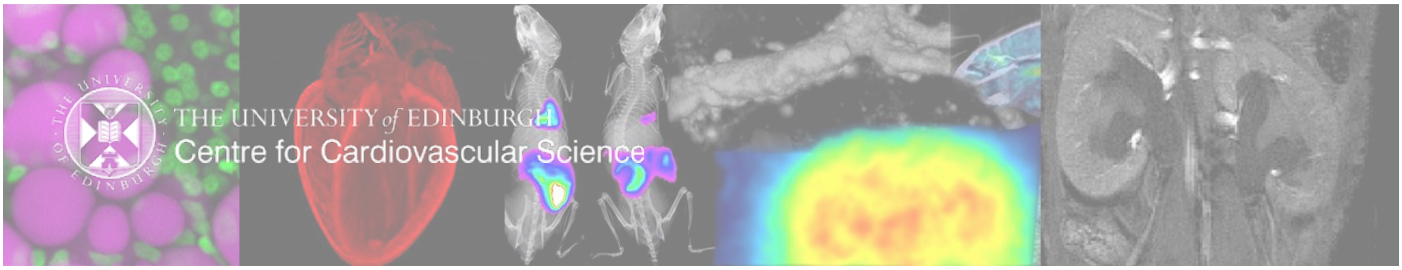
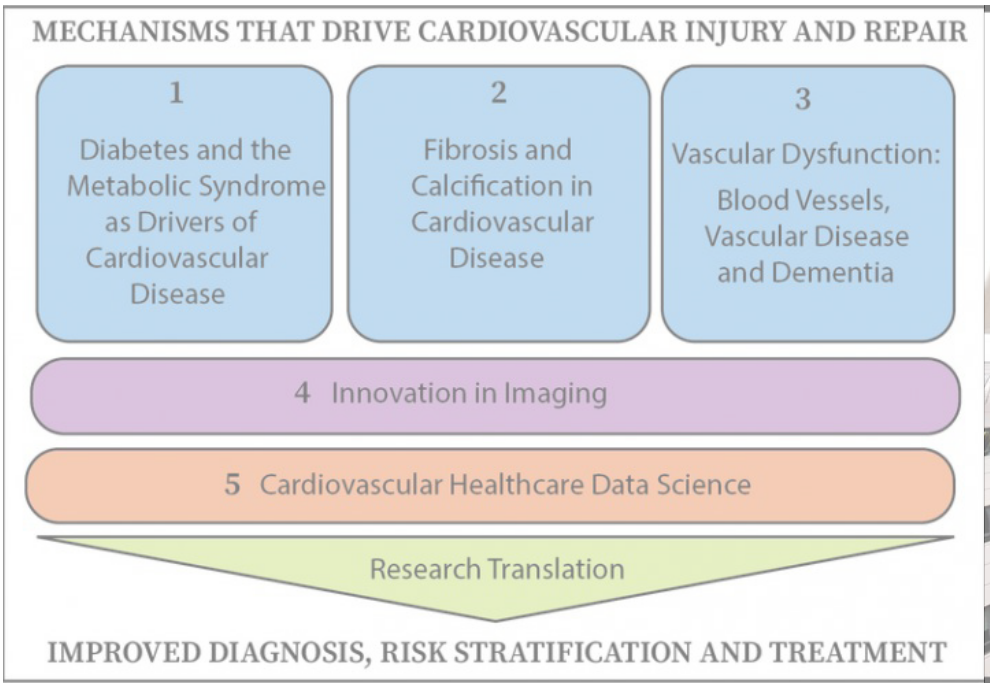
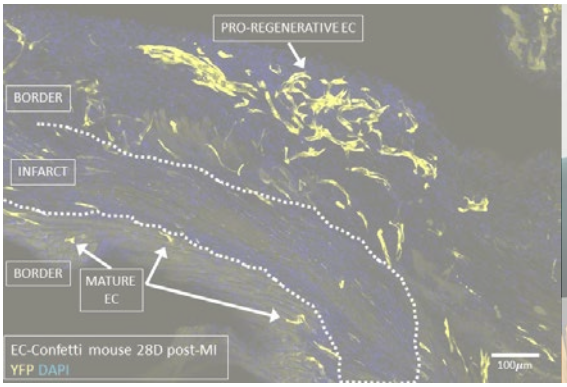


