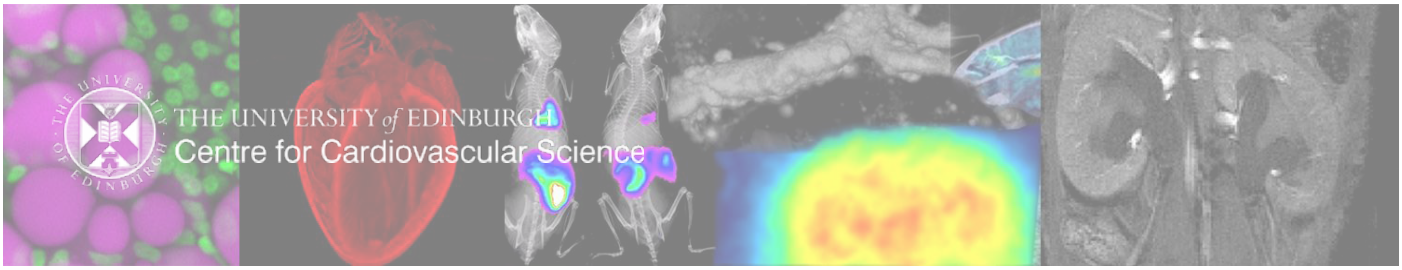
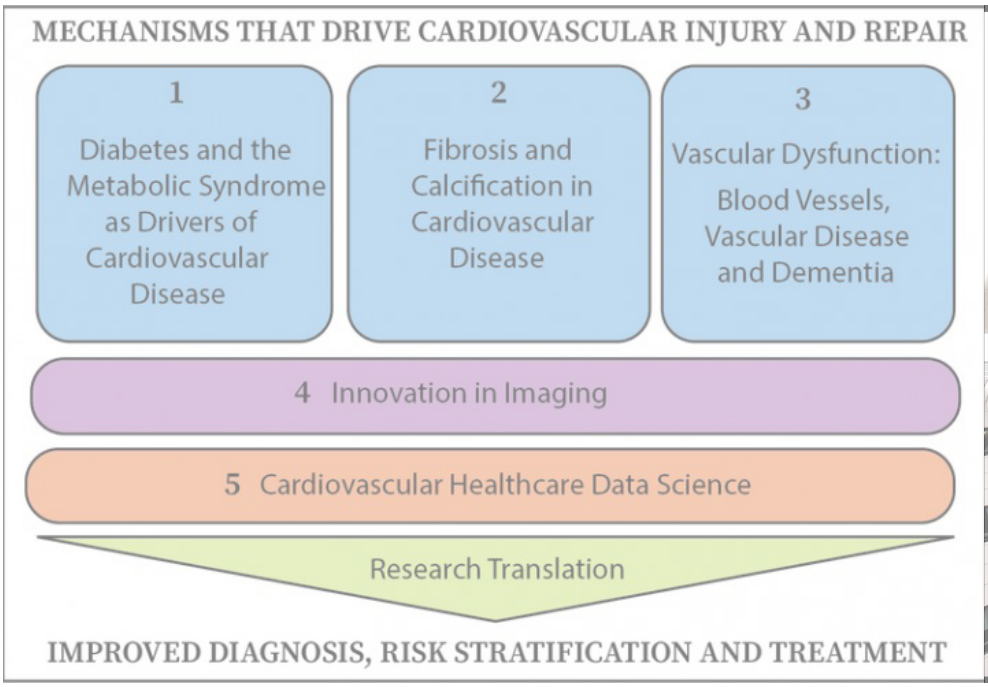
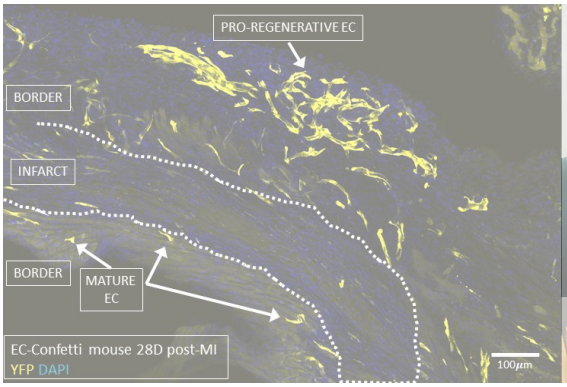


