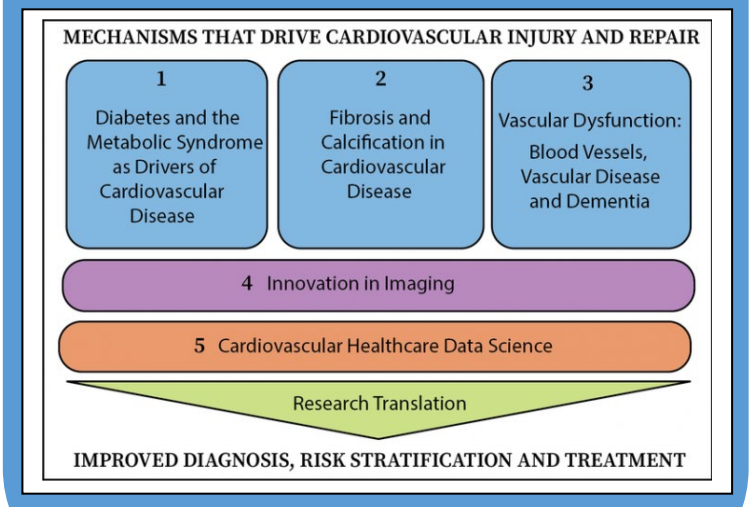
REA3 BIMONTHLY NEWSLETTER JANUARY 2020

The BHF Centre of Research Excellence in Edinburgh is a five year award from the British Heart Foundation to foster excellence in cardiovascular research.

Our research is driven through 3 pillars of research excellence and are closely aligned with 2 major cross-cutting themes:



If you would like to contribute to future REA3 newsletters, please contact Gillian Joyce: Gillian.Joyce@ed.ac.uk

Introduction

Welcome to the inaugural newsletter of the University of Edinburgh's British Heart Foundation Research Excellence Award 2019-2023 (REA3). This is the first of a series of newsletters that will feature throughout the year. In this first issue, we thought it would be most helpful if we outlined the overall strategic direction for the REA3, the progress so far and the plans for 2020. Please also ensure you visit the website for further information.

We have a breadth of Principal Investigators (PIs) within REA3, but of course, the Centre spans researchers across the campus who align to our strategic direction. Our current PIs, who drive the direction of the project, are listed here. We will evolve the leadership of REA3 on an annual basis to ensure we maintain the optimal input, direction and health of the REA3.

While some of our strategic areas are mature, others are an early stage. For example, the intersection of REA3 with the Dementia Research Institute in Edinburgh. Our focus for this is in the area of vascular dementia. We are honoured to be working with Professor Joanna Wardlaw and Professor Giles Hardingham as Centre PIs and many others more widely in the Centre to ensure we maximise this terrific opportunity.

Strategic recruitments are also critical to the success of REA3. We are fortunate to have been able to secure the collaboration of Professor Trian Chavakis from the University of Dresden, Germany. Trian joins the University on a 0.2 FTE contract, initially for 3 years. He is a global authority in immunometabolic health and trained immunity. We feature Trian's work (page 3) and his intersection with REA3 later in this newsletter. In the next issue, we will feature our work with Rafael Kramann, who is also impacting on the direction of REA3.

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

PUMP PRIMING

Part of our strategy is to prime early projects that are aligned to our pillars and cross-cutting themes, which would benefit from funds to initiate/perform key experiments that will lead to larger additional funding externally.

We have had, to date, two successful rounds of pump priming and the awarded applications can be found here.

Within this newsletter we feature two successful applicants:

Dr Maurits Jansen (Co-applicants Professor Carmel Moran, Adrian Thomson, Dr Gillian Gray and Dr Adriana Tavares) – Page 4:

"Optimisation, validation and quantative alignment of novel preclinical cardiac ultrasound and magnetic resonance imaging methods"

Dr Mairi Brittan (Co-applicants Professor Andrew Baker, Professor Dave Newby, Professor Nick Mills and Dr Julie Rodor) – Page 5:

"Exploring the transcriptional landscape of pro-regenerative vascular endothelial progenitor cells in the fibrotic myocardium"

A third round will be forthcoming, with this targeted **towards research fellows and translational projects**. We will highlight additional projects in the next issues.

PEOPLE

We have been able to fund a number of key posts to enable research to progress efficiently in key areas. These include retinal imaging, mass spectrometry and in vivo animal model deep phenotyping.