REA3 BIMONTHLY NEWSLETTER

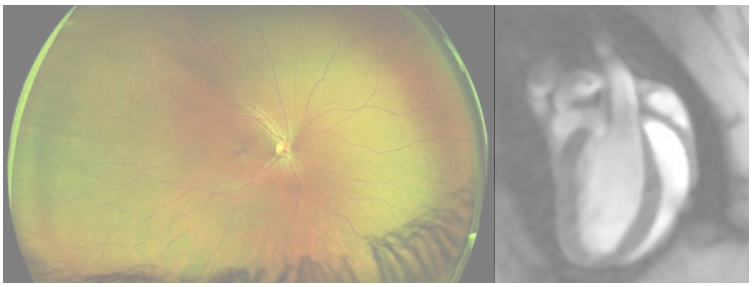
May 2020

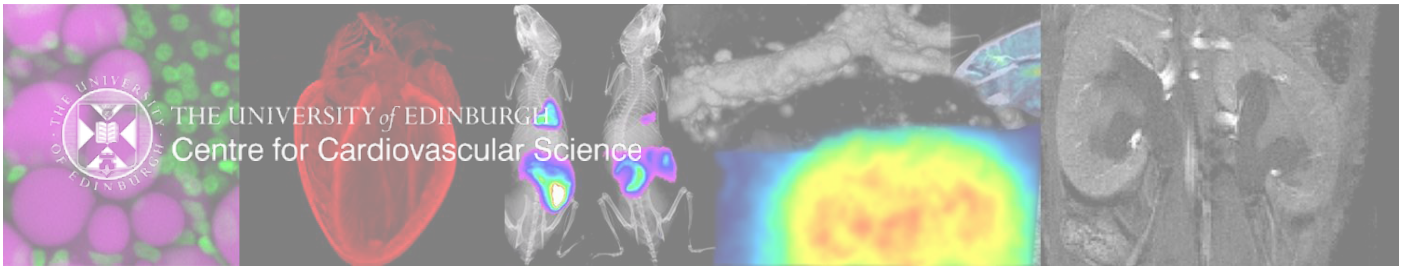




THE UNIVERSITY of EDINBURGH

British Heart Foundation





INTRODUCTION

Welcome to our third edition of the bimonthly REA3 Newsletter.

The disruption continues within the research community and beyond,which no-one could have predicted or anticipated. With many projects currently suspended until research facilities are fully open, everyone within REA3 have been working really hard to keep projects on track. There is some optimism that our laboratories will start to reopen. However, this is still in the face of a pandemic that still causes worry and concern for many.

Earlier in April, the REA3 Centre was approached by BHF to redistribute some of the funds awarded towards COVID-19 research. An open call was circulated within the university and 6 very strong applications were received. After a thorough review process, 4 of these research projects have been awarded funds to help with the local and national response to COVID-19. Further information regarding the COVID-19 awards can be found within page 2.


Dr Trisha Singh

Among one of the COVID-19 awardees was one of our REA3 Clinical Research Fellows, Dr Trisha Singh. Trisha was an ST5 in Cardiology who was based at University Hospital Southampton when she joined us in August 2019. She shares some of her work over the last few months.


Dr Antoine Vallatos

The rest of the REA3 research continues to be just as important and from our Spring 2019 Pump Priming Awards, Dr Antoine Vallatos was successful in his application for his project, "*MRI biomarkers of cerebral small vessel disease in rodent models in vivo*". Antoine has provided some insight into his current research. Though to illustrate the current situation, which many researchers find themselves in, histology data is excluded due to the necessary building closures.

Finally, Robert Chang-Chih Chou*, who is funded by REA3 and appointed to Dr Adriana Tavares' Group, gives us a small insight into his background and what the appointment means to him.

