Faculty of Health Sciences

and

Faculty of Life Sciences

MRes in Health Sciences Research

Research Projects

2022/23

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Lab Based Projects:

1. Molecular and cellular studies in congenital gene defects that cause congenital skeletal malformation

Primary supervisor: Nobue Itasaki

Secondary supervisor (for day-to-day support): N/A as primary supervisor provide supports daily

School / Faculty: Bristol Veterinary School / Faculty of Health Sciences (Langford Campus)

Summary of project:

Cerebro-Costo-Mandibular syndrome (CCMS) is a congenital disorder comprising skeletal malformations in branchial arch derivatives and the ribs and vertebrae. Affected patients often have respiratory difficulties, associated with upper airway obstruction, reduced thoracic capacity and scoliosis[1].

The genetic cause of CCMS was recently identified as mutations in the gene called *SNRPB,* encoding Small Nuclear Ribonucleoprotein-associated Protein B and the isoform B'[2]. SNRPB are components of the major spliceosome required for RNA splicing. The importance of accurate splicing is evident, as 15-50% of human genetic diseases arise from mutations involved in splicing. Interestingly, many craniofacial disorders were found as spliceosomal gene defect. Although, it is not known how mutations in such fundamental genes can cause specific phenotypes in the skeletal system during embryogenesis.

Our group recently found that knock-down of SNRPB *in vitro* by siRNA causes inhibition of Wnt signalling and enhancement of BMP signalling, two pathways required for bone development. In fact, inhibiting Wnt signals or enhancing BMP signals cause rib abnormalities in model animals[3].

To investigate the role of spliceosomes in cells relevant to CCM syndrome phenotypes, in this project, we use Mesenchymal Stem Cells (MSCs) and osteoblastic cells that mirror developing chondrogenic and osteogenic cells. We will employ siRNA and CRISPR-mediated approaches in cells at various differentiation stages, including chondrogenic precursors and osteoblastic precursors, and investigate how knock-down of *SNRPB* and other spliceosomal genes affects cell differentiation. Along with other ongoing projects using *in vivo* models in the lab, we aim to elucidate the mechanism for CCMS.

Techniques to be used:

- In vitro cell culture of Mesenchymal stem cells and osteoblast-like osteosarcoma cells
- Induction of cell differentiation in vitro
- knock-down of *SNRPB* and other spliceosomal defect genes by siRNA transfection and CRISPR method
- mRNA and protein analyses of the obtained cells

3 Key references:

1 Tooley, M. *et al.* Cerebro-Costo-Mandibular syndrome: Clinical, Radiological and Genetic Findings. *American Journal of Medical Genetics* **170**, 1115-1126, doi:10.1002/ajmg.a.37587 (2016).

2 Lynch, D. C. *et al.* Disrupted auto-regulation of the spliceosomal gene SNRPB causes cerebro-costo-mandibular syndrome. *Nature communications* **5**, 4483, doi:10.1038/ncomms5483 (2014).

3 Turner, B. R. H. & Itasaki, N. Local modulation of the Wnt/beta-catenin and bone morphogenic protein (BMP) pathways recapitulates rib defects analogous to cerebro-costo-mandibular syndrome. *J Anat*, doi:10.1111/joa.13144 (2019).

Specific requirements for the project:

Immunisations (e.g. Hepatitis B)? No

HO licence? No

Other? N/A

2. Can non-invasive ultrasound change the course of Alzheimer's disease pathology through gamma entrainment?

Primary supervisor: Daniel Whitcomb

Secondary supervisor (for day-to-day support): Ben Clennell

School / Faculty: Bristol Medical School

Summary of project (<300 words / ~ half-page):

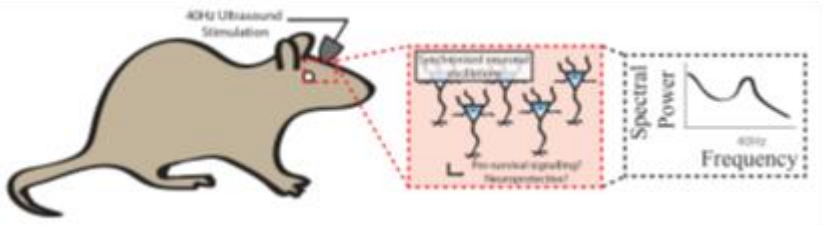

Fig. 1. Characterising the effects of ultrasound-induced gamma entrainment on neuronal function. With a transducer placed on the skull, ultrasound is delivered. We anticipate 40Hz stimulation will induce gamma frequency neural oscillations. We will investigate the consequences this has on intracellular signalling mechanisms and whether this is neuroprotective.

Neural activity follows repetitive, rhythmic patterns, caused by oscillations in membrane potentials or synchronised action potential firing. These neural oscillations are defined by their frequency band, such as alpha (8-12Hz), beta (13-30Hz) and gamma (30-100Hz). Gamma oscillations are linked to normal neurocircuit function and information processing. Aberrant gamma oscillations are observed in Alzheimer's disease patients and Alzheimer's disease animal models. Interestingly, stimulating the brain to induce gamma oscillations through so-called 'gamma entrainment' can have significant beneficial effects in animal models of Alzheimer's disease, including reducing amyloid load and improving cognition. Therefore, restoring gamma oscillations may be a useful therapeutic approach. However, translating this experimental intervention into patients is currently limited by a lack of appropriate brain stimulation tools. We have recently shown that ultrasound can reversibly modulate the activity of neurons *in vitro*, consistent with a growing number of studies *in vivo*. In this project, **we will determine if ultrasound can be used for gamma entrainment, establishing the potential of this approach for use in Alzheimer's disease (Fig. 1).**

We previously found that just 40 seconds of ultrasound stimulation changes the excitability profile of cortical neurons *in vitro* (Clennell et al., 2021). We are now exploring how this mechanism might be exploited *in vivo*. This project will therefore involve analysing the effects of 40Hz (gamma) transcranial ultrasound stimulation on key molecular and protein targets. We will non-invasively stimulate Wistar rats with transcranial ultrasound, and you will explore the consequences of this on intracellular signalling mechanisms using Western blotting assays. We will focus on pro-cell survival and neurotrophic signalling. In parallel, we will use our *in vitro* neuron model of Alzheimer's disease to test whether pathology is modified by the ultrasound-mediated gamma entrainment, and by which mechanisms.

Techniques to be used:
Gel electrophoresis, immunocytochemistry, electrophysiology

3 Key references:
Adaikkan & Tsai *Trends in Neurosci.* 43, 24-41 (2020)
Iaccarino *et al. Nature* 540, 230–235 (2016)
Clennell *et al. Brain Stimul.* 14, 217–225 (2021)

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? N/A
HO licence? N/A
Other? N/A

3. Development of gene therapy targeting the glomerular endothelium
Primary supervisor: Aldara Martin Alonso (secondary: Dr Natalie Finch, Dr Becky Foster)
Secondary supervisor (for day-to-day support): Aldara Martin Alonso
School / Faculty: **Bristol Medical School (THS)**
Summary of project (<300 words / ~ half-page):

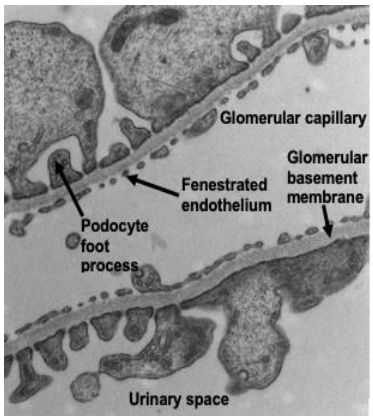

Figure 1: Transmission electron micrograph of the glomerular filtration barrier illustrating the fenestrated glomerular endothelium, glomerular basement membrane and podocytes with foot processes. Image by Dr Finch

Introduction

Glomerular endothelial cells (GEnCs) line the glomerular capillaries in the kidney and form part of the glomerular filtration barrier (**figure 1**). The glomerular filtration barrier works as biological sieve to filter water and small solutes from the blood, whilst retaining macromolecules. The glomerular endothelium is the first barrier in direct contact with blood.

GEnC dysfunction is important in different glomerular diseases. Crucially, they are implicated in the development of diabetic kidney disease (DKD). However, GEnC-specific therapies have not been possible due to the lack of GEnC-specifc promoters. Adeno associated virus (AAV)-based gene therapy is a promising therapeutic tool due to its cell-specificity, stability and safety profile and we have preliminary data showing utility in GEnC (**figure 2)**.

We are currently developing an AAV using our novel promoter that will allow specific targeting to GEnCs, and this project aims to support this work. In the future, and if pre-clinical studies are successful, this tool has potential to be translated into gene therapy in glomerular diseases.

Project

Aim 1: To optimise techniques to quantify AAV transduction in glomerular endothelial cells (GEnC).

Transfection conditions will be optimised in HEK using the same transgene as in the GEnC-targeted AAV. Transgene expression will be determined by assessing gene expression (e.g., real-time quantitative PCR) and/or protein expression (e.g., Western blot, immunofluorescence). Different reagents (e.g., antibodies) and conditions might be compared at this step.

Aim 2: To compare GEnC-targeted AAV with different serotypes.

GEnC-targeting AAV candidates, with different serotypes, will be compared to identify the AAV that show the highest transduction efficiency and specificity in GEnC. This will involve applying the optimised methods (above) to quantify expression of the transgene in GEnCs infected with these different AAVs. The student will support this work.

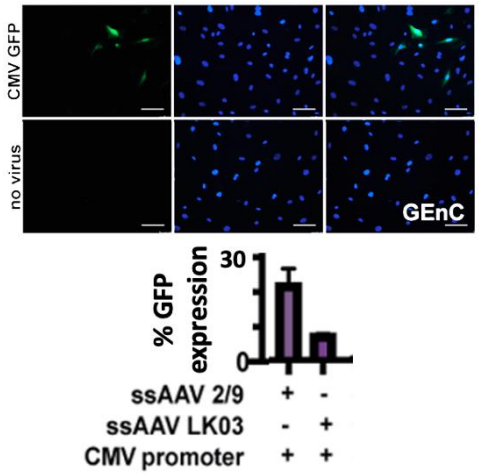

Figure 2: Successful transduction of GEnC with serotype adeno-associated virus 2/9 (ssAAV 2?9) and cytomegalovirus (CMV) promoter. Green staining is green fluorescence protein (GFP) expression in successfully transduced cells. Blue staining shows DAPI nuclear counterstain.

Techniques to be used:
Cell culture, transfection, BCA assay, SDS-PAGE, western blot, immunostaining, real-time quantitative PCR.

3 Key references:

- Wang D, Tai PWL, Gao G. Adeno-associated virus vector as a platform for gene therapy delivery. Nat Rev Drug Discov. 2019; 18:358-378. doi:10.1038/s41573-019-0012-9
- Patrakka, J, Xiao, Z, Nukui, M, Takemoto, M, He, L, Oddsson, A, Perisic, L, Kaukinen, A, Szigyarto, CA, Uhlen, M, Jalanko, H, Betsholtz, C, Tryggvason, K. Expression and subcellular distribution of novel glomerulus-associated proteins dendrin, ehd3, sh2d4a, plekhh2, and 2310066E14Rik. J Am Soc Nephrol. 2007; 18:689-697.
- Barbon E, Kawecki C, Marmier S, Sakkal A, Collaud F, Charles S, Ronzitti G, Casari C, Christophe OD, Denis CV, Lenting PJ, Mingozzi F. Development of a dual hybrid AAV vector for endothelial-targeted expression of von Willebrand factor. Gene Ther. 2021. doi: 10.1038/s41434-020-00218-6.

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)?
HO licence?
Other?

4. Is increased neuroinflammation the missing link between Alzheimer's disease and depression?

Primary supervisor: Dr Lindsey Sinclair

Secondary supervisor (for day-to-day support): Professor Seth Love

School / Faculty: Translational Health Sciences

Summary of project (<300 words / ~ half-page):

Alzheimer's disease and depression are both common diseases. Depression is much more common in individuals suffering from Alzheimer's disease (AD) and other forms of dementia than in older adults without dementia. Depression in AD is difficult to treat and currently available antidepressants have been shown to do more harm than good in this population.

There is a clear need to identify potential targets for treatment development.

The student will use human brain tissue, obtained from brain banks across the UK, from two groups:

1. Individuals with depression and AD
1. Individuals with AD alone

After FACS sorting RNA will be extracted from brain cells sorted into neurons/non neurons. The student will use this RNA to study gene expression in neurons using microarrays (run by the Bristol Genomics Facility). This project is more refined than previous studies in this area which have looked at bulk tissue changes in gene expression, making it impossible to tell whether any changes observed in gene expression were driven by neurons or other cell types.

This will allow the student to identify whether there are any differences between individuals with AD who do and do not have depression. This would allow us to begin to disentangle the relationship between depression and Alzheimer's disease

Techniques to be used:

Bioinformatics
RNA extraction
Sample preparation for microarray study

3 Key references:

Asmer MS, et al. J Clin Psychiatry. 2018;79(5).
Gibson J et al. Translational psychiatry. 2017;7(4):e1094-e.
Khundakar et al. J Alzheimers Dis 2015; 44(1):27-41

Specific requirements for the project:

Evidence of Hepatitis B immunisation

5. Interrogating protein pathways involved in depression in Alzheimer's Disease.

Primary supervisor: Dr Lindsey Sinclair

Secondary supervisor (for day-to-day support): Professor Seth Love

School / Faculty: Translational Health Sciences

Summary of project (<300 words / ~ half-page):

Alzheimer's disease and depression are both common diseases. Depression is much more common in individuals suffering from Alzheimer's disease (AD) and other forms of dementia than in older adults without dementia. Depression in AD is difficult to treat and currently available antidepressants have been shown to do more harm than good in this population.

There is a clear need to identify potential targets for treatment development.

Dr Sinclair has recently obtained gene expression data from a large US cohort and is at present analysing which genes have different levels of expression in those with depression and AD versus AD alone. Using pathway analysis she will identify which pathways appear to be differentially activated in individuals with depression and AD. This analysis should be complete this autumn.

This project aims to identify whether these changes in gene expression are associated with any differences in protein levels. The student will use human brain tissue from two groups:

1. Individuals with depression and AD
1. Individuals with AD alone

The student will measure key proteins in the pathways that look, from the gene expression data, to have increased or decreased activity in those with depression and AD. Ideally this would be using multiplex assays to measure multiple proteins from each pathway, but for some targets multiplex assays are not available.

Techniques to be used:

Tissue homogenisation
Total protein quantification
ELISA or multiplex assay (target dependent)
Immunohistochemistry if required

3 Key references:

Asmer MS, et al. J Clin Psychiatry. 2018;79(5).
Gibson J et al. Translational psychiatry. 2017;7(4):e1094-e.
Khundakar et al. J Alzheimers Dis 2015; 44(1):27-41

Specific requirements for the project:

Hepatitis B immunisation

6. Induction of reparative angiogenesis in a limb ischaemia model.

Primary supervisor: Prof Paolo Madeddu

Secondary supervisor (for day-to-day support): Dr Sadie Slater

School / Faculty: Translational Health Sciences

Summary of project (<300 words / ~ half-page):

Our work focuses on the role of pericytes (a vascular cell with stem cell-like properties) in promoting reparative angiogenesis, primarily focusing on treating critical limb ischaemia. We have previously shown injecting pericytes into mouse models of limb ischaemia promotes an increase in blood vessel formation[1]. In this project the aim is to further investigate the pericyte molecular mechanisms which promote angiogenesis and how we can manipulate these mechanisms to promote greater reparative angiogenesis *in vivo*. In particular we are interested in the role of the transcription factor BACH1. We have previously demonstrated BACH1 can regulate angiogenesis by controlling pericyte expression of the pro-angiogenic growth factor angiopoietin-1[2]. BACH1 is also known to repress expression of many antioxidant genes and this may also have an impact on angiogenesis[3]. Here we plan to investigate the effect of inhibiting BACH1 expression in a mouse model of limb ischaemia. We will silence BACH1 expression in mice and then induce hind limb ischaemia. Effects on blood flow will be measured every 7 days until day 21 when the mice will be sacrificed and tissues collected. We predict inhibiting BACH1 expression will induce greater expression of antioxidant factors leading to improved reparative angiogenesis compared to control animals. This work will involve the collection of mouse gastrocnemius muscles after induction of ischaemia for further analysis. Tissues will be collected for staining and quantification of capillary density to assess the effect on angiogenesis. Expression of antioxidant genes and proteins in tissue samples will be quantified using qPCR and Western blotting techniques. We hope this work will lead to the development of Bach1 inhibitory drugs which will aid reparative angiogenesis.

Techniques to be used:

- Isolation of RNA from tissues, making cDNA, qPCR analysis of gene expression.
- Isolation of protein from tissues, Western blotting for protein expression.
- Collection and preparation of animal tissues for histological analysis.
- Immunohistological staining of capillaries in animal tissue samples.
- Fluorescent microscopy to quantify capillary density.

3 Key references:

1. Transplantation of human pericyte progenitor cells improves the repair of infarcted heart through activation of an angiogenic program involving micro-RNA-132. Katare R, et al. Circ Res 2011.
1. MicroRNA-532-5p Regulates Pericyte Function by Targeting the Transcription Regulator BACH1 and Angiopoietin-1. Slater SC, et al. Mol Ther 2018.
1. Zhang X, Guo J, Wei X, Niu C, Jia M, Li Q and Meng D. Bach1: Function, Regulation, and Involvement in Disease. *Oxid Med Cell Longev*. 2018.

Specific requirements for the project:
Immunisations: Hepatitis B

7. Light-powered antimicrobial surfaces to reduce nosocomial infections

Primary supervisor: Prof Bo Su

Secondary supervisor (for day-to-day support): Dr Nihal Bandara

School / Faculty: Dental School/Health Sciences

Summary of project (<300 words / ~ half-page):

Contamination of hospital surfaces plays an important role in the transmission of healthcare-associated pathogens. Careful cleaning and disinfection of environmental surfaces, especially high touch surfaces in hospitals are essential for effective infection prevention. However, traditional cleaning and disinfection methods which are often reliant on the use of chemicals or detergents are proven ineffective for complete decontamination of hospital surfaces by microbes, particularly multidrug-resistant 'superbugs'.

Photocatalysis has recently emerged as an effective green solution for antimicrobial applications because it does not rely on the release of any chemicals or antimicrobials [1,2]. Rather, bacterial pathogens are inactivated through a contact-killing mechanism, whereby the generated ROS disrupt or damage their cell membrane. This will provide a safe and environmentally friendly solution to help prevent the spread of microbes, especially AMR pathogens, which is particularly important in a hospital setting where many patients already have weakened immune systems.

This project is aimed at developing highly efficient antimicrobial coatings that possess photocatalytic activity powered by visible light (sunlight or artificial light), enabling effective removal of microbes and any other bio-contamination to reduce the transmission of bacterial infection primarily via touch surfaces in hospitals, such as door handles.

In this project, the photocatalytic effect of heterojunctions comprising 2D graphite carbon nitride (g-C_3N_4) with TiO_2 nanoparticles under visible light will be investigated. The heterojunctions at the interface between TiO_2 nanoparticles and g-C_3N_4 nanosheets can efficiently reduce the recombination of photoinduced electron-hole pairs and increase the lifetime of charge carriers, with significantly enhanced photocatalytic activity [3]. The coatings based on TiO_2/g-C_3N_4 heterojunctions will be formulated and optimised. The microstructure, photocatalytic activity and antimicrobial performance of the coatings will be characterised using SEM, UV-vis and microbiology assays. An atmospheric pressure plasma (APP) technology will be explored to further enhance the photocatalytic activity and antimicrobial performance of the coatings.

Techniques to be used:
Spray coating, plasma, high-intensity ultrasound, high-speed mixing, UV-vis spectroscopy, scanning electron microscopy (SEM), antimicrobial performance evaluation

3 Key references:

1. C. Chambers, S.B. Stewart, B. Su, H.F. Jenkinson, J.R. Sandy, A.J. Ireland, *Dental Materials*, 33 (2017) 115–123
1. N.A. Ahmad Fauzi, A.J. Ireland, M. Sherriff, H. M. H. N. Bandara, B. Su, *Dental Materials*, 38 (2022) 147-157
1. K. Li, Z. Y. Huang, X. Q. Zeng, B. B. Huang, S. M. Gao, J. Lu, *ACS Appl. Mater. Interfaces*, 7 (2015) 9023−9030

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? No
HO licence? No
Other?

8. Understanding the communal interactions of emerging multidrug resistant fungus *Candida auris* with coinhabiting bacterial pathogens

Primary supervisor: Dr Nihal Bandara (primary Supervisor) and Dr Angela Nobbs (Co-Supervisor)

Secondary supervisor (for day-to-day support):

School / Faculty: Bristol Dental School, Faculty of Health Sciences

Summary of project (<300 words / ~ half-page):

The Surge of superinfections in COVID19 patients highlight another rapidly escalating pandemic, antimicrobial resistance (AMR). *Candida auris*, an emerging multidrug resistant fungal pathogen commonly known as 'white fungus', has been reported to cause life-threatening infections in COVID19 patients. Particularly, with its unique adhesion mechanisms and ability to form biofilms, *C. auris* persists on different surfaces for a long time, causing invasive outbreaks in nosocomial settings. Such pathologies include superficial infections of wounds, skin, ears, respiratory and genitourinary tracts and indwelling devices, and systemic infections such as invasive candidiasis, leading to significant mortality rates, longer hospital stays, poor quality of life and increased medical care costs. *C. auris* is frequently misidentified and capable of evading host immunity, therefore, perceived as a pathogen in disguise.