REA3 BIMONTHLY NEWSLETTER

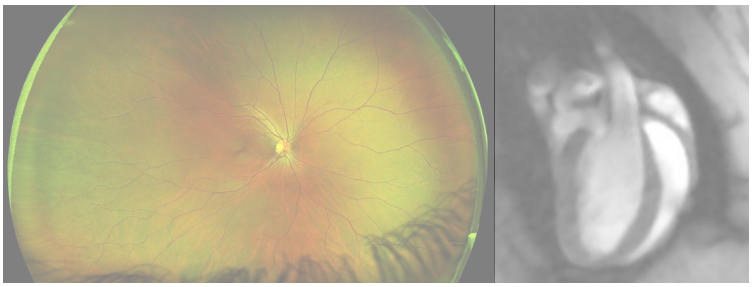
March 2020

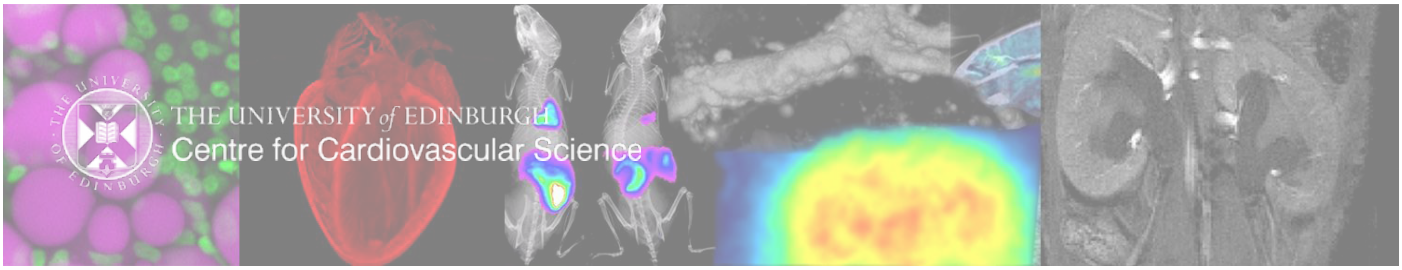




THE UNIVERSITY of EDINBURGH

British Heart Foundation





INTRODUCTION

Welcome to our second edition of the bimonthly REA3 Newsletter.

As everyone is aware, the Covid-19 pandemic is profoundly affecting our personal and work lives and for the moment, we are unsure how long this disruption will last. This has been a particular issue for our early career researchers, our research students as well as clinical staff who have been deployed into the National Health Service. Regarding BHF-funded research, the latest update can be found here: https://www.bhf.org.uk/for-professionals/information-for-researchers/bhf-research-position-statement-on-covid-19 and we are talking to other REA3-funded Centres of Research Excellence to try and develop plans, strategies and solutions to mimimise the impact where possible. For up-to-date information regarding the situation in the UK, please do follow the UK and Scottish Government guidelines. For those of you who are part of the University of Edinburgh family, there will be continued updates via the university website and of course, to our extensive mailing lists regarding any developments.


Professor Kramann

Within this issue we feature Dr Rafael Kramann, who is Professor of Medicine and Chair of Nephro-Cardiology at RWTH Aachen University. Professor Kramann is also one of our Principal Investigators within REA3 and he presents an overview of his research regarding kidney disease and cardiovascular diseases. Currently, Rafael has also been working hard on the frontline regarding treatment of Covid-19 patients in Germany.


