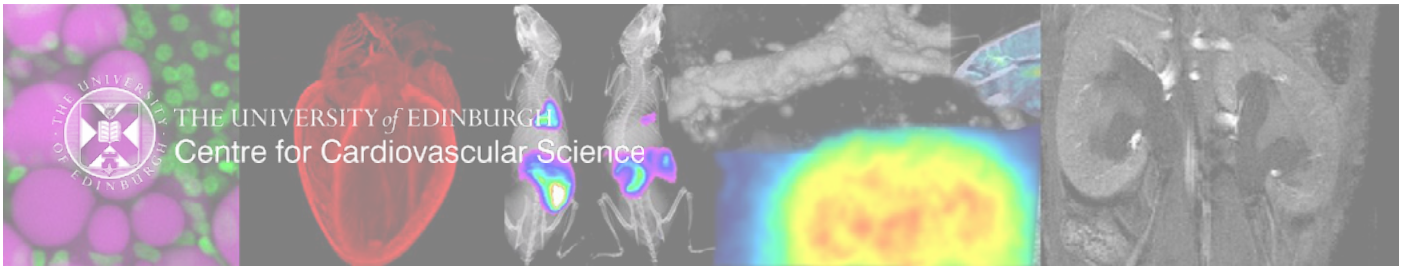
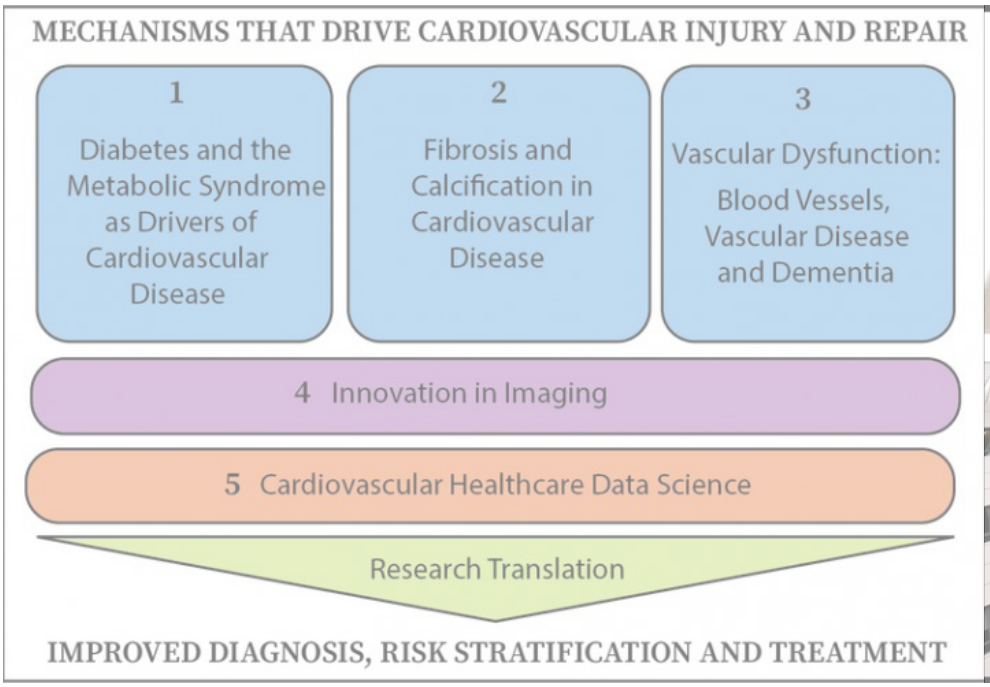
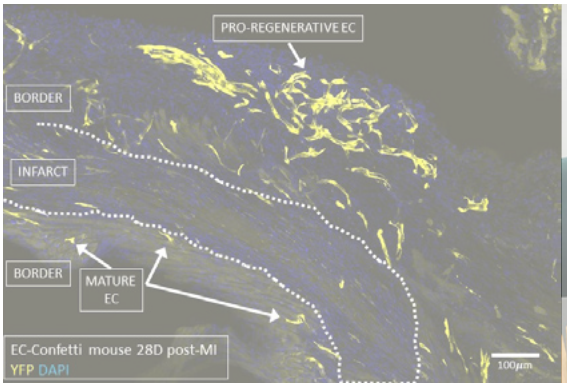



