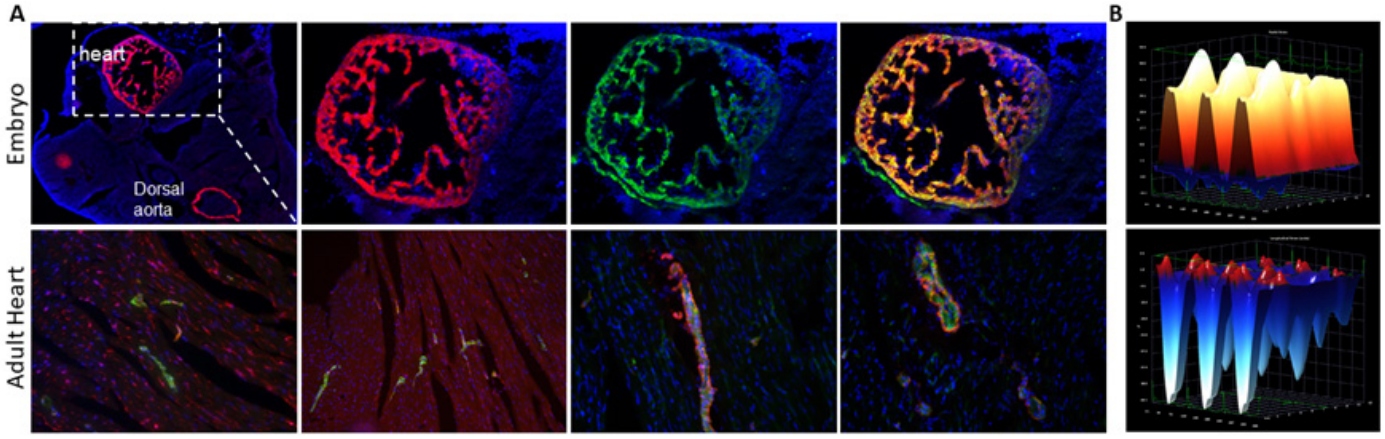
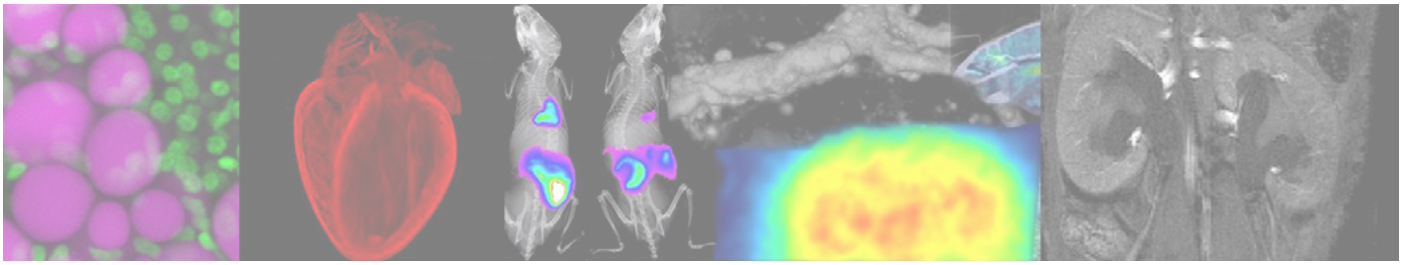
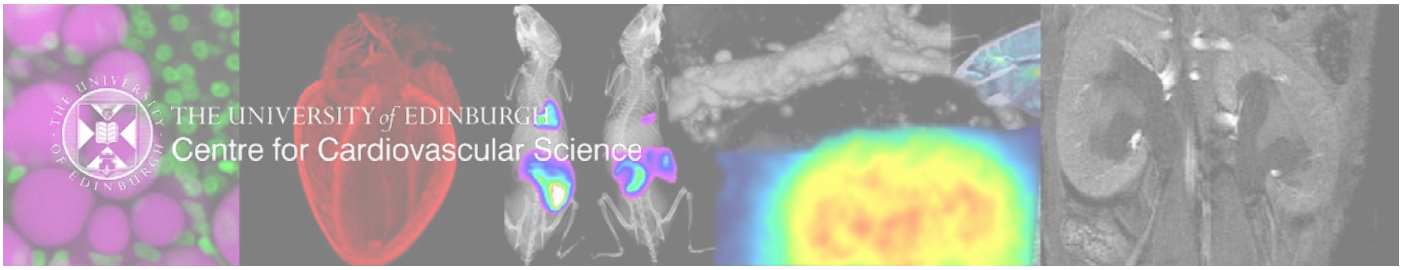