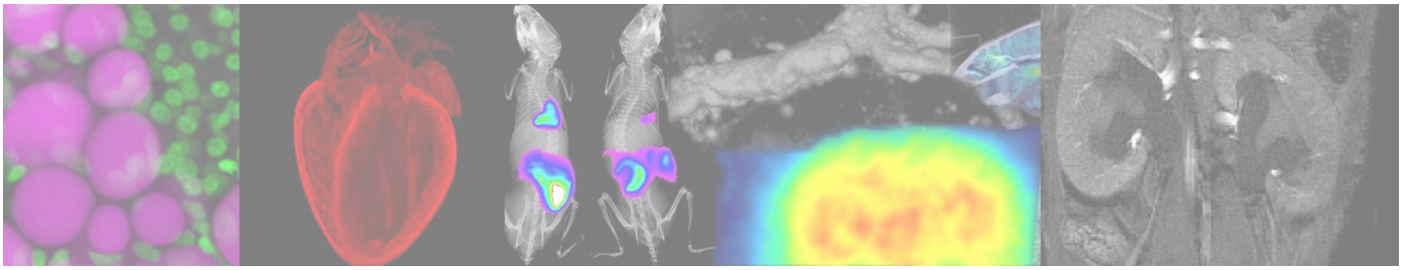
Our Spring Pump Priming Awards closed on 24 April 2020. We received 6 Early Career Researcher applications and 5 translational proposals. All applicants will be notified of the outcome on 2 June 2020. A round up of those awarded will be provided in the next issue.

As always, Gillian Joyce, Research Project Co-ordinator is always looking for volunteers for articles or any points of interest in the REA3 remit. Please contact her if you wish to include anything in July's edition of the REA3 Newsletter: Gillian.Joyce@ed.ac.uk

In the meantime, we hope that everyone remains safe and well during these times and thank everyone for their commitment to the REA3 Centre.

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

**Mr Chang-Chih Chou is currently furloughed by the university. This information was provided before that period commenced.*



REA3 Covid-19 (SARS-CoV-2) Awards 2020

On 15 April 2020, the University of Edinburgh's REA3 centre requested applications for COVID-19 research as part of the REA3 centre. The research proposals had to fulfill the following criteria:

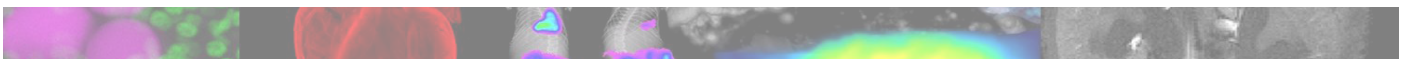
1. Necessitates research activity during the pandemic.
2. Can involve collection of samples, images or data, but needs to be designed to answer a specific question effectively with associated power.
3. Be of direct clinical relevance for patient treatment or care: diagnosis, risk stratification, management and treatment
4. Be of direct cardiovascular relevance, for example: investigating the impact or consequences of (i) COVID-19 infection on the heart or circulation, (ii) cardiovascular disease on the outcomes of patients infected with COVID-19, and (iii) the unintended consequences of diverting resources away from the management or treatment of cardiovascular diseases as a result of the COVID pandemic.
5. Be aligned to the themes of the REA and within BHF funding remit.