# REA3 BIMONTHLY NEWSLETTER

## September 2020

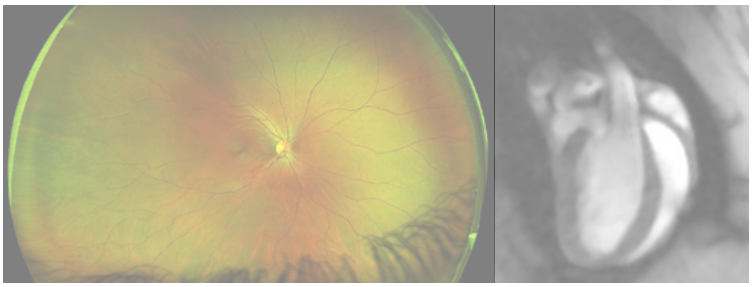


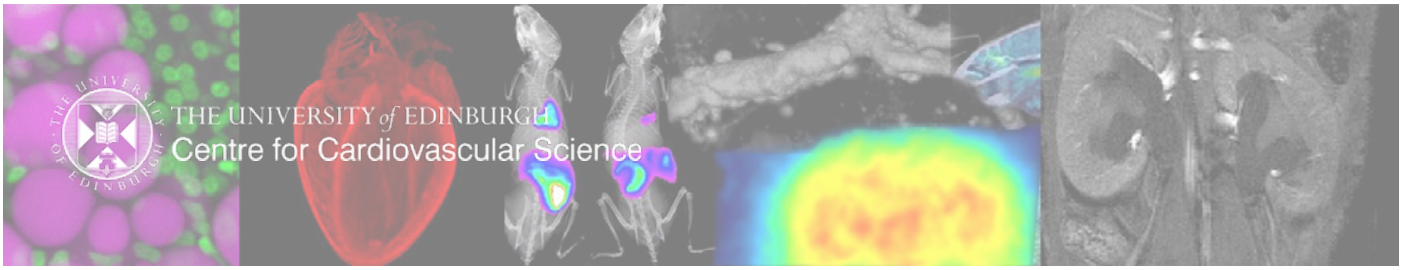





THE UNIVERSITY of EDINBURGH

British Heart Foundation






# INTRODUCTION

Welcome to our fifth edition of the bimonthly REA3 Newsletter.

Since the easing of lockdown, many of our researchers have been able to access the buildings and laboratories necessary to facilitate the continued success of the projects they are working on. However, the University as a whole is still maintaining strict social distancing measures to ensure that the work environment remains safe and adheres to the current rules. As a Centre we remain vigilant regarding any new announcements from the Scottish and UK Governments, which may impact on our current working ethos. We will continue to adapt, if required, and appreciate that these times may bring further disruption. However, there will always be a commitment to try and minimise any changes with future-proofing and planning being integral to REA3 and beyond.


Professor Scott Webster

In our September issue, we feature Professor Scott Webster who is one of our Principal Investigators (PI) within REA3 and also Personal Chair of Medicines Discovery. He provides an overview of his translational drug discovery research, including a summary of those colleagues that have collaborated and contributed to his drug discovery work.


Dr Ryan Wereski

One of our Clinical Fellows, Dr Ryan Wereski, has contributed a piece regarding his current work, which is focused on the role of cardiac biomarkers and how they can be used to assess the risk of a patient admitted with suspected acute coronary syndrome.

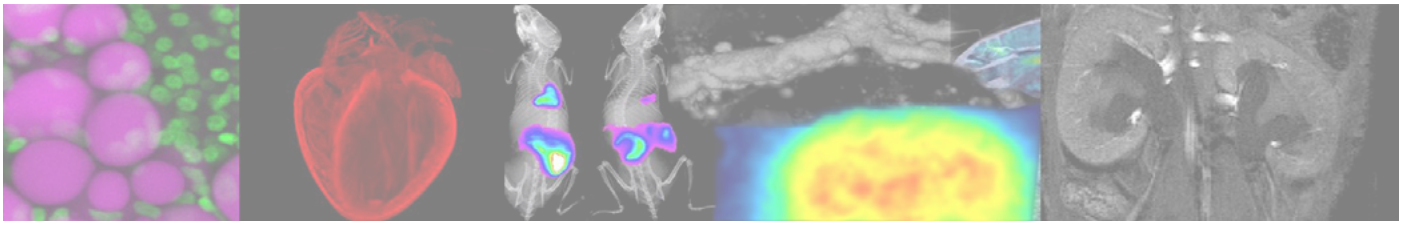

Professor Roland Stimson

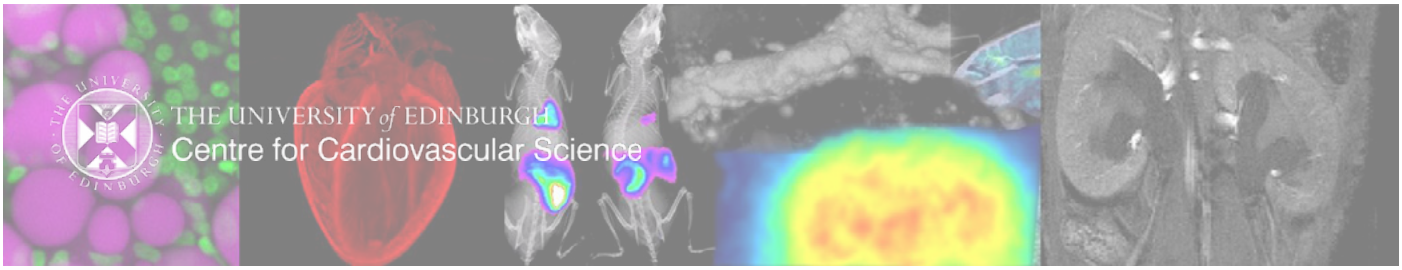
In our Pump Priming round in Autumn 2019, Professor Roland Stimson was one of the applicants who was successful in securing funds for his project entitled, ***"Investigating the genetics of human adipose brown tissue, a novel target for metabolic disease"***. Professor Stimson and his team have felt the impact COVID-19 has had on their research. **However, now the project has commenced, though delayed, he has provided us with a small summary of his project and its aims.**

