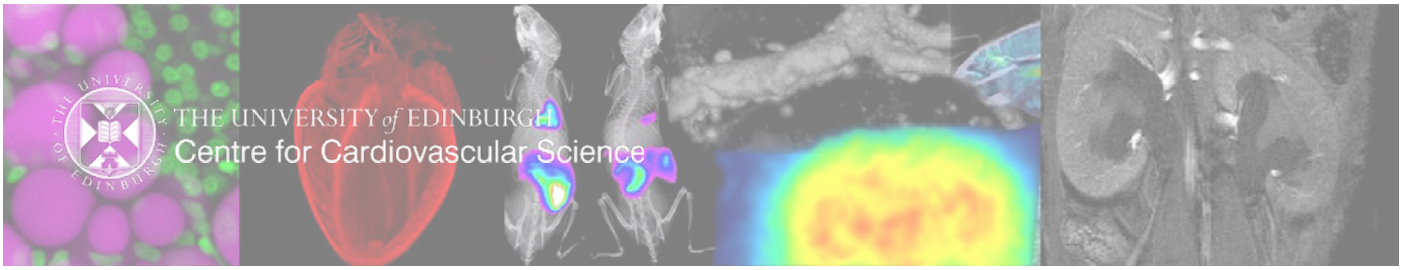
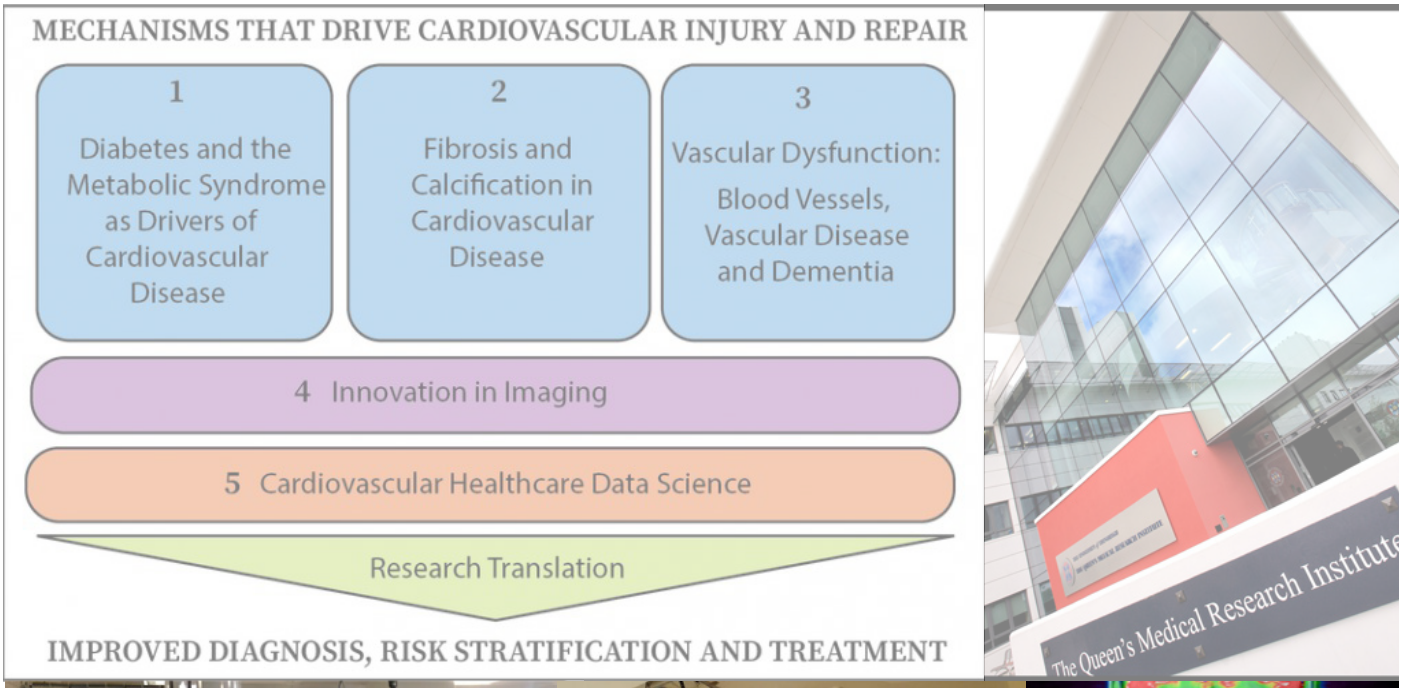