List of appointments approved and recruited:

- *Charlene Hamid – Retinal Imaging Specialist – in post (see Page 6)*
- *Dr Catherine L Stables – Programmer – DataLoch – in post*
- *Dr Trisha Singh – Clinical Fellow – in post*
- *Dr Amy Ferguson – Postdoctoral Research Fellow on pump priming project (Rannikmäe)*
- *Mario Salazar Gomez – Research Technician on pump priming project (Chavakis/Michailidou/Morton)*
- *Dr Ryan Wereski – Clinical Fellow – in post, REA3 funding from February 2020*
- *Dr Peter Aldiss – In-Vivo Specialist – starting March 2020*

VACANCIES – CHANCELLOR'S FELLOWS

We are in the fortunate position to be able to advertise two Chancellor's Fellows across the research base of the REA3. The advert can be found at the following link:

https://www.vacancies.ed.ac.uk/pls/corehrrecruit/erq_jobspec_version_4.jobspec?p_id=050055

We encourage you all to seek possible candidates.

SUMMARY OF THE REA3-FUNDED POSITIONS:

- Two Clinical Fellows
- Translational Fellows
- Retinal Imaging Specialist
- In-Vivo Specialist in Metabolic Modelling
- Mass Spectrometry Specialist

EVENTS FUNDED BY REA3:

- Public Engagement Awards
- Training and workshops – Small bursaries

PROJECTS FUNDED BY REA3:

- Pump Priming
  - Spring Round 2019 – 5 projects
  - Autumn Round 2019 – 4 projects
  - Spring Round 2020 – targeting Early Career Researchers (ECRS)

PROFESSOR TRIAN CHAVAKIS – University Hospital Carl Gustav Carus, Dresden

The scientific focus of Prof. Chavakis is in the field of Inflammation, especially at the crossroads of Innate Immunity and Immunometabolism.

Inflammation in the adipose tissue (AT) or the liver has emerged as a major player in the development of obesity-related insulin resistance, diabetes and non-alcoholic fatty liver disease (NAFLD). In this regard, the group of Prof. Chavakis studies inflammatory mechanisms that are involved in the pathogenesis of aforementioned obesity-related metabolic-inflammatory pathologies. His group investigates the molecular mechanisms underlying the accumulation and activation of inflammatory cells in the AT and the liver in obesity. For instance, his group has recently identified a novel mechanism, by which alpha4-integrin-dependent adhesive interactions between macrophages and adipocytes not only promote macrophage (MΦ) pro-inflammatory activation and thereby AT inflammation in obesity, but also contribute to metabolic dysfunction by inhibiting beige adipogenesis (*Chung et al. Nat Immunol. 2017*) (Figure). In addition, his group is interested in understanding mechanisms involved in resolution of inflammation and utilising them against metabolic-inflammatory pathologies. For example, his group has recently demonstrated a role of the homeostatic, anti-inflammatory, secreted protein Developmental endothelial locus-1 in mediating phagocytic clearance of apoptotic cells by macrophages and thereby resolution of inflammation (*Kourtzelis et al. Nat Immunol. 2019*). Currently, Prof Chavakis focuses on different inflammation-related mechanisms contributing to AT and liver metabolic dysfunction in obesity, as well as on pathways that may promote resolution of metabolic inflammation, and he collaborates with different REA groups in this regard.

A further current focus is on understanding the mechanisms underlying trained innate immunity. Recent studies have shown that certain stimuli, such as western high fat diet or fungal-derived components may promote an increased response of myeloid cells to a secondary inflammatory challenge. This process is designated “trained innate immunity” or “innate immune memory” and may contribute to chronicity of inflammation (*Chavakis et al., Nature Immunology 2019*). Trained immunity involves changes in cellular metabolism, as well as epigenetic and transcriptomic alterations in innate immune cells. Trained immunity has long-term effects on mature myeloid cells although these cells have a relatively short lifespan in the bloodstream. This paradox was solved by Prof. Chavakis’ group that demonstrated that trained immunity modulates long-lived progenitors of myeloid cells, specifically, hematopoietic stem and progenitor cells (HSPCs), in a manner that involves innate immune signaling and adaptations in cellular metabolism of HSPCs, particularly cholesterol biosynthesis (*Mitroulis et al., CELL, 2018*). The Prof. Chavakis’ group continues to analyse regulation of innate immune cell generation (myelopoiesis) in the bone marrow by trained immunity and also collaborates with REA PIs in this regard.