Research Project Co-ordinator, Gillian Joyce, is still looking for REA3 Newsletter contributions and the next issue will be released in November. If you would like to provide some insight to your research, highlight an event/seminar or anything that is related to REA3, please contact her: Gillian.Joyce@ed.ac.uk

As always we are extremely grateful to everyone's commitment to REA3 and hope that over the next few months that our high-level research will be able to continue to deliver through these challenging times.

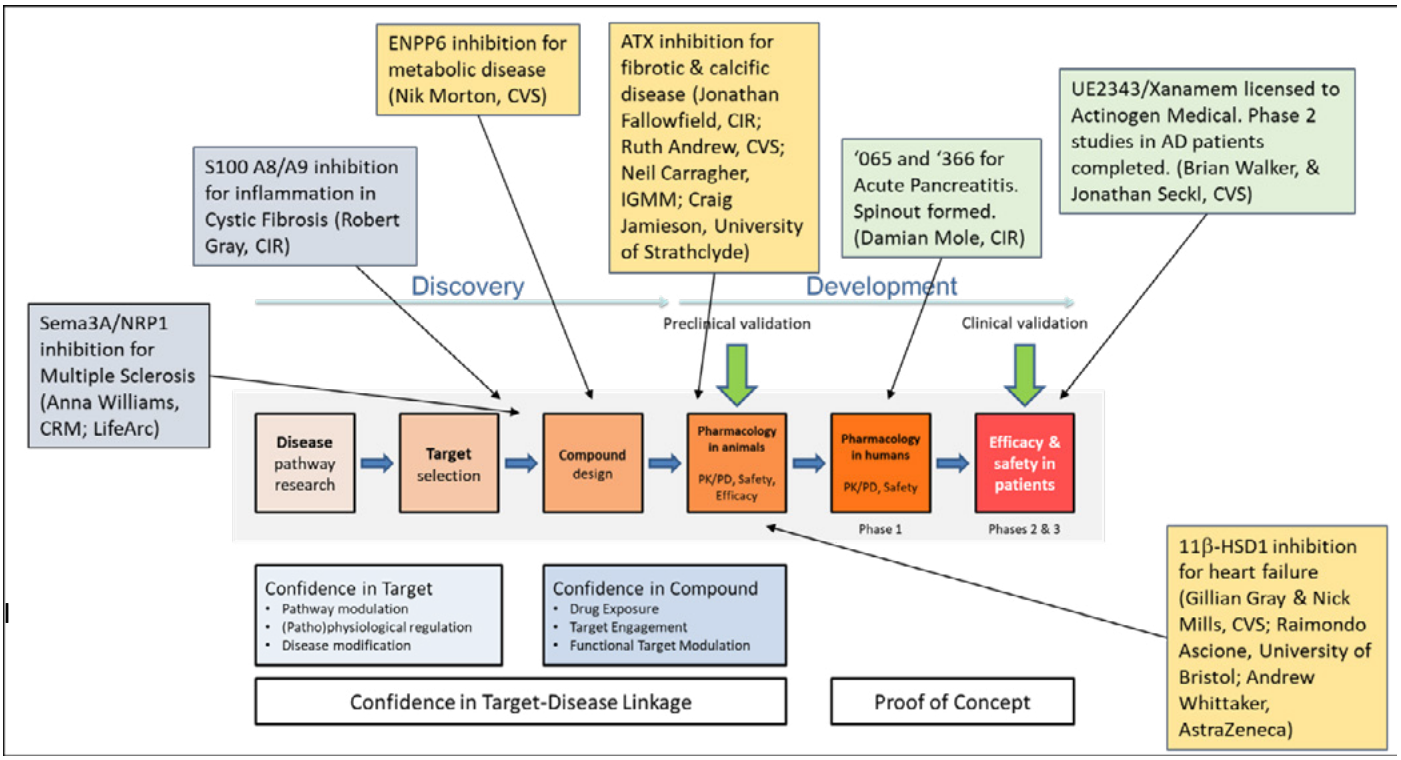
**Professor Andrew H Baker, Director REA3**
**Professor David Newby, Deputy Director REA3**