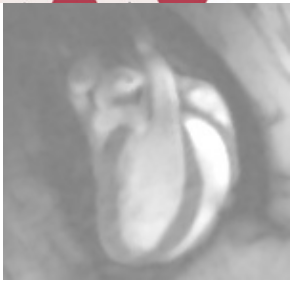
REA3 BIMONTHLY NEWSLETTER

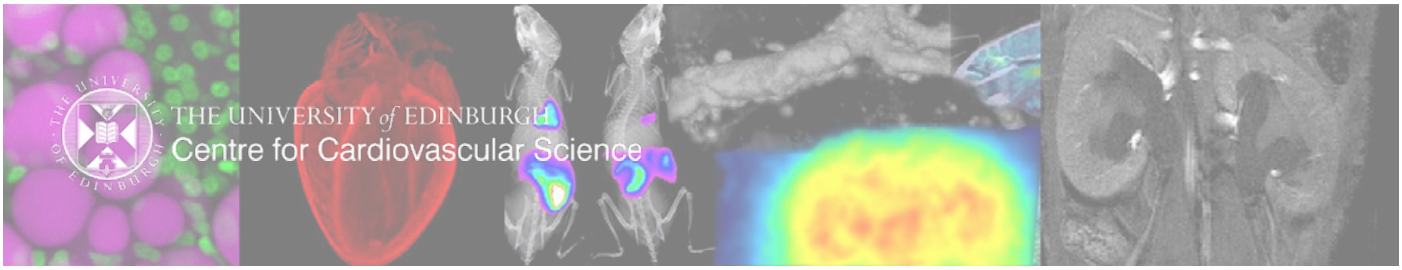
July 2021



THE UNIVERSITY of EDINBURGH

BHF Research Excellence Award University of Edinburgh





INTRODUCTION

Welcome to the latest edition of the REA3 Newsletter.

As it is summer, hopefully most people are managing to have a well-deserved break over this period. The vaccination programme in the UK continues to be rolled out with pop-in centres "popping" up to capture as many people as possible. For those in the Lothian area you can find out more at the following link:

https://www.nhslothian.scot/Coronavirus/Vaccine/Pages/Drop-in-Clinics.aspx


Dr Caelan Taggart

In this issue we have two contributors providing an update about their projects and positions within REA3. Dr Caelan Taggart was recently appointed as a Clinical Fellow and is currently helping in the development of risk scores so that doctors can use it to help identify patients with type 2 myocardial infarction, which is less well understood in comparision to type 1 myocardial infarction.


Dr Tijana Mitić,

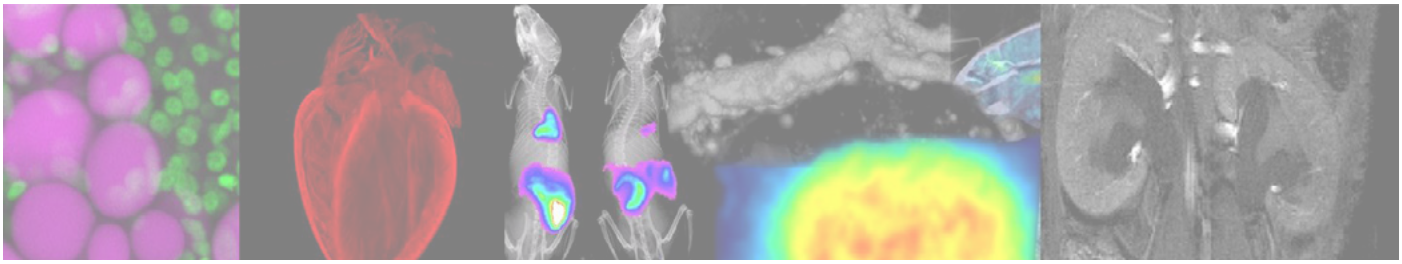
We also just recently recruited transitional fellows to REA3 and one of those appointments, Dr Tijana Mitić, provides us with some insight into her research in epigenetic mechanisms of endothelial dysfunction in ischaemia/hypoxia.