Figure. Heart: from embryo to adult and back? A. *Images showing cardiomyocytes and blood vessels during wild-type mouse heart ontogeny*. **B.** *Wild-type radial (up) and longitudinal strain analysis (bottom) following high-resolution 3D echocardiography of an adult heart.*

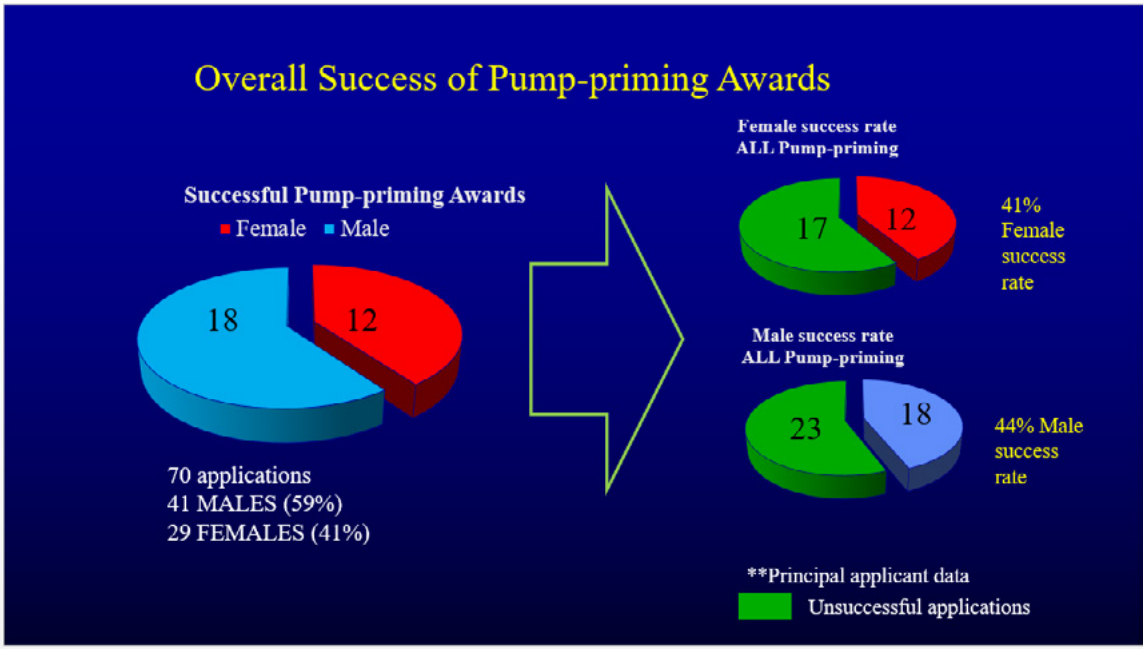
Our long-term objective is to establish novel therapeutic strategies through identification of pericyte subsets and molecular pathways that influence blood vessel remodelling and fibrosis leading to heart failure following myocardial infarction. This REA3 pump-priming grant is an essential first step towards achieving such important goals. We identified CD248 as a potential therapeutic target in heart disease; understanding its role in cardiovascular disease is essential and over the long term may lead to the development of drugs to treat cardiovascular disease and thus to improve human health.