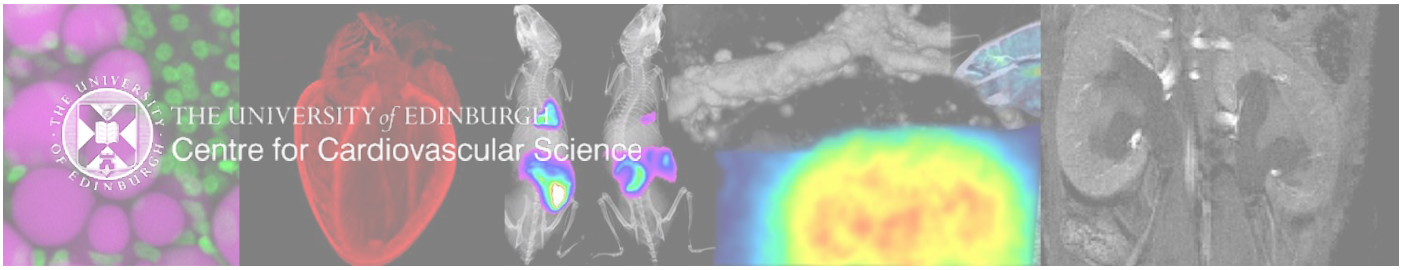
Additionally

6. Funding of any proposals will be dependent on relevant CMVM/ACCORD/Building access approvals. A College proforma must have been completed and submitted to Professor David Dockrell and the clinical research approved by ACCORD.
7. Can involve other Centres/Institutes but needs to bring parallel funds.
8. Evidence of commitment to gain other funds if not already obtained.

A COVID-19 panel, who were external to the REA3 Executive, first evaulated each of the 6 applications. All applications were then presented at the Executive meeting on 30 April. After careful consideration and discussion the following applications were successful:

Name of main applicant	Co-applicants	Title of Covid-19 proposal	Amount Awarded
Dr Trisha Singh	Prof David Newby	Manganese-Enhanced Magnetic resonance imaging of myOcardial injuRY in COVID 19 MEMORY - COVID Study	£50,000.00
Dr Mairi Brittan & Prof Andrew Baker	Prof Nick Mills, Dr David Dorward, Dr Christopher Lucas, Mr Ian McCracken, Dr Cass Li & Prof Neil Henderson	Single cell RNA-sequencing of heart cells from patients with COVID-19 with and without associated acute myocardial injury	£37,253.00
Prof Nick Mills & Prof Dave Newby	Dr Anda Bularga, Dr Marc Dweck, Dr Andrew Chapman,Dr Martin Denvir, Dr Anoop Shah (collaborators: Dr Annemarie Docherty & Dr Kenny Baillie)	Direct and Indirect effects of COVID-19 on acute cardiac care	£99,570.00
Prof Joanna Wardlaw	With Dr Fergus Dougal on behalf of the R4aD Investigator group	Impact of COVID-19 on short and long term outcomes after stroke: R4VaD and COVID-19	£23,988.00





Dr Trisha Singh - Clinical Research Fellow

Trisha was successful in securing one of the clinical fellowships advertised in 2019. Recently her MRC funding was approved. Trisha will, however, continue within the REA3 sphere, building on her success in securing COVID-19 funding. A small insight into her current work and research:

Manganese-enhanced magnetic resonance imaging (MEMRI) is a novel imaging technique, which allows us to directly track calcium activity within the myocardium. Manganese is a calcium analogue which actively enters viable cells with intact calcium-handling mechanisms and its uptake is evident by an increase in MRI-detectable T1 relaxivity of tissues. Proof of concept studies have demonstrated the utility of MEMRI in assessing infarct size more accurately than with standard cardiac MRI protocols using gadolinium enhancement (Figure 1) and have shown reduced myocardial manganese uptake in patients with cardiomyopathies suggesting abnormal calcium handling (Figure 2).

Understanding the potential for myocardial recovery is key in guiding revascularisation therapies in ischaemic cardiomyopathy, in addition to novel therapies used in heart failure. Being able to monitor calcium handling and therefore myocardial function in different types of cardiomyopathies has the potential to guide management in these patients. We look to the use of MEMRI to assess myocardial calcium handling in reversible causes of cardiomyopathy, namely ischaemic cardiomyopathy, myocarditis and takotsubo cardiomyopathy.

The British Heart Foundation REA3 promotes multi-disciplinary collaboration and provides flexible funding opportunities to researchers who are early in their academic career, such as myself. This award meant that I could continue my research whilst applying for pre-doctoral clinical research fellowship funding from the British Heart Foundation and Medical Research Council. The REA3 Clinical Fellow opportunity has provided me with resources and training to progress as a researcher. In the current climate, COVID-19 has had a significant impact on our healthcare system, highlighting the need for COVID-19 related research in order to better understand the impact on cardiovascular health. REA awards will have an important role to play in progressing researchers during this time.