We also would like to welcome Professor Scott Webster to the REA3 Executive. Scott has already provided invaluable insight as a PI to REA3 and we are pleased that he has accepted our invitation to help shape the remainder of the funding, especially with his expertise in translation.

Gillian Joyce welcomes any new articles or ideas that perhaps you would like to have included in the next REA3 newsletter. Do get in contact with her: Gillian.Joyce@ed.ac.uk

Please enjoy the rest of the summer break and we look forward to providing more updates in the next edition.

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



Dr Caelan Taggart - Clinical Research Fellow

Caelan joined the Centre for Cardiovascular Science in August 2020 after completing his core medical training. Since then, he has been working closely with colleagues in the cardiac biomarker team and his supervisors Professor Nicholas Mills and Dr Andrew Chapman.

Heart attacks remain one of the most common reasons for death or admission to hospital in the UK. The two most common types of heart attack are known as type 1 and type 2 myocardial infarction. We have effective treatments for type 1 myocardial infarction, which occurs when a clot forms in the artery and blocks the blood supply to the heart. However, type 2 myocardial infarction is less well understood and occurs when the heart muscle cannot get enough oxygen due to an alternative condition and is damaged in the absence of a clot forming in the artery.

Despite this being common (around 20% of all heart attacks) there are currently no guidelines for doctors on how to manage type 2 myocardial infarction and most patients do not receive any additional treatment or follow up. The focus of my PhD studies is to improve the management of these patients.

My initial work has been the development of risk score that doctors can use to identify patients with type 2 myocardial infarction to identify those at higher risk of future heart attacks or death. We will develop this by performing an analysis of this patient population in the High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome (High-STEACS) trial cohort.

As there are no evidence-based therapies for this condition, we will gather a panel of medical experts who have conducted research into type 2 myocardial infarction and design a complex intervention, in this case a care pathway, for these patients. We will do this by conducting a Delphi study. A Delphi study is a survey method consisting of open and closed questioning over several rounds until a consensus is reached **(Figure 1)**. This care pathway will mainly focus on identifying and treating underlying coronary disease and heart failure which we know is common in these patients.

Once we have developed our care pathway, we will test this by implementing it into the intervention arm of a small local, randomised trial to determine whether it is acceptable to both patients and doctors **(Figure 2)**. We hope this research will inform the design of a large multi-centre trial, assessing the impact of this intervention on clinical outcomes in patients with type 2 myocardial infarction.

I am thankful to the British Heart Foundation Research Excellence Award (REA/18/5/34216) for providing me with funding whilst I await the outcome of my fully funded Clinical Research Training Fellowship proposal.

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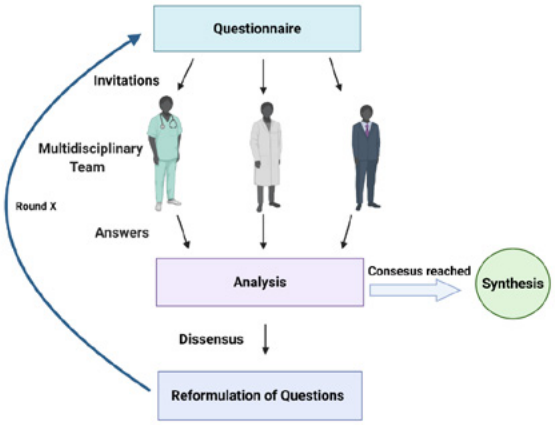

Figure 1: Design of Delphi study aimed at creating consensus statements on the assessment and management of type 2 myocardial infarction