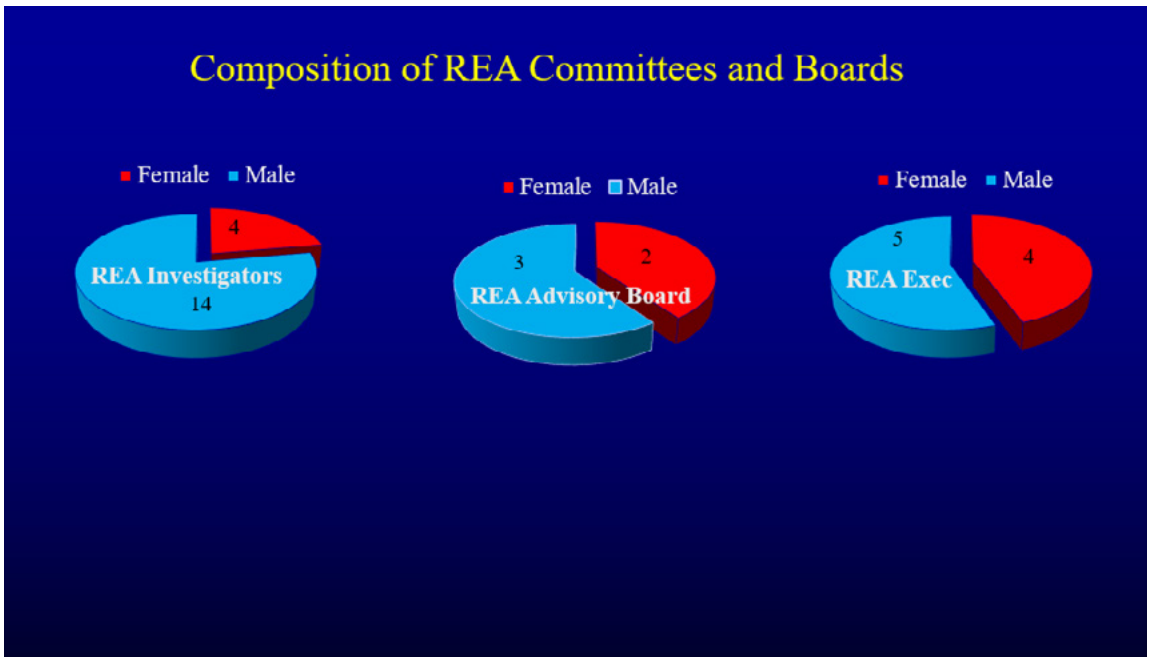




Professor Carmel Moran, Chair of Translational Ultrasound, Director of Preclinical Ultrasound Imaging Facility, CCVS

At the External Advisory Board meeting on 23 November, Professor Carmel Moran provided a gender analysis of REA3. The call for pump-priming awards is sent to distribution lists across CMVM in Edinburgh (CVS, 47-LF, 49-LF and crm-bio) and it was difficult to get gendered data on these site-specific range of Centres. Analysis has been restricted to CVS and assumed this was typical across the site.