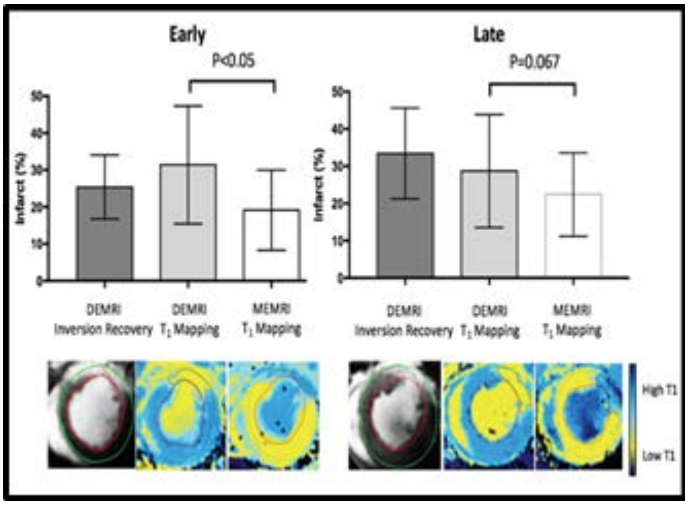


Figure 1. DEMRI and MEMRI infarct quantification by T1 mapping. Mean infarct as percentage pf LV myocardium at maximum infarct short axis slice in rats. DEMRI and MEMRI T1 mapping early (3 weeks, n=13, left panel) and late post-MI (12 weeks, right panel) Infarct size by MEMRI T1 mapping is lower than DEMRI T1 mapping at 3 weeks (P<0.005), attenuated at 12 weeks(P=0.067). Error bars represent SD. With example T1 maps.

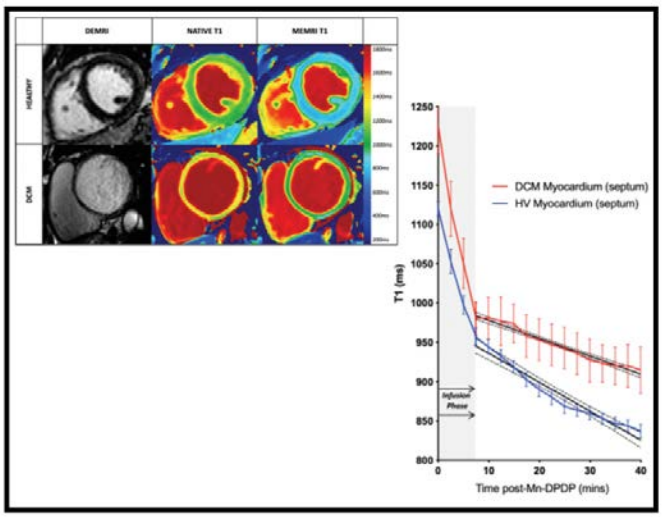
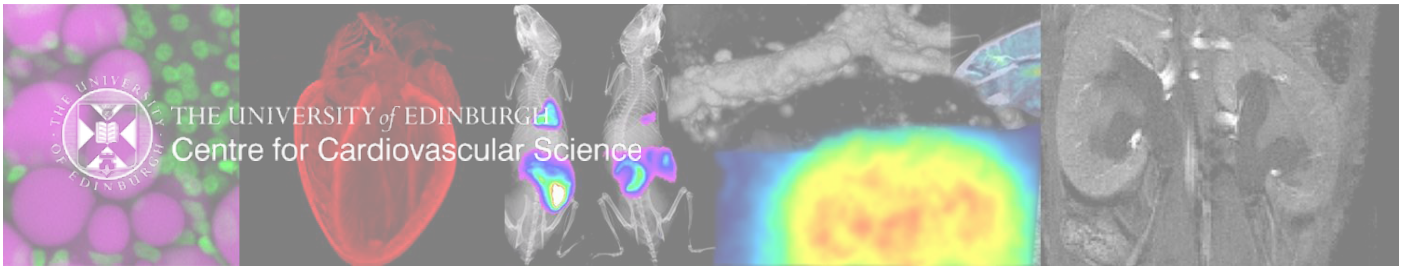