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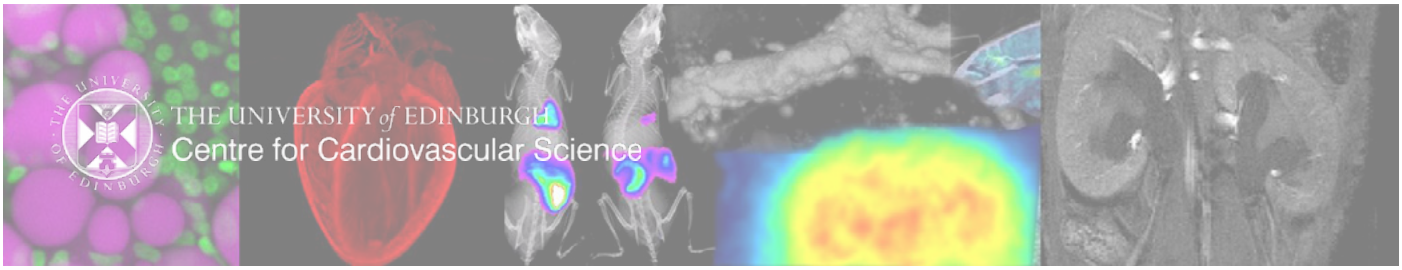


Dr Caelan Taggart - Clinical Research Fellow

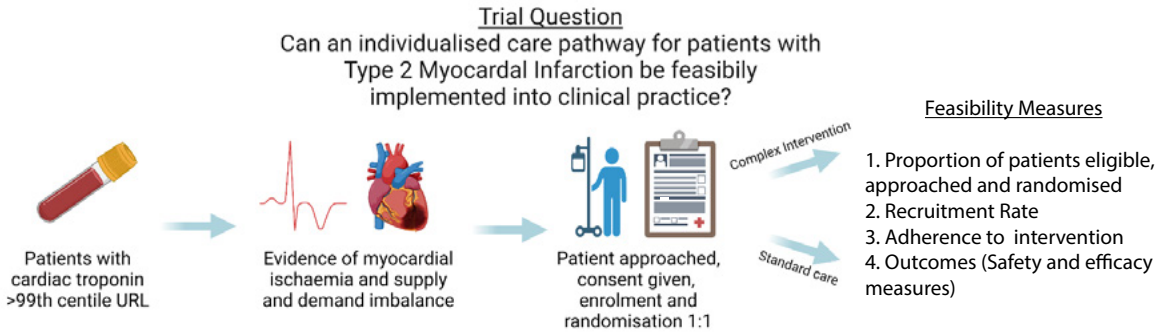
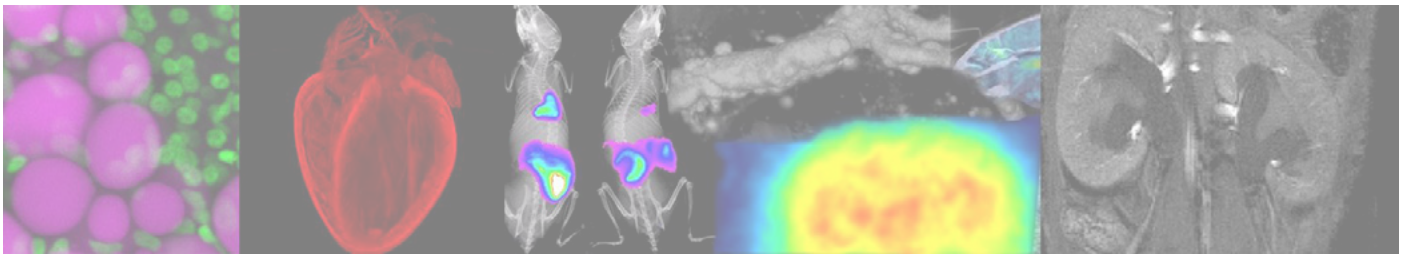
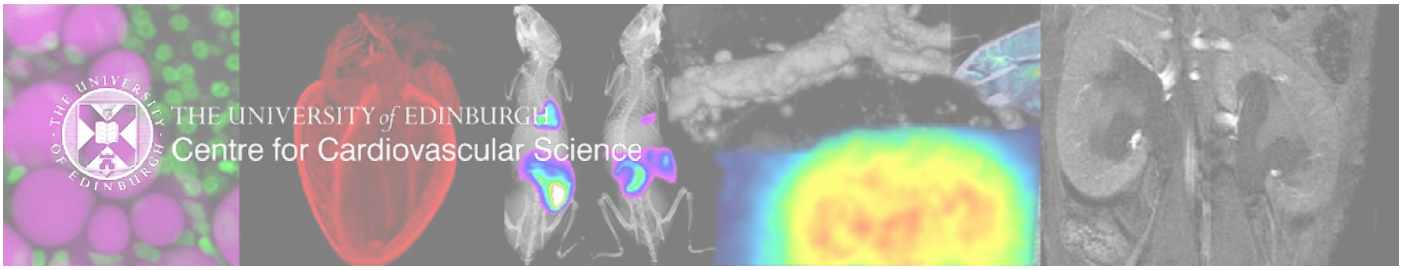