The global incidence of polymicrobial infections caused by coinhabiting fungal and bacterial pathogens is steeply rising. The physical and chemical interactions (mediated by quorum sensing; QS) between these fungal and bacterial pathogens at infection sites govern their virulence, pathogenicity, and antimicrobial sensitivity, thus, significantly impacting on the pathogenesis of the infection and treatment outcomes. Interactions between *Candida* species and bacteria are well-studied, however, due to its recent emergence as a pathogen, largely unknown communal behaviour, and frequent misidentification with other *Candida* species, there have yet to be reports of such interactions of *C. auris* with coinhabiting bacterial pathogens at infection sites.

The proposed project will therefore investigate the physical and chemical interactions of *C. auris* with major bacterial pathogens commonly isolated from *C. auris* infection sites, *Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis,* and *Streptococcus pneumoniae*, and their QS molecules, using an *in vitro* interkingdom biofilm model. The findings will not only reveal the communal behaviour and mechanisms of antimicrobial resistance of *C. auris* but also may uncover potential antifungal targets for future therapeutic developments.

Techniques to be used:

Microbiology techniques: *in vitro* biofilm development, aggregation assays, apoptosis assays, microbial quantification via colony forming units and microbial viability testing, biofilm biomass assays, antimicrobial sensitivity assays

Microscopy techniques: Confocal laser scanning microscopy, scanning electron microscopy, light microscopy

Molecular biology: protein assays, qPCR, bioinformatics

3 Key references:

1. Allison DL, Willems HME, Jayatilake J, Bruno VM, Peters BM, Shirtliff ME: *Candida*-Bacteria Interactions: Their Impact on Human Disease. Microbiol Spectr 2016, 4(3). doi:10.1128/microbiolspec.VMBF-0030-2016.
1. ElBaradei A: A decade after the emergence of *Candida auris:* what do we know? Eur J Clin Microbiol Infect Dis 2020. doi:10.1007/s10096-020-03886-9.
1. Bandara N, Samaranayake L. Emerging and future strategies in the management of recalcitrant *Candida auris*. Med Mycol. Feb 10 2022;doi:10.1093/mmy/myac008

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? Yes
HO licence? No

9. Studying Alzheimer's disease using the kidney

Primary supervisor: Richard Coward

Secondary supervisor (for day-to-day support): Jenny Hurcombe (JH) and Rob Pope (RP) (post-docs)

School / Faculty: THS

Summary of project (<300 words / ~ half-page):

There are strong links between protein losing kidney disease (proteinuria) and dementia1. Patients with long-term leak of protein into the urine are more likely to develop dementia including Alzheimer's disease. Our lab has recently discovered that a suspected key protein implicated in the brain in Alzheimer's disease called Tau (or MAPT [Membrane Associated Protein Tau] is highly expressed in a key kidney cell called the podocyte. Podocytes have several neurological features, including being terminally differentiated, having vesicular secretions and foot processes.
In this project we propose studying MAPT phosphorylation in detail as it appears when this protein is phosphorylated it accumulates and damages cells.

This project will use conditionally immortalised human podocyte cell lies we have developed2 to assess if we are able to find new treatments that prevent MAPT from becoming phosphorylated in basal and diabetic states (diabetes also causes MAPT to become phosphorylated, proteinuria and is linked to dementia3). It will consist of cell culture, generating and transfecting viral protein constructs into cells, Western blotting, immunofluorescence and the use of a high throughput computer-based microscope called the IN-Cell analyser to screen a drug library. It will form part of two Medical Research Council (MRC) funded grants we are currently working on. The student will work with two highly talented and highly supportive post-doctoral researchers on this project (JH and RP).

3 Key references:

1. Mid-life proteinuria and late-life cognitive function and dementia in elderly men: the Honolulu-Asia Aging Study. Higuchi, M., et al., Alzheimer Dis Assoc Disord, 2015. 29(3): p. 200-5.

1. A Conditionally Immortalized Human Podocyte Cell line demonstrating Nephrin and Podocin expression. Saleem MA, O'Hare MJ, Reiser J, Coward RJ, Inward CD, Farren T, Ni L, Mathieson PW, Mundel P. J Am Soc Nephrol; 13: 630-8. 2002

1. Mid- and late-life diabetes in relation to the risk of dementia: a population-based twin study. Xu, W., et al., Diabetes, 2009. 58(1): p. 71-7.

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? No
HO licence? No
Other? No

10. Cardioprotective efficacy of cAMP signalling during ischaemic cardioplegic arrest

Primary supervisor: Prof Saadeh Suleiman

Secondary supervisor (for day-to-day support): Dr Katie Skeffington & Megan Young

School / Faculty: Bristol Medical School (THS)

Summary of project (<300 words / ~ half-page):

During open heart surgery, blood is diverted away from the heart and the heart is rendered ischaemic and susceptible to reperfusion injury. This injury is caused by Ca^{2+} loading and generation of reactive oxygen species which trigger the opening of mitochondrial permeability transition pore (MPTP) and cause distortion of mitochondrial ultrastructure. The mitochondria become uncoupled and unable to produce ATP leading to cardiomyocyte death. However, to help arresting the heart and reduce the injury, a high-K^{+} solution (cardioplegia) is infused in the coronaries.

Cardiac sympathetic activation increases cardiac contractility to pump more blood around the body. This can occur under physiological conditions which include exercise or during a fight-or-fright response. We have shown that transient stimulation of β1-Adrenergic Receptor (β-AR) is cardioprotective against ischaemia and reperfusion (I/R) and this effect is mediated by cAMP signalling pathways. However, taking advantage of this intervention in the setting of diseased (e.g. failing) heart is not feasible as these hearts tend to be the target of excessive β-AR stimulation and they become desensitized to this activity. To overcome this problem, we used membrane permeable cAMP analogues which we showed can be protective against I/R in anormal heart. To translate this finding into relevant clinical setting, it is important to show that this treatment is also protective during ischaemic cardioplegic arrest. Therefore, the aim of this project is to investigate the cardioprotective efficacy of cAMP analogues when added before cardioplegic arrest of isolated perfused hearts.

Techniques to be used:
Rodent hearts will be excised & cannulated via the aorta onto the Langendorff perfusion apparatus. Cardiac function will be monitored, and hearts will be arrested using cardioplegic solution and reperfusion. Heart function will be monitored (developed pressure and heart rate) and injury will be assessed using cardiac protein release and finally, the heart will be fixed and stained for identification of infarcted zones.

3 Key references:
Lewis MJ, Khaliulin I, Hall K, Suleiman MS. Cardioprotection of Immature Heart by Simultaneous Activation of PKA and EPAC: A Role for the Mitochondrial Permeability Transition Pore. Int J Mol Sci 2022, 23, 1720.
Khaliulin I, Bond N, James AF, Dyar Z, Amini R, Johnson JL, Suleiman M-S. Functional and cardioprotective effects of simultaneous and individual activation of Protein Kinase A and Epac. Br J Pharmacol 2017 DOI: 10.1111/bph.13709.
Halestrap, AP & Richardson, AP. The mitochondrial permeability transition: a current perspective on its identity and role in ischaemia/reperfusion injury. J Mol Cell Cardiol 2015, 78, 129-41.

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)?N/A
HO licence? N/A
Other?

11. A novel combination therapy promotes cell survival in the ischemic heart.

Primary supervisor: Professor Raimondo Ascione

Secondary supervisor: Dr Sarah Smith

School / Faculty: Bristol Medical School, Translational Health Sciences

Summary of project (<300 words / ~ half-page):

Heart failure (HF) following acute myocardial infarction (MI) impacts 30 million people worldwide and is attributed to >70,000 annual deaths in the UK (1). Following an MI, a complex series of cellular and molecular myocardial changes take place. An ischemic MI event may trigger necrosis in up to a million cardiomyocytes, and the immune system activates an inflammatory response to repair the damage, thus resulting in a fibrotic scar to replace the loss of cardiomyocytes. This process resolves itself over a few weeks yet adverse changes in cardiac function and pathological LV remodelling sets the trajectory for the progression of HF (2). Limiting the damage to the myocardium and the size of the fibrotic scar during the first few weeks following an MI is integral to preventing HF in patients. However, it has been postulated that modulating myocardial inflammatory and fibrotic events following an MI might reduce LV scar size and preserve LV function (3), there are no established therapies in this emerging field to treat patients with MI.

We have identified a novel combination therapy which results in a 50% reduction in scar size and 20% improvement in LV function in a porcine MI model, compared to control animals.

We are delighted to offer an extension of this project to investigate how this novel combination therapy prevents cellular death in *human* cardiomyocytes. The project student will investigate how the therapy promotes survival in ischemic/hypoxic cardiomyocytes, thus reversing the cells fate. Cardiomyocytes make up 70% of cells within the myocardium therefore understanding how this therapy influences both molecular and functional changes will contribute in the development of a potential new therapy to treat ischemic heart failure.

Techniques to be used:
Tissue culture, qPCR, Western blotting, Immunocytochemistry, cell viability and cell cycle assays

3 Key references:

1. Cardiovascular Disease Statistics: British Heart Foundation; 2014;
2. *Nature* 522, 62-67 (2015);
3. Atheroscler. Thromb. 20, 9–22 (2013);

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)?
HO licence?
Other?

12. How do you become hard hearted? The Role of NFY in biomechanical regulation of cardiac fibroblast proliferation.

Primary supervisor: Dr Mark Bond

Secondary supervisor (for day-to-day support): Dr Reza Ebrahimighaei

School / Faculty: Health Sciences/THS

Summary of project (<300 words / ~ half-page):

Cardiac fibrosis is one of the main pathophysiological processes contributing to heart failure, which affects 26 million people worldwide and half a million in the UK alone, where almost 2% of the NHS budget is spent managing this syndrome. For some conditions that lead to fibrosis, such as volume or pressure overload, treatments that target risk factors may help limit its progression, but new therapeutic strategies are urgently needed to directly inhibit the mechanisms that lead to fibrosis, particularly in patients where risk factor management is ineffective.

Cardiac fibrosis is caused, at least in part, by a proliferative expansion of resident cardiac fibroblasts (CF), which then deposit increased amounts of extracellular matrix (ECM) proteins, such as collagen. This causes the myocardium to stiffen, which contributes to systolic and diastolic dysfunction. Increased myocardial-stiffness also influences cardiac fibroblast behaviour by activating mechano-sensitive transcription factors.

We hypothesise that increased myocardial stiffness activates expression of genes that promote CF proliferation and ECM deposition. This in turn enhances fibrosis, creating a feed-forward cycle of tissue fibrosis. Our preliminary next generation sequencing data has identified over 1000 genes induced by increased ECM stiffness in cardiac fibroblasts, which are associated with cell proliferation. Our analysis of the regulatory promoter regions of these genes identified enrichment of binding elements for the transcription factor NFY. The NFY transcription factor has previously been shown to promote proliferation of other cell types, suggesting that this factor may play a major role in promoting CF proliferation in response in increased myocardial stiffness.

Aims:

1. Characterise the regulation of NFY expression and activity in cardiac fibroblasts in response the ECM stiffness.
1. Characterise the role of NFY in regulating cardiac fibroblasts proliferation and fibrosis related gene expression.

Techniques to be used:

Cardiac fibroblasts will be cultured *in vitro* on collagen-coated acrylamide hydrogels of tunable stiffness. NFYA expression will be quantified using qPCR and western blotting. NFYA activity will be quantified using NFY-dependent reporter gene analysis. NFYA activity will be modulated using siRNA-silencing, expression of dominant-negative NFYA mutants and decoy oligonucleotides. Effects on cell proliferation will be quantified using Edu incorporation and flow cytometry. Effects on expression of ECM genes (e,g, collagen) will be quantified using qPCR. Novel NFY target genes will be identified using RNA-seq. Expression of NFYA target genes in a porcine *in vivo* model of cardiac myocardial infarction will be tested using qPCR.

Key references:

1. Ly, L.L., Yoshida, H., Yamaguchi, M. (2013) Nuclear transcription factor Y and its roles in cellular processes related to human disease. *Am. J. Cancer*. 3:339-346

2. Alabert, C., Rogers, L., Kahn, L., Niellez, S., Fafet, P., Cerulis, S., Blanchard, J.M., Hipskind, R.A., Vignais, M-L. (2006) Cell type-dependent control of NF-Y activity by TGF-beta. *Oncogene* 25. 3387-96.

3. Li, Y., Xioa, X., Chen, H., Hu, K., Yin, D. (2020) Transcription factor NFYA promotes G1/S cell cycle transition and cell proliferation by transactivating cyclin D1 and CDK4 in clear cell renal cell carcinoma. *Am. J. Cancer Res*. 10: 2446-2463.

Specific requirements for the project:

No specific requirements beyond an interest in cell biology and cell signalling.

13. Exploring the role of ROS in transcription regulation of tick-borne pathogens

Primary supervisor: Dr Ian Cadby

Secondary supervisor (for day-to-day support): Dr Jamie Mann

School / Faculty: Bristol Veterinary School

Summary of project (<300 words / ~ half-page):

The main focus of this project is Anaplasma: a tick-borne pathogen that causes disease in humans and animals and is an expert in immune evasion and host cell manipulaton. Within the mammalian host, Anaplasma phagocytophilum survives and replicates inside neutrophils. To achieve this paradoxical living arrangement this bacterium makes many changes the host cell, particularly they efficiently diminish the neutrophil ability to produce reactive oxygen species (ROS), which would otherwise kill bacteria.

Whilst Anaplasma have a means of deactivating host ROS production, researchers have noted that Anaplasma isolated from host cells are able to detoxify exogenous ROS, indicating that these bacteria have proteins dedicated to this process and must therefore encounter some ROS in their lifecycle, probably from the host. Consistent with these observations, when Anaplasma meets a mammalian immune cell, they are seen to bind and remain outside the host cell for a prolonged period of time during which host ROS production is actually stimulated until the host cell capacity to do so is diminished. An important aspect of ROS is that it is a ubiquitous signalling molecule that is sensed by transcription factors (proteins that control gene expression) and mediates host-pathogen cross-talk in a range of pathogenic bacteria by turning on expression of virulence factors and defence mechanisms. The role of ROS as a signalling molecule has not been explored in Anaplasma. Based on these observations we hypothesise that Anaplasma encounter ROS during their lifecycle and have sensory mechanisms to turn on the expression of their ROS defence genes. Since ROS is likely to be encountered at the point of host recognition, the subset of genes activated are probably also involved in adaptation to and entry into the host cell. In support of this hypothesis, we have identified an *Anaplasma* gene that encodes a homologue of LexA (called APH1100), a transcription factor that controls gene expression in response to DNA damage that occurs as a result of ROS.

Your task in this project will be to characterise this predicted ROS-sensitive transcription factor and explore its potential in regulating expression of genes involved in host cell subversion.

Techniques to be used:

Protein expression and purification, crystallography, in vitro DNA binding assays (EMSAs), western blotting, reporter assays, cultivation of Anaplasma, RNA purification and downstream analysis.

3 Key references:

Salje *et al.* (2021) Cells within cells: Rickettsiales and the obligate intracellular bacterial lifestyle. ***Nature Reviews Microbiology*** 19:375–390

Cadby *et al.* (2016) Regulation, sensory domains and roles of two Desulfovibrio desulfuricans ATCC27774 Crp family transcription factors, HcpR1 and HcpR2, in response to nitrosative stress. ***Molecular microbiology*** 102:1120-1137.

Carlyon *et al.* (2004) *Anaplasma phagocytophilum* Utilizes Multiple Host Evasion Mechanisms To Thwart NADPH Oxidase-Mediated Killing during Neutrophil Infection. ***Infection and immunity*** 72:4772-4783.

Specific requirements for the project: None, the project will mainly be conducted on the Langford campus.

14. Myocardial fibrosis assessment and association with quantitative evaluation of coronary artery occlusion by 3D coronary volume reconstruction in a large animal model of acute myocardial infarction.

Primary supervisor: Vito Domenico Bruno

Secondary supervisor (for day-to-day support): Daniel Baz Lopez

School / Faculty: School of Medicine – Translational Health Science

Summary of project (<300 words / ~ half-page):

Large animal models of myocardial infarction (MI) are valuable to understand the pathophysiology of the disease and in this study, we aim to correlate the amount of coronary volume occluded with the amount of myocardial fibrosis in a large animal model of MI. 22 Yorkshire pigs underwent a closed chest MI model, followed by cardiac magnetic resonance imaging (CMR). 3D quantitative coronary assessment (3DQCA) reconstruction was used to determine the segment length in occluded and non-occluded vessels. In a preliminary analysis, we demonstrated a direct correlation between the occluded coronary volume and the size of the MI scar measured with CMR in the acute phase(1). Abnormal cardiac fibrosis has a major role after MI with reactive oxidative species (ROS) being direct regulators of interstitial ECM production(2). At the same time, mitochondria have been pointed as the main ROS generator in cardiac fibrosis(3). We aim to correlate the occluded coronary volume with the amount of cardiac fibrosis after the MI. We also aim to evaluate the associative determination of ventricular dysfunction and levels of fibrosis with mitochondrial variables of the genetic function. Snap-frozen myocardial porcine and formalin fixed samples will be used in this project: these samples were collected from the infarcted area and from the border zone, transitional and undamaged area at the time of the termination of the 22 animals and left ventricular samples from 8 healthy animals will serve as controls. Samples will be processed for the differential isolation of total DNA and proteins. Relative mitochondrial genome copy number and mutation frequency will be assessed from the total DNA isolated fraction. The protein quantification of fibrosis markers fibrillar type I and type III collagen, Matrix metalloproteinase 1 (MMP1), Tissue inhibitor of metalloproteinase 1 (TIMP1), and TGF-beta receptor levels will be determined out of the total protein isolation.

Techniques to be used:

- Accumulation of fibrillar type I and type III collagen in the extracellular matrix of the cardiac interstitial space in each of the MI myocardial portions and in healthy myocardium: Western blot quantification of the protein levels and immunohistochemical determination of the histological distribution.

- Determination of the protein levels of Matrix metalloproteinase 1 (MMP1) and Tissue inhibitor of metalloproteinase 1 (TIMP1) in each of the MI myocardial portions and in healthy myocardium: Western blot quantification of the protein levels and immunohistochemical determination of the histological distribution.

- Determination of the protein levels of TGF-beta receptor in each of the MI myocardial portions and in healthy myocardium: Western blot quantification of the protein levels and immunohistochemical determination of the histological distribution.

- Determination of the relative mitochondrial genome copy number in each of the MI myocardial portions and in healthy myocardium: qPCR assay.

- Determination of the level of location specific genomic mitochondrial DNA mutation rate in each of the MI myocardial portions and in healthy myocardium: Quantification of the frequency mutation by qPCR-RMC assay.

3 Key references:

1. Bruno VD, Sammut E, Gall A, Baz-Lopez D, Ascione R, Johnson TW. Quantitative evaluation of coronary artery occlusion by 3D coronary volume reconstruction in a large animal model of acute myocardial infarction. Eur Heart J. 2021;42(Supplement_1):3257.
2. Hill MF, Singal PK. Antioxidant and oxidative stress changes during heart failure subsequent to myocardial infarction in rats. Am J Pathol. 1996;148(1):291–300.
3. Dai DF, Johnson SC, Villarin JJ, Chin MT, Nieves-Cintron M, Chen T, et al. Mitochondrial oxidative stress mediates Angiotensin II-induced cardiac hypertrophy and Gαq overexpression-induced heart failure. Circ Res [Internet]. 2011;108(7):837–46. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? NA
HO licence? NA
Other? NA

15. The effect of endocannabinoid receptor 1 agonist, WIN-55, 212-2, on excitation-inhibition of hippocampal dentate gyrus circuitry and pattern separation behaviour in mice

Primary supervisor:
Dr Denize Atan, Consultant Senior Lecturer in Neuro-Ophthalmology, University of Bristol

Secondary supervisor (for day-to-day support):
Yingxin Li, final year PhD student, Translational Health Sciences, Bristol Medical School
Professor Zafar Bashir, Physiology, Pharmacology, Neuroscience, Life Sciences, University of Bristol

School / Faculty: Translational Health Sciences, Faculty of Health Sciences

Summary of project (<300 words / ~ half-page):

The discrimination of similar episodes and places and their representation as distinct memories depend on a process called pattern separation. In the hippocampus, pattern separation relies on the circuitry of the dentate gyrus (DG). Hence, pathologies involving the DG, like temporal lobe epilepsy and mild cognitive impairment, are associated with pattern separation deficits.

We have found that mossy cells (MCs) are key neurons in DG circuitry and regulate excitation-inhibition of the network in a highly dynamic frequency-dependent manner. Using a novel genetically modified mouse model that selectively lacks MCs, we found:

1. In electrophysiology field recordings of the DG in acute hippocampal slices, MCs have a net inhibitory effect at stimulation frequencies connected with learning and memory but a net excitatory effect at higher frequencies
2. In behavioural tasks, the absence of MCs is associated with deficits in spatial memory and pattern separation behaviour but protects against seizures.