Professor Anna Williams

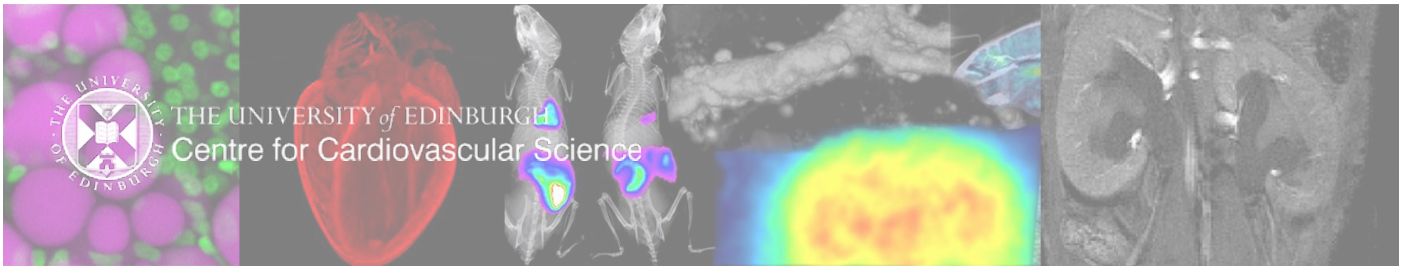
In our Spring 2019 REA3 Pump Priming Round, £47,666.10 was awarded to Professor Anna Williams' project, *Can human embryonic-derived endothelial-like cells specify to brain microvasculature?* Anna provides some insight into the project and how the work links the Williams and Baker labs together. Dr Kristiina Rannikmäe, who was also awarded money in the Spring 2019 round, has appointed Dr Amy Ferguson to join her study, *Clinical consquences of rare variants in Cerebral Disease genes***.** We feature a small section on Amy's appointment and work.

Our Spring 2020 Pump Priming Round is currently open with a closing date of 5pm Friday 24 April. We will be targeting Early Career Principal Investigators and translational research. You can find out more within this newsletter.

If you wish to contribute anything to any future editions of the newsletter then do get in contact with Gillian Joyce, Research Project Co-ordinator, Gillian.Joyce@ed.ac.uk She will be looking for any interesting articles to feature from the May issue onwards.

Finally, we want to extend our thanks to the REA3 community, our colleagues in other areas of research and for everyone's commitment during this challenging time and for pulling together.