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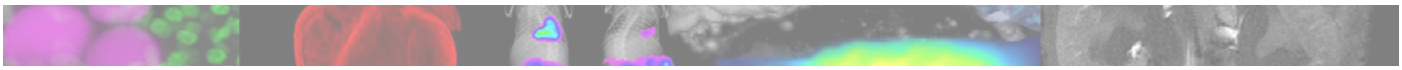
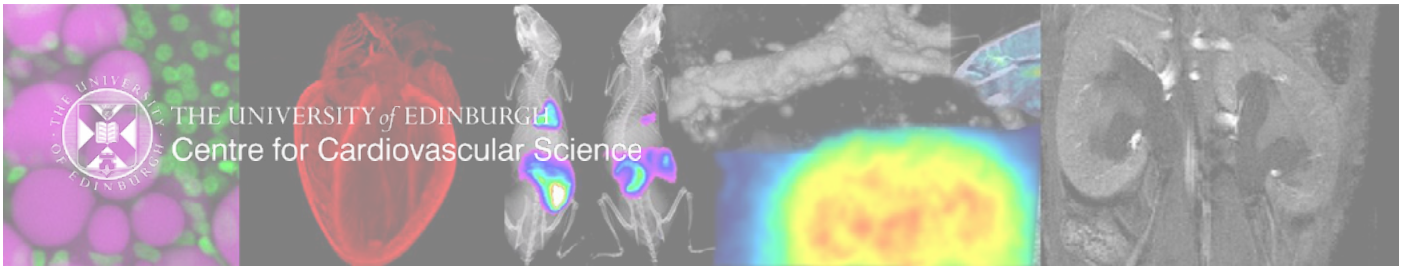
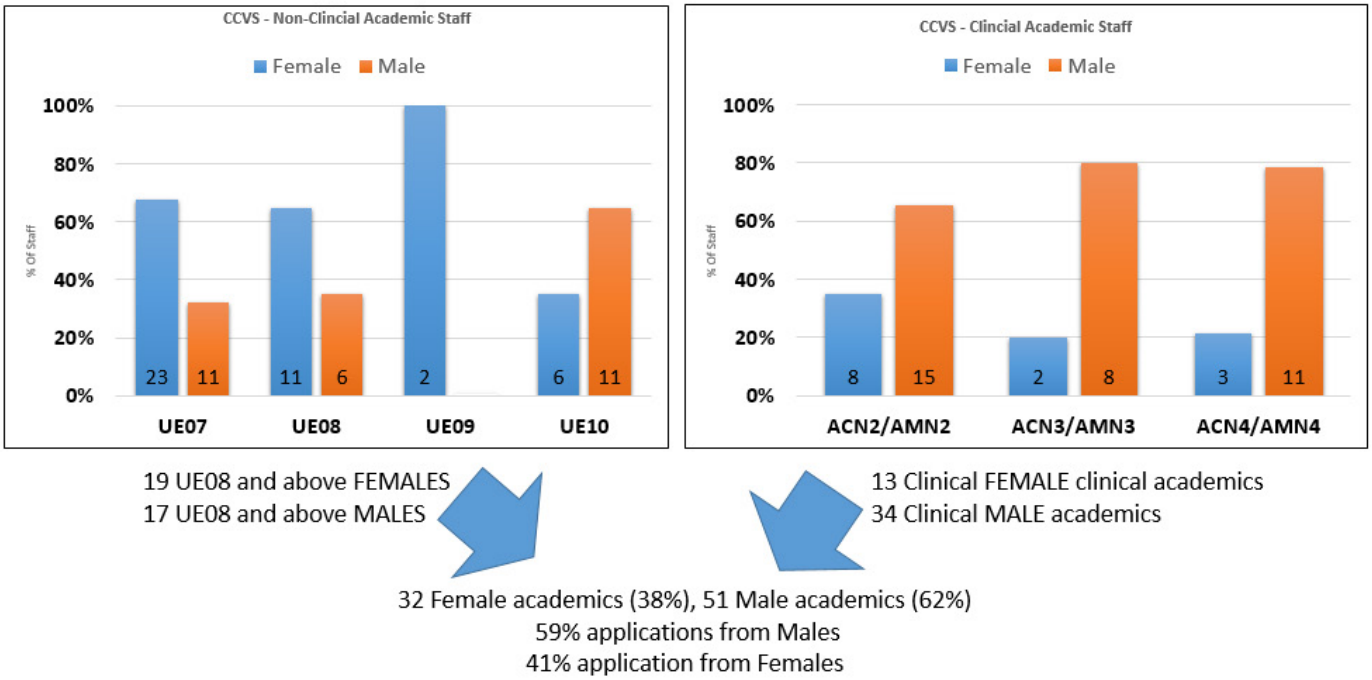




Professor Carmel Moran, Chair of Translational Ultrasound, Director of Preclinical Ultrasound Imaging Facility, CCVS

Distribution of CVS Academic Staff



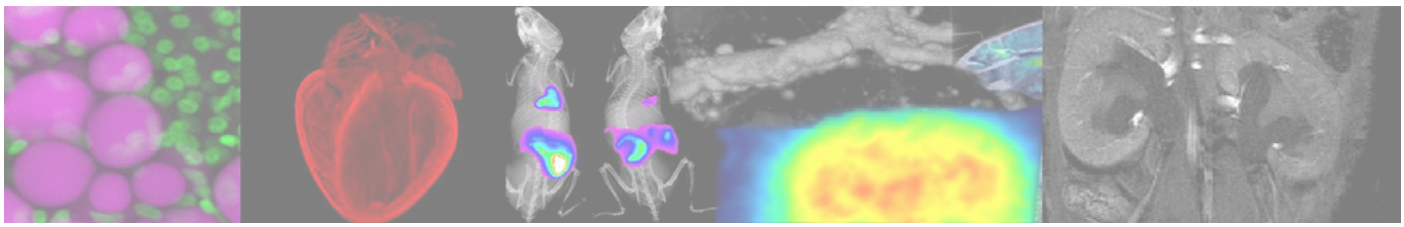
19 UE08 and above FEMALES
17 UE08 and above MALES