Figure 2: Brief flow chart of feasibility trial testing a complex intervention for type 2 myocardial infarction





Dr Tijana Mitić - Career re-entry Fellow and Transitional Fellow

As a BHF career re-entry research fellow and a REA transitional fellow, I am delighted and grateful to be able to share my research scope. Recently, I have been awarded a REA Transitional Fellowship to support my research into epigenetic mechanisms of endothelial dysfunction in ischaemia/hypoxia. Through applying molecular, biochemical, synthetic biology and bioinformatics approaches my research interests comprise epigenetic mechanisms that regulate endothelial gene expression and activation of endothelial cells function following injury. Such approaches could be translated to clinical practice and of relevance also for cerebral and cardiac ischaemic diseases. This topic aligns with the REA3 pillars and CVS strategy but has the potential for development of innovative pharmacological agents, gene therapies, and repurposing of existing drugs for alternative use in-human.

My lab uses human genetic/genomic and physiological data to find human relevance for non-coding RNAs (ncRNAs). Long non-coding RNAs (lncRNAs) are new players in epigenetic regulation of endothelial cell gene expression. It is currently unknown how lncRNA-chromatin interactions contribute to endothelial physiology during ischaemia, to regulate gene expression. Some lncRNAs are translated and some are likely to express functional proteins. About 20% of all lncRNAs can interact with Polycomb repressive complex 2 (PRC2) in a context dependent manner. PRC2 is a transcriptional repressor, and Enhancer of Zeste Homolog 2 (EZH2) is a catalytic core of PRC2 responsible for di-/tri- methylation of lysine 27 of histone 3 (H3K27me2/3), that is generally very well studied in cancer cells. The EZH2 also acts as an RNA-binding protein. There is still very little conclusive evidence on ncRNA-guided targeting of PRC2 onto endothelial genes, and role in chromatin looping organisation. Recent work had shown that reversal of EZH2 regulates chromatin remodelling de-represses key genes leading to repair post ischaemic injury, aortic aneurism and heart failure, and the mechanisms behind this protection suggests involvement of lncRNAs. Targeting PRC2 protein:ncRNA interactions is now at the forefront of repurposing existing EZH2 inhibitors for CVDs. Together with mapping the cell type specific expression of chromatin accessibility this is very topical and novel work.

As a BHF Fellow, through the past 4 years I have developed methodologies, conceptual frameworks and tools that could benefit my research into epigenetic mechanisms of endothelial dysfunction. The named studies required two kind of approaches, a protein-centric one, that involves immunoprecipitation of target protein with RNA purification, or secondly, a lncRNA-centric approach using biotinylated probes that hybridise against lncRNA of interest followed by RNA, DNA or protein purification and sequencing or mass/spec. Over the past year, we have done exciting work with Prof. David Tollorvey lab and the Wellcome Trust bioinformatics team to generate and map the endothelial PRC2 transcriptome. These findings disclosed the relationship between ncRNA and PRC2 in endothelial biology, whereby many EZH2 bound lncRNA were found to directly interact with one other lncRNA or mRNA target, whereas a small fraction (0.4%) was bound to miRNA and antisense RNA.