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

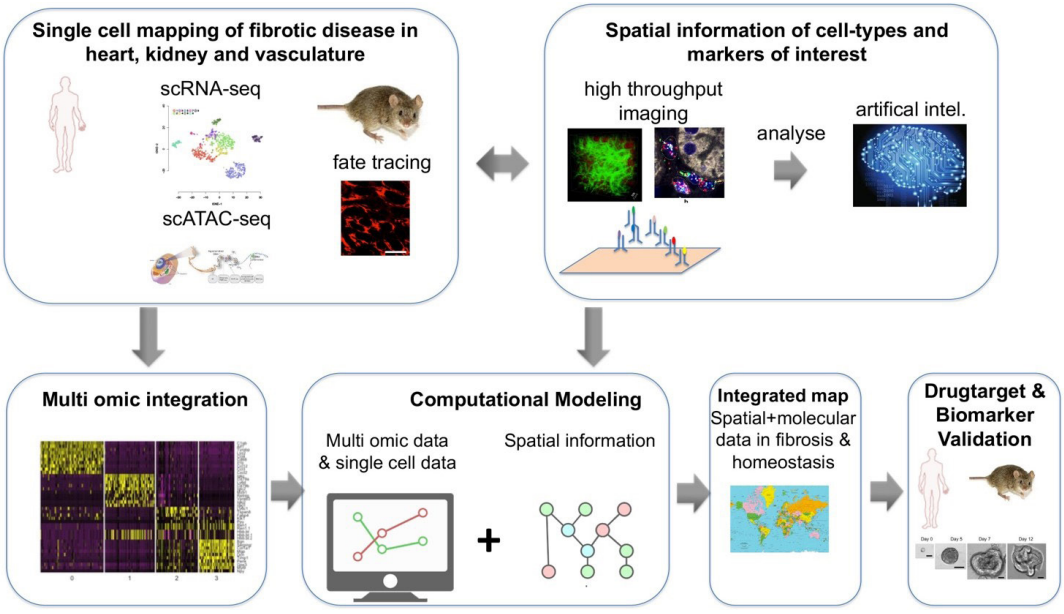


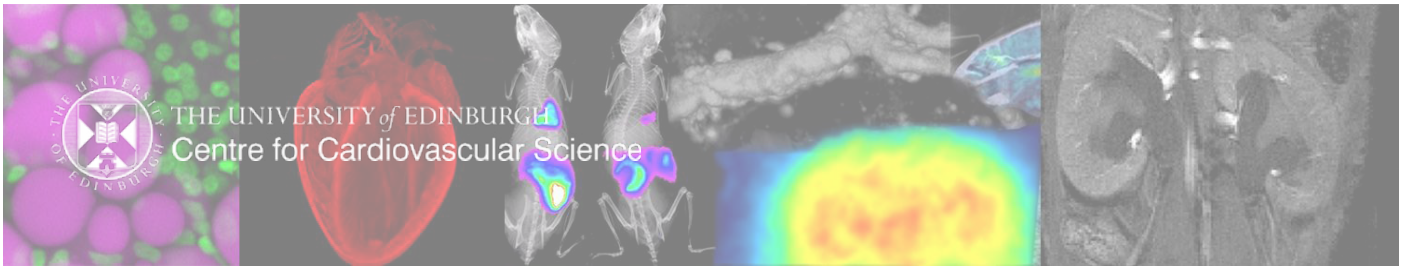
Professor Rafael Kramann - RWTH Aachen University and Erasmus Medical Centre

Rafael Kramann´s laboratory (www.kramannlab.com) at RWTH Aachen University (Aachen, Germany) and Erasmus Medical Center (Rotterdam, The Netherlands) works on kidney disease and cardiovascular diseases with a particular focus on tissue fibrosis driving end-stage renal disease, heart failure as well as vascular disease (vascular sclerosis and calcification). Another interest of the lab is developing novel computational and wet lab tools in the single cell genomic field.

Tissue fibrosis, or scar formation, is the common final pathway of virtually all progressive diseases and inflicts damage in every major solid organ including kidney, heart, lung and liver as well as soft tissues such as blood vessels, skin, and skeletal muscle. Scar tissue can form after an acute insult, or more slowly as a result of years of chronic injury/agitation from a separate underlying malady. A fibrotic matrix may initially aid in the tissue repair process, and even subside in cases of mild injury as functional tissue regenerates. However, during chronic or repetitive injury, fibrotic matrix deposition goes unchecked, slowly disrupting tissue architecture, preventing normal function, and inhibiting repair ultimately leading to organ failure. It has been estimated that fibrosis contributes to as much as 45% of mortality in the developed world. Myofibroblasts are the cells that cause fibrosis but their cellular origin, regulation and mechanism of activation and expansion is incompletely understood.

The Kramann laboratory combines genetic fate tracing studies in mice with single cell genomic technologies and single cell mapping of human tissue to dissect the cellular source and heterogeneity of myofibroblasts and to further understand their mechanism of activation by cross-talk to other cells. The generated single cell and single nucleus RNA-sequencing and ATAC-seq data is validated using cell-culture models with novel cell-lines generated particular for this purpose, 3D cell culture models and organoids. The major goal is to generate high resolution molecular and spatial maps of fibrotic disease in heart and kidney to understand disease and identify novel biomarkers and therapeutic targets. The single cell data is mapped to space using multiplex and sequential immunostaining, in situ hybridization and spatial transcriptomics. Dr. Kramann collaborates with various groups within the REA and outside with a particular focus on single cell technologies and multi-omic integration (single cell genomic data with e.g. proteomics and metabolomics as well as spatial information) to achieve these goals. His group has recently discovered Gli1^{+} cells as a major source of fibrosis causing cells in heart, kidney and vasculature (Cell Stem Cell 2015) and the bone marrow (Cell Stem Cell 2017).