Figure 2. MEMRI in non-ischaemic cardiomyopathy. Representative myocardial T1 mapping in healthy volunteers and patients with non-ischaemic dilated cardiomyopathy using Shortened Look-Locker Inversion Recovery (above panel) Native T1 in DCM is higher than HV and the rate of T1 reduction following the perfusion phase is lower (right panel)



Dr Antoine Vallatos - MRI biomarkers of cerebral small vessel disease in rodent models in vivo

Amount awarded: £47,095

Co-applicants Dr. Maurits Jansen, Dr. Michael Stringer, Prof. Joanna Wardlaw & Prof. Anna Williams

Small vessel disease (SVD) is the commonest cause of vascular dementia, it affects 1 in 10 people over 60 years and triples the risk of stroke. Structural magnetic resonance imaging (MRI) is key for diagnosis, with white matter abnormalities and evidence of blood-brain barrier (BBB) impairment. We recently showed (Rajani *et al.*,2018) a mechanistic pathological link between small blood vessels and white matter myelin changes in a rat SVD model (SHRSP). Specifically, the first pathological change involves an endothelial cell (EC) dysfunction (reduced tight junctions and endothelial proliferation) which leads to a block in oligodendroglial differentiation via secreted molecules. The EC dysfunction is caused by a loss of ATP11B, with a single nucleotide polymorphism in this gene associated with sporadic human SVD. An ATP11B knock out transgenic rat (ATP11BKO) has since been developed (A.Williams' lab) as a new SVD model.

Conventional structural MRI alone will not be able to characterise the new model, as it typically fails to detect the initial microvascular dysfunction in SHRSP rats, with visible lesions appearing only in late disease stages. Advanced MRI sequences could provide with early biomarkers of SVD: diffusion tensor imaging (DTI) can be used to probe subtle white matter changes, while recently, dynamic contrast enhanced (DCE) MRI was shown to detect subtle BBB permeability changes in an SVD model (Nation *et al.*, 2019).

We hypothesised that BBB integrity loss in SVD models is a biomarker of EC dysfunction and subsequent white matter changes that can both be tracked by combining structural MRI (Fig.a), with DTI (Fig.b) and DCE (Fig.c). We are currently testing this by assessing the ability of translational MRI protocols to identify BBB integrity and white matter changes in the clinically-relevant ATP11BKO model group and a Sprague-Dawley group acting as a wild type control. At each timepoint, animals are sacrificed for histopathologic MRI assessment using a novel method based on immunohistochemistry sections cut in the MRI plane and stacked to account for MRI thickness (Al-Mubaral *et al.*, 2019).

We aim to characterise the imaging phenotype of a novel SVD model, and assess correlation between BBB integrity, white matter changes and myelin alterations that occur in SVD. The robust histopathologic assessment of MRI measurements proposed here will hopefully set the ground for the quantitative validation of new MRI biomarkers allowing translational preclinical SVD studies (e.g. drug development).