## Professor Scott Webster - REA3 PI and Personal Chair of Medicines Discovery

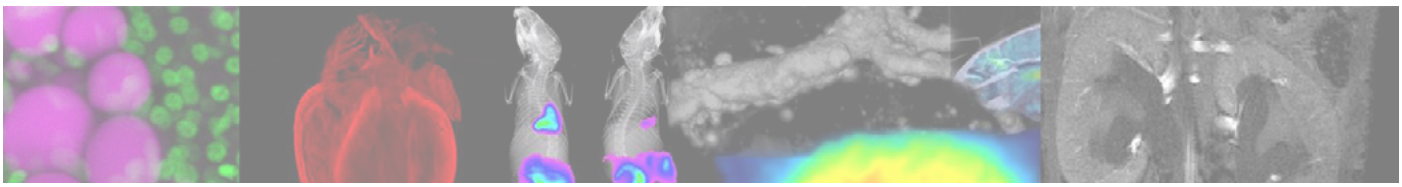
I am grateful for the opportunity to provide an overview of my translational drug discovery research. First of all I would like to highlight that none of this work is done in isolation and I am indebted to all of my colleagues, who have completed years of hard graft to get to the point where potential therapeutic targets are ready to begin the drug discovery process. Below is a diagram that I often share to explain the drug discovery process and which also shows some of the projects I am involved in either as PI or co-PI. I have been lucky to work in various disease areas and with many brilliant colleagues. Those projects with particular relevance to REA3 are highlighted in the gold boxes, while those in green are at the commercial/partnering stage.

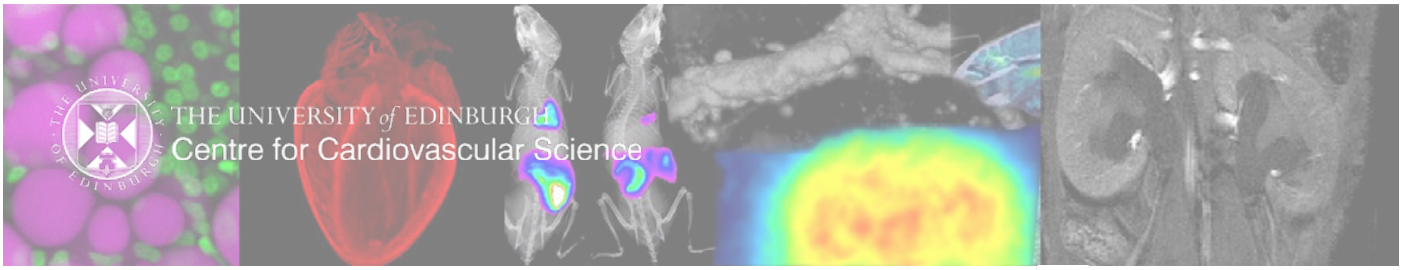


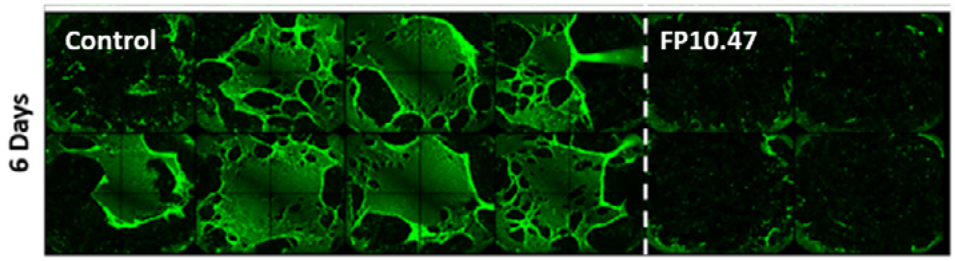

I initially became interested in the ENPP family of enzymes through two coincidental and separate routes. Professsor Jonathan Fallowfield and I had been working together on a GSK-sponsored project to discover new RXFP1 agonists for the treatment of fibrotic liver disease and, following the completion of the project, we were interested in new therapeutic targets that could benefit from the experience our teams had built up. This led to a collaboration with Dr Craig Jamieson at the University of Strathclyde, who had generated highly potent ENPP2/ATX inhibitors with potential in fibrotic disease.

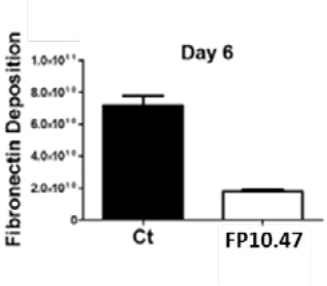
We also formed a team around this and with Professor Neil Carragher developed a phenotypic screening platform to profile compounds in a range of cell types. The effect of one compound (FP10.47) on extracellular matrix deposition in human hepatic stellate cells is shown on the following page:

*Continued Overleaf/*

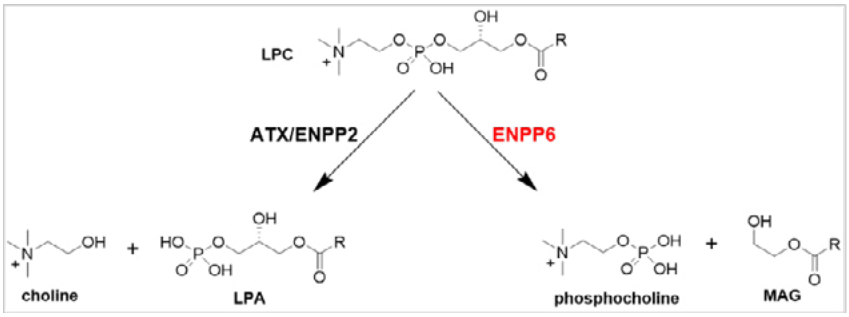


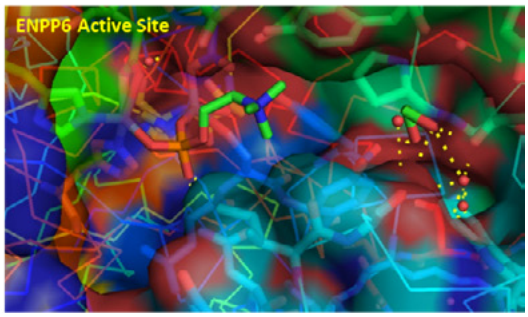


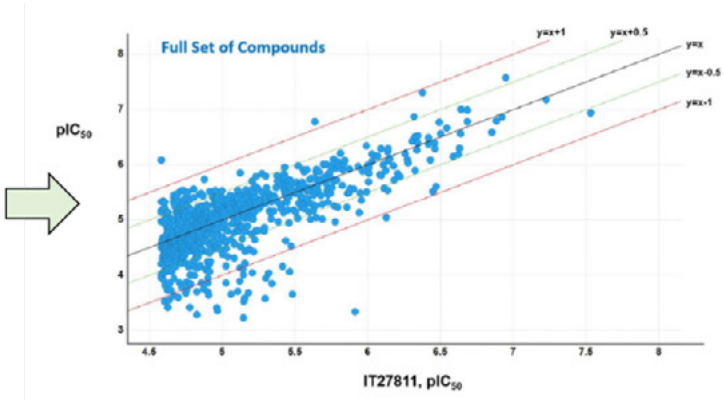




To bolster our ATX screening platform we joined with Professor Ruth Andrew to develop a mass spectrometric imaging technique to determine pharmacodynamic activity of ATX inhibitors in tissue slices. This has been technologically challenging, but is now producing excellent results and will allow us to assess in vivo inhibition of lead compounds in target tissues. Further work will be initiated soon in collaboration with Dr Vicky Macrae and Dr Paddy Hadoke to determine the efficacy of FP10.47 in models of calcification and atherosclerosis. This work has been funded via REA3 pump-priming:

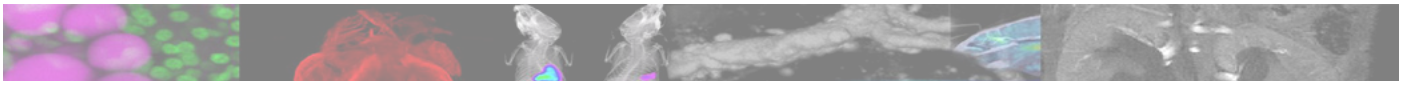


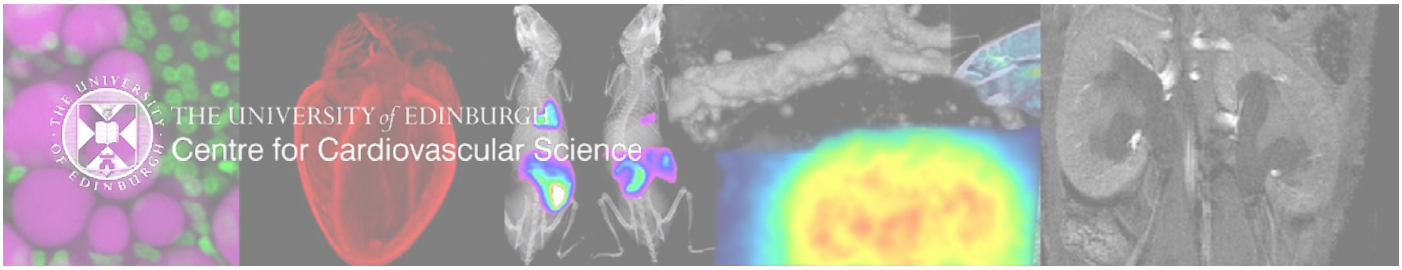




Around the same time that we were initiating plans for ENPP2/ATX I was approached by Professor Nik Morton about ENPP6. Nik had compelling GWAS and rodent data that supported it as a novel target for the treatment of cardiometabolic disease. We quickly produced recombinant enzyme by expressing human and mouse protein in mammalian suspension cultures and developed a colourometric screening assay. With further funding we developed a fluorescent screen for ENPP6 in 384-well format and expressed human ENPPs 1 - 5 and 7. Screens for each of these enzymes were developed so that selectivity of emerging hits from an initial 12k compound screen could be assessed. This work led to a collaboration with AstraZeneca in which we were able to rapidly adapt our screening assay to 1536-well format to enable to the screening of the AstraZeneca small molecule screening deck (~1M compounds). A second assay was also developed and transferred to AstraZeneca to perform follow-up testing. This ultimately yielded several series of ENPP6 inhibitors with $IC_{50}$s as low as 25nM:




*Continued Overleaf/*

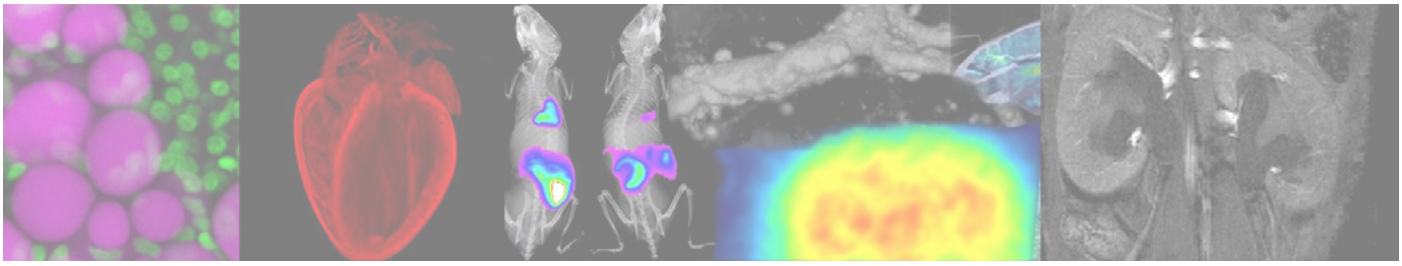


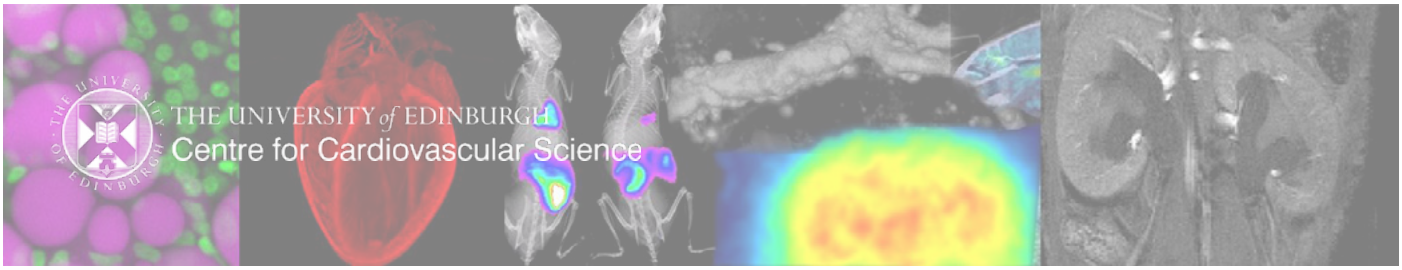



We are currently focused on positioning our ENPP assets for investment and expanding drug discovery activities on other members of the family for conditions such as aortic stenosis and cancer.

Finally, I am excited to be working with Dr Robert Gray to develop potential new therapies for Cystic Fibrosis patients. This is a particularly challenging project since we are aiming to disrupt a protein-protein interaction. Following a Covid-19 induced hiatus we recently started work to produce proteins that will be sent to our industry partner DyNABind Gmbh, who will perform a DNA-encoded library (DEL) screen on several million compounds. Subsequent work will be carried out in Edinburgh to profile hits emerging from the DEL screen in cell-based assays before seeking funding for hit-to-lead optimisation activities.

I hope that I have provided a flavour of my current drug discovery work and that I have highlighted the importance of a team-based approach with complementary skills and experience. I am thankful to all of the skilled colleagues who have completed the technical work on the projects described above, most notably Andrew McBride (ENPPs), Pierre Rome (ENPPs), Shazia Khan (ATX), John Marwick (ATX) and Gareth Hardisty (S100). I also thank Rongling Wang (ENPP6) and the countless others who have produced the data that underpins each of these projects.






## Dr Ryan Wereski - Clinical Research Fellow

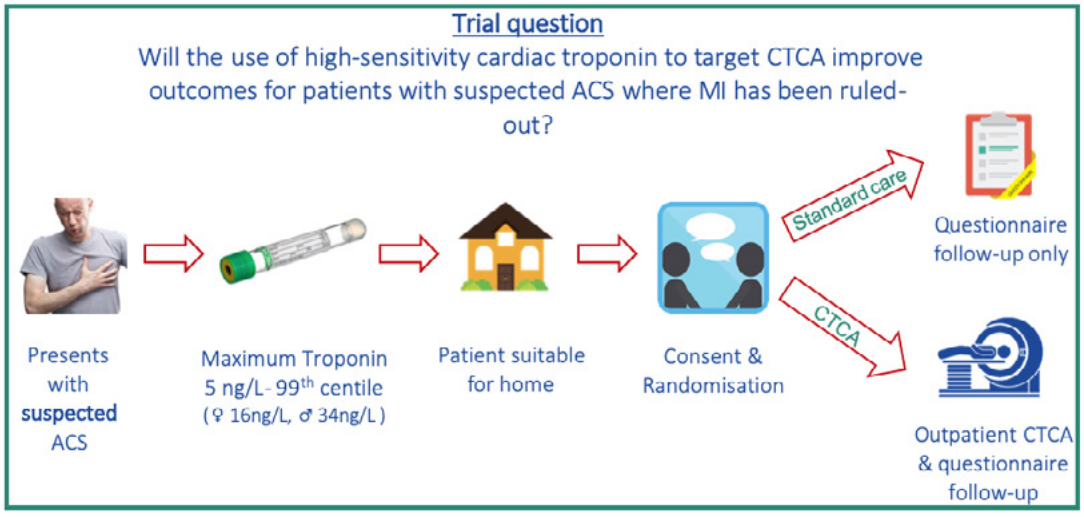
I joined the Centre for Cardiovascular Science in August 2019 after securing a place on the REA3 clinical fellowship programme. Since then I have been working closely with colleagues in the Cardiac Biomarker team led by Professor Nick Mills at the Centre for Cardiovascular Science.