THE UNIVERSITY of EDINBURGH

British Heart Foundation

"Optimisation, validation and quantative alignment of novel preclinical cardiac ultrasound and magnetic resonance imaging methods"

Amount awarded: £11,628.00

Dr Maurits Jansen (Co-applicants Professor Carmel Moran, Adrian Thomson, Dr Gillian Gray and Dr Adriana Tavares)

Assessment of cardiac structure and function is an invaluable tool in preclinical research and indices obtained with imaging methods like magnetic resonance imaging (MRI) and echocardiography (EC) are directly comparable with clinical measures. Within REA, this will be important to understand the impact of enhancing vessel regeneration following MI, of creating and modifying aortic stenosis and of altering the metabolic phenotype.

In the past, an ECG trigger was required to acquire 3D cardiac MRI data. The scanner upgrade has made a new technique (IntraGate) available that does not require placement of the needle electrodes and images can be reconstructed retrospectively by means of a navigator signal acquired with each scan.

We will optimise and compare different MRI sequences: conventional cine MRI, IntraGate MRI and Ultra-Short Echo Time (UTE) IntraGate MRI. Potential benefits, like reduced scan time and improvement of the quality of imaging data will be assessed and explored.

High-resolution ultrasound has offered an alternative to MRI for structural and functional imaging that has been widely used as it requires shorter imaging time, and is less expensive. However, usually only one slice through the centre of the left ventricle (LV) is acquired and geometric assumptions are made to calculate cardiac volumes. This method is prone to errors, particularly when ventricular remodelling is asymmetric e.g. following MI.

The recently acquired VEVO3100 scanner, funded by the Wellcome Trust multi-user equipment grant in 2019, now offers the possibility to generate 3D images of the heart. We will optimise the 3D EC technique and compare it with the 2D EC technique. Reproducibility of the methods will also be assessed. Subsequently, we will compare EC derived parameters for function and structure with MRI derived parameters in the same animal in order to quantitatively assess the strengths and weaknesses of each technique.

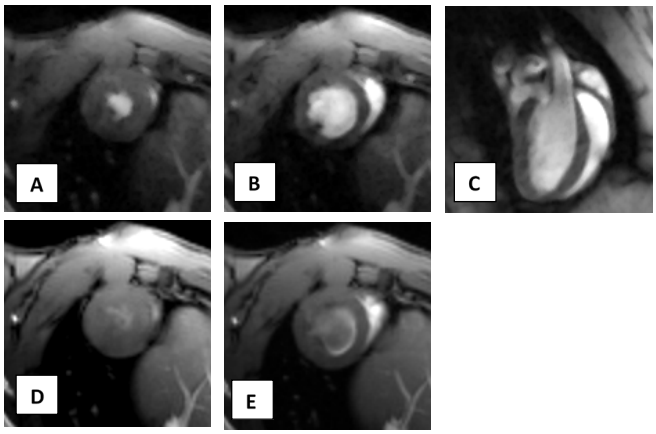


Figure. MRI assessment of cardiac function in rats using prospective (A-C) and retrospective (D-E) gating. Left ventricle of a rat at end systole (A and D) and end diastole (B and E). C: 4-chamber view of the heart. The retrospectively gated images show a better signal-to-noise ratio and improved sharpness.