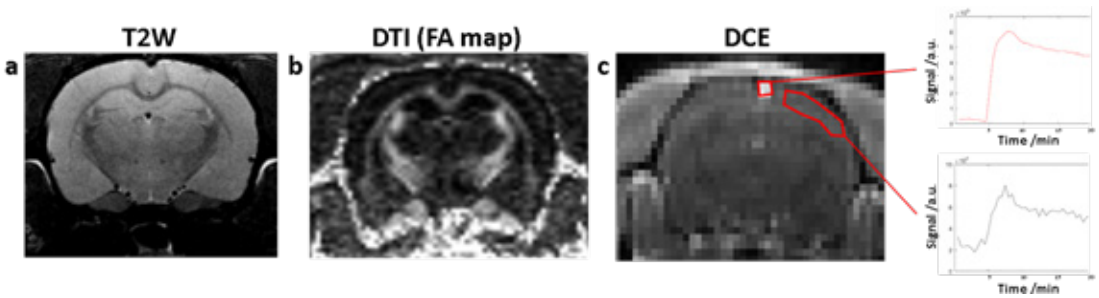
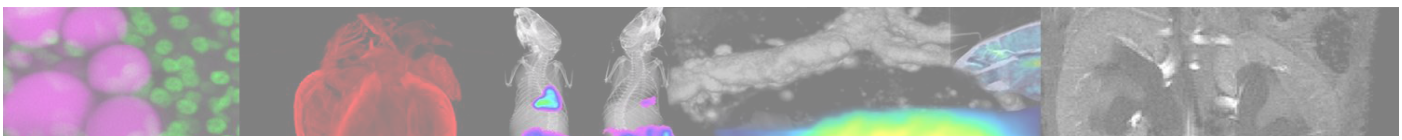
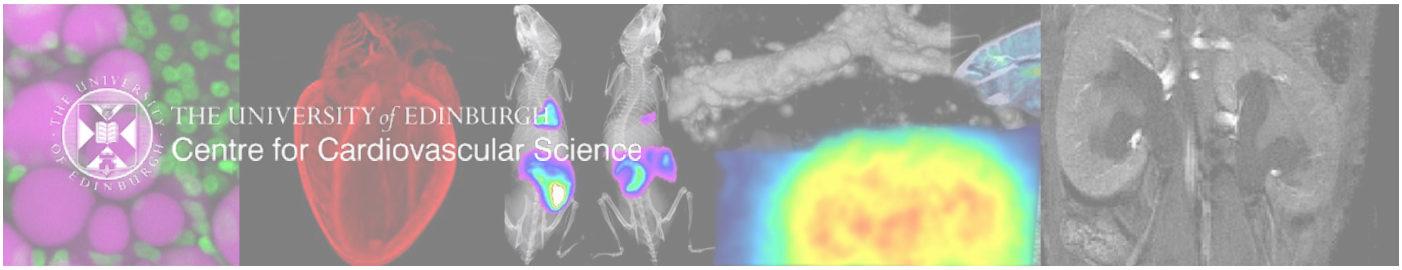


Figure. (a) Structural T2W (b) Fractional Anisotropy maps produced using DTI data allow probing white matter integrity. (c) Dynamic signal enhancement following the injection of contrast agent (Gd) is sensitive to BBB permeability.





Robert Chang-Chih Chou

" I have several years' laboratory experience in academia and in the pharmaceutical industry. I was granted a Taiwan's pharmacist license and worked as a GMP Pharmaceutical Inspector for FDA Taiwan. I also received classic training in Pharmacy, Pharmacology, Neuroscience and Stem Cell Biology.

Before joining CVS, I worked with Professor Richard Ribchester at the Centre for Discovery Brain Science within the University of Edinburgh. We had been studying the fate of neuromuscular junctions after their exposure to organophosphate containing pesticides. After the end of the MRC grant, I joined Dr. Adriana Tavares' group in June 2019 funded by the BHF REA3 award. Currently, I have been in a team working on studying the expression of an 18 KDa translocator protein (TSPO) locating in outside membrane of mitochondria.

My part of the project focuses on analysis of TSPO expression in human samples from a human brain and tissue bank by performing Histology and Autoradiography. I have always had interests in understanding the progression of neurodegenerative disorders and subsequently develop a treatment strategy to slow down the progression of the neurodegeneration, even cure the patients. Recently, the research of neurodegenerative diseases focuses on Neuroimmunity, which studies the immunological activities in patients or models of neurodegenerative diseases. The TSPO project mentioned previously is a pioneering study in this subfield. It has been a great opportunity for me to apply my skills and knowledge in Pharmacology, Histology and Neuroscience into a research environment. I am learning how to develop a radioactive tracer to study the immunological activities in patients or models of neurodegenerative diseases. This is a great platform for me to develop my profession in Immunology"

VIRTUAL SEMINARS

Professor Ruth Andrew and Dr Cecile Benezech are currently working hard to deliver a range of virtual seminars over the summer period. Please keep an eye on these being advertised. Some of the REA3 SAB members will be scheduled to speak including Professor Calum MacRae based at Brigham and Women's Hospital and Harvard Medical School.

FINALLY.....

Lockdown has seen wildlife flourish in many cities and towns, including Edinburgh. Below is a selection of photographs from Gillian Joyce's travels around town (adhering to the rules!):