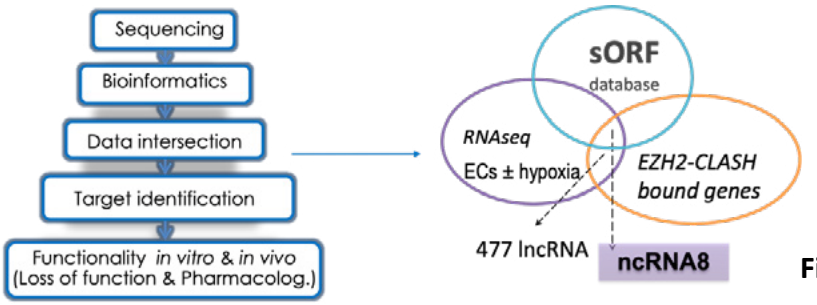


Figure 1

The summary of the approach we took in the lab includes the above pipeline. Through data intersection we have been able to identify 477 lncRNA candidates and a novel ncRNA8, to take forward. We wish to investigate how it influences EC epigenome in vascular complications and during PRC2 inhibition.

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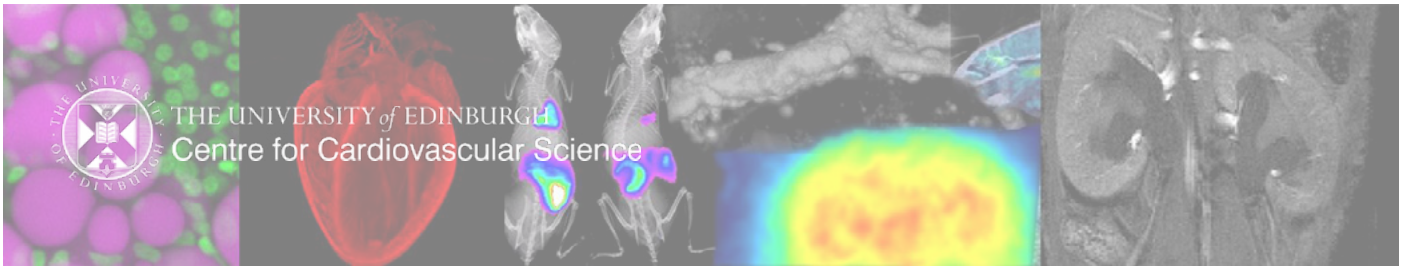
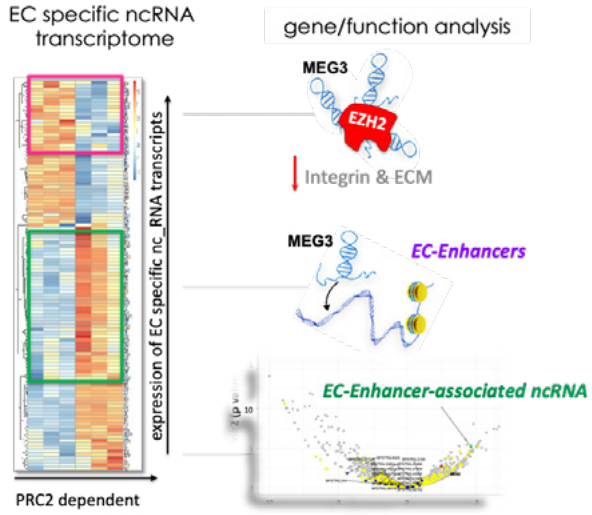


Dr Tijana Mitić - Career re-entry Fellow and Transitional Fellow

Moreover chromatin isolation by RNA purification and sequencing (ChIRP-Seq) with MEG3-biotinylated probes to hybridise them onto endogenous lncRNA in culture system, I identified unique binding locations to genomic regions in the vascular endothelial cells that MEG3 associates with and leads to repression of gene transcription through recruitment of PRC2. These new mechanistic aspects have helped me inform good science in the area of microvascular diseases.