Professor Anna Williams - Professor of Regenerative Medicine, Honorary Consultant Neurologist, University of Edinburgh

Can human embryonic-derived endothelial-like cells specify to brain microvasculature?

Endothelial cells (ECs) from different organs are similar in that they all form blood vessels, but also increasingly recognised as different, suggesting functional differences important for the biology and pathology of their surrounding tissue. This project working between the Williams and the Baker labs, will address these differences and how they are generated/maintained – an important question for our REA3.

The Baker lab has derived human endothelial-like cells from embryonic stem cells (hESC), and analysed their transcriptomes by scRNAseq analysis. We compared these published transcriptomes from human organ-specific vascular ECs. Essentially, and perhaps unsurprisingly, these organ-specific cells have different RNA transcriptional landscapes to each other and to the hESC-derived ECs (Figure 1). This project depends on the belief that understanding these differences will allow us to coax ES-derived endothelial-like cells into cells with an organ-specific endothelial phenotype and function. Our overarching hypothesis is therefore that "*Specification of human ES cell-derived ECs can be achieved by co-culture in organ-specific environments*".

The Williams lab has recently published transcriptome analysis of single human brain nuclei including ECs and has identified the importance of brain ECs in development of vascular dementia. Brain ECs are notably distinct, forming the blood-brain barrier with specialised tight junctions. In this project, we will define the 'ground state' transcriptomes of hESC-derived EC, human post mortem brain EC nuclei and fresh human brain ECs from neurosurgical biopsies aiming to then determine links and transition paths between these states. This may generate pathways we can manipulate to generate more 'brain-like' ECs, which we can test in culture. Previous work suggests that co-culture of hESC-derived ECs with astrocytes can induce some EC changes suggestive of a more brain-like phenotype, giving us a starting point, and so we will culture our hESC-derived ECs on transwell membranes, with underlying astrocytes. These cells will be examined at the RNA and protein level and compared with our 'ground' states generated above.

Development of such a model system will provide us with essential new information that provides the unique opportunity to understand the molecular cues that drive maturation and specification of hES-EC into brain microvascular ECs, assess the impact of other brain cells e.g. astrocytes on brain EC transcriptome and function and use a relevant human model system to drive innovation in strategies to target key molecular pathways in brain ECs that underpin vascular dementia; e.g. small molecule screens.

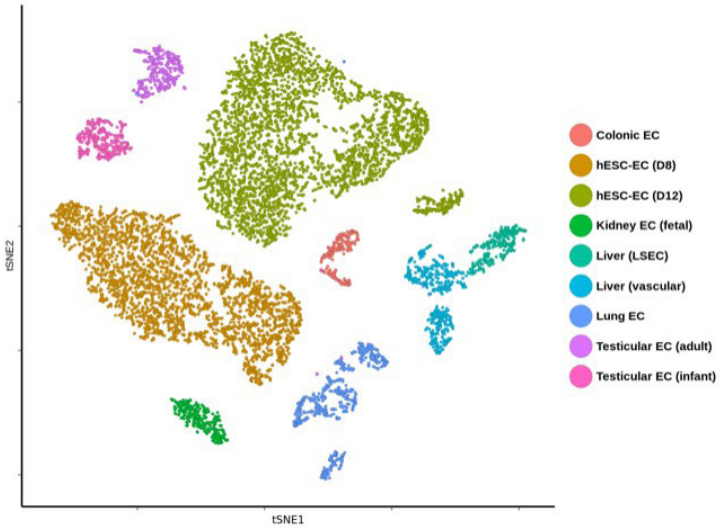
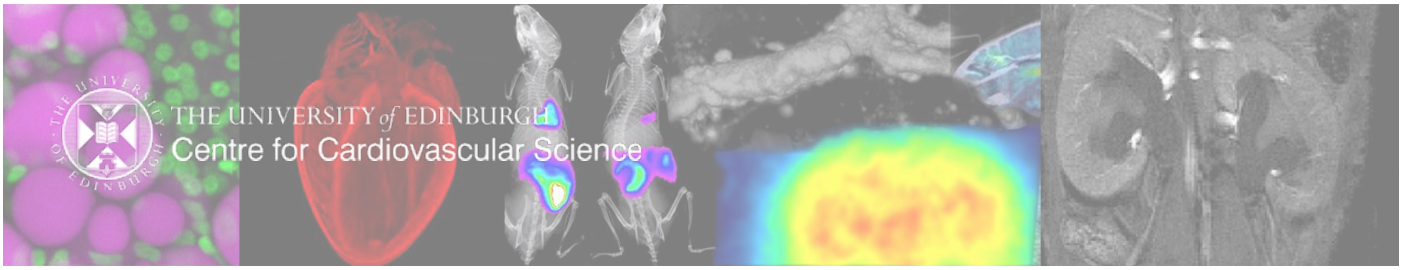