MCs express endocannabinoid receptor 1 (CB1), a target for cannibidiol treatments of epilepsy.

Because of the effect on MCs, our hypothesis is that treatment with CB1 agonist, WIN-55, 212-2, will be associated with deficits in pattern separation behaviour in wild type mice but will protect against seizures.

Techniques to be used:

1. The student will learn how to perform field electrophysiological recordings in the DG of acute hippocampal slices. Recordings will be performed with the addition of WIN-55, 212-2 to the bath of acute wild type hippocampal slices and compared against control experiments in which recordings are made of the DG in untreated wild type slices and slices taken from genetically modified mice that selectively lack mossy cells.
2. The student will use the behavioural paradigms we have already developed to test memory and pattern separation behaviour in mice. They will perform surgeries to implant transfusion tubes to administer WIN-55, 212-2 directly to the hippocampal DG of wild type and genetically modified mice to compare their performance on the behavioural tasks during transfusion of WIN-55, 212-2 versus placebo.

3 Key references:

1. Van Hagen, et al. The object pattern separation (OPS) task: a behavioural paradigm derived from the object recognition task. Behavioural brain research, 2015.
2. Reyes, A. et al. Impaired spatial pattern separation performance in temporal lobe epilepsy is associated with visuospatial memory deficits and hippocampal volume loss. Neuropsychologia, 2018.
3. Bui, A. D. *et al.* Dentate gyrus mossy cells control spontaneous convulsive seizures and spatial memory. Science, 2018.

Specific requirements for the project:

Immunisations (e.g. Hepatitis B)? No

HO licence: Not absolutely necessary, but would be helpful

16. Heparan sulphate in the glomerular endothelial glycocalyx: importance in diabetes and potential as a therapeutic target.

Primary supervisor: Prof Simon Satchell

Secondary supervisor (for day-to-day support): Dr Raina Ramnath

School / Faculty: Bristol Medical School/ Translational Health Sciences

Summary of project (<300 words / ~ half-page):

Diabetes is the commonest cause of kidney failure in England. In addition, 75% of all people with diabetes die from some form of blood vessel disease. The endothelial glycocalyx (outlined in yellow in Fig 1) is a key determinant of vascular function.1,2 In diabetes, glycocalyx damage contributes to glomerular and kidney damage.

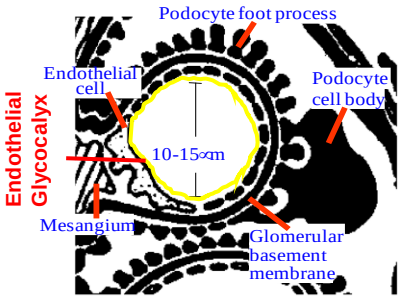

Fig 1. Cross section through a glomerular capillary

Understanding of the contributions of particular glycocalyx components (Fig 2), and which are damaged in diabetes, is limited but data suggest the importance of heparan sulphate (HS)

Exostosin (EXT) 1 is an essential and rate-limiting enzyme involved in HS chain elongation. We have successfully established
(i) an inducible Ehd3 Cre EXT1fl/fl mouse model, in which Ext1 is deleted specifically in glomerular endothelial cells, therefore HS is specifically knockdown in glomerular endothelial cells.
(ii) a conditionally immortalised human glomerular endothelial cells (ciGEnC) overexpressing EXT1 to rigorously examine the protective role of HS.

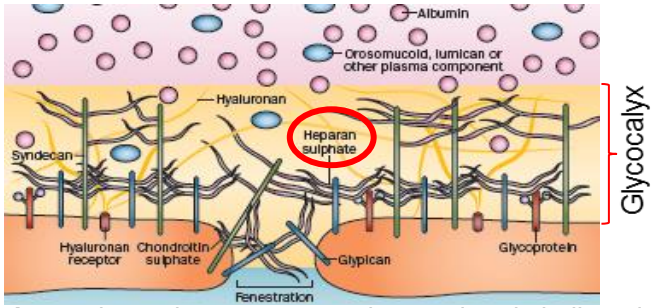

Fig 2. Glycocalyx, present on the renal endothelium, is a negatively charged gel composed of different components. Amongst them is the glycosaminoglycan heparan sulphate.[2]

We hypothesise that HS is a key component of the GEnC glycocalyx and represents a potential therapeutic target in diabetes.
Aim 1. Determine whether damage to GEnC glycocalyx and the glomerular capillary is exacerbated by diabetes in HS knock-down mice.
Aim 2. Investigate whether overexpression of HS restores the glycocalyx and protects the endothelial cells in diabetic conditions.
Outcome. Confirming the importance of HS in the GEnC glycocalyx and capillary function will pave the way to therapies targeted at glycocalyx protection and restoration. These will be of benefit to diabetic kidney disease and systemic vascular disease patients.3

Clinical impact.
Technology is available to design and manufacture HS which can be taken in tablet form so once we have confirmed the importance and potential of HS, progress towards it being used to maintain healthy glycocalyx and protect people with diabetes will be relatively rapid.

Techniques to be used:

The researcher/student will contribute to this project but will not be expected to complete all this work on their own.

Models
In vivo: Ehd3 Cre EXT1fl/fl, mice will be injected with streptozotocin to induce Type 1 diabetes

In vitro: EXT1 overexpressing ciGEnC will be stimulated in a diabetic milieu

The aims will be investigated by performing the following assays:
i) Transmission electron microscopy will be used to assess glomerular ultrastructure (Fig 3) by quantifying endothelial glycocalyx depth, basement membrane thickness and slit diaphragm width.

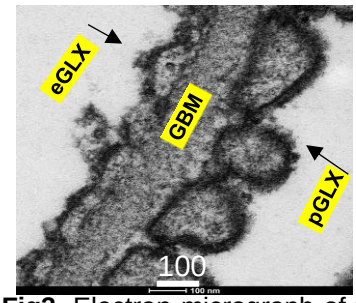

Fig3. Electron micrograph of the glomerular capillary wall shows endothelial glycocalyx (eGLX) on the luminal side of the vessel, glomerular basement membrane (GBM) and podocyte glycocalyx (pGLX)

ii) Confocal microscopy will be used to determine glomerular and peritubular eGLX depth and coverage by our innovative peak to peak technique. Kidney sections will be stained with MOA lectin and endothelial membrane label R18. The distance between the peak signals MOA- 488 and the R18 labels is an index of glycocalyx thickness (Fig 4). Macros will be used for automated eGLX analysis.

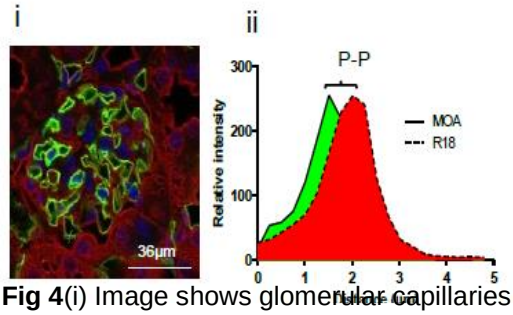

Fig 4(i) Image shows glomerular capillaries labelled red (R18) and the luminal endothelial glycocalyx labelled green (MOA). (ii) Peak to Peak (P-P), an index of glycocalyx thickness,will be determined from an average of 3 lines in a loop, 3 loops in a glomerulus, 3 glomeruli in a mouse and n=4 mice in each group.

iii) A novel isolated glomerulus assay (Fig 5) will be used to determine glomerular albumin permeability. It will establish the relationship between glycocalyx damage and altered glomerular permeability.

iv) Urinary albumin creatinine ratio will assess kidney function.

v) In vitro assays such as transendothelial albumin permeability and in cell analyser will be used to determine the endothelial function and glycocalyx expression respectively

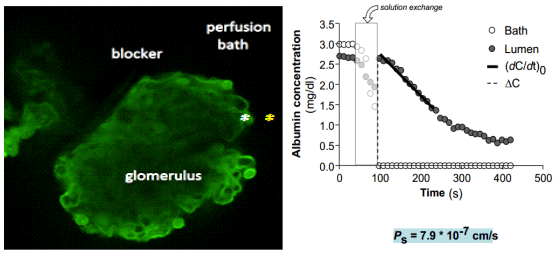

Fig 5. A single glomerulus isolated from a mouse, perfused with Alexa 488-labelled BSA. Single capillary loops (*) were identified. The diffusive albumin solute permeability (P_S^{alb}) for that capillary lumen was calculated from the decay in capillary lumen fluorescence intensity.

This project will provide fantastic training opportunities using cutting-edge technologies including confocal microscopy. High-quality imaging will be carried out in our state-of-the-art Wolfson bioimaging facility. The researcher will learn different lab techniques, develop independent critical thinking skills, develop skills in analysing the data and interpretation of the results. They will get to develop their communication skills by attending Bristol Renal weekly lab meetings to present their data.

It is anticipated that the results obtained from this proposal will add to already available data on this project, therefore accelerating the submission of a manuscript.
3 Key references: 1. Reitsma S, Slaaf DW, Vink H, van Zandvoort MA, oude Egbrink MG. The endothelial glycocalyx: composition, functions, and visualization. Pflugers Arch. 2007;454(3):345-59. 2. Satchell S. The role of the glomerular endothelium in albumin handling. Nature reviews Nephrology. 2013;9(12):717-25. 3. Becker BF, Chappell D, Bruegger D, Annecke T, Jacob M. Therapeutic strategies targeting the endothelial glycocalyx: acute deficits, but great potential. Cardiovasc Res. 2010;87(2):300-10.
Specific requirements for the project: This project will use samples derived from mouse work conducted by other researchers and human cells grown in vitro and does not require a personal animal licence. However, there is the opportunity to undertake animal licence training and licencing, and so contribute directly to the animal work, if the student would like to do so. Immunisations (e.g. Hepatitis B): No HO licence: PPL (Dr Becky Foster): P855B71B4

17. Endothelial glycocalyx and PAR1 interplay in glomerular endothelial cells

Primary supervisor: Prof Simon Satchell

Secondary supervisor (for day-to-day support): Dr Raina Ramnath

School / Faculty: Bristol Medical School/ Translational Health Sciences

Summary of project (<300 words / ~ half-page):

The vascular endothelium, including the glomerular endothelial cells, is lined on the luminal side of the vessel by a gel-like structure called the glycocalyx (eGLX), (**Fig 1**, outlined in yellow). EGLX plays an important role in maintaining vascular homeostasis, exhibiting antithrombotic, anti-inflammatory properties, and regulating vascular permeability.

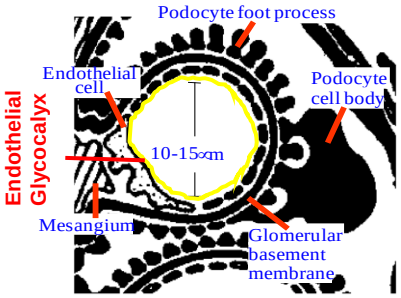

Fig 1. Cross section through a glomerular capillary

Central to its role are the antithrombotic properties of the glycocalyx. EGLX comprises heparan sulphate (amongst others, **Fig 2**) which increases the anticoagulant action of antithrombin. It also harbours anticoagulant and anti-inflammatory compound thrombomodulin, which is triggered in response to procoagulant stimuli. In addition to its key anti-coagulation functions, it plays an important role in maintaining blood flow in microcirculation. However, in disease conditions eGLX disruption has been associated with platelet adhesion and microthrombi formation and disseminated intravascular coagulation. Hemolytic uremic syndrome (HUS) affecting the kidney glomeruli is characterised by a triad of anemia, thrombocytopenia and acute kidney injury. The role of eGLX in HUS has not been elucidated.

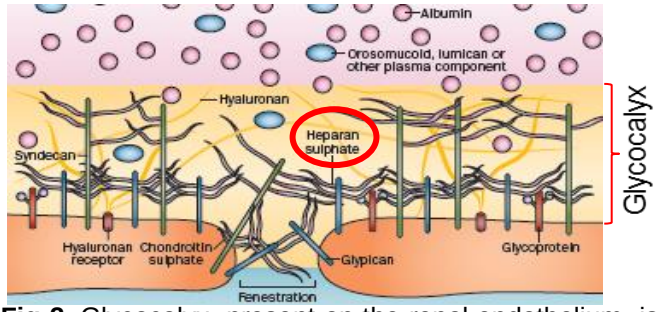

Fig 2. Glycocalyx, present on the renal endothelium, is a negatively charged gel composed of different components. Amongst them is the glycosaminoglycan heparan sulphate.[2]

Thrombin binds and activates its receptor protease-activated receptor-1 (PAR1), initiating the process of thrombosis. PAR1 has been demonstrated to be expressed on the glomerulus. Understanding the interplay between PAR1 activation and glycocalyx could lead to the identification of key therapeutic targets in the treatment of HUS.

We hypothesise that **PAR1 activation disrupts eGLX in the glomerulus contributing to thrombosis, inflammation and vascular permeability**

Aim 1. Determine whether eGLX is damaged in transgenic mice expressing an overactive form of PAR1 in the glomerular endothelial cells.

Aim 2. Investigate whether these mice exhibit signs of thrombosis, inflammation and vascular permeability.

Techniques to be used:

Model

In vivo: An inducible Ehd3CrePAR1 transgenic mice whereby PAR1 is constitutively active in glomerular endothelial cells, resembles aspects of an HUS model.

***The aims will be investigated by performing the following assays*:**

i) Confocal microscopy will be used to determine glomerular eGLX depth and coverage by our innovative peak to peak technique. Kidney sections will be stained with MOA lectin and endothelial membrane label R18. The distance between the peak signals MOA- 488 and the R18 labels is an index of glycocalyx thickness (**Fig 3)**. Macros will be used for automated eGLX analysis.

ii) Immunofluorescence staining, western blot and real-time qPCR will be used to determine changes in haemostatic markers, anticoagulant and fibrinolytic markers (antithrombin, PAI-1), endothelial markers (syndecans, VCAM-1, E-selectin), and inflammatory markers (IL-1β, IL-6, IL-8, HMGB-1, histone-H3)

iii) A novel isolated glomerulus assay **(Fig 4)** will be used to determine glomerular albumin permeability. It will establish the relationship between glycocalyx damage and altered glomerular permeability.

iv) Urinary albumin creatinine ratio will assess kidney function.

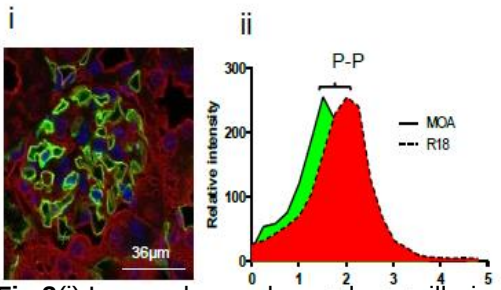

Fig 3(i) Image shows glomerular capillaries labelled red (R18) and the luminal endothelial glycocalyx labelled green (MOA). (ii) Peak to Peak (P-P), an index of glycocalyx thickness,will be determined from an average of 3 lines in a loop, 3 loops in a glomerulus, 3 glomeruli in a mouse and n=4 mice in each group.

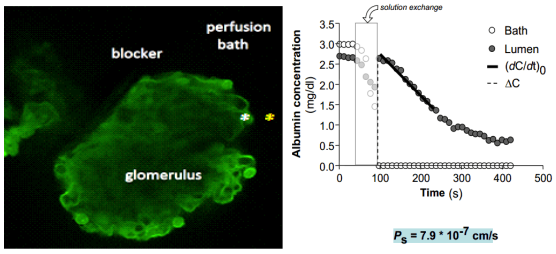

Fig 4. A single glomerulus isolated from a mouse, perfused with Alexa 488-labelled BSA. Single capillary loops (*) were identified. The diffusive albumin solute permeability (P_S^{alb}) for that capillary lumen was calculated from the decay in capillary lumen fluorescence intensity.

This project will provide fantastic training opportunities using cutting-edge technologies including confocal microscopy. High-quality imaging will be carried out in our state-of-the-art Wolfson bioimaging facility. The researcher will learn different lab techniques, develop independent critical thinking skills, develop skills in analysing the data and interpretation of the results. They will get to develop their communication skills by attending Bristol Renal weekly lab meetings to present their data.

3 Key references:

1. Satchell S. The role of the glomerular endothelium in albumin handling. Nature reviews Nephrology. 2013;9(12):717-25.
2. Becker BF, Chappell D, Bruegger D, Annecke T, Jacob M. Therapeutic strategies targeting the endothelial glycocalyx: acute deficits, but great potential. Cardiovasc Res. 2010;87(2):300-10.
3. Ikeda M, Matsumoto H, Ogura H, Hirose T, Shimizu K, Yamamoto K, Maruyama I, Shimazu T. Circulating syndecan-1 predicts the development of disseminated intravascular coagulation in patients with sepsis. J Crit Care 2018; 43: 48–53.

Specific requirements for the project: This project will use samples derived from mouse work conducted by other researchers and does not require a personal animal licence. However, there is the opportunity to undertake animal licence training and licencing, and so contribute directly to the animal work, if the student would like to do so.

Immunisations (e.g. Hepatitis B): No

HO licence (Dr Becky Foster): P855B71B4

Other?

18. A 3D bioprinted model of tissue resident macrophages in the subcutaneous tissue

Primary supervisor: Asme Boussahel

Secondary supervisor (for day-to-day support): Asme Boussahel

School / Faculty: School of Cellular and Molecular Medicine

Summary of project (<300 words / ~ half-page):

Tissue resident macrophages are immune cells present in distinct phenotypes in most tissues with a range of functions e.g. clearance of cellular debris and iron processing, immune surveillance, response to infection and the resolution of inflammation. Tissue-resident macrophages are extremely heterogeneous. This is the result of both the heterogeneity of their origins and the influence of the environment in which they reside. So far, studying tissue resident macrophages *in-vitro* has been very challenging due to the difficulty in isolating them and differentiating them. Recent research has shed some light on SC tissue resident macrophages and their function. They are involved in altering adipocyte morphology in obese animals. They also play a role in adipose tissue inflammation, ectopic fat deposition, and insulin resistance and are thought to control drug absorption following SC delivery. This new understanding of SC macrophages provides opportunities for developing new therapies for treating obesity and Type 2 diabetes. However, we are still unable to use them efficiently as drug targets or study their interactions with drugs effectively due to the inability to study them *in-vitro*.

I propose to develop a comprehensive model of the SC tissue resident macrophages by 3D bioprinting them into a SC tissue model that captures both the origins of macrophages and the SC tissue environment that shapes their function. This will be the first attempt to model the heterogenous nature of tissue resident macrophages *in- vitro*.

This master project will be the first step towards this by 3D bioprinting human monocytes isolated from blood with a SC tissue biomimetic hydrogel and optimising their differentiation into SC tissue resident like macrophages. 3D bioprinting will enable this work to be translatable to other fields enabling more in-depth study of tissue resident macrophages in other tissues e.g. brain, kidneys.

Techniques to be used:

3D Bioprinting
Primary human cells isolation and culture
Advanced bioimaging techniques
Physical and chemical characterisation of hydrogels and cells
Histology and staining including immunostaining
Macrophage polarisation studies

3 Key references:

Davies, L., Jenkins, S., Allen, J. Yaylor, PR. Tissue-resident macrophages. Nature Immunology 14**,** 986–995 (2013).

Derakhshanfar, S., Mbeleck, R., Xu, K., 3D bioprinting for biomedical devices and tissue engineering: a review of recent trends and advances. Bioactive Materials 3: 144-156 (2018)

Bystronova, J., Scigalkova, I., Wolfova, L., Pravda, M., Vrana, N E., Velebny, V. Creating a 3D microenvironment for monocyte cultivation: ECM-mimicking hydrogels based on gelatine and hyaluronic acid derivatives. RSC Advances 8: 7606-7614 (2018)

Specific requirements for the project:

Immunisations (e.g. Hepatitis B)

19. Deciphering the pathogenic and immune evasion strategies of bacterial endocarditis pathogens

Primary supervisor: Dr Angela Nobbs; Co-supervisor: Dr Borko Amulic

Secondary supervisor (for day-to-day support): Dr Jane Brittan

School / Faculty: Faculty of Health Sciences / Faculty of Life Sciences

Summary of project (<300 words / ~ half-page):

When oral *Streptococcus* bacteria enter the bloodstream, they have the capacity to evade our immune defences, colonise damaged heart valves and activate platelets. This leads to undesirable thrombus (clot) formation and the development of severe cardiovascular disease, infective endocarditis (IE), with high treatment failure and mortality rates (<30%). Signals released from activated platelets assist recruitment and activation of neutrophils, which exude granular and nuclear materials in neutrophil extracellular traps (NETs). NETs can then serve as a scaffold to further enhance and entrap bacteria-platelet aggregates on injured heart valves, exacerbating the disease.
Our recent studies with *Streptococcus gordonii* have characterised two cell-surface proteins, Hsa and PadA, that can bind directly to platelets and contribute to survival in blood. However, the specific mechanisms by which these proteins mediate bacterial survival are unknown. It is also not known if these proteins can interact with neutrophils. By addressing these knowledge gaps, this project will provide novel insights into the molecular mechanisms that underpin the progression of this severe heart condition, and indicate the potential for bacterial proteins to serve as targets for the prevention or management of IE.
The overall aims of this project are to determine the role of *S. gordonii* proteins Hsa or PadA in evading neutrophil- or complement-mediated killing within blood, and in triggering neutrophil activation and NET formation, either directly or via platelets. Using streptococcal knockout mutants, together with *Lactococcus lactis* heterologous expression strains, the specific objectives of this project are to investigate the capacity for Hsa and PadA:

1. To protect *S. gordonii* from phagocytic killing
1. To induce the release of cytokines and neutrophil extracellular traps
1. To bind complement factors/inhibitors and serum proteins

Where specific functions are identified, there will be scope to utilise molecular biology-based tools to generate targeted deletions in PadA or Hsa, and so further refine molecular understanding of the functional regions of these proteins.