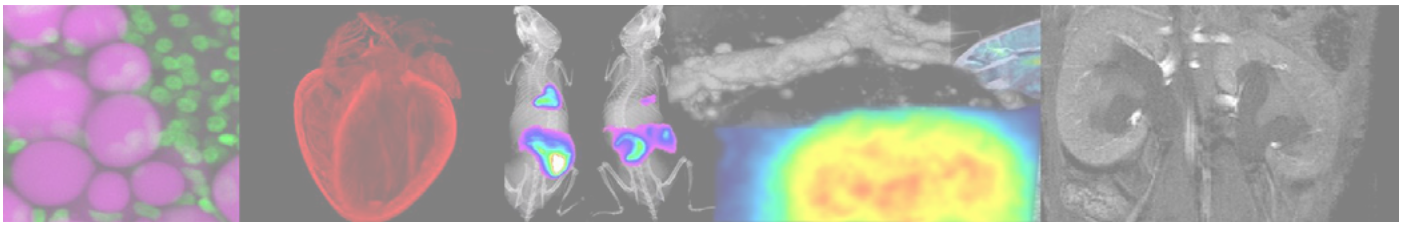
Figure 2

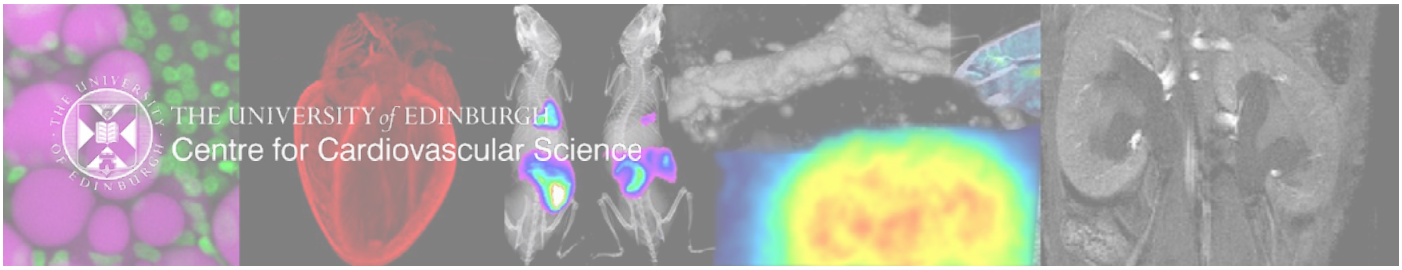


We generated endothelial specific PRC2-dependent transcriptome and a genome-wide MEG3-lncRNA profiles, which we associated with specific enhancer regions. Both comprehensive expression analysis also revealed EZH2-bound ncRNAs and mRNA targets belonging to specific functional pathways including integrin signalling and regulation of extracellular matrix.

Through bioinformatics analyses we have also identified enhancer regions within the PRC2-regulated RNAs. This work helped me identify ncRNAs that could be studied further to inform the mechanisms behind PRC2-regulation i.e. binding to chromatin to induce remodelling in endothelial cells via specific enhancer inhibition. Further, in collaboration with Prof Frontini, from Cambridge BLUEPRINT project we have identified and categorised open reading frames (ORFs) within our novel datasets. Amongst novel ncRNAs we identified the ones with small ORFs and explored their coding potential to produce micropeptide. This gives rise to two approaches really, to understanding the actions of ncRNA and that of the micropeptide in endothelial cell biology.

For my Transitional Fellowship, I will be studying above data that have contributed to my Fellowship plan and program of research. My intention is to use established tools to characterize specific ncRNA candidates and to underpin their pathological mechanisms in controlling vascular disease. This funding has really paved the way for me to try and secure the Intermediate Fellowship at the next stage and I grateful to be able to get this this opportunity.





Professor Joanna Wardlaw - Interview featured in the Daily Mail

Professor Joanna Wardlaw's expertise about minimising risks of developing dementia, was featured recently in an article entitled, *"What the experts do to stave off dementia: after exciting new drug breakthrough, our guide to precautions you can take to lessen your chances of the condition"*.

Further information can be found on the Row Fogo Centre for Research into Ageing and the Brain website:

https://www.ed.ac.uk/clinical-brain-sciences/research/row-fogo-centre/news-and-events/news/professor-joanna-wardlaw-daily-mail-dementia

FINALLY.....

It's growing season again and Gillian Joyce's kitchen resembles a still from the film, "The Day of the Triffids". But fear not, it's just cucumbers (and other bits and bobs):