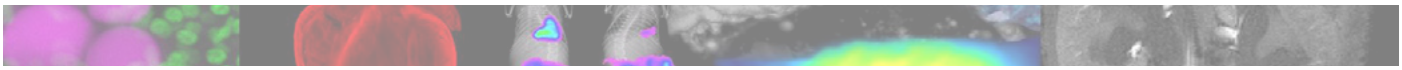
The current focus of my research is on the role that cardiac biomarkers, such as cardiac troponin, can play in the risk-stratification of patients who attend hospital with suspected acute coronary syndrome.

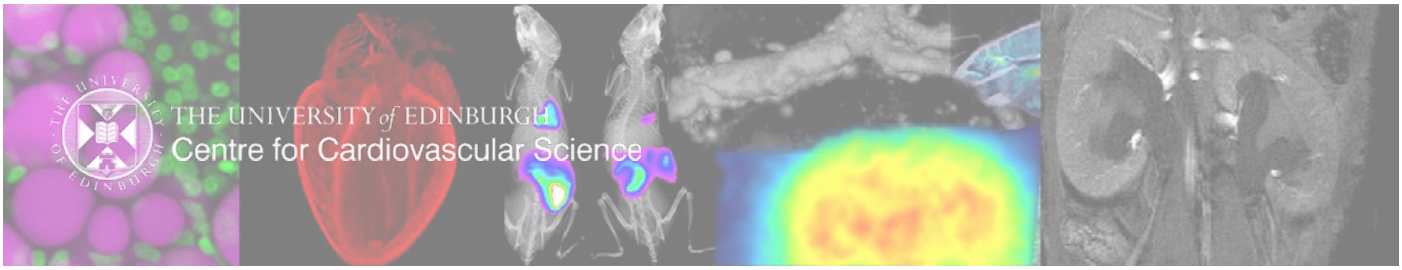
Chest pain and suspected myocardial infarction is one of the commonest reasons for people to attend the Emergency Department. High-sensitivity troponin assays have revolutionised how these patients are assessed and managed, and now the majority of patients can be safely discharged from the Emergency Department without a diagnosis of myocardial infarction.

However, there is no current international consensus on how those without a diagnosis of myocardial infarction should be assessed, investigated, or managed for underlying coronary disease. The assessment and follow-up of these patients varies around the globe, and often patients are discharged with no further evaluation for coronary artery disease after presenting with symptoms suggestive of acute coronary syndrome. This is despite evidence from the High-STEACS trial showing that incremental elevations in the concentration of troponin in patients without myocardial infarction can predict myocardial infarction or cardiac death at 1-year.

To assess this, I am currently helping to deliver the BHF-funded multi-centre randomised control trial, TARGET-CTCA, between NHS Greater Glasgow and Clyde and NHS Lothian. The TARGET-CTCA trial aims to assess whether the concentration of high sensitivity cardiac troponin, even when below the reference range used to diagnose myocardial infarction, can be used to inform the selection of patients for further coronary investigation. As part of this randomised trial, patients will be allocated to receive either standard-care, or additional coronary investigation with CT Coronary Angiography (Figure). Investigators believe that biomarker-led risk-stratification will help identify the patients at highest risk of significant underlying coronary disease, and help inform the selection of patients for secondary prevention therapies to ultimately reduce the future incidence of adverse cardiovascular outcomes.






# Professor Roland Stimson - Investigating the genetics of human brown adipose tissue, a novel target for metabolic disease