Figure 1. tSNE plot of human vascular endothelial types.

Plot illustrates the heterogeneity of human adult cells between organs (lung, liver, testes available in 10X) and the cells derived from hES cells in culture for either 8 or 12 days.



The British Heart Foundation (BHF) Research Excellence (REA3) Spring 2020 Pump Priming Awards

The aim of the REA3 pump priming fund is to provide small grants which will directly aid successful grant and fellowship applications, initiate new collaborations, or establish new research directions that will be fundable from other sources within the period of the REA3 award. These should be aligned to REA3 pillars and cross-cutting themes. **The Spring 2020 call is specifically for proposals from Early Career Principal Investigators (within 5 years of their first position as principal investigator), and for requests for funds to support all stages of translational research.**

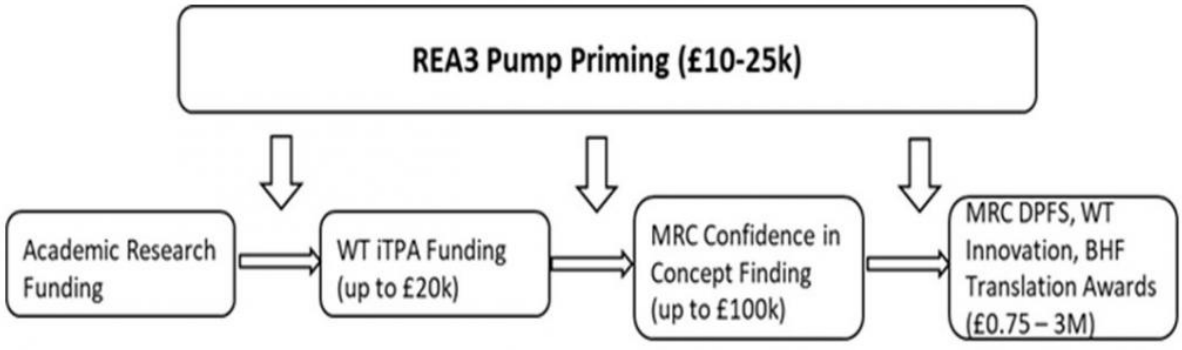
Guidance for Applicants – Early Career PI Proposals

Priority will be given to proposals that have one or more of the following:

- are clearly aligned to REA3 pillars and cross-cutting themes.
- seek to link research between one or more research pillars or themes.
- contain an element of healthcare data science.
- show a clear and tangible route to further funding.

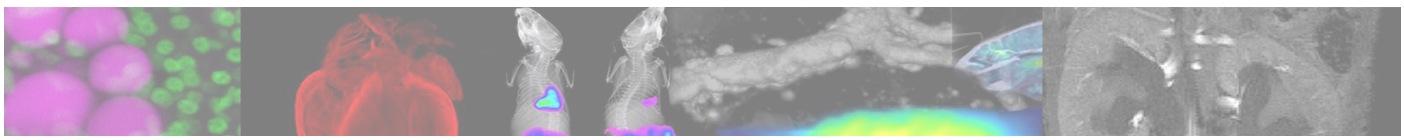
Guidance for Applicants - Translational Applications