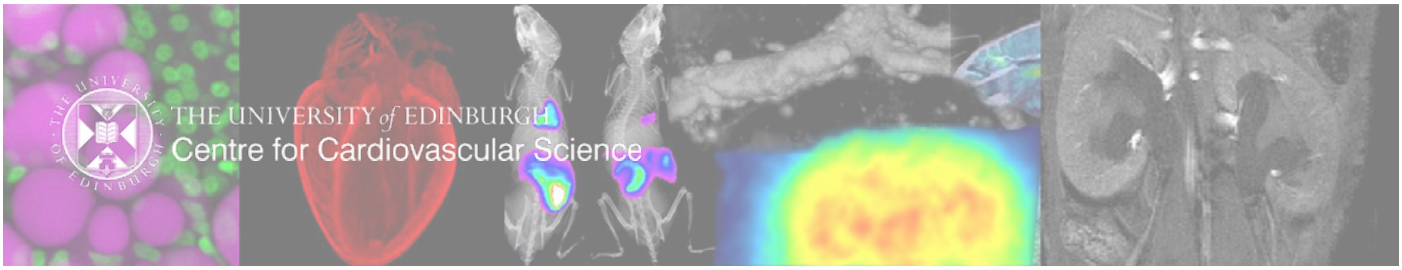
13 Clinical FEMALE clinical academics
34 Clinical MALE academics

32 Female academics (38%), 51 Male academics (62%)
59% applications from Males
41% application from Females

ED&I within REA3

- Pump-priming awards
  - 41% success rate for Females and 44% success rate for Males.
  - 41% of applications came from Females, 59% of applications from Males – consistent with CCVS eligible to apply
- Collecting diversity data – including gender and also protected characteristics





Additional £200,000 funding from BBSRC IAA

BBSRC support has been provided to enable translational and commercialisation activities and engagement with industry, policy making bodies or other stakeholders, from BBSRC funded research. The new fund aims to increase, advance and accelerate the achievement of impact from BBSRC investments in excellent bioscience research and capabilities.
An extension has been applied to the latest BBSRC IAA to enable allocation of an additional £200,000 of funding on a competitive basis. This is the second and final round.
The award will support direct costs only and be associated with a range of activities including:

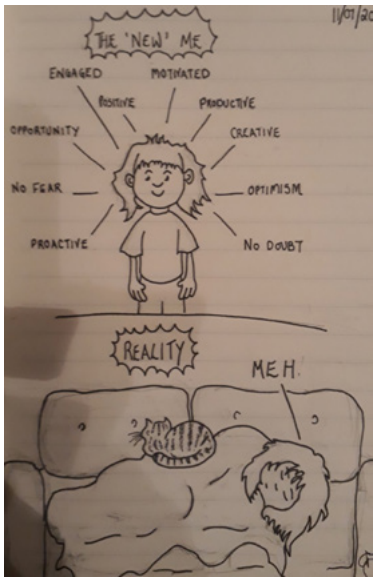
- ***Proof of principle or proof of concept studies (up to £30,000)***
- ***Market research (up to £10,000)***
- ***Secondments, placements and people exchange (up to £5,000)***

Open now, closes 10 March 2021 17:00.

More information

FINALLY.....
New year and new goals! Each year Gillian Joyce starts January with the mantra, "I'm going to do this" and "I'll make more time for this" and then by February things begin to wane a bit. However, she's trying to return to her love of drawing and art, which provides a focus and relaxation. A few bits and bobs below, mainly for friends and family, but it's a start:


Samuel Beckett




Birthday pressie - Diego

Remember there is a range of services provided within the university for staff and students to access regarding health and wellbeing:
https://www.ed.ac.uk/staff/health-wellbeing
https://www.ed.ac.uk/students/health-wellbeing