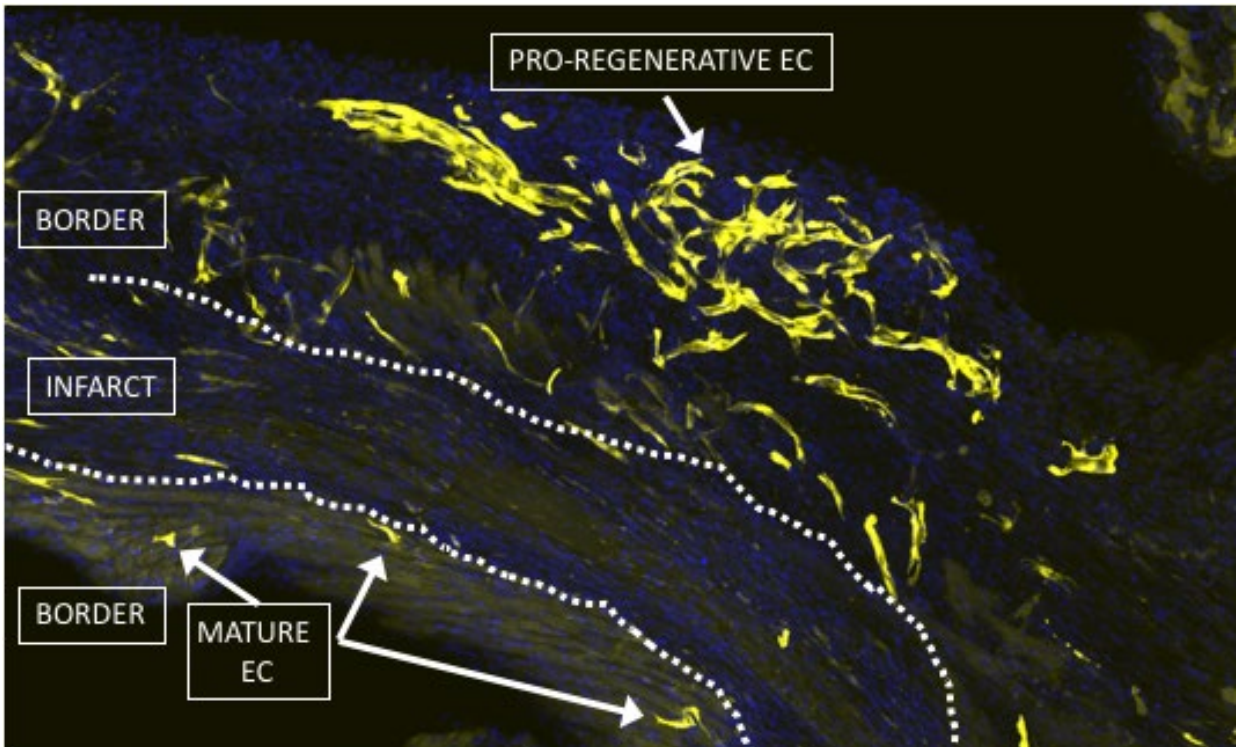
"Exploring the transcriptional landscape of pro-regenerative vascular endothelial progenitor cells in the fibrotic myocardium"

Amount awarded: £43,518.21

Dr Mairi Brittan (Co-applicants Professor Andrew Baker, Professor Dave Newby, Professor Nick Mills and Dr Julie Rodor):

Our previous studies using an endothelial cell (EC)-specific 'Confetti' mouse combined with single cell RNA-sequencing have identified a putative 'pro-regenerative' EC subpopulation that resides in the adult mouse heart and drives endogenous vascular regeneration following myocardial infarction (Li Z et al., European Heart Journal 2019). Here we aim to use spatial transcriptomics technology combined with laser capture microdissection and deep RNA-sequencing to elucidate the molecular signature of pro-regenerative EC in the context of the tissue microenvironment.

We predict that this study will identify a unique phenotype of pro-regenerative EC to permit their isolation for functional validation, including in human cardiac tissues. Moreover, this project will identify potential novel targets that regulate myocardial neovasculogenesis and therefore may guide future therapeutic strategies for patients with heart disease.



"Figure showing clones derived from proliferation of pro-regenerative and mature (non-regenerative) endothelial cells in the infarct border region of an endothelial cell-specific multispectral lineage-tracing 'Confetti' mouse at 28 days post-MI"

RETINAL IMAGING SPECIALIST – CHARLENE HAMID

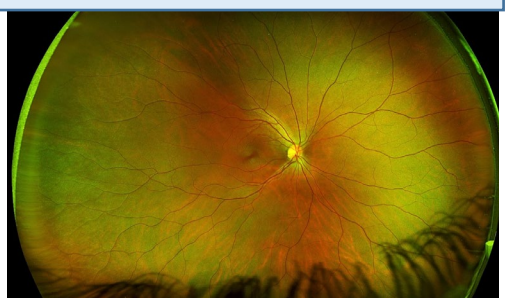
Charlene Hamid joined the REA3 project as our Retinal Imaging Specialist in November 2019. She will be working with Dr Tom MacGillvray and Professor Joanna Wardlaw.

"Before joining the University of Edinburgh, I worked for a number of years as an experienced ophthalmic photographer and diabetic retinal grader within the NHS.

I have always had a specialist interest in research and retinal image analysis. I applied for the role of ophthalmic imager and analyst as I felt it would enable me to further specialise in these areas and to develop my experience and knowledge in this field.

It has been an opportunity to apply my skills working in ophthalmology into a research environment where I am learning how the retina can give us an insight into cardiovascular and brain health. I hope to expand the role and collaborate as the level of research develops and grows."

