University of BRISTOL

Faculty of Health Sciences
and
Faculty of Life Sciences

MRes in Health Sciences Research

Research Projects

2024/25

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1: Project title: Identifying novel CSF markers of pericyte injury in Alzheimer's disease

Primary supervisor: Dr Robbie Fisher/Dr Scott Miners

Secondary supervisor (for day-to-day support): Dr Dan Asby/Dr Rob MacLachlan

School / Faculty: BMS/THS

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

Pericytes are vascular mural cells that play a central role in regulating cerebral blood flow and blood-brain barrier (BBB) permeability. Reduced cerebral blood flow and BBB leakiness are major early features of Alzheimer's disease (AD) associated with pericyte injury and neurovascular uncoupling. Previous studies have shown that the levels of soluble platelet-derived growth factor receptor B (sPDGFRB), a protein that is released from injured pericytes, were elevated in clinical CSF samples from patients with AD (1) and in individuals in the initial stages of AD (2). These studies raise the tantalising possibility that CSF markers of pericyte injury can be used to detect neurovascular injury and track cognitive decline in individuals in the very early pre-clinical stages of AD. PDGFRB is, however, expressed in multiple cell types throughout the CNS and therefore concerns over specificity have been raised.

A recent single-nuclei transcriptomic analysis of the human cerebrovasculature (3) has identified a panel of novel gene markers that are enriched in pericytes. In this study, the student will determine which of the novel 'pericyte' markers are expressed in human brain-derived primary pericyte cultures. They will determine whether any of the markers are secreted upon exposure of primary pericytes to experimental conditions that model AD i.e. hypoxia and beta-amyloid and then investigate whether the expression of the best candidate markers are elevated in clinical CSF samples from individuals at different stages of AD.

Techniques to be used: Primary cell culture; immunofluorescence; ELISA-based measurement of targets in cell conditioned medium; ELISA based measurement of selected targets in CSF (may require development/optimisation of ELISAs).

3 Key references:

1. CSF evidence of pericyte damage in Alzheimer's disease is associated with markers of blood-brain barrier dysfunction and disease pathology | Alzheimer's Research & Therapy | Full Text (biomedcentral.com)
2. Blood–brain barrier breakdown is an early biomarker of human cognitive dysfunction | Nature Medicine
3. A human brain vascular atlas reveals diverse mediators of Alzheimer's risk | Nature

Specific requirements for the project: Immunisations (e.g. Hepatitis B)? Hep B will be required to work with CSF samples HO licence? NA Other? NA

02: Project title: Modelling glial cell polarisation in multiple sclerosis – influence of the mesenchymal stromal cell secretome

Primary supervisor: **Dr Claire Rice**

Secondary supervisor (for day-to-day support): **Dr Kelly Hares**

School / Faculty: **Bristol Medical School**

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

In the central nervous system (CNS), tissue-resident macrophages include microglia and mononuclear cell-derived macrophages. Both can be polarised to either a proinflammatory 'M1' phenotype or an anti-inflammatory 'M2' phenotype. M1 cells are associated with damage to neuronal cells, primarily through oxidative stress and lipid peroxidation but M2 cells promote repair in the CNS *via* recruitment of stem cells to sites of injury and supporting oligodendrocyte precursor cells, which are responsible for axonal myelination.

Mesenchymal stromal cells (MSCs) are pluripotent cells with important roles within the bone marrow microenvironment, including provision of support for haematopoietic stem cells. The MSC secretome refers to the trophic factors and anti-inflammatory cytokines produced by MSCs. Recently, it has been recognised that the MSC secretome has a host of immunomodulatory and neuroprotective qualities, including differential effects on macrophage activation and promotion of myelination.

Multiple sclerosis (MS) is an immune-mediated, inflammatory, demyelinating and neurodegenerative disease that causes progressive neurological disability. In MS, the inflammatory response is associated with breakdown of the blood-brain barrier (BBB) which allows circulating cells, including monocyte-derived macrophages, to enter the CNS. Both demyelination and axonal loss have been associated with activated macrophages. The effect of MSCs on macrophage polarisation in MS has not been examined previously.