Techniques to be used:
General microbiology techniques for culturing bacterial cells; isolation of primary neutrophils from human blood and/or maintenance of cell line PLB-985; killing assays by viable count; immunolabelling of cells; flow cytometry; ELISA; fluorescence/confocal microscopy; Western immunoblotting; [bacterial mutagenesis and cloning]

3 Key references:

1. Haworth, J.A., et al., Concerted functions of *Streptococcus gordonii* surface proteins PadA and Hsa mediate activation of human platelets and interactions with extracellular matrix. *Cell Microbiol*, 2017. 19: e12667.
1. Jung, C.J., et al., Endocarditis pathogen promotes vegetation formation by inducing intravascular neutrophil extracellular traps through activated platelets. *Circulation*, 2015. 131: 571-81.
1. Keane, C., et al., Multiple sites on *Streptococcus gordonii* surface protein PadA bind to platelet GPIIbIIIa. *Thromb Haemost*, 2013. 110: 1278-87.

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? Hepatitis B

20. A novel strategy to combat Group B Streptococcus neonatal disease by targeting interkingdom interactions with fungus Candida albicans

Primary supervisor: Dr Angela Nobbs

Secondary supervisor (for day-to-day support): Dr Jane Brittan

School / Faculty: Faculty of Health Sciences

Summary of project (<300 words / ~ half-page):

Group B Streptococcus (GBS) is a major cause of infant death and morbidity worldwide, resulting in 147,000 stillbirths and infant deaths annually. Of those infants who survive, up to 50% will suffer neurological sequelae such as seizures, sight or hearing loss, and cerebral palsy. The primary ecological niche for GBS is the genitourinary (GU) tract, and maternal colonisation represents the principal route of GBS transmission from mother to child. As such, therapeutic strategies that diminish GU tract colonisation by GBS could prevent infant disease and death on a global scale. For this to be achieved, there is a need for better understanding of the molecular basis of GU tract colonisation by GBS so that critical targets may be identified.

There is strong clinical evidence that the presence of fungus Candida albicans is a major risk factor for GU tract colonisation by GBS. However, the reason for this link is poorly understood. We have shown that C. albicans significantly enhances attachment to and invasion of vaginal mucosa by GBS, an outcome that would increase the risk of GBS transmission and disease. What we now need to decipher, and which is the aim of this project, is exactly how C. albicans mediates these effects, for which two mechanisms are proposed: i) via direct coadhesion and ii) via modulation of the host mucosal response. Specifically, the experimental objectives are to:

1. Exploit a mutant library and a collection of isolates taken from pregnant women in high- and low-income countries to identify the key GBS and C. albicans adhesin profiles associated with co-colonisation (coadhesion) in pregnancy
1. Determine the capacity for dual species infection to enhance GBS colonisation through modulation of mucosal tissue interactions (e.g. autophagy, cytokine release) and the immune response (e.g. neutrophil engagement)
1. Explore the feasibility of targeting C. albicans-GBS co-colonisation via peptide mimetics to diminish GBS carriage within the GU tract

Ultimately, it is anticipated that information arising from this project could inform development of novel future strategies to impair GBS colonisation and disease by targeting this interkingdom interaction.

Techniques to be used:

General microbiology techniques for culturing bacterial and fungal cells; tissue (mammalian cell) culture; biological assays of microbial coaggregation and adhesion/invasion of epithelial tissue; fluorescence/confocal microscopy to visualise host-microbe interactions; ELISA and flow cytometry to analyse host responses (e.g. cytokine release); pull-down assays/proteomics; use of in silico tools to design function-blocking peptides; [mutagenesis approaches]

3 Key references:

- G.R. Pidwill, S. Rego, H.F. Jenkinson, R.J. Lamont & A.H. Nobbs (2018). Co-association between Group B Streptococcus and Candida albicans promotes interactions with vaginal epithelium. Infect Immun 86: e00669-17
- S. Rego, T.J. Heal, G.R. Pidwill, M. Till, A. Robson, R.J. Lamont, R.B. Sessions, H.F. Jenkinson, P.R. Race & A.H. Nobbs (2016). Structural and functional analysis of cell wall-anchored polypeptide adhesin BspA in Streptococcus agalactiae. J Biol Chem 291: 15985-16000
- P. Cools, V. Jespers, L. Hardy, T. Crucitti, S. Delany-Moretlwe, M. Mwaura et al. (2016). A multi-country cross-sectional study of vaginal carriage of Group B streptococci (GBS) and Escherichia coli in resource-poor settings: prevalences and risk factors. PLoS One 11: e0148052-e

Specific requirements for the project: Immunisations (e.g. Hepatitis B)? Hepatitis B HO licence? N/A Other? N/A

21. Bioengineering complex *in vitro* models of the kidney

Primary supervisor: **Dr James Armstrong, Prof. Gavin Welsh**

Secondary supervisor (for day-to-day support): **Martha Lavelle**

School / Faculty: **Bristol Medical School, Faculty of Health Sciences**

Summary of project (<300 words / ~ half-page):

Kidneys are complex multicellular organs with a number of critical functions in waste removal and homeostasis. Blood circulating through the kidneys is filtered at the glomerulus, a capillary network that allows water and small aqueous substrates to pass into an extracellular space known as the Bowman's capsule. This selective permeability is enabled by three interconnected barriers in the glomerular capillaries: a highly fenestrated endothelium surrounded by a collagen-rich basement membrane, and an epithelial lining of interdigitated podocytes.[1]

Recreating the glomerulus *in vitro* would provide a high-throughput, tractable system to study renal diseases and screen therapeutics without the need for animal models. However, this endeavour is limited by the technical challenge associated with assembling endothelial cells and podocytes into a natural configuration. Bristol Renal have previously shown that these two cell types can spontaneously assemble in co-culture, a process that can be guided using nanofibrous hydrogels (fibrin) and microfibrous scaffolds (polyglycolic acid) (**Figure 1A**).[2] This model effectively recreated some of the microscale cellular interactions and supported the deposition of collagen IV, a key basement membrane component. However, this model could not replicate the macroscopic architecture of the native glomerulus and did not provide any user control over cellular assembly.

This project will address this enduring challenge through the use of an acoustic cell patterning technology previously developed by the Armstrong Group (www.TheArmstrongGroup.co.uk).[3] This method uses ultrasound standing waves to exert acoustic radiation forces that can controllably aggregate living cells into user-defined geometric assemblies (**Figure 1B**). We will use this technology to remotely assemble podocytes and endothelial cells into programmed "capillary networks." Hydrogels will be used to encapsulate the patterned cell arrays and provide biomaterial cues for coculture. We will use confocal fluorescence microscopy to assess the cell motility, morphology, and reorganization, and immunostaining to determine the distribution of collagen IV. If successful, this project will output a new *in vitro* model for studying renal physiology and disease.

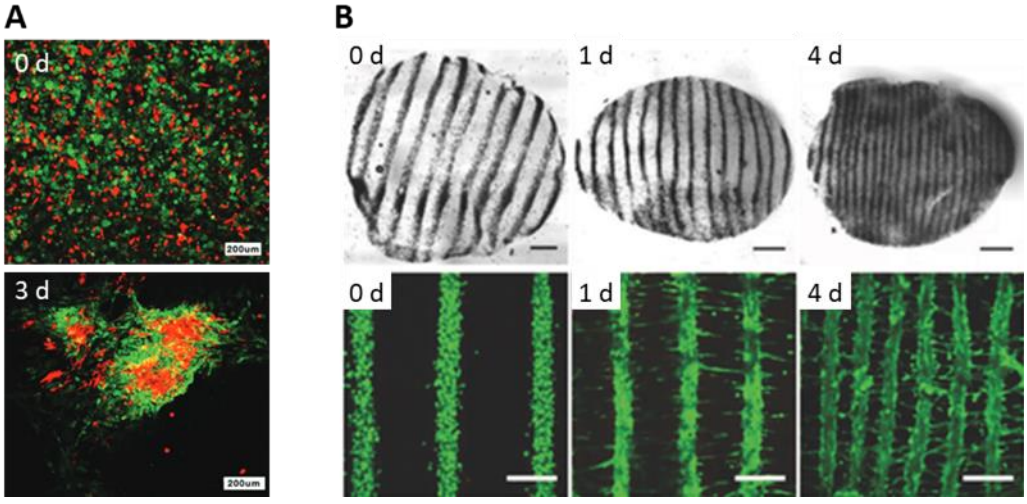

Figure 1. (A) Glomerular endothelial cells (red) and podocytes (green) cocultured in fibrin and supported by a polyglycolic acid scaffold, scale bars 200 µm. (B) Cells patterned in a hydrogel using 2.2 MHz ultrasound standing waves, brightfield scale bars 500 µm, fluorescence scale bars 200 µm.

Techniques to be used:

- Sterile cell culture of glomerular endothelial cells and podocytes. - Assembly and operation of acoustic cell patterning devices. - Synthesis, characterization, and casting of hydrogel biomaterials. - Immunostaining and confocal fluorescence microscopy. - Biological assays (*e.g.*, alamarBlue, PicoGreen).
3 Key references: 1. Welsh & Saleem *Nature Reviews Nephrology* (2011). 1. Tuffin *et al. Advanced Healthcare Materials* (2019). 1. Armstrong *et al. Advanced Materials* (2018).
Specific requirements for the project: Immunisations (e.g. Hepatitis B)? No HO licence? No Other? No

22. Effects of RCAN1 gene transfer on endothelial function

Primary supervisor: Dr Kerry Wadey

Secondary supervisor (for day-to-day support): Prof Sarah George

School / Faculty: Bristol Medical School, Faculty of Health Sciences

Summary of project:

Coronary artery bypass grafting is the mainstay treatment for patients with ischaemic heart disease. Autologous saphenous vein conduits are most commonly grafted owing to their length and ease of harvest; however, their long-term success is hindered by re-blockage. Re-blockage is a product of neointima formation – resulting from hyper-proliferation of VSMCs – coupled then with superimposed atherosclerosis. The major health and economic burden of vein graft failure necessitates the development of novel alternative therapies, especially those that target VSMC proliferation. Gene therapy is a particularly attractive approach as the accessibility of the vein graft conduit during surgery presents good opportunity for the application of *ex vivo* gene transfer technology.

Accumulating evidence indicates that RCAN1 exerts divergent effects across various cardiovascular diseases. Our findings have shown that, in cultured human saphenous vein VSMCs, introduction of the *rcan1* transgene markedly suppresses proliferation and promotes apoptotic cell death. Uniformly, siRNA-mediated silencing of RCAN1 facilitated cell proliferation and enhanced cell survival. These initial findings present delivery of the *rcan1* transgene as a potential strategy for reducing neointima formation and prolonging the patency of vein grafts.

In designing novel therapies for vein graft failure, it is important to investigate any potential detrimental effects of an intervention on endothelial function. Firstly, using cationic nanotechnology as a means of gene transfer, we would like to examine the effect of overexpression of RCAN1 on endothelial cell survival, proliferation and migration. Findings would be indicative of whether this approach would disrupt re-endothelialisation following CABG surgery. Secondly, we would assess the outcome of RCAN1 overexpression on inflammatory responses including pro-inflammatory cytokine production and monocyte recruitment. Thirdly, we would evaluate whether introduction of the RCAN1 transgene would compromise endothelial barrier function; and finally, we would like to investigate any adverse effects of introducing RCAN1 on thrombus formation by examining platelet adhesion. Evaluation of these parameters in cultured human endothelial cells, as well as in segments of surplus human saphenous vein collected from consenting CABG patients, will provide good evidence for the suitability of RCAN1 overexpression as a treatment for vein graft failure.

Techniques to be used:
Tissue and organ culture, cell transfection, apoptosis assay, proliferation assay, migration assay, ELISA, monocyte adhesion assay, permeability assay, platelet adhesion assay, Western blotting

3 Key references:

Katz MG, Fargnoli AS, Kendle AP, Hajjar RJ, Bridges CR. Gene Therapy in Cardiac Surgery: Clinical Trials, Challenges, and Perspectives. Ann Thorac Surg. 2016;101(6):2407-16.

Wang S, Wang Y, Qiu K, Zhu J, Wu Y. RCAN1 in cardiovascular diseases: molecular mechanisms and a potential therapeutic target. Mol Med. 2020;26(1):118.

Ward AO, Caputo M, Angelini GD, George SJ, Zakkar M. Activation and inflammation of the venous endothelium in vein graft disease. Atherosclerosis. 2017;265:266-74.

Specific requirements for the project:

none

23. Early detection of neuropathy in the community - SenseCheQ

Primary supervisor: Prof Tony Pickering

Secondary supervisor (for day-to-day support): Dr Juim Dunham and Dr Anna Sales

School / Faculty: PPN, FLS

Summary of project (<300 words / ~ half-page):

Peripheral neuropathy is a common and disabling complication of chemotherapy treatment for cancer – over half of patients have some nerve damage and many will go on to have severe persistent symptoms like pain, numbness and postural hypotension (Flatters et al 2017). This nerve damage often goes undetected at the time of treatment as our current sensory testing techniques are either rather insensitive or are complex, time-consuming research tools that are not used in clinic. Early detection of the neurotoxicity could allow changes to treatment regime or protective therapeutic interventions.

We are undertaking a MRC-Versus arthritis funded study – SenseCheQ – to develop a novel approach to test the sensory function of peripheral nerves in the community. This is a collaboration with engineering colleagues in Newcastle University and experts in Chemotherapy-induced Neuropathy in Dundee University to develop haptic and Peltier-based stimulators that could be wearable by patients during their treatment. The student will be testing prototype stimulators in healthy volunteers of a range of ages to characterise their sensory psychophysics and the comparative performance with gold standard quantitative sensory test devices (Rolke et al 2006) with these low-cost, miniaturised, wearable stimulators and sensors (see also Reimer et al 2020 for a similar approach).

Techniques to be used:

The student will work with the research team to develop and iteratively test thermal and vibration devices and will also use models of gain and loss of sensory function to assess their sensitivity to detect damage early in human volunteer studies and towards patient testing. It will involve interactions with engineers and with patient partners as we work through the design challenges to develop the SenseCheQ device. The devices will be controlled, and the data captured using Arduinos and analysis will be in Matlab and Prism.

3 Key references:

Flatters SJL, Dougherty PM & Colvin LA. (2017). Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): a narrative review. *Br J Anaesth* **119,** 737-749.

Rolke R, Baron R, et al (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* **123,** 231-243.

Reimer M, Forstenpointner J, Hartmann A, Otto JC, Vollert J, Gierthmuhlen J, Klein T, Hullemann P & Baron R. (2020). Sensory bedside testing: a simple stratification approach for sensory phenotyping. *Pain Rep* **5,** e820.

Specific requirements for the project:

Immunisations (e.g. Hepatitis B)? Will need to do ICH-GCP training.

HO licence? No

Other?

24. Does Synthetic Torpor in rats confer protection against myocardial ischaemia/ reperfusion injury?

Primary supervisor: Prof Tony Pickering

Secondary supervisor (for day-to-day support): Dr Mike Ambler & Dr Timna Hitrec

School / Faculty: PPN, FLS

Summary of project (<300 words / ~ half-page):

Torpor is a naturally occurring hypothermic, hypometabolic protective state in which animals tolerate extremes of heart rate and breathing and their temperature falls to ambient, such that oxygen consumption falls to as little as 1% of active levels (Heldmaier, Ortmann, & Elvert, 2004). Recent advances in our understanding of the central control of torpor have enabled the induction of a torpor-like state in the rat, a species that does not naturally enter torpor, and establishes the principle that synthetic torpor might be achievable in humans (Takahashi et al., 2020).

Myocardial ischaemia, in which the blood supply the muscle of the heart is interrupted, is a major cause of death and disability worldwide. Hence, treatments that enable the heart to tolerate ischaemia are vitally important. We have some intriguing pilot data indicating that inducing a synthetic torpor-like state in the rat protects its heart from ischaemia.

This student will further investigate the potential for synthetic torpor to protect hearts from ischaemia/reperfusion injury, using an ex-vivo Langendorf preparation. Initial experiments will aim to confirm the pilot observations, with subsequent work investigating whether the hypothermia, the bradycardia, or both are required for the observed protection.

Techniques to be used:

The student will be trained in the methods of cardiac perfusion and measurement of ventricular performance pre & post ischaemia, as well as biochemical markers of injury and infarct size. They can also learn stereotaxic injection of viral vectors to the hypothalamus. Analysis will be conducted in Labview, Matlab, and standard statistical analysis packages.

3 Key references:

Heldmaier, G., Ortmann, S., & Elvert, R. (2004). Natural hypometabolism during hibernation and daily torpor in mammals. *Respiratory Physiology & Neurobiology*, *141*(3), 317–329.

Takahashi, T. M., Sunagawa, G. A., Soya, S., Abe, M., Sakurai, K., Ishikawa, K., . . . Sakurai, T. (2020). A discrete neuronal circuit induces a hibernation-like state in rodents. *Nature, 583*(7814), 109-114.

Ambler, M., Hitrec, T., Wilson, A., Cerri, M., & Pickering, A. (2022). Neurons in the Dorsomedial Hypothalamus Promote, Prolong, and Deepen Torpor in the Mouse. *J Neurosci, 42*(21), 4267-4277.

Specific requirements for the project:

Immunisations (e.g. Hepatitis B)? No

HO licence? Yes

Other?

Project title: Does Synthetic Torpor in rats confer protection against myocardial ischaemia/ reperfusion injury?

Primary supervisor: Prof Tony Pickering

Secondary supervisor (for day-to-day support): Dr Mike Ambler & Dr Timna Hitrec

School / Faculty: PPN, FLS

Summary of project (<300 words / ~ half-page):

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a torpor-like state in the rat, a species that does not naturally enter torpor, and establishes the principle that synthetic torpor might be achievable in humans (Takahashi et al., 2020).
Myocardial ischaemia, in which the blood supply the muscle of the heart is interrupted, is a major cause of death and disability worldwide. Hence, treatments that enable the heart to tolerate ischaemia are vitally important. We have some intriguing pilot data indicating that inducing a synthetic torpor-like state in the rat protects its heart from ischaemia.
This student will further investigate the potential for synthetic torpor to protect hearts from ischaemia/reperfusion injury, using an ex-vivo Langendorf preparation. Initial experiments will aim to confirm the pilot observations, with subsequent work investigating whether the hypothermia, the bradycardia, or both are required for the observed protection.

Techniques to be used:
The student will be trained in the methods of cardiac perfusion and measurement of ventricular performance pre & post ischaemia, as well as biochemical markers of injury and infarct size. They can also learn stereotaxic injection of viral vectors to the hypothalamus. Analysis will be conducted in Labview, Matlab, and standard statistical analysis packages.

3 Key references:
Heldmaier, G., Ortmann, S., & Elvert, R. (2004). Natural hypometabolism during hibernation and daily torpor in mammals. Respiratory Physiology & Neurobiology, 141(3), 317–329.
Takahashi, T. M., Sunagawa, G. A., Soya, S., Abe, M., Sakurai, K., Ishikawa, K., . . . Sakurai, T. (2020). A discrete neuronal circuit induces a hibernation-like state in rodents. Nature, 583(7814), 109-114.
Ambler, M., Hitrec, T., Wilson, A., Cerri, M., & Pickering, A. (2022). Neurons in the Dorsomedial Hypothalamus Promote, Prolong, and Deepen Torpor in the Mouse. J Neurosci, 42(21), 4267-4277.

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? No
HO licence? Yes
Other?

25. Improving the translatability of Laser-Evoked Potentials (LEPs) recorded in freely moving rats.

Primary supervisor: Prof Tony Pickering

Secondary supervisor (for day-to-day support): Dr Tony Blockeel, Dr Anna Sales

School / Faculty: PPN, FLS

Summary of project (<300 words / ~ half-page):

Laser stimulation is routinely used in human studies to evoke acute thermal pain in a temporally precise and reproducible manner. This is often coupled with EEG recordings of brain activity to objectively quantify the response of the central nervous system to noxious stimuli, with stimulus-locked EEG responses termed laser-evoked potentials (LEPs). To bridge the divide between these clinical studies and preclinical research we have recently employed similar techniques in freely moving rats. Initial experiments have shown that as in humans, the amplitude of LEPs in the rodent brain are correlated with stimulus intensity. We have also demonstrated that the latency of the LEP response falls into two distinct categories dependent on the signal transduction mechanisms in the periphery: fast responses are due to Aδ activation (rapidly conducting), while the more frequent slow responses and are due to C-fibre mediated responses (slowly conducting) (see Sales, Blockeel *et al* 2021).