Professor Joanna Wardlaw: *"The retinal imaging post is invaluable for facilitating the use of retinal imaging in cardiovascular and cerebrovascular research, while ensuring very high quality and consistent data capture, with state of the art analysis to extract the most detailed information about microvessels and nerve fibres.*
It also provides training to short term researchers and facilitates development of new analysis methods, unlocking information in large datasets to address causes of stroke, dementia and cardiovascular disease.''



WORKSHOPS AND EVENTS

Part of the funding supports workshops and events that are clearly aligned to the REA3 pillars. Financial support was provided towards the costs of **The Small Vessel Disease (SVD) Research Network, which was held on 28 November 2019** and aligns with Pillar 3, Vascular Dysfunction: Blood Vessels, Vascular Disease and Vascular Dementia.

The two joint Stroke Association/BHF/Alzheimer's Society funded UK-wide priority programmes in vascular dementia, which happen to be led from Edinburgh, one a large clinical study and the other a multicentre lab models study, were presented back to back at the meeting and were very complementary. It really emphasised what a big place Edinburgh occupies in cerebrovascular disease and vascular dementia research in the UK.

There were attendees from as far afield as Sheffield! Points to Dr Rosalind Brown also for getting junior researchers to do a lot of the organisation. And, as a measure of enthusiasm, it was not too derailed by the strike.

Dr Rosalind Brown:
"We had 48 attendees from different departments across the University, as well as some external attendees.

Talks covered a range of local SVD-related research, including ongoing clinical studies, research using rodent models of SVD and how retinal imaging may provide insight into blood vessel changes in the brain.

We held a feedback session at the end and there was a lot of enthusiasm for further network events and hope to hold the next one before the summer.

We are grateful to both the BHF REA and the Row Fogo Centre for Research into Ageing and the Brain for their support."

EVENTS & MEETINGS

- 3 February 2020 – Edinburgh Diabetes Day – Further information on Page 8
- 20 February 2020 – REA3 Executive Meeting
- 26 March – One-day Symposium – Research & Development – Developing and supporting Gene Therapies in Edinburgh
- 18 June 2020 – CVS Annual Symposium

NEXT ISSUE – MARCH 2020

We will bring you more updates concerning the progress of some of our pump priming projects and a feature concerning one of the posts REA3 has funded.

If you wish to contribute anything or have any ideas as to how to shape any future newsletters, please contact Gillian Joyce, Research Project Co-ordinator, Gillian.Joyce@ed.ac.uk

THE UNIVERSITY of EDINBURGH
Centre for Cardiovascular Science

Edinburgh Diabetes Day

February 3rd 2020

Join us for the inaugural Edinburgh Diabetes Day to celebrate the growing strength and depth of the network of diabetes researchers in Edinburgh.

This event will provide an overview of the key hubs of basic, clinical, epidemiological, big-data/e-health, medicines and translation in diabetes research across the University of Edinburgh, providing networking opportunities and further strengthening University-wide collaborations

Image credit: Zebrafish adipocytes, J. Minchin

Keynote speaker

Elizabeth Robertson, Director of Research, Diabetes UK

Speakers (topic)

Introduction by Andrew Morris, Vice Principal Data Science
Helen Colhoun (Genetics of Type 1 Diabetes)
Shareen Forbes (Stem cells in islet transplantation)
Fraser Gibb (Advances in diabetes medicines)
Nik Morton (Genetics of Obesity/ Type 2 diabetes)
James Minchin (Model systems and high throughput genetic screens)
Scott Webster (Developing new medicines)
Robert Semple (Monogenic insulin resistance)
Laura Denby (Mechanisms of nephropathy)
Ruth Andrew (Cutting edge mass spectrometry and endocrine factors)
Roland Stimson (Human brown adipose tissue)
Brendan Gabriel (Human skeletal muscle and circadian rhythms)
Jonathan Fallowfield (NAFLD)
Rebecca Reynolds (Early life, obesity, diabetes)
Nick Mills (Exploring the Data Loch)
Debbie Wake (MyDiabetesMyWay)
Sum up by Jonathan Seckl, Vice Principal Planning, Resources and Research Policy

VENUE

Henry Wellcome Lecture Theatre,
The Queens Medical Research Institute
Little France Crescent
Edinburgh, EH16 4TJ

TIME

08:50-17:00 followed by wine and nibbles until 18:00 in the Fyffe Room QMRI

BOOKING

https://www.eventbrite.co.uk/e/edinburgh-diabetes-day-2020-tickets-89783180911

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