We hypothesise that MSCs isolated from people with MS preferentially induce polarisation of CNS tissue-resident macrophages to a pro-inflammatory M1 phenotype, and reversing this to promote an M2 phenotype will be neuroprotective and pro-reparative in MS.

This study will examine the effect of the MSC secretome on macrophage polarisation under culture conditions simulating inflammation and will include a comparison of secretome when MSCs are isolated from people with MS and from control subjects. Overall, the aim is to promote M2 polarisation of CNS tissue-resident macrophages and identify potential novel treatment interventions for people with MS.

Techniques to be used:

Cell culture – mononuclear cells and glia
Phase contrast microscopy
Immunocytochemistry
In vitro models of inflammation (cytokine-induced)
MTT assay

Enzyme-linked immunosorbent assay (ELISA) Statistical analysis
3 Key references: 1. Rice, C. M., Kemp, K., Wilkins, A. & Scolding, N. J. Cell therapy for multiple sclerosis: an evolving concept with implications for other neurodegenerative diseases. The Lancet 382: 1204–1213 (2013). 2. Yan, K. et al. Bone marrow-derived mesenchymal stem cells maintain the resting phenotype of microglia and inhibit microglial activation. PLoS One 8(12): e84116 (2013). 3. Sarkar, P. et al. Reduced neuroprotective potential of the mesenchymal stromal cell secretome with ex vivo expansion, age and progressive multiple sclerosis. Cytotherapy 20: 21–28 (2018).
Specific requirements for the project: Immunisations : Hepatitis B HO licence? No Other? N/A

03: Project title: Do antidepressants show potential to protect against Alzheimer's disease?

Primary supervisor: Dr Lindsey Sinclair, Professor Pat Kehoe

Secondary supervisor (for day-to-day support): Dr Mizuki Morisaki

School / Faculty: Translational Health Sciences

Alzheimer's disease (AD) is the most common form of dementia. There is no cure and there is an intense research focus on prevention of Alzheimer's and other forms of dementia. Depression in mid to later life has been identified as a modifiable risk factor for the later development of AD. The extent to which it is actually modifiable and which treatments might best modify the risk are unknown.

It is not known whether depression is treated with psychotherapy, medication, or whether it is treated at all, affects dementia risk. A meta-analysis found only 5 articles and reported that antidepressant use was associated with a doubling in the odds of dementia/cognitive impairment, but this may have been confounded by more severe depression in those who took antidepressants. Long-term treatment seems to have a greater effect on reducing dementia risk. There are different theories about how antidepressants may modulate dementia risk, very few human humans, which all lack mechanistic insight, and studies in preclinical models are limited to a small number of studies in genetic models.

This project aims to determine whether antidepressants show any potential to protect neurons against amyloid beta. The student will culture commercially available primary hippocampal neurons with and without exposure to antidepressants and amyloid beta for up to 4 weeks. Synapse numbers will be assessed using ELISAs to measure synaptophysin and PSD-95. Dendrite length will be assessed using live cell imaging.

Techniques to be used:

Human cell culture, fluorescence-based assays and confocal microscopy
Only if time permits: ELISA

3 Key references:

Livingston et al. Lancet 2020 8-14 August; 396(10248): 413–446.
Bartels C et al. Am J Psychiatry. 2018;175(3):232-41.
Moraros J et al. Depress Anxiety. 2017;34(3):217-26.
Correia AS et al. Int J Mol Sci. 2022;23(9).

Specific requirements for the project:
Hepatitis B immunisation

04: Project title: Do antidepressants show potential to protect against Alzheimer's disease?

Primary supervisor: Dr Lindsey Sinclair, Professor Pat Kehoe

Secondary supervisor (for day-to-day support): Dr Mizuki Morisaki

School / Faculty: Translational Health Sciences

Alzheimer's disease (AD) is the most common form of dementia. There is no cure and there is an intense research focus on prevention of Alzheimer's and other forms of dementia. Depression in mid to later life has been identified as a modifiable risk factor for the later development of AD. The extent to which it is actually modifiable and which treatments might best modify the risk are unknown.

Some antidepressants (e.g. SSRIs) have been reported to show neuroprotective effects against AD pathology via promoting mitochondrial health. It is not surprising that antidepressants may promote neuronal survival by improving mitochondrial health as mitochondrial dysfunction is seen in both depression and AD pathology.

This project aims to determine whether antidepressants show any potential to protect neurons against common stresses seen in the ageing brain such as hypoxia and amyloid beta. The student will culture commercially available primary hippocampal neurons with and without exposure to antidepressants for up to 4 weeks. Hypoxia will be modelled using a hypoxic chamber. Outcome measures will include measuring proteins in the cell media by ELISA and measures of mitochondrial function including the MTT assay.

Techniques to be used:

Human cell culture, fluorescence-based assays and confocal microscopy
Only if time permits: ELISA

3 Key references:

Livingston et al. Lancet 2020 8-14 August; 396(10248): 413–446.
Bartels C et al. Am J Psychiatry. 2018;175(3):232-41.
Moraros J et al. Depress Anxiety. 2017;34(3):217-26.
Correia AS et al. Int J Mol Sci. 2022;23(9).

Specific requirements for the project:
Hepatitis B immunisation

05: Project title: Investigating the glioma microenvironment and role neural activity plays in tumour development

Primary supervisor: Dr Daniel Whitcomb

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

School / Faculty: Bristol Medical School

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

The tumour environment – which in the broadest sense refers to the cellular surroundings of a tumour – is a key determinant of tumour development and growth (1). Here, various factors including immune cells, components of the extracellular matrix, and secreted molecules, have all been implicated in regulating or impacting on the growth dynamics of tumours. Indeed, a major avenue of therapeutic research focuses on understanding how manipulation of the tumour environment can be utilised for therapeutic effect.

Gliomas have a particularly complex microenvironment, encompassing the various cell types of the central nervous system and their many secreted factors. Here, neurons themselves are key contributors in shaping the glioma microenvironment. Previous study has shown that neuronal activity actually promotes tumour growth, likely via mechanisms involving secreted factors and glutamatergic synaptic transmission (2,3). This presents a significant therapeutic opportunity, and something we propose to explore in this project:

Does localised, transient suppression of neuronal activity in regions surrounding a tumour remove a major growth-inducing impetus, and therefore slow the progression of gliomas?

Using organotypic brain slice cultures, we will explore the relationship between glioma development and neural activity. We will characterise the synaptic integration of gliomas and determine how the synapse influences tumour proliferation. Importantly, we will test the hypothesis that transiently reducing neural activity slows tumour growth, potentially paving the way for a novel avenue of therapeutic research.

Techniques to be used:

Organotypic brain slice cultures; glioma cell culture; immunohistochemistry

3 Key references:

(1) de Visser et al. Cancer Cell 41, 374–403 (2023)
(2) Venkataramani et al. Nature 573, 532–538 (2019)
(3) Venkatesh et al. Nature 549, 533–537 (2017)

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

06: Project title: Nerve growth factor in cervical and thoracolumbar canine intervertebral disc herniation and its association with spinal pain, a preliminary study.

Primary supervisor: Angela Fadda

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

School / Faculty: Langford Vets – University of Bristol

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

Clinical features of intervertebral disc herniation (IVDH) in dogs range from spinal pain to motor and sensory loss. Whilst neurological deficits are consequence of spinal cord injury, the exact pathogenesis of pain in IVDH is unclear. Severity of pain in affected dogs varies largely, and despite similar pathophysiology for cervical and thoracolumbar IVDH, there are considerable clinical differences which have only been partially explained. Indeed, most of cervical cases present with signs of hyperpathia, guarding of the neck, vocalisation, muscle fasciculations without neurologic deficits; in thoracolumbar IVDD neurological deficits often prevail (Brisson, 2010).
Nerve Growth Factor (NGF) plays a crucial role in the growth and survival of certain nerve cells. Current research supports that elevated levels of NGF may contribute to various pain conditions. More recently, treatments targeting circulating levels of NGF and specific receptors are successfully employed to alleviate pain in dogs suffering from osteoarthrosis(Lascelles et al., 2015).

NGF is increased in IVDs after disc injury in animal models (Nakawaki et al., 2019) and its expression is upregulated in degenerated IVD in dogs (Bitterli et al., 2024) but its