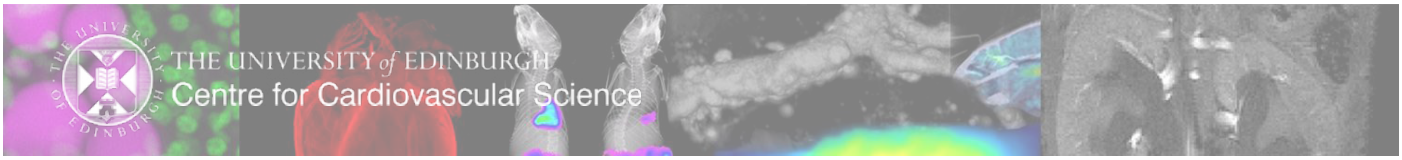
We request applications for pump-priming to support all stages of translational research. For very early stage projects funding may be sought to establish 'reason to believe' to conduct specific experiments that will provide evidence of a new approach to a specific problem. In this case projects will be expected to be in a position to seek follow-on funding for a more substantive programme of translational research. Funding may also be sought to support more established translational research where 'proof of concept' is required to leverage larger follow-on funding investment. Funding will also considered for projects that require a specific datasets to bridge the funding gap. The typical translational funding pathway is shown below:



CLOSING DATE
5pm Friday 24 April 2020. Outcome announced: 2 June 2020

Further information, including the application form, can be found on the BHF Centre of Research Excellence pages (MyEd login required)





Dr Kristiina Rannikmäe successfully applied for funding in the first round of REA3 pump priming in Spring 2019. The title for her study, "*Clinical consequences of rare variants in Cerebral Small Vessel Disease genes*" was awarded £45,375.31 and included a bid to help fund a postdoctoral research assistant to work on the project with the collaborating team (Drs K. Rannikmäe and K. Rawlik, Professors A. Tenesa and C. Sudlow).

After advertising, a successful appointment was made and Dr Amy Ferguson commenced employment with the university in January this year.

Welcome Dr Ferguson!

Dr Kristiina Rannikmäe, *"Amy is a Postdoctoral Researcher who joined the University of Edinburgh from the University of Glasgow after completing her PhD in psychiatric genetics. Amy has a background in molecular genetics, as well as population and statistical genetics. The title of her BHF REA3 funded project led by me is "Clinical consequences of rare variants in Cerebral Small Vessel Disease genes". Decreasing price and increasing availability of genotyping will lead to the discovery of many rare genetic variants among those tested for any indication. However, the interpretation of the variant's consequences – the probability that an individual will develop a disease (i.e. variant penetrance) – is one of the most pressing challenges in genetic medicine. To date, knowledge of variants' potential to cause disease comes predominantly from small disease cohort studies which suffer from biases and overestimate penetrance. Amy's research will focus on investigating the broad spectrum of clinical manifestations associated with rare genetic variation in monogenic cerebral small vessel disease genes in the UK Biobank study, which will complement the knowledge obtained from small disease cohort studies. Amy is based in the Centre for Medical Informatics in the Usher Institute, but collaborates closely with Professor Albert Tenesa's statistical genetics team in the Roslin Institute."*

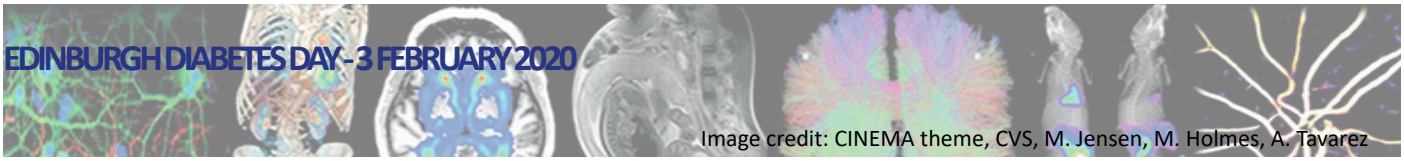


Image credit: CINEMA theme, CVS, M. Jensen, M. Holmes, A. Tavarez

REA3 were pleased to provide financial support towards the inaugural Edinburgh Diabetes Day (EDD)