Notably the observation that slow responses are the most prevalent response type in rodents is contrary to the situation in human volunteers, where fast Aδ-driven LEPs predominate. We hypothesise that this difference is due to the skin type stimulated in each species: in humans laser stimuli are typically applied to the hairy skin of the forearm, whereas in our rodent experiments glabrous (hair-free) skin of the hind paw was targeted. These two skin types express different profiles of thermally sensitive receptors and therefore may exhibit differential responses to laser stimulation.

The primary aim of this project is to obtain *in vivo* recordings of LEPs in rats following stimulation of both hairy and glabrous skin types to ascertain whether targeting hairy-skin in rodents leads to a more human-like and therefore translatable response. Additional aims of the project include investigating whether modulation of the laser characteristics (e.g. energy, beam width & duration) also affect the relative probabilities of Aδ vs C-fibre mediated responses. Again, the results of this secondary study will allow experimental parameters to be optimised for experiments testing novel analgesics.

Techniques to be used:

During the course of the project training will be provided in animal handling and recovery surgical procedures as well as assays of nociception. The project involves the use of wireless EEG recording systems and clinical-grade lasers. Data analysis will be performed in Matlab using pre-written analysis routines, with the option for students to develop a foundation in scientific programming

3 Key references:

1. Sales, A., Blockeel, A *et al.* (2021) Trial by trial, machine learning approach identifies temporally discrete Aδ- and C-fibre mediated laser evoked potentials that predict pain behaviour in rats. bioRxiv 2021.08.10.455801
2. Valeriani, M., Pazzaglia, C., Cruccu, G. & Truini, A. (2012) Clinical usefulness of laser evoked potentials. *Neurophysiol. Clin.* **42**, 345–53.
3. Xia, X.L., Peng, W.W., Iannetti, G.D., and Hu, L. (2016). Laser-evoked cortical responses in freely-moving rats reflect the activation of C-fibre afferent pathways. Neuroimage 128, 209-217.

Specific requirements for the project:

Immunisations (e.g. Hepatitis B)? No

HO licence? Yes

Other? No known allergies to animals or atopy.

Desk Based Projects

26. Development of Core Outcome Set for Deep Venous Insufficiency of the Lower Limb
Primary supervisor: Professor Robert Hinchliffe
Secondary supervisor (for day-to-day support): Mr Baris Ozdemir (Honorary Senior Lecturer)
School / Faculty: Bristol Centre for Surgical Research, Bristol Medical School, University of Bristol
Summary of project (<300 words / ~ half-page):

Summary of project

Background: Surgical treatment of venous disease of the lower limbs was until recently largely limited to removal or ablation of superficial varicose veins. Surgical innovation in minimally invasive stent placement has more recently allowed surgeons to successfully re-open blocked deep veins in the legs with the intention of preventing post thrombotic syndrome (PTS), a condition which is associated with significant impairment in quality of life due to leg pain, swelling and ulceration. Consequently, patients who have developed acute proximal (iliac veins / inferior vena cava) deep vein thrombosis (DVT) or chronically occluded deep veins due to previous proximal DVT are now routinely being offered stenting in many vascular centres rather than standard therapy, which comprises anti-coagulation and compression stockings.
The data to underpin the clinical effectiveness of treatments for deep venous disease remains weak and guidelines conflicting, in large part because outcome reporting in trials assessing the clinical effectiveness of therapeutic interventions is heterogeneous.[1,2] The heterogeneity of outcomes makes meaningful comparison between different therapeutic interventions difficult and suggests a need to improve outcome selection and reporting. A solution to this problem is the development of a core outcome set (COS) for deep venous disease. A COS represents the minimum outcomes that should be reported in research trials for a specific condition.[3] They have been widely accepted as part of robust trials methodology as their use allows meaningful comparison between separate trials for the same condition and includes both clinician and patient influenced outcomes. An iBSc student performed a systematic review and developed a long list of outcomes and was awarded the Richard Wood Prize for her work by the Vascular Society of Great Britain & Ireland.[4]

Aim: To develop a core outcome set for use in the reporting of clinical studies of people with chronic deep venous insufficiency of the lower limbs.

Project plan:
The long list of outcomes for consideration of inclusion in a core outcome set for assessing clinical trials in patients with chronic deep venous insufficiency of the lower limb will be generated from three sources.
i) A systematic review of reported outcomes in clinical studies of chronic deep venous insufficiency of the lower limb has been completed and submitted for publication.[4]
ii) Outcomes identified by an international steering committee.
iii) Semi-structured patient interviews.

The candidate will obtain research ethics committee approval using the integrated research application system for the patient interviews.

In the second phase a Delphi consensus questionnaire will be developed of using the standard COMET system. This will be followed by a Delphi consensus meeting to finalise the core outcomes for inclusion.[5]

Techniques to be used:
The core outcome set development will fulfil the requirements for the MRes in Health Sciences Research project. It is anticipated that the project will be considered for submission for publication in a surgical journal. During the project the student will learn Delphi consensus methodology and be exposed to qualitative interview techniques. They will receive guidance and training on scientific writing.

Key references:

1. Kakkos SK, Gohel M, Baekgaard N, Bauersachs R, Bellmunt-Montoya S, Black SA, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. Eur J Vasc Endovasc Surg. 2021 Jan;61(1):9-82. https://doi: 10.1016/j.ejvs.2020.09.023.

1. National Institute for Health and Care Excellence. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing (NG158) [Internet]. London: National Institute for Health and Care Excellence (UK); 2020 [cited 2020 Jun 5]. (National Institute for Health and Care Excellence: Clinical Guidelines). Available from: http://www.ncbi.nlm.nih.gov/books/NBK556698/

1. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Devane D, et al. (2016) Core Outcome Set-STAndards for Reporting: The COS-STAR Statement. PLoS Med 13(10): e1002148 doi:10.1371/journal.pmed.1002148

1. Eleanor McNally, Robert Hinchliffe, Baris Ozdemir, Sarah Rudd. A systematic review of reported outcomes in patients with chronic deep venous insufficiency of the lower limb. PROSPERO 2021 CRD42021236795 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021236795

1. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, Clarke M, Gargon E, Gorst S, Harman N, Kirkham JJ, McNair A, Prinsen CAC, Schmitt J, Terwee CB and Young B. The COMET Handbook: version 1.0 Trials 2017 18(Suppl 3):280 https://doi.org/10.1186/s13063-017-1978-4

Specific requirements for the project: None

27. Interventions and approaches to support physical activity of people with heart failure: a systematic review and contribution to the funded HAPPY Study

Primary supervisor: Dr Alyson Huntley

Secondary supervisor (additional support if needed): Dr Lorna Duncan

School / Faculty: PHS

Summary of project

Dr Alyson Huntley has been funded by NIHR RfPB to conduct the study Heart failure And Participation in Physical activitY (the HAPPY study) (May 2022-August 2023). This involves evidence synthesis, information gathering, and working with local clinicians, commissioners, logic model development with the aim to improve community heart failure services.

This MRes project would support this process and the student would both conduct their own publishable systematic review as well as be involved in the consultation process and logic model development by the HAPPY study.

The student will become part of the HAPPY study and will conduct a systematic review on the interventions and approaches to support physical activity of people with heart failure. This review will complement the qualitative evidence synthesis that will be conducted by the research team. Both reviews will be used in the consultation process to produce a logic model and guiding principles to feedback to commissioners of heart failure services in Bristol, and it is hoped also the South-West commissioning region.

The student will gain experience in all these methods above but will get hands training in systematic review methodology. The supervisors have significant experience in systematic review methodology and data analysis and both members of the HAPPY team. We also have a health psychologist, GP heart failure consultant, and three heart failure nurses on the team.

Techniques to be used:

Hands on experience of systematic review from inception to publication potentially meta-analysis of data. Experience of being involved in stakeholder consultation and production of a logic model for future intervention development/service improvement.

3 Key references:

1. Doukky R, Mangla A, Ibrahim Z et al. Impact of physical inactivity on mortality in patients with heart failure. Am J Cardiol 2016; 117: 1135– 1143.
1. Taylor CJ, Huntley AL, Burden J et al. Research priorities in advanced heart failure: James Lind alliance priority setting partnership. Open Heart 2020;7(1): e001258.
1. Harkness K, Spaling MA, Currie K et al. A systematic review of patient heart failure self-care strategies. J Cardiovasc Nurs 2015;30(2):121-35

Specific requirements for the project:

None

28. To determine the acceptability and usefulness of Breathing Space in helping people in crisis

Primary supervisor: Jonathan Banks, Research Fellow, NIHR ARC West and Population Health Sciences, 9th Floor, Whitefriars, Lewins Mead, Bristol, BS1 2NT. Email: Jon.Banks@Bristol.ac.uk

Secondary supervisor (for day-to-day support): Heather Brant, Senior Research Associate, NIHR ARC West and Population Health Sciences, 9th Floor, Whitefriars, Lewins Mead, Bristol, BS1 2NT. Email: Heather.Brant@Bristol.ac.uk

School / Faculty: Population Health Science

Summary of project (<300 words / ~ half-page):

The Bath & North East Somerset (B&NES) Breathing Space[1] was commissioned in 2019 and started in March 2020. In B&NES the Breathing Space offers a non-clinical safe space for people (from 18 years) at the point of, or experiencing, a mental health crisis. The service aims to provide community-based access to a calm, relaxing, and comfortable safe space out of hours, where people can spend quality time meeting and talking with practitioners one to one about their immediate issues and get help in putting together a package of support which meets their immediate and longer-term needs. Breathing spaces have the potential to support individuals at a community level with mental health issues and also reduce attendances at A&E.

This qualitative research study will examine,

- How the service is delivered from the perspectives of key staff
- Which components of the service were helpful in managing mental health and life crises
- Which components of the service could be improved and were there areas that the service could not provide support
- How service users accessed the service
- How service users compared the service to other support services they may have used
- How have the lives of service users changed since using the service

These objectives will enable us to understand how the breathing space works on an individual level and will complement quantitative research evaluating the effectiveness of the service in preventing hospital attendance or admission and will help policy makers and commissioners to shape the intervention going forward.

The supervisor is working with B&NES local authority and Bath Mind who are delivering the service, these organisations will support research access and recruitment.

The project will be written up as a report, a peer review publication and MRes thesis.

Techniques to be used:

- Semi-structured interviews with key staff to facilitate in-depth understanding of how the service is delivered, estimate n=3-4
- Semi-structured interviews with service users of breathing space, sample size to be determined by information power,[2] estimate n=15-20
- Purposive sampling will ensure a range of service users will be interviewed. Sampling criteria could include: age, gender, ethnicity and mode of contact (phone versus face to face).
- Interviews to be transcribed, anonymised and analysed thematically[3]
- The supervisory team will apply for UoB Faculty ethical approval before the MRes formally starts so that the research can start promptly

3 Key references:

1. https://www.bathmind.org.uk/our-services/evening-support-breathing-space/
    1. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. Qualitative Health Research. 2016;26(13):1753-1760. doi:10.1177/1049732315617444
    1. Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qualitative Research in Sport, Exercise and Health 2019;11(4):589-97. doi: 10.1080/2159676X.2019.1628806

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)?
HO licence?
Other?
An enhanced DBS check will be required.

29. Is breast pain associated with breast cancer? A systematic review

Primary supervisor: Shelley Potter

Secondary supervisor (for day-to-day support): TBC

School / Faculty: Bristol Medical School, Faculty of Health Sciences

Summary of project (<300 words / ~ half-page):

At present, patients with breast symptoms that may be suggestive of breast cancer are routinely referred to one stop breast clinics on 'two-week wait referral' pathways for urgent assessment. This pathway was established to promote the rapid diagnosis and treatment of breast cancer to improve outcomes for patients. Over the last 10 years, however, the numbers of referrals to NHS breast clinics have more than doubled. Over 700,000 women are referred each year in England and breast clinics are struggling to meet demand with only half of all units currently meeting 14-day referral targets. Despite these dramatic increases, the percentage of women diagnosed with breast cancer has only increased by 14% over the same period.

Patients with breast pain make up more than 40% of all breast clinic referrals as patients and primary care teams are concerned that breast pain may indicate an underlying breast cancer. Breast pain alone, in the absence of any other breast symptoms, however, is not a common symptom of breast cancer. A recent large single centre study of over 10,000 patients suggested that only 0.4% of women presenting with breast pain alone were subsequently diagnosed with breast cancer (1). A systematic review of 7 studies suggested the incidence of breast cancer in women with breast pain and a normal examination was between 1-2% but this only included women over 30 (2).

Women with breast pain may be more appropriately managed outside of the one stop breast cancer assessment clinic, but before service redesign can be proposed, the safety of this approach must be determined.

The aim of this project is to undertake a systematic review +/- meta-analysis to determine the incidence of breast cancer in women presenting with breast pain alone and how this varies with age to inform recommendations for the optimal management of this group.

Techniques to be used: Systematic review +/- meta-analysis

3 Key references:

1. Dave RV, Bromley H, Taxiarchi VP, et al No association between breast pain and breast cancer: a prospective cohort study of 10 830 symptomatic women presenting to a breast cancer diagnostic clinic. Br J Gen Pract. 2021 Dec 13:BJGP.2021.0475. doi: 10.3399/BJGP.2021.0475

1. Martín-Díaz M, Maes-Carballo M, Khan KS, Bueno-Cavanillas A. To image or not in noncyclic breast pain? A systematic review. Curr Opin Obstet Gynecol. 2017 Dec;29(6):404-412. doi: 10.1097/GCO.0000000000000407.

1. Walker S, Hyde C, Hamilton W. Risk of breast cancer in symptomatic women in primary care: a case–control study using electronic records British Journal of General Practice 2014; 64 (629): e788-e793. DOI: https://doi.org/10.3399/bjgp14X682873

Specific requirements for the project: None

30. Supporting conversations with young people about their online activities and mental health – a university-based pilot of Good Practice Indicators.

Primary supervisor: Dr Lucy Biddle

Secondary supervisor (for day-to-day support): Dr Myles-Jay Linton

School / Faculty: Bristol Medical School, Faculty of Health Sciences

Summary of project (<300 words / ~ half-page):

The impact of social media and other online activities on young people's mental health has caused concern among clinicians and within educational establishments such as universities. Particular areas of concern include possible impacts on body image, disordered eating, sleep-disturbance, socioemotional functioning and self-harm.

The Royal College of Psychiatrists have suggested that practitioners who support young people's mental health should inquire about online behaviour during consultations since this may allow them to contribute to online safeguarding and enable them to detect risk. However, how such conversations should take place is not well-understood. Recent research conducted at Bristol University found that 93% of mental health practitioners surveyed (n=98) have no protocol for discussing online activity with young people, 71% expressed a wish for training or guidance, and only 54% covered this topic routinely during mental health consultations. Meanwhile qualitative work with young people revealed a tendency for young people to feel stigmatised or blamed for 'bad online behaviour' if conversations are not conducted in an appropriate or supportive manner.

In response to these findings, we used Delphi (consensus) methods to develop a set of good practice indicators (GPIs) for mental health practitioners to support them to conduct effective, safe and acceptable conversations with young people about their online activities (submitted). The Delphi was based upon consensus across two panels - clinical mental health practitioners and young people with lived experience of mental health problems – and derived GPIs covering the key domains of 'when and who' a practitioners should ask about online activities, 'how' they should do this, 'what' they should ask and how they should 'respond'.

The aim of this project is to pilot our GPIs and explore their applicability across a range of university support service settings. Specifically, the project will: i) explore the utility and transferability of our GPIs within a university setting by obtaining the views and experiences of practitioners who provide wellbeing/ mental health support to students at Bristol and have used these in their practice; ii) gather university practitioners' recommendations for improving/ refining our GPIs.

Techniques to be used:

This is a qualitative project. Prior to the project, practitioners in University Wellbeing services, Residential life and other settings will be introduced to our good practice indicators via a workshop session and online resource. They will then be invited to use these in their interactions with students. The project will involve conducting and analysing focus group discussions and/ or 'think aloud' interviews with practitioners about their experiences of using the guidance, perceptions of effectiveness and ideas for improvement. Groups/ interviews will be semi-structured, using a topic guide and open-ended questioning. Data will be audio-recorded, transcribed and analysed thematically.

3 Key references:

Abi-Jaoude E, Naylor KT, Pignatiello A. Smartphones, social media use and youth mental health. Canadian Medical Association Journal. 2020;192(6): E136-E141.

Hollis C, Livingstone S, Sonuga-Barke E. The role of digital technology in children and young people's mental health–a triple-edged sword?. Journal of Child Psychology and Psychiatry. 2020 Aug;61(8):837-41. Kim B, White K. How can health professionals enhance interpersonal communication with adolescents and young adults to improve health care outcomes?: systematic literature review. International Journal of Adolescence and Youth. 2018 Apr 3;23(2):198-218.
Specific requirements for the project: Immunisations (e.g. Hepatitis B)? No HO licence? No Other? No

31. Should pain be included in the Patient Orientated Eczema Measure?

Primary supervisor: Matthew Ridd

Secondary supervisor: Stepanie MacNeill

School / Faculty: Population Health Science

Summary of project:

Atopic eczema/dermatitis ("eczema") is a common (1 in 5 children) long-term condition. It is characterised by dry and inflamed itchy skin, and it has a greater impact on quality of life than diabetes and cystic fibrosis. In the UK, around 14% of GP consultations are for skin problems, and most children with eczema are managed by their GP.
It is recommended that the seven item Patient Orientated Eczema Measure is included in all trials of eczema treatments, as a core outcome measure of eczema symptoms. However, patients have voiced concern that pain, as an important symptom, is not included in this scale.
Using data already collected, the student will determine whether an eighth item, asking about pain, improves the validity of the scale. The student will analyse completion and distribution of responses to the pain scale question and compare the distributions of the existing seven and proposed eight item POEM scales.

Techniques to be used:

Secondary analysis of data from the Trial of Eczema allergy Screening Tests study (https://www.bristol.ac.uk/eczema-allergy-study), using STATA.

Key references:

Spuls PI, Gerbens LA, Simpson E, Apfelbacher CJ, Chalmers JR, Thomas KS, Prinsen CA, von Kobyletzki LB, Singh JA, Williams HC, Schmitt J. POEM a core instrument to measure symptoms in clinical trials. Br J Dermatol. 2017 Apr;176(4):979-984. DOI: 10.1111\bjd.15179

Chalmers J, Simpson E, Apfelbacher C et al. Report from the fourth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). Br J Dermatol 2016; 175: 69-79. DOI: 10.1111/bjd.14773

Ridd MJ, Webb D, Roberts K, Santer M, Chalmers JR, Gilbertson A, et al. Test-guided dietary management of eczema in children: A randomized controlled feasibility trial (TEST). Clin Exp Allergy. 2021;(December 2020) :452–62. DOI: 10.1111/cea.13816

Specific requirements for the project: None.

32. Understanding the relationships between radiographic osteoarthritis at the knee and hip joints in 40,000 UK Biobank participants

Primary supervisor: Dr Monika Frysz

Secondary supervisor (for day-to-day support): Prof Jon Tobias, Dr Benjamin Faber

School / Faculty: THS

Summary of project (<300 words / ~ half-page):

Osteoarthritis (OA) is a degenerative condition of the joints that is commonly seen at the knee and hip. End-stage disease is treated with total joint replacement (TJR) accounting for the majority of the £10 billion spent on musculoskeletal services in the UK annually[1]. OA is a complex multifactorial disease caused by an interplay between systemic influences and local biomechanical risk factors[2]. It is thought that OA of the knee and hip may be associated with different risk factors and should be regarded as unique diseases, however it is unclear to what extent co-existing OA at weight-bearing joints is part of a common process predicted by joint risk factors.

Our recent work in UK Biobank conducted as part of the AUGMENT study (PI Prof Jon Tobias) has shown that radiographic hip OA (rHOA) (based on a novel classification of osteophytes and joint space narrowing measured on dual-energy X-ray absorptiometry (DXA) scans) was associated with hip pain and was strongly predictive of total hip replacement (THR)[3].
This work initially focused on available 40,000 left hip DXA scans, however right hip, and bilateral knee DXA scans are also available. We are currently in the process of automatically deriving radiographic features of OA on the remaining knee and hip DXAs with results from 160,000 scans expected by the end of Summer 2022.

The project we are proposing would harness this data to achieve the following aims:

1. Describe the prevalence of co-existing radiographic OA (rOA) and its individual features at the knee and hip joint in the UK Biobank study
1. Explore sex differences and other risk factors (i.e., height and BMI) in rOA at the knee and hip
1. Explore relative associations between knee and hip rOA, with clinical outcomes such as joint pain, hospital diagnosed OA and TJR

Techniques to be used:

1. Managing and cleaning large data sets
1. Experience with using registry data (such as Hospital Episode Statistics)
1. How to use STATA software to perform large scale observational analyses
1. Basic statistics: descriptive analyses, regression analyses (linear, logistics)
1. Drafting an abstract +/- paper. (Including using referencing software, EndNote)

3 Key references:

1. England N. https://www.england.nhs.uk/blog/tackling-the-elephant-in-the-room/. 2018
2. Calce SE, Kurki HK, Weston DA, et al. The relationship of age, activity, and body size on osteoarthritis in weight-bearing skeletal regions. *Int J Paleopathol* 2018;22:45-53. doi: 10.1016/j.ijpp.2018.04.001 [published Online First: 2018/04/22]
3. Faber BG, Ebsim R, Saunders FR, et al. A novel semi-automated classifier of hip osteoarthritis on DXA images shows expected relationships with clinical outcomes in UK Biobank. *Rheumatology (Oxford)* 2021 doi: 10.1093/rheumatology/keab927 [published Online First: 2021/12/18]

Specific requirements for the project: Unlimited data internet connection if working from home. The data download requirements can be high for this type of analysis.

33. Previous stillbirth or miscarriage as a predictor of adverse maternal and neonatal outcomes in a subsequent pregnancy

Primary supervisors (Day to Day): Dr Danya Bakhbakhi & Dr Kate Birchenall

Secondary supervisors: Prof Abigail Fraser & Dr Christy Burden

School / Faculty: Faculty of Health Sciences

Summary of project (<300 words / ~ half-page):

Background

We know that within a year over 50% of parents will become pregnant again following a prenatal loss such as a miscarriage or stillbirth. Parents would like to be counselled correctly about the chance of a prenatal loss recurrence and any other possible negative outcomes, so they can be prepared in a subsequent pregnancy. Although some literature exists about the risk of a prenatal loss recurrence, there is varied evidence about the risk of other pregnancy outcomes such as, preterm birth, growth restriction, pre-eclampsia, gestational diabetes, operative birth (caesarean section or instrumental delivery) or neonatal complications. Parents would like to know their chances of having a normal live birth. No previous studies analysing adverse subsequent pregnancy outcomes/stillbirth recurrence after stillbirth have been conducted using cohort data from England. Furthermore, very few studies have adjusted for important confounding variables such as BMI and ethnicity.

Clinical relevance
This study will better inform healthcare professionals, so they provide correct information about risks to women in a subsequent pregnancy after stillbirth or miscarriage. This study will aim to ultimately improve management of care in a subsequent pregnancy

- Aim
  This study aims to examine the association of a previous prenatal loss and the development of adverse pregnancy outcomes in a subsequent pregnancy.

Objectives: To estimate

- The association of a miscarriage and the development of adverse maternal and neonatal outcomes in a subsequent pregnancy;
- The association of a stillbirth and the development of adverse maternal and neonatal outcomes in a subsequent pregnancy
- The likelihood of a normal live birth following a miscarriage or stillbirth;
- If maternal age, BMI, social class, ethnicity, education, smoking and inter-pregnancy interval affect the risk of developing an adverse maternal or neonatal outcomes following a stillbirth or miscarriage.
- The influence of obstetric delivery management in a subsequent pregnancy on maternal and neonatal outcomes

Techniques to be used:
ALSPAC collected data on previous stillbirth and miscarriage in their pregnancy cohort.
Demographic and obstetric characteristics of women with previous prenatal loss will be analysed e.g. age, ethnicity, socio-economic status
Adverse pregnancy outcomes in the next pregnancy will be analysed: stillbirth or miscarriage recurrence; live birth rate; pre-eclampsia; gestational diabetes; fetal growth restriction; placental abruption; placenta praevia; antepartum haemorrhage; malpresentation; induction of labour;

instrumental birth; emergency or elective caesarean section; preterm birth; neonatal death; birth weight; Apgar score and neonatal intensive care admission.
Stratification according to gestational age of stillbirth recurrence
Statistical methods will include univariate and multivariate analysis, logistic regression modelling, calculation of odds ratios, adjustments for confounders with support from a medical statistician
Analysis of influence of obstetric management (e.g induction, mode of delivery and antenatal encounters) on subsequent pregnancy perinatal survival outcome e.g stillbirth and neonatal death

Triangulation with Born in Bradford data and the Norwegian Mother, Father and Child Cohort Study may be possible.

3 Key references:

Nijkamp, J.W., Ravelli, A.C.J., Groen, H. et al. Stillbirth and neonatal mortality in a subsequent pregnancy following stillbirth: a population-based cohort study. BMC Pregnancy Childbirth 22, 11 (2022). https://doi.org/10.1186/s12884-021-04355-7

Lamont K, Scott N W, Jones G T, Bhattacharya S. Risk of recurrent stillbirth: systematic review and meta-analysis BMJ 2015; 350 :h3080 doi:10.1136/bmj.h3080

Black, M., Shetty, A. and Bhattacharya, S. (2008), Obstetric outcomes subsequent to intrauterine death in the first pregnancy. BJOG: An International Journal of Obstetrics & Gynaecology, 115: 269-274. https://doi.org/10.1111/j.1471-0528.2007.01562.x

Specific requirements for the project:
Access to ALSPAC data

34. Opioid prescribing rates in NHS GP surgeries employing clinicians with additional training in acupuncture, or other complementary or alternative therapies

Primary supervisor: Dr Lorna Duncan

Secondary supervisor (additional support if needed): Dr Tanzeela Khalid

School / Faculty: Population Health Sciences

Summary of project:

Chronic non-cancer pain has been shown to affect between one-third and one-half of adults in the UK and is a presenting condition in around 20% of primary care consultations. Related opioid prescribing more than doubled between 1998 and 2018 in Primary Care in England.[1] However, with a lack of evidence for its long-term effectiveness, and concerns about the safety of prescription opioid use, NICE does not recommend such management and other, safer treatment options are necessary. Acupuncture, a popular adjunct therapy in England, is one such option used commonly to treat chronic pain. Recently revised NICE guidelines for chronic primary pain management (7th April 2021) include the recommendation of a course of acupuncture by a suitably qualified healthcare professional.[2]

Previously, using retrospective cross-sectional analysis, we showed that antibiotic prescribing rates in NHS GP surgeries employing GPs with additional training in complementary or alternative medicine (CAM) were lower than those in other GP surgeries across England.[3] It is possible that opioid prescribing rates also differ in such surgeries.

In this project, similar methodology to that employed in the above study will be used to determine differences in opioid prescribing rates between conventional NHS GP surgeries and those employing staff additionally trained in acupuncture, or other complementary or alternative therapies. This methodology is outlined in the following section.

Findings will be presented at a meeting or focus group to which members of the local Chronic Pain Health Integration Team, a local CCG, and members of our PPI team with experience of chronic pain, will be invited. Their feedback will be used to prepare the study findings for publication.

Techniques to be used:

- Registers of the British Medical Acupuncture Society and the British Acupuncture Council will be used to identify GPs and other primary care staff trained in acupuncture. Registers of staff trained in the remaining 'big 5' CAM therapies as defined in a House of Lords report into CAM (chiropractic, osteopathy, herbal medicine and homoeopathy) will also be searched if time permits.
- Currently active, working links to NHS GP surgeries will be checked for all primary care staff identified in this way.
- Opioid prescribing data will then be obtained for each practice employing these staff, and compared with national data obtained from NHS Digital. Possible confounders will be assessed and statistical analyses used to evaluate associations between 'CAM GP' practices and opioid prescribing.

3 Key references:

1. Curtis, H. *et al* (2019): Opioid prescribing trends and geographical variation in England, 1998–2018: a retrospective database study. Lancet Psychiatry 6:140-150
1. https://www.nice.org.uk/guidance/ng193/chapter/Recommendations#managing-chronic-primary-pain
1. Van der Werf, E.T., Duncan, L.J., von Flotow, P., and Baars, E.W. (2018): Do NHS GP surgeries employing GPs additionally trained in integrative or complementary medicine have lower antibiotic prescribing rates? BMJ Open 8: e020488

Specific requirements for the project:

None

35. Understanding unexplained general practice prescribing variation

Primary supervisor: Dr Lorna Duncan

Secondary supervisor (additional support if needed): Dr Tanzeela Khalid

School / Faculty: Population Health Sciences

Summary of project:

It is estimated that in English primary care, where most NHS prescribing occurs, at least 10% of the prescriptions issued in 2019/20 may have been unnecessary, and potentially harmful. Overprescribing, which occurs when people are given medicines they don't need or want, or where their harms outweigh their benefits, is a complex multi-factorial issue involving regulatory and organisational factors, in addition to the views, experience and knowledge of both prescribers and patients.[1] Large variations in prescribing rates exist between GP practices in England.

In September 2021, the Department for Health and Social Care published its plan to reduce medicines overprescribing, with overarching aims to reduce the incidence of adverse events, sub-optimal polypharmacy and waste; and to promote person-centred care, financial savings and carbon net zero targets.[2]

This project is part of an investigation into the factors impacting on current unexplained differences in GP practice prescribing rates. It will consider regulatory and patient-related factors which may be influencing prescribing decisions through the use of Freedom of Information requests[3] to the 42 Integrated Care Systems co-ordinating health and care services across England, and an online survey of the public. It may also be possible for the student to assist with other aspects of the broader study (which includes analysis of organisational and prescriber-level data, and cross-sectional analysis of prescribing data).

Project findings will be written up as two reports. These findings will then be incorporated into a mixed methods paper of the larger study for publication in a peer-reviewed journal. Preparation of an infographic(s) for patients and/or other stakeholders may also be possible from this project.

Techniques to be used:

- Local policies, initiatives and incentives relating to the reduction of over-prescribing in general practice will be identified through the submission of freedom of information requests to the 42 Integrated Care Systems in England. Relevant data will be extracted into a spreadsheet and thematic analysis of its potential impacts on general practice prescribing will be made, including identification of variations across the country.
- An online survey will also be developed using JISC online surveys and made available to consider public understanding and perspectives on medicines overuse, and the potential impacts of this on health and the environment in terms of waste and greenhouse gas emissions. Focus groups with patients may also be held to ascertain the perspectives of patient without internet access.
- Focus group and survey data will be analysed using descriptive statistics and thematic analysis to identify barriers and enablers to optimum prescribing, and possible interactions.

3 Key references:

1. Carter M, Chapman S, Watson MC. Multiplicity and complexity: a qualitative exploration of influences on prescribing in UK general practice. BMJ Open 2021;11(1): e041460.
2. Department of Health & Social Care. Good for you, good for us, good for everybody. Sept 2021. https://www.gov.uk/government/publications/national-overprescribing-review-report
3. Duncan LJ, Cheng KFD. Modifications to the delivery of NHS face-to-face general practice consultations during the COVID-19 pandemic in England. F1000Res 2021;10:261.

Specific requirements for the project:
None

36. Non-invasive imaging of the eye to predict Alzheimer's disease

Primary supervisor:
Dr Denize Atan, Consultant Senior Lecturer in Neuro-Ophthalmology, University of Bristol

Secondary supervisor (for day-to-day support):
Dr EL Anderson, post-doctoral research fellow, MRC Integrative Epidemiology Unit (IEU), University of Bristol
Prof K Tilling, Professor of Medical Statistics, Population Health Sciences, Bristol Medical School.
Prof P Kehoe, Gestetner Professor of Translational Dementia Research, Institute of Clinical Neurosciences
Prof George Davey Smith, Professor of Clinical Epidemiology, MRC IEU

School / Faculty: Translational Health Sciences, Bristol Medical School, Faculty of Health Sciences

Summary of project (<300 words / ~ half-page):
Alzheimer's Disease (AD) is an increasing global health burden. Several genetic, health and lifestyle factors are associated with increased AD risk and it is estimated that ~1/3 AD cases are attributable to modifiable lifestyle factors. Given the long prodrome of AD of up to 20 years, identifying high risk individuals for drug trials and lifestyle changes to prevent the onset of disease may be the best strategy to combat the disease; however, screening programmes, e.g., based on MRI scans, are currently prohibited by their cost, impracticality, and limited availability.
AD is associated with pathological changes in the retina and there is now exciting evidence that retinal imaging using optical coherence tomography (OCT) scans may be a rapid low-cost and non-invasive alternative to screening for AD, particularly since OCT imaging is now available at most optician practices.
Our hypothesis is that OCT is a sensitive, objective, and quantitative method to assess AD risk. Our aim is to determine the genetic, environmental, and lifestyle factors which increase the risk of OCT changes typically associated with AD and neurodegeneration of the brain.

Techniques to be used:

UK Biobank is a UK population cohort study of 502,656 people aged 40-69 years at recruitment, of whom 133668 had an eye exam and 87633 had OCT scans. Given the long prodrome of AD and the 6.5% prevalence of AD among people >65 years, we anticipate that ~31,000 Biobank participants are currently in the prodrome of AD (~1700 have already been diagnosed with AD).
We have obtained UK Biobank data on participant genotypes, physical and cognitive assessments, demographic factors, education, job, lifestyle, environmental exposures, and medical history as well as image-derived phenotypes (IDPs) taken from OCT and MRI scans. Using this data, we will test the statistical associations and causal effects of genetic (e.g., APOE), health (e.g., diabetes, hypertension, BMI), lifestyle and environmental exposures (e.g., smoking) on these IDPs using standard univariate and multivariate statistical analysis methods and Mendelian Randomization (MR). Additional hypothesis-free analyses using MR-base and machine learning algorithms will be used to identify other exposures in UK Biobank linked to neurodegenerative IDPs as the outcomes.

3 Key references:

1. Larsson SC, et al. Modifiable pathways in Alzheimer's disease. BMJ 2017.
1. Ko F, et al. Association of Retinal Nerve Fiber Layer Thinning With Current and Future Cognitive Decline. JAMA Neurol 2018.
1. Mutlu U, et al. Retinal neurodegeneration and brain MRI markers. Neurobiol Aging 2017.

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? No
HO licence? No
Other? Online training in Information Governance

37. Brain tumour diagnoses by eye health specialists: is there evidence of a Barker effect?

Primary supervisor:
Dr Denize Atan, Consultant Senior Lecturer in Neuro-Ophthalmology, University of Bristol

Secondary supervisor (for day-to-day support):
Dr Tim Jones, Senior Research Associate & former cancer analyst at Public Health England, Applied Research Collaboration-West
Dr Teresa Redaniel, Data Lead, Applied Research Collaboration-West
Dr Beth Stuart, Medical Statistician, University of Southampton
Dr Samiel Merriel, GP with expertise in early cancer diagnosis and prevention, University of Exeter

School / Faculty: Translational Health Sciences, Bristol Medical School, Faculty of Health Sciences

Summary of project (<300 words / ~ half-page):
Brain tumours affect 8 per 100,000 people in the UK each year. Brain tumours often affect vision before causing any other symptoms. Unless diagnosed early, many people with brain tumours will die or suffer long-term disabilities, like permanent sight loss.

In 2016, an 8-year-old boy called Vincent Barker was in the news. During a routine sight test, his optometrist, Honey Rose, failed to detect optic nerve swelling at the back of his eyes - a sign indicating raised intracranial pressure. He died soon afterwards. As a result, Honey Rose was convicted for gross negligence manslaughter.

Since the widespread media coverage of the Rose/Barker case, optometrists have been referring more people to hospital over concerns they might have optic nerve swelling. Because of this, we think more patients with brain tumours are diagnosed earlier and more frequently by eye specialists than 5 years ago.

The primary aim of this project is to find out the number of people diagnosed with brain tumours every year between 2013 to 2018 in England and the proportion who were diagnosed by eye specialists before and after the Rose/Barker case in 2016.

Our secondary aim is to determine whether patients with brain tumours were diagnosed earlier by hospital eye specialists compared with other routes-to-diagnosis and whether they lived longer and had better treatment outcomes as a result.

Techniques to be used:
Public Health England and the National Cancer Registry and Analysis Service (NCRAS) routinely collect data on everyone diagnosed with benign and malignant brain tumours in England. We have National Research Ethics Committee approval to access NCRAS data linked to Hospital Episode Statistics; and we have obtained the data on all new cases of benign and malignant brain tumours diagnosed between 2013 and 2018.

Trends in the data will be investigated in the 3 years before and after exposure to the widespread media coverage Rose/Barker case in 2016 by generalised linear regression techniques. We will determine the change in:

i. Adjusted odds ratios for the number of brain tumours diagnosed via hospital eye services
i. Time to diagnosis
i. WHO tumour grade at diagnosis
i. Cancer stage at diagnosis
i. Time between diagnosis and treatment
i. Mortality

Age, sex, ethnicity, geographical location, deprivation index, and smoking history will be used as covariates in these analyses.
3 Key references: 1. Poostchi A, et al. Spike in neuroimaging requests following the conviction of the optometrist Honey Rose. Eye 2018. 1. Elliss-Brookes L, et al. Routes to diagnosis for cancer. B J Cancer 2012. 1. Koo MM, et al. Presenting symptoms of cancer and stage at diagnosis. Lancet Oncol 2020.
Specific requirements for the project: Immunisations (e.g. Hepatitis B)? No HO licence? No Other? Online training in Information Governance

38. Assessing the impact of published guidelines for reporting pilot trials; application in the field of physical activity

Primary supervisor (and day-to-day support): Sam Leary

Secondary supervisors: Kate Tilling

School / Faculty: Health Sciences

Summary of project (<300 words / ~ half-page):

Pilot trials play a crucial role in the design of randomised controlled trials (RCT). They provide an opportunity to identify and address feasibility issues prior to the main RCT, thus avoiding the wasted resources and unnecessary participant burden that can incur from poorly designed RCTs. Since the early 2000s, a number of publications in the medical literature have highlighted inadequacies in the design, conduct and reporting of pilot trials. This work led to two notable publications in 2016: a conceptual framework for defining feasibility studies (Eldridge, Lancaster et al.) and an extension to the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement to include pilot trials (Eldridge, Chan et al.). It was hoped that these publications would educate researchers, leading to better use of pilot trials and thus more rigorously planned and informed RCTs. The impact of these publications requires evaluation in a variety of fields.

We undertook a review of the reporting of pilot trials published before 2016 (i.e. pre-CONSORT extension) in physical activity journals (Horne et al. 2018), and found the standard to be low across most reviewed articles. The aim of this project is to assess the impact of the CONSORT extension in the field of physical activity.

Objectives –

1. Undertake a follow-up review using articles published after the CONSORT extension, based on the same methods as the 2016 review such as presenting descriptive statistics (Horne et al.)
2. Within these articles, explore factors associated with better reporting, for example year and country of publication, number of centres, type of funding, and journal endorsement of CONSORT, using a statistical analysis method such as Poisson regression.
3. Identify a collection of articles reporting full-scale RCTs, and look backwards to find whether appropriate pilot work was published, and if so, how it influenced the design of the full-scale RCT.

Techniques to be used:

Thorough review of relevant literature through comparison with published guidelines
Identification of relevant RCTs and evaluation of any available pilot work
Analysis of data using Stata, including generation of summary statistics and performing regression analysis
Contribution to writing up the results for publication in a peer-reviewed journal.

3 Key references:

1. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. PLoS One. 2016;11:3. 6.
2. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355:i5239.
3. Horne E, Leary G, Matson R, Cooper A, Ness A, Leary S. Pilot trials in physical activity journals: a review of reporting and editorial policy. Pilot and Feasibility Studies. 2018;4-125.

Specific requirements for the project:

An interest in improving the standard of reporting of research studies, learning a statistics package and performing secondary data analysis is required to undertake this project.

Data Based Projects

39. Early life exposures and antibody status in children with Down's Syndrome

Primary supervisor (and day-to-day support): Sam Leary

Secondary supervisors: Georgina Williams and Julian Hamilton-Shield

School / Faculty: Health Sciences

Summary of project (<300 words / ~ half-page):

Children with Down's syndrome (DS) are at increased risk of autoimmune conditions including diabetes, coeliac and thyroid disease (Gillespie at al. 2006). Autoimmune diabetes occurs earlier in children with DS compared with the general population, despite decreased levels of the typical genetic susceptibility factors (Aitken et al. 2013). Therefore alternative predictors of the development of autoimmunity in children with DS need to be identified.

The Feeding and Autoimmunity in Down Syndrome Evaluation Study (FADES) is a UK wide cohort study for which infants with DS are recruited under eight months of age. Recruitment began in September 2014, and parents complete detailed feeding and medical questionnaires at recruitment, seven months, 12 months and yearly thereafter. To date there are just over 100 participants in the study.

The aim of this project is to investigate which modifiable early life exposures are associated with antibody status in the FADES cohort. Potential exposures could include, but are not limited to, the early introduction of formula (containing cow's milk protein, children with DS have higher levels of Bovine albumin antibodies (Brown et al. 2012)), early weaning onto solid food which may relate to early gluten exposure, and also antibiotic use in the first year of life which influences the developing gut microbiome, itself linked to a range of adverse health conditions including autoimmunity.

Objectives –

1. Summarise the current literature on modifiable early life exposures and developing autoimmunity of islet cell, small gut and thyroid gland in children
1. Identify which early life exposures recorded in the FADES cohort will be investigated
1. Describe these exposures, comparing with the general population where possible
1. Assess and compare the associations between each exposure and antibody status.

Techniques to be used:

Review of existing literature
Management of a dataset, including selecting existing variables, creating new variables
Analysis of data using Stata, including generation of summary statistics, performing regression analyses
Application of epidemiology concepts to interpret findings
Contribution to writing up the results for publication in a peer-reviewed journal.

3 Key references:

Gillespie KM, Dix RJ, Williams AJK, Newton R, Robinson ZF, Bingley PJ, Gale EAM, Shield JPH. Increased islet autoimmunity in children with Down's syndrome. Diabetes 2006;55(11):3185-8.

Aitken RJ, Mehers KL, Williams AJ, Brown J, Bingley PJ, Holl RW, Rohrer TP, Schober E, Abdul-Rasoul MM, Shield JPH, Gillespie KM. Early-onset diabetes in children with Down's syndrome is autoimmune. Diabetes Care 2013;36(5):1181-5.

Brown J, Aitken J, Newton R, Uibo R, Bingley P, Shield J, Williams A, Gillespie K. Increased levels of low affinity anti-BSA antibodies in individuals with Down's syndrome at genetic risk for autoimmunity: Immunity 2012: W20. 006;137 (https://onlinelibrary.wiley.com/doi/pdf/10.1111/imm.12001)

Specific requirements for the project:

This is a clinically relevant project that has the potential to benefit patients, but does not involve any data collection. An interest in learning a statistics package and performing secondary data analysis is required to undertake this project.

40. Investigating the eating behaviour and nutrition of patients with Idiopathic Intracranial Hypertension

Primary supervisor:
Dr Denize Atan, Consultant Senior Lecturer in Neuro-Ophthalmology, University of Bristol

Secondary supervisor (for day-to-day support):
Dr Elanor Hinton, Senior Research Associate, Clinical Research and Imaging Centre (CRIC)
Professor Julian Hamilton Shield, Professor in Diabetes and Metabolic Endocrinology, UHB Education Centre

School / Faculty: Translational Health Sciences, Bristol Medical School, Faculty of Health Sciences

Summary of project (<300 words / ~ half-page):

Idiopathic Intracranial Hypertension (IIH) is a neurological disorder characterized by raised intracranial pressure (ICP) of unknown cause. Although IIH is not life-threatening, the condition causes significant disability from visual loss and headaches.

IIH is strongly associated with obesity and the prevalence of IIH is rising in tandem with the rising prevalence of obesity in Western countries. Hence, IIH management usually involves behavioural changes, medications and/or bariatric surgery to promote weight loss. But as obesogenic diets are high in calories and nutrient-poor, there may be associated nutritional deficiencies that contribute to the clinical presentation of IIH that may be exacerbated by dietary restrictions.

The aim of this proposal is to investigate the eating behaviour and nutrition of IIH patients and their clinical response to treatment with nutritional supplements. The student will analyse the eating behaviour and nutrition of IIH patients compared with healthy age-, sex- and BMI- matched controls, using a range of validated questionnaires available online in REDCap as well as an online food choice task, an online food-related response inhibition task and an online 24-hour food recall diary (Intake 24). We shall also investigate how patients with IIH respond to treatment with nutritional supplements. Magnetic resonance imaging (MRI) scans will be performed on a subset of IIH patients at the CUBRIC in Cardiff that will include arterial spin labelling, phase contrast and fMRI to investigate CSF dynamics, cerebral blood flow and eating behaviour.

Hypothesis:
Our hypothesis is that IIH is exacerbated by nutritional deficiencies associated with the obesogenic diet.

The primary objectives are:
1. To compare the eating behaviour and nutrition of IIH patients versus healthy controls
2. To investigate the effects of nutritional supplements on the symptoms and signs of patients with IIH

The secondary objectives are:
1. To investigate CSF dynamics in IIH patients
2. To investigate cerebral blood flow in IIH patients
3. To investigate eating behaviour in IIH patients with fMRI

Techniques to be used:
The MRes student will join the Nutrition theme of the Bristol Biomedical Research Centre. Patients with IIH will be identified and recruited from the clinics of four neuro-ophthalmology consultants at Bristol Eye Hospital and North Bristol Trust (there are ~110-130 adult IIH patients under current follow-up and ~2 new patients diagnosed per month).

Inclusion criteria:
1. Diagnosis of IIH meeting modified Dandy criteria

2. Age range: 18 to 45 years

Exclusion criteria:

1. Subjects who have undergone surgical treatment for IIH.
2. Subjects with MRI contraindications

A power calculation was performed which determined a minimum of 26 participants per group (IIH vs control) is required to detect a two tailed difference between two independent means (given alpha = 0.05, power of 80%).

Analyses will include comparisons between IIH patients and healthy matched controls in their responses to:

1. Eating Disorder Examination Questionnaire 6.0
2. Adult Eating Behaviour Questionnaire
3. Taste preference questionnaire
4. Visual functioning questionnaire + 10 item neuro-ophthalmology supplement
5. SF36 Quality of Life questionnaire
6. Food choice task
7. Food-related No-go/Go task (response inhibition)
8. Macronutrient and micronutrient intake recorded by Food Intake 24.

3 Key references:

1. Burkett JG, Ailani J. An Up to Date Review of Pseudotumor Cerebri Syndrome. *Curr Neurol Neurosci Rep* 2018; 18(6): 33.
1. Hinton EC, Birch LA, Barton J, et al. Using neuroimaging to investigate the impact of Mandolean® training in young people with obesity: a pilot randomised controlled trial. *BMC Pediatrics* 2018 Nov 22;18(1):366.
1. Reynolds G, Epps S, Huntley A, Atan D. Idiopathic intracranial hypertension - why we should screen patients for micronutrient deficiencies: a systematic review. 2022 [in preparation].

Specific requirements for the project:

Immunisations (e.g. Hepatitis B)? Hep B

HO licence? No

Other? Honorary contract with NBT and UHB. Online training in Good Clinical Practice

41. The Impact on Memory of Epilepsy – the TIME Study

Primary supervisor:
Dr Denize Atan, Consultant Senior Lecturer in Neuro-Ophthalmology, University of Bristol

Secondary supervisor (for day-to-day support):
Dr Kasia Sieradzan, Consultant Neurologist, Southmead Hospital, Bristol
Dr Jiaxiang Zhang, Senior Lecturer, Cardiff University Brain Research Imaging Centre, Cardiff
Dr Helen Thorburn, Clinical Psychologist, Southmead Hospital, Bristol
Dr Kathryn Urankar, Consultant Neuropathologist, Southmead Hospital, Bristol
Dr Mallar Chakravarty, Computational Neuroscientist, Brain Imaging Centre, Douglas Institute & Assistant Professor, Departments of Psychiatry and Biomedical Engineering, McGill University, Canada

School / Faculty: Translational Health Sciences, Bristol Medical School, Faculty of Health Sciences

Summary of project (<300 words / ~ half-page):

Epilepsy, characterised by recurrent seizures, is a common neurological disorder affecting 1% of the UK population. Temporal lobe epilepsy (TLE) is one of the most common forms of epilepsy, and hippocampal sclerosis, a structural abnormality of the hippocampus, is a hallmark feature of TLE. Due to the role of the hippocampus in memory formation and retrieval, the most common cognitive problems experienced by TLE patients are in episodic memory.

Previous studies have shown that the hippocampal subfield called the dentate gyrus (DG) acts as the "gateway" to the hippocampus and has a specialised role in memory known as pattern separation (PS). PS refers to the process of representing highly similar memories in a distinct way, allowing them to coexist with minimal interference[1]. It can be thought of as the process of encoding 'where I put my car keys today' in a manner distinct from 'where I put them yesterday'.

Deficits in PS are known to correlate with age-related changes in the hippocampus, mild cognitive impairment, dementia and more recently, TLE[2] . Recent work by the Atan group and others has shown that mossy cells in the DG are the main cells responsible for PS in mice[3]. We have also found that there is an age-related decline in mossy cells in the human brain, which might explain why PS problems become more common with age. Furthermore, young epilepsy patients have pathological changes in their brains, e.g., fewer mossy cells, that are more typical of older adults. Preliminary work by the research team has shown that PS deficits in young epilepsy patients linearly correlate with the degree of DG volume loss on their MRI scans.

Hypothesis:
Our hypothesis is that people with TLE will be impaired in PS because of the death of mossy cells from recurrent seizures.

The aims are:
1. To measure PS in people with TLE and compare the results with healthy controls
2. To correlate deficits in PS with structural changes in the DG on MRI scans
3. To correlate deficits in PS with histological changes in the DG of epilepsy surgical specimens

Techniques to be used:

Bristol is one of the most active epilepsy surgery centres in the UK. After a standard inpatient work-up that includes EEG/video-telemetry, 3T MRI and neuropsychological tests, ~50% of patients referred to the service are found to have an epileptic focus suitable for surgery.

The student will recruit patients with TLE referred to Bristol for epilepsy surgery. They will also recruit healthy age-and sex-matched volunteer subjects.

After informed consent, the student will ask subjects recruited to the study to perform a simple online memory task, called the Mnemonic Similarity Task (developed by the Stark lab)[1]. The student will analyse hippocampal subfields on their MRI scans to determine whether PS performance is correlated with the shape and volume of the DG.

For those patients who do undergo epilepsy surgery, histological stains will be performed on their surgical samples to quantify the number of mossy cells and other cell populations in the DG. The student will correlate these pathological changes with the patients' pre-operative PS ability. As the memory task is available online, the participant will be asked to complete the memory task again after surgery to determine the impact of the epilepsy surgery on their PS performance.

3 Key references:

1. Bakker A, Brock Kirwan C, Miller M, Stark CEL. Pattern Separation in the Human Hippocampal CA3 and Dentate Gyrus. Science 2008;319:1640-2.
2. Reyes A, Holden HM, Chang YA, et al. Impaired spatial pattern separation performance in temporal lobe epilepsy is associated with visuospatial memory deficits and hippocampal volume loss. Neuropsychologia 2018;111:209-15.
3. Bui AD, Nguyen TM, Limouse C, et al. Dentate gyrus mossy cells control spontaneous convulsive seizures and spatial memory. Science 2018;359:787-90.

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? Hep B
HO licence? No
Other? Honorary contract with NBT. Online training in Good Clinical Practice

42. Working with Bristol communities to co-produce a dietary advice/support toolkit

Primary supervisor: Dr Sarah Sauchelli Toran

Secondary supervisor (for day-to-day support): Dr Alexandra Mitchell

School / Faculty: Bristol Dental School/Faculty of Health Sciences

Summary of project (<300 words / ~ half-page):

Adopting healthy dietary habits is fundamental for the prevention and management of multiple non-communicable diseases[1]. Although NHS England and NICE have published extensive guidelines to facilitate a transition to healthier dietary habits, much of the advice that is readily available is not tailored to the needs, capacity, culture, and knowledge of diverse communities. It often focuses on food groups rather than dishes or meals that play an important role in certain cultures, and it does not account for the additional challenges of people who live in food deserts (limited access to supermarkets, normally of higher cost) or food swamps (high density of fast-food outlets), exacerbating health inequalities.

In this project, the student will work closely with a Bristol community of their choice to:

a. better understand the barriers the community faces in adopting healthier dietary patterns.

a. design with members of the community an advice/support toolkit tailored for their community.

The student will receive comprehensive support to engage with the community, and if they wish a sub-set of people with a specific medical condition. They will review the literature[2] to identify relevant existing resources and work closely with supervisors to organise a set of workshops to be run from local community spaces or a university micro-campus. During the workshops the student will gather both qualitative and quantitative data, which will be collated to produce the blue-print of a toolkit, as well as the final project report. The students who wish to do so, will be assisted in working with community organisations to obtain funding to develop and disseminate the toolkit.

Dr Sarah Sauchelli Toran has extensive networks with community organisations and healthcare teams in South, East and Inner City Bristol. Dr Alex Mitchell is a research dietitian with clinical and research expertise in the provision of dietary advice.

Techniques to be used:

Community-Based Participatory Research[3]: This is a collaborative approach to research that is based in community settings, directly engages with members of the community as equal partners, and focuses on promoting change in that community. It is applied research.

Focus groups: This is a type of qualitative research, where data is collected by bringing a group of people together to discuss a given topic. The researcher facilitates the discussion.

Co-design: This is a method used for designing interventions, technologies, materials etc. where everyone involved equally contributes to the decision making. It is a very important aspect of Community-Based Participatory Research.

3 Key references:

1. World Cancer Research Fund. THE SCIENCE ON THE CONNECTION BETWEEN NUTRITION AND NCDs Dietary patterns. www.wcrf.org/NOURISHING. Published 2014.
2. Leung G, Stanner S. Diets of minority ethnic groups in the UK: influence on chronic disease risk and implications for prevention. *Nutr Bull*. 2011;36(2):161-198. doi:10.1111/J.1467-3010.2011.01889.X
3. Holkup PA, Tripp-Reimer T, Salois EM, Weinert C. Community-based Participatory Research: An Approach to Intervention Research With a Native American Community. *ANS Adv Nurs Sci*. 2004;27(3):162-175.

Specific requirements for the project:

No specific requirements.

43. Using canonical correlation analysis (CCA) to identify genetic variants correlated with clinical markers of kidney disease phenotypes

Primary supervisor: Professor Moin Saleem

Secondary supervisor (for day-to-day support): Dr Amy Osborne

School / Faculty: Bristol Medical School, and SCEEM (School of Computer Science, Electrical and Electronic Engineering and Engineering Mathematics)

Summary of project (<300 words / ~ half-page):

Canonical Correlation Analysis (CCA) is a statistical technique that can be used to identify single or combinations of common-frequency genetic markers, such as single nucleotide polymorphisms (SNPs), that show significant correlation with multiple phenotype variables (considered jointly). This method can be used to prioritise genes with possible small modifying effects on the phenotypes (not causal genes) for further analysis. CCA uses linear combinations of variables derived from two sets of data objects and finds those combinations which are maximally correlated with each other. The sets of data objects can be genotype count data from SNP arrays (typically used for a genome-wide association study; GWAS) and multiple continuous phenotypic variables (multidimensional datasets).

CCA has previously been applied to a cardiovascular disease genotype dataset and confirmed already established SNP-phenotype results with improved statistical power, as well as identified potentially novel genotype-phenotype associations (1). CCA for association analysis was proposed initially by Ferreira and Purcell (2) and subsequently extended (3). Both these papers apply CCA to multiple trait/single genotype analysis (pleiotropy analysis), while the latter also considers the case of several markers (gene centered pleiotropy analysis) and several traits, or several markers and one trait (epistasis analysis).

This project will use CCA to identify SNPs that show significant correlation with multiple clinical markers for either chronic kidney disease (CKD) or nephrotic syndrome (NS). SNPs can be analysed individually (univariate-SNP analysis) or multiple SNPs in the same gene region can be considered (gene-based). Relevant clinical variables and pre-processed genotype data are available for analysis in the INS and CKD NURTuRE datasets. After running CCA, any identified putative genes will be subjected to statistical enrichment analyses using both Gene Ontology and published expression datasets. Any identified SNPs can be further analysed using variant prediction tools, expression quantitative trait loci (eQTL) databases, fine-mapping and case/control analyses.

Techniques to be used:

- canonical correlation analysis (CCA) and associated statistics in R
- gene enrichment analysis in R
- bash command line scripting for data preparation
- database searches
- data visualization in R
- use of high performance computing (HPC)

3 Key references:

Seoane J. A., Campbell C., Day I. N., Casas J. P., Gaunt T. R. Canonical correlation analysis for gene-based pleiotropy discovery. *PLoS Computational Biology.* 2014; 10 (10, article e1003876)
Ferreira M. A., Purcell S. M. A multivariate test of association. *Bioinformatics.* 2009; 25: 132-133.
Tang C.S., Ferreira M.A. A gene-based test of association using canonical correlation analysis. *Bioinformatics.* 2012; 28: 845–850.

Specific requirements for the project: none

44. Evaluation of the prevalence, risk factors, clinical relevance and impact of telangiectases in systemic sclerosis

Primary supervisor: John D Pauling

Secondary supervisor (for day-to-day support): Emma Clark

Qualitative supervisor: Sarah Drew and Katie Whale

School / Faculty: Bristol Medical School (THS)

Summary of project (<300 words / ~ half-page):

Systemic sclerosis (SSc) is an autoimmune rheumatic disease characterised by cutaneous vascular manifestations including Raynaud's phenomenon and digital ulceration. An important but largely overlooked vascular cutaneous manifestation of SSc is the formation of telangiectasia. These small dilated dermal capillaries form at areas of intense cutaneous ischaemia. Telangiectases are, in isolation, harmless but when clustered in eposed areas of the face and hands, they can cause major body image dissatisfaction in SSc and have been considered a potential harbinger of internal organ vascular complications such as pulmonary arterial hypertension.

Obtaining reimbursement/commissioning approval for local treatments for SSc-telangiectases is an issue worldwide.

A novel PRO instrument has been devised by our group to capture the lived experience of SSc-RP (ASRAP questionnaire)1,2. The international multicentre ASRAP validation study has collected data from over 430 patients with SSc. The ASRAP study has collected data on the presence, number and distribution of telangiectases in patients with SSc.

This MRes dissertation project shall:

1. Evaluate the prevalence, risk factors and clinical relevance of teleagiectases in SSc.
1. Examine the reliability of a patient self-scoring method for quantifying telangiectases in exposed areas of the hands, forearms and face
1. Better understand the patient experience of telangiectasia in SSc as justification for local treatment and future assessment

Techniques to be used:

1. A comprehensive scoping review on the prevalence, risk factors, clinical evaluation and treatment of telangiesctases in SSc shall ensure the student understands the existing literature on this subject.
2. The ASRAP study dataset of >430 patients with SSc includes a physician assessment of number and distribution of telangiectases in a carefully phenotyped SSc cohort. The descriptive analysis shall examine the prevalence, risk factors and clinical relevance of telangiectases in SSc. The student shall develop skills in statistical analyses such as logistic regression analysis.
3. The ASRAP dataset also includes a patient-reported assessment of the number and distribution of telangiectases. An additional highly novel analysis shall examine the reliability of a patient-reported vs. physician assessment of telangiectases.
4. A qualitative focus group study of people with systemic sclerosis and telangiectases shall be undertaken to explore patient experiences associated with the presence of these cutaneous manifestations of SSc. The study shall be undertaken with NHS ethics and HRA approval, giving the student an understanding of NHS regulatory frameworks and the principles of research governance. An inductive thematic analysis of data will be led by the student with support and guidance from experienced qualitative researchers.

Key references:

1. Pauling J, Yu L, Denton C, Frech T, Herrick A, Hummers L, Saketkoo L, Shah A, Khanna D, Domsic R. Preliminary Assessment of Internal Reliability and Construct Validity of Long and Short-form Assessment of Systemic Sclerosis-associated RAynaud's Phenomenon (ASRAP) Questionnaires [abstract]. Arthritis Rheumatol. 2021; 73 (suppl 10). https://acrabstracts.org/abstract/preliminary-assessment-of-internal-reliability-and-construct-validity-of-long-and-short-form-assessment-of-systemic-sclerosis-associated-raynauds-phenomenon-asrap-questionnaires/. Accessed March 15, 2022
2. Pauling JD, Domsic RT, Saketkoo LA, Almeida C, Withey J, Jay H, Frech TM, Ingegnoli F, Dures E, Robson J, McHugh NJ, Herrick AL, Matucci-Cerinic M, Khanna D, Hewlett S. A multi-national qualitative research study exploring the patient experience of Raynaud's phenomenon in systemic sclerosis: A Scleroderma Clinical Trials Consortium Vascular Working Group initiative. Arthritis Care & Research 2018 Sep;70(9):1373-1384

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)?
HO licence?
Other?

NHS ethics and HRA approval for the planned qualitative research study.

The student shall undertake training in Good Clinical Practice.

45. Life-space and physical function in a sample of community-dwelling older adults

Primary supervisor: Dr Emily J Henderson

Secondary supervisor (for day-to-day support): Dr Mícheál Ó Breasail

School / Faculty: Population Health Sciences, Bristol Medical School

Summary of project (<300 words / ~ half-page):

Life-Space Mobility (LSM) is a holistic concept which describes how an individual interacts with their surroundings, capturing many aspects of physical, mental, and social health (1). This is typically captured using self-reported questionnaires. This project will explore the relationships between participant-reported LSM captured using the Life Space Assessment (LSA) tool and how it relates to measures of physical function (in-person assessment), physical activity behaviours (accelerometry) and physical activity questionnaires (IPEQ-WA) collected from community-dwelling older adults.

While the LSA is a subjective measure it has been widely-validated in different populations of older adults. Accelerometry using wrist-worn sensors can provide complementary data about the physical activity behaviours people perform within the life-space zone they report, for instance if people who venture further from home does so for leisure (2). Further nuance can be obtained by incorporating measures of physical function (3), for which population normative data are widely available providing us the ability to stratify the participants further by their capability to perform a series of physical tests i.e. short physical performance batter (SPPB), timed up and go (TUG), and hand grip strength (HGS).

This project will provide valuable hands on experience in data manipulation, data processing, and statistical analysis using a variety software and/or programming languages such as STATA, R, and/or Python. This will entail the initial cleaning and processing of raw accelerometry data to generate a dataset of physical activity behaviours and diurnal rhythms through to subsequent statistical analysis.

The student will be based in the Ageing and Movement Research Group (AMRG) in Population Health Sciences. Previous intercalating students and master's students have successfully presented their work at conferences and published findings in peer reviewed journals. You can follow our progress on Twitter @AMRG_Bristol, @PdPRIME, @chiefpd2 or our website. We welcome potential students to make contact with us if they are considering any of the projects we offer.

Techniques to be used:
This project involves data manipulation and processing in R/STATA and additional packages as required and students should ideally be familiar with data processing in STATA or similar statistical software packages along with the coding for cleaning, describing and performing e.g., basic statistical tests of association, using regression analysis.

3 Key references:

1. Baker, P. S., Bodner, E. V., & Allman, R. M. (2003). Measuring life-space mobility in community-dwelling older adults. Journal of the American Geriatrics Society, 51(11), 1610–1614.
1. Tsai, L. T., Portegijs, E., Rantakokko, M., Viljanen, A., Saajanaho, M., Eronen, J., & Rantanen, T. (2015). The association between objectively measured physical activity and life-space mobility among older people. Scandinavian journal of medicine & science in sports, 25(4), e368–e373.
1. Lee JQ, Ding YY, Latib A, et alINtrinsic Capacity and its RElAtionship With Life-SpacE Mobility (INCREASE): a cross-sectional study of community-dwelling older adults in SingaporeBMJ Open 2021;11:e054705

Specific requirements for the project:
See above, previous use of R/STATA etc. highly desirable.

46. Exploring the relationships between the health of people with Parkinson's and caregiver health.

Primary supervisor: Dr Emily J Henderson

Secondary supervisor (for day-to-day support): Dr Mícheál Ó Breasail

School / Faculty: Population Health Sciences

Summary of project (<300 words / ~ half-page):

Patients with parkinsonism (PwP) are more likely than individuals of the same age without PD to be admitted to hospital and admission is associated with significant morbidity and excess mortality (1). Up to 75% of PwP are thought to have a co-resident partner or relative who may fulfil a caregiver role, to a greater or lesser extent, for the PwP. Many of such caregivers may themselves be older adults and may have their own complex health needs and the burden of caring for someone with the condition is well described (2).

This project will involve the analysis of routinely collected primary care data from the Clinical Practice Research Datalink (CPRD)(3) with linkage to other important data sources such as Hospital Episode Statistics (HES). STATA will be used to investigate whether the caregiver's health status is associated with risk of hospital attendance and admission for the individual with Parkinson's and thus flag the need for respite or temporary support to prevent the PwP being admitted due to non-medical reasons.

The student will be based in the Ageing and Movement Research Group (AMRG) in Population Health Sciences. We are a group of multidisciplinary researchers with three main themes a) innovating undergraduate medical education in ageing b) clinical trials in older adults and c) innovating care and treatments for Parkinson's and other related neurodegenerative diseases. Previous intercalating students and master's students have successfully presented their work at conferences and published findings in peer reviewed journals. You can follow our progress on Twitter @AMRG_Bristol, @PdPRIME, @chiefpd2 or our website. We welcome potential students to make contact with us prior to considering any of the projects we offer.

Techniques to be used:
This project involves data manipulation and processing in STATA and additional packages as required and students should ideally be familiar with data processing in STATA or similar statistical software packages along with the coding for cleaning, describing and performing e.g., basic statistical tests of association using regression analysis.

3 Key references:

1. Low, V., Ben-Shlomo, Y., Coward, E., Fletcher, S., Walker, R., & Clarke, C. E. (2015). Measuring the burden and mortality of hospitalisation in Parkinson's disease: A cross-sectional analysis of the English Hospital Episodes Statistics database 2009-2013. Parkinsonism & related disorders, 21(5), 449–454.
1. Schrag, A., Hovris, A., Morley, D., Quinn, N., & Jahanshahi, M. (2006). Caregiver-burden in parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. Parkinsonism & related disorders, 12(1), 35–41.
1. Herrett, E., Gallagher, A. M., Bhaskaran, K., Forbes, H., Mathur, R., van Staa, T., & Smeeth, L. (2015). Data Resource Profile: Clinical Practice Research Datalink (CPRD). International journal of epidemiology, 44(3), 827–836.

Specific requirements for the project:
Previous use of STATA or equivalent essential

47. Better understanding the musculoskeletal phenotype of people with Parkinson's disease

Primary supervisor: Dr Emily J Henderson

Secondary supervisor (for day-to-day support): Dr Mícheál Ó Breasail

School / Faculty: Population Health Sciences, Bristol Medical School

Summary of project (<300 words / ~ half-page):

Osteoporosis and bone fractures are approximately twice as likely in Parkinson's Disease compared to the general population (1), and in women, PD is the strongest single contributor to fracture risk (2). For people with Parkinson's (PwP) falls and fractures are a cause of substantial morbidity (3).

As part of an RCT looking at improved pathways of care for PwP we will measure bone density using dual-energy x-ray absorptiometry (DXA) at several skeletal sites (hip, spine, whole body). DXA is the gold standard for the diagnosis of osteoporosis but also provides additional information on bone mass and geometry. Our trial is planned to represent PwP across all PD stages, including those typically excluded from clinical trials. As such a detailed description of bone at multiple skeletal sites, across the disease spectrum, will greatly improve our understanding of how best to target interventions future to maintain bone health and prevent future fractures.

This project will provide hands on experience of analysing DXA scans, data extraction and processing, and statistical interpretation of these data. This will entail the initial preparation of DXA images for extraction, followed by the extraction of bone data for statistical analysis.

The student will be based in the Ageing and Movement Research Group (AMRG) in Population Health Sciences. Previous intercalating students and master's students have successfully presented their work at conferences and published findings in peer reviewed journals. You can follow our progress on Twitter @AMRG_Bristol, @PdPRIME, @chiefpd2 or our website. We welcome potential students to make contact with us if they are considering any of the projects we offer.

Techniques to be used:
This project will provide hands on experience of analysing DXA scans, data extraction and processing, and statistical analysis.

3 Key references:

1. Torsney, K. M., Noyce, A. J., Doherty, K. M., Bestwick, J. P., Dobson, R., & Lees, A. J. (2014). Bone health in Parkinson's disease: a systematic review and meta-analysis. Journal of neurology, neurosurgery, and psychiatry, 85(10), 1159–1166.
1. Dennison, E. M., Compston, J. E., Flahive, J., Siris, E. S., Gehlbach, S. H., Adachi, J. D., Boonen, S., Chapurlat, R., Díez-Pérez, A., Anderson, F. A., Jr, Hooven, F. H., LaCroix, A. Z., Lindsay, R., Netelenbos, J. C., Pfeilschifter, J., Rossini, M., Roux, C., Saag, K. G., Sambrook, P., Silverman, S., … GLOW Investigators (2012). Effect of co-morbidities on fracture risk: findings from the Global Longitudinal Study of Osteoporosis in Women (GLOW). Bone, 50(6), 1288–1293.
1. Henderson, E. J., Lyell, V., Bhimjiyani, A., Amin, J., Kobylecki, C., & Gregson, C. L. (2019). Management of fracture risk in Parkinson's: A revised algorithm and focused review of treatments. Parkinsonism & related disorders, 64, 181–187.

Specific requirements for the project: Interest and enthusiasm in working with older adults with neurodegenerative disease participating in clinical trials. Completion of NIHR training (~4 hours) on Good Clinical Practice. Able to meet the requirements for working with clinical populations (DBS / immunisations etc) in the NHS.

48. A randomised controlled trial of augmented care in Parkinson's disease

Primary supervisor: Dr Emily J Henderson

Secondary supervisor (for day-to-day support): Dr Matthew Smith

School / Faculty: Population Health

Summary of project (<300 words / ~ half-page):

People living with Parkinson's disease experience progressive motor and non-motor symptoms, which negatively impact on health-related quality of life and can lead to an increased risk of hospitalisation. It is increasingly recognised that the current care models are not suitable for the needs of people with parkinsonism whose care needs evolve and change as the disease progresses. This trial aims to evaluate whether a complex and innovative model of integrated care will increase an individual's ability to achieve their personal goals, have a positive impact on health and symptom burden, and be more cost-effective when compared with usual care.

PRIME RCT is a single centre, randomised controlled trial where people with parkinsonism and their informal caregivers are randomised into one of two groups: either PRIME Parkinson multi-component model of care; or usual care. Adults ≥18 years with a diagnosis of parkinsonism, able to provide informed consent or the availability of a close friend or relative to act as a personal consultee if capacity to do so is absent, and living in the trial geographical area are eligible. Up to three caregivers per patient can also take part, must be ≥18 years, provide informal, unpaid care and able to give informed consent. The primary outcome measure is goal attainment, as measured using the Bangor Goal Setting Interview. The duration of enrolment is 24 months. The total recruitment target is n=214 and the main analyses will be intention to treat.

The student will be part of the team recruiting to the trial and delivering the active intervention to participants randomised in 'PRIME RCT'. The intervention in delivered in community and secondary care settings from intensive care through to residential and nursing homes. It would suit an individual with an interest in geriatric medicine, neurology and movement disorders and there is an opportunity to develop and pursue the student's specific interests within the scope of the trial. The student will be based in the Ageing and Movement Research Group (AMRG) in Population Health Sciences. We are a group of multidisciplinary researchers with three main themes a) innovating undergraduate medical education in ageing b) clinical trials in older adults and c) innovating care and treatments for Parkinson's and other related neurodegenerative diseases. Previous intercalating students and master's students have successfully presented their work at conferences and published findings in peer reviewed journals and we anticipate these will be outcomes from this project. You can follow our progress on Twitter @AMRG_Bristol, @PdPRIME, @chiefpd2 or our website. We welcome potential students to make contact with us prior to considering any of the projects we offer.

Techniques to be used:

- Recruitment of participants into an interventional clinical trial
- Adherence to the principles of Good Clinical Practice (GCP)
- Data collection using electronic clinical record systems
- Statistical analysis of quantitative data using Stata

3 Key references:

- Tenison, E., Smink, A., Redwood, S., Darweesh, S., Cottle, H., van Halteren, A., ... & Henderson, E. (2020). Proactive and integrated management and empowerment in Parkinson's disease: Designing a new model of care. Parkinson's Disease, 2020.
- Bloem BR, Henderson EJ, Dorsey ER, Okun MS, Okubadejo N, Chan P, Andrejack J, Darweesh SK, Munneke M. Integrated and patient-centred management of Parkinson's disease: a network model for reshaping chronic neurological care. The Lancet Neurology. 2020 Jul 1;19(7):623-34.

• Tenison E, Henderson EJ. Multimorbidity and frailty: Tackling complexity in Parkinson’s disease. Journal of Parkinson's Disease. 2020 Jan 1;10(s1):S85-91.
Specific requirements for the project: Interest and enthusiasm in working with older adults with neurodegenerative disease participating in clinical trials. Completion of NIHR training (~4 hours) on Good Clinical Practice. Able to meet the requirements for working with clinical populations (DBS / immunisations etc) in the NHS.

49. Atypical Parkinson's disorders: new horizons in Parkinson's care

Primary supervisor: Dr Emily J Henderson

Secondary supervisor (for day-to-day support): Dr Matthew Smith

School / Faculty: Population Health Sciences

Summary of project (<300 words / ~ half-page):

Parkinson's disease (PD) the second most common neurodegenerative condition, typically associated with a host of movement symptoms including tremor, bradykinesia and dysfunction of gait.PD exists clinically in a spectrum with a selection of related "atypical" parkinsonian disorders that includes progressive supranuclear palsy (PSP) and multiple system atrophy (MSA), historically considered to be much rarer and often taking several years for a diagnosis to be reached. Differentiating these conditions is important, as each can have specific care needs, provides important prognostic information for patient and family and is vital to establish as we head towards an era of novel disease modifying treatments.

Our fundamental understanding of the underlying pathology behind these conditions has changed markedly over the years, including through linkage studies between phenotype and neuropathological findings post-mortem. This has led to a dramatic world-wide "rethink" of clinical criteria with new guidelines published in 2017 for PSP. With criteria expanded, many patients previously labelled as having PD are seeing their diagnosis changed as a result, in particular encompassing individuals with predominant problems with gait and balance.

This project aims to explore the effect that new guidelines have exerted on the cohort of patients seen in the movement disorder clinic serving the Bath area. This will involve the prospective assessment of clinical records over an extended period, exploring the process and rate at which patients are diagnosed with atypical parkinsonian disorders as well as retrospective analysis of those already with a diagnosis.

The goals of project will be to use this data to facilitate the following:

1. Development of the "Bath Atypical Cohort" (PRIME atypical)
1. Describe the phenotype of atypical parkinsonian disorders within the region
1. Describe the patient journey to diagnosis, including imaging (MRI/PET CT/cardiac MIBG)
1. Reimagine care pathways and structures

Dependent on progress and interest, the opportunity to contribute to the STRIPE interventional trial of neuromodulation for bladder symptoms in PD and the other portfolio of clinical trials in the PRIME programme may also be available to the student. The student will be based in the Ageing and Movement Research Group (AMRG) in Population Health Sciences. We are a group of multidisciplinary researchers with three main themes a) innovating undergraduate medical education in ageing b) clinical trials in older adults and c) innovating care and treatments for Parkinson's and other related neurodegenerative diseases. Previous intercalating students and master's students have successfully presented their work at conferences and published findings in peer reviewed journals and we anticipate these will be outcomes from this project. You can follow our progress on Twitter @AMRG_Bristol, @PdPRIME, @chiefpd2 or our website. We welcome potential students to make contact with us prior to considering any of the projects we offer.

Techniques to be used:

- Data collection using electronic clinical record systems
- Statistical analysis of quantitative data using Stata

3 Key references:

1. Höglinger, G. U., Respondek, G., Stamelou, *et al.* Movement Disorder Society-endorsed PSP Study Group (2017). Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Movement disorders : official journal of the Movement Disorder Society*, *32*(6), 853–864.
1. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology*. 2008;71(9):670-676.
1. Smith MD, Brazier DE, Henderson EJ. Current Perspectives on the Assessment and Management of Gait Disorders in Parkinson's Disease. *Neuropsychiatr Dis Treat*. 2021;17:2965-2985. Published 2021 Sep 21. doi:10.2147/NDT.S304567

Specific requirements for the project:
Interest and enthusiasm in working with older adults with neurodegenerative disease participating in clinical trials. Completion of NIHR training (~4 hours) on Good Clinical Practice. Able to meet the requirements for working with clinical populations (DBS / immunisations etc) in the NHS. Basic clinical skills (examination and history taking).

50. Investigating cleft lip and/or palate and mental health using observational data from the Cleft Collective and Mendelian randomization

Primary supervisor: Evie Stergiakouli

Secondary supervisor (for day-to-day support): Amy Davies, Gemma Sharp, Sarah Lewis

School / Faculty: Bristol Medical School, Population Health Sciences

Summary of project (<300 words / ~ half-page):

Cleft lip and/or cleft palate (CL/P) affects one in 700 in the UK. While prognosis is generally good, CL/P is associated with a wide range of health problems, including breathing, feeding, speech, dental and hearing problems.

Research is beginning to focus on the wider implications of cleft, particularly the psychological and social impacts on children and their families. Our previous work suggested elevated levels of behavioural problems, particularly hyperactivity-related problems in children born with CL/P. In this study, we aim to use data from the Cleft Collective to describe early life development using the Ages and Stages Questionnaire (ASQ) and mental health in children born with cleft and their parents. In addition, we will use Mendelian randomization to investigate if being born with cleft can cause mental health problems in children. The Cleft Collective is an ongoing UK-wide longitudinal study investigating the causes, best treatments, and the psychological impact of cleft, on affected individuals and their families using questionnaire data, biological samples and linkage with other data sources. Mendelian randomization is a method of causal analysis which utilizes genetic variants to proxy exposures and investigate their causal effects on health outcomes. Mendelian randomization overcomes the problems of confounding by known or unknown confounders and selection bias that are present in observational analysis. In this project, we will use genetic variants associated with CL/P from large genome-wide association studies (GWAS) to proxy being born with CL/P. These genetic variants can then be identified in large GWAS of mental health problems (ADHD, autism spectrum disorder, major depression, anxiety) to causally test if they are linked to CL/P. This approach has been used effectively to test if CL/P is causing educational underachievement in cleft. Identifying if children born with CL/P are at higher risk for mental health problems is essential to providing the necessary support required to improve outcomes.

Techniques to be used:

Epidemiological analysis, Mendelian randomization, genetic epidemiology

3 Key references:

Dardani et al (2018). bioRxiv 434126; doi: https://doi.org/10.1101/434126

Davey Smith, Ebrahim (2003). IJE 32(1):1–22. doi:10.1093/ije/dyg070

Ludwig et al. (2012). Nat Genet. 44(9):968–71. doi:10.1038/ng.2360

Veterinary Projects

51. Does hunger affect how dairy calves value milk?

Primary supervisor: Dr. Benjamin Lecorps

Secondary supervisor (for day-to-day support): Prof. Mike Mendl

School / Faculty: Bristol Veterinary School / Faculty of health sciences

Summary of project (<300 words / ~ half-page):

Our understanding of mental experiences and mental health of animals is still very limited, despite these being core to modern conceptions of Animal Welfare. This knowledge gap is even more problematic given that captive animals, including most common farm species, are typically subjected to many stressors (e.g., feed-restrictions)[1]. It is important to address this research gap to guide future animal husbandry procedures. This project is part of a research programme aiming to understand how commonly applied, and arguably quite severe, feed restrictions impact dairy calves, especially at the emotional level. Hunger states may be especially intense when dairy calves are weaned off milk to force transition to solid feeds. Here we propose to explore whether calves perceive a milk reward differently as a function of how hungry they are (state-dependent learning). For this, calves will be trained to associate specific cues (e.g., colours) with specific states (very hungry vs. hungry), leading to the delivery of milk. We expect that calves will prefer the cue associated with the greater hunger state because greater deprivation typically increases the value attributed to a reward[2]. If these predictions hold true, it may completely change the way we understand and induce weaning in dairy calves. For instance, current scientific recommendations argue that milk provision should be gradually decreased to push animals to feed from other sources (i.e., solid feed) in opposition to abrupt reduction in milk allowance[3]. However, this may lead calves to increase the value they put on milk and thus be counterproductive. Instead, weaning strategies based on decreased milk attractiveness may help redirect the rewarding properties of milk towards other food sources. This work would be the first to use state-dependent learning in cattle and has the potential to lead to important changes in animal husbandry practices.

Techniques to be used:

State-dependent learning involves training animals to associate different cues (predicting the same reward) under different hunger states. This methodology has not been developed in cattle and will be based on previous work in other species.

3 Key references:

1. B. Lecorps, D. M. Weary, M. A. G. von Keyserlingk, *Trends Cogn. Sci.* (2021), doi:https://doi.org/10.1016/j.tics.2021.03.010.
2. L. A. Buckley, V. Sandilands, P. M. Hocking, B. J. Tolkamp, R. B. D'Eath, *Appl. Anim. Behav. Sci.* **165**, 124–132 (2015).
3. P. P. Nielsen, M. B. Jensen, U. Halekoh, L. Lidfors, *Appl. Anim. Behav. Sci.* **109**, 223–237 (2008).

Specific requirements for the project:

Immunisations (e.g. Hepatitis B)? No

HO licence? No

Other? No

52. Factors associated with decisions to start dogs presumed to have myxomatous mitral valve disease on cardiac medications in primary-care practice

Primary supervisor: Melanie Hezzell (UoB); Dan O'Neill (RVC)

Secondary supervisor (for day-to-day support): Melanie Hezzell

School / Faculty: Vet / Health Sciences

Summary of project (<300 words / ~ half-page):

Myxomatous mitral valve disease (MMVD) is the most common heart disease in adult dogs, accounting for three-quarters of a veterinary cardiologist's caseload. It is most common in middle-aged and older, small- and medium-sized dogs. Guidelines have been published with recommendations for the diagnosis and treatment of MMVD. However, these guidelines were written by specialist cardiologists and describe "gold standard" investigations that may not always be achievable in primary-care practice, for various reasons (e.g., access to specialist equipment or expertise, financial constraints). Ideally these guidelines could be adapted to be more applicable to a primary-care setting. To achieve this, we must first characterise how MMVD is currently managed in primary-care practice.

The Veterinary Companion Animal Surveillance System (VetCompass) collects anonymised electronic clinical data from >30% of all UK veterinary practices. We can use these stored data to investigate how primary-care veterinarians manage MMVD, including information about the animals, their presenting signs, physical examination findings, plus diagnostic tests performed and medications prescribed. We will collect data obtained in one calendar year (2019) from dogs likely to be affected by MMVD (small- and medium-sized dogs ≥5 years old) that had not previously received cardiac medications. Dogs will be divided into 3 groups (during 2019, group x. no cardiac medications received, group y. diuretics initiated (required for treatment of congestive heart failure) and group z. other cardiac medications initiated (as expected in advanced preclinical disease)). Analysis of these data will identify factors associated with animals being started on a. diuretics and b. other cardiac medications. This is the first step towards understanding how this very common disease is managed in primary-care practice. We plan eventually to develop MMVD guidelines with primary-care veterinarians, which will allow a higher proportion of affected dogs to benefit from optimal care, improving their health and welfare.

Techniques to be used:

Data collection. Use of VetCompass. Statistical analysis (using R).

3 Key references:

Keene BW, Atkins CE, Bonagura JD, et al. ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. Journal of Veterinary Internal Medicine 2019; 33(3): 1127-1140

Mattin MJ, Boswood A, Church DB, et al. Prognostic factors in dogs with presumed degenerative mitral valve disease attending primary-care veterinary practices in the United Kingdom. Journal of Veterinary Internal Medicine 2019;33:432-444.

Mattin MJ, Brodbelt DC, Church DB, et al. Factors associated with disease progression in dogs with presumed preclinical degenerative mitral valve disease attending primary care veterinary practices in the United Kingdom. Journal of Veterinary Internal Medicine 2019;33:445-454.

Specific requirements for the project:

Immunisations (e.g. Hepatitis B)?

HO licence?

Other?