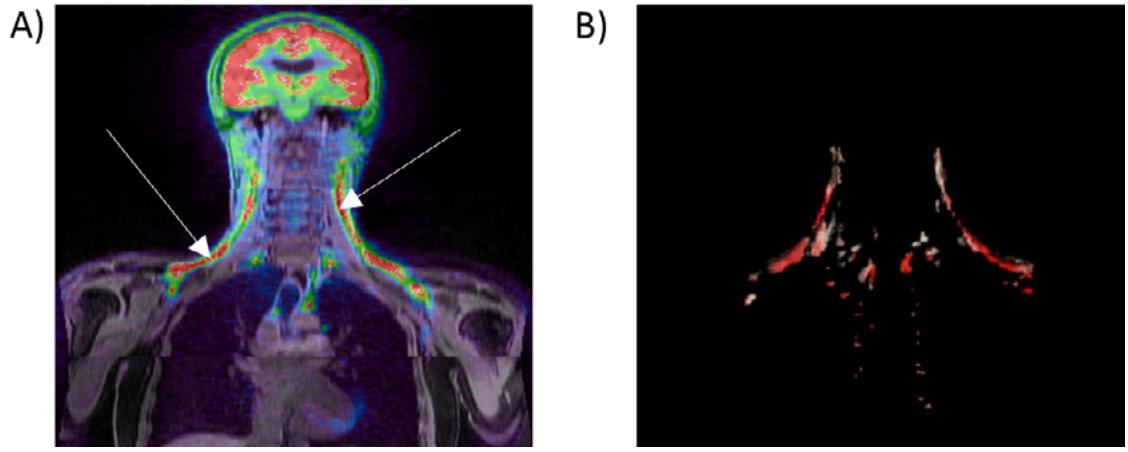
## Amount awarded: £37,830.95

**Co-applicants: Dr Tom MacGillivray, Dr Scott Semple and Professor Edwin van Beek**

The recent identification of brown adipose tissue (BAT) in adult humans offers therapeutic potential to activate this thermogenic tissue to increase energy expenditure, improve insulin sensitivity, improve dyslipidaemia and prevent cardiovascular disease. BAT is present in several depots in adults but primarily in the supraclavicular and paraspinal regions. Lean individuals have more BAT than obese subjects, however the quantity of BAT mass varies widely between individuals even in those with the same body fat content but the reasons for this are unclear. We hypothesize that genetic variation is in part responsible for these differences in BAT mass and that identifying the genes controlling BAT mass/ activation might identify novel therapeutic targets. Positron emission tomography (PET), most commonly using the metabolic tracer $^{18}$F-fluorodeoxyglucose ($^{18}$FDG), is the 'gold standard' technique to quantify BAT mass and activity in humans, however this is an intensive technique and requires subjects to be exposed to cold prior to scanning so is not easily performed in large numbers of subjects. In this BHF-funded project, we are determining whether magnetic resonance (MR) scanning can accurately quantify BAT mass. BAT has higher mitochondrial and water and lower fat content than white adipose tissue (WAT), this lower fat fraction can be quantified using MRI. In addition, MR scanning is a quick non-invasive technique that can be undertaken in large numbers of subjects. We are using $^{18}$FDG-PET/MR in lean and obese subjects during warm and cold exposure to determine the supraclavicular fat fraction in BAT positive and negative subjects (see Figure). In addition, we are developing a semi-automated technique to quantify BAT mass using MR that can be applied to large datasets to determine the genetic predictors of BAT mass and whether this confers protection against development of obesity, diabetes and cardiovascular disease. Understanding the genetic regulators of BAT will hopefully lead to the development of novel treatments for metabolic and cardiovascular disease.

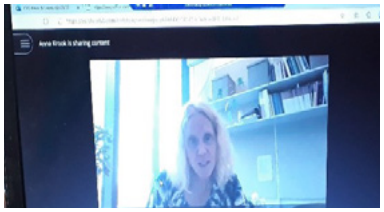
***Figure Quantification of fat fraction in human BAT***

***A)*** *Fused PET/MR image of $^{18}$FDG uptake by supraclavicular BAT (white arrows) in a subject during mild cold exposure (17°C).* ***B)*** *Fat fraction map of an individual's supraclavicular BAT generated using MR scanning.*

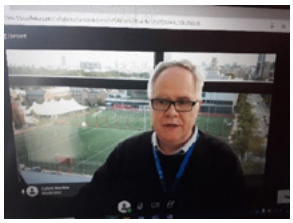



**CVS VIRTUAL EXTERNAL SEMINARS**

On the 3 and 17 September, two of our REA3 SAB members joined us by Blackboard Collaborate to provide two well-attended virtual lunch time seminars. We had the pleasure of welcoming Professor Anna Krook of the Karolinska Institute, whose seminar was entitled, ***"Skeletal microRNAs and regulation of metabolism"*** plus Professor Calum Macrae of Brigham and Women's Hospital and Harvard Medical School with his lecture entitled, ***"Left-right signalling and the mechanisms of atrial fibrillation"***. There was an opportunity after each event to engage with both Professors and find out more about their current research.



Professor Anna Krook
3 September



Professor Calum Macrae
17 September

**The REA3 Executive would like to extend its thanks to Professor Anna Krook and Professor Calum Macrae for giving up their time to deliver these important online sessions for our scientific community.**

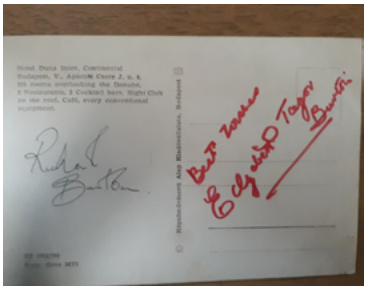
**FINALLY.....**

Weekends are a fairly subdued event now for Gillian Joyce so what to do if not out for food or being turfed out a pub at 10pm? Have a tidy out of "stuff" and see what's there:

An old postcard.....

Dodgy fleece, one wearer.

But the reverse has some interesting movie star autographs



Oooh happier times