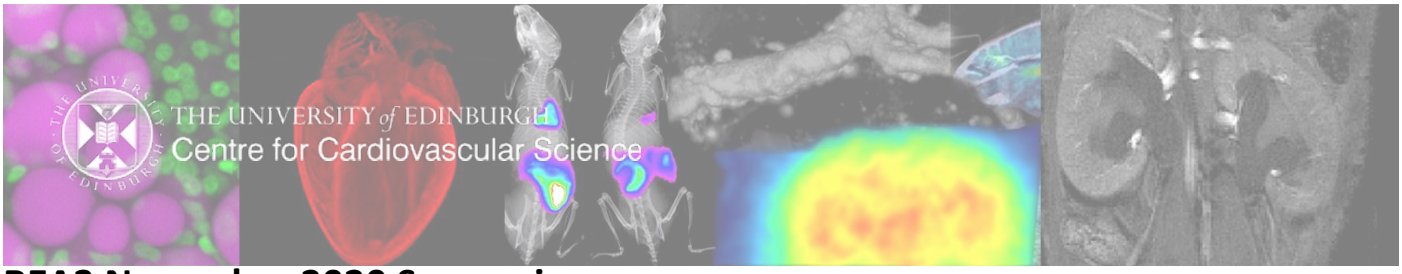
Professor Nik Morton, *"Of > 100 delegates, we had representations from industry, the e-health sector and other key academic stakeholders, Scottish National Blood Transfusion Transplant Centre, Roslin/Vet School Large Animal Research Facility and Centre for Discovery Brain Sciences. Professor Andrew Morris, Chair of Medicine/Vice-Principal of Data Science launched the day and noted the potential for making diabetes research "greater than the sum of its parts" in Edinburgh.*

This was a clear endorsement of our activities and intent, and a sign of our increasing interaction with data science resources, exemplified by cross-cutting REA3 data science leader and speaker Professor Nick Mills.

Elizabeth Robertson, Director of Research at Diabetes UK (DUK), gave an excellent keynote speech about "future perspectives" in the diabetes research areas. She remarked on the high number of young scientists in the audience and at the poster and networking sessions. A highlight of the keynote was the explicit steer from her that joint funding of grants with other charities such as the British Heart Foundation (BHF) is a priority.

Our closing speech, provided by Professor Jonathan Seckl, Moncrieff Arnott Professor of Molecular Medicine and Senior Vice-Principal, shared keen interest to support new initiatives in diabetes research among our expanding community. His challenge was "what will we do" with this newly marshalled grouping and momentum.

Overall,the day was a great success. It will lead to further interaction among our related disciplines locally and beyond"



REA3 November 2020 Symposium

The REA3 Executive are pleased to announce that we will be holding our first REA3 Symposium/Workshop on Tuesday 24 November at QMRI. Details surrounding this event will be announced in later editions of the newsletter. The day will focus on data driven innovation and will be led by Professor Nick Mills.,

Future Opportunities

In June 2019 we advertised Clinical Research Fellowship (ClinRF) vacancies and successfully appointed 3 individuals. It is intended to advertise this year's ClinRF opportunities over the coming weeks. Please do keep an eye on our website for updates: https://www.ed.ac.uk/cardiovascular-science/research/cvs-bhf-centres/bhf-centre-of-research-excellence/fellowships

And finally.....

Gillian Joyce, Research Project Co-ordinator, is keen to hear from anyone who would like to contribute any information that can feature in the REA3 Newsletter. If you would like to feature any news or articles that link in with REA3, please get in touch, particularly those individuals/groups who are receiving funding from REA3.

You can contact Gillian using her email address: Gillian.Joyce@ed.ac.uk

Like many of you, Gillian has experienced disruption to her working life and is now propping up a laptop on her dining table at home with two children. So for some light relief for all the new home workers and also to those who are adjusting to a different working ethos, here is a selection of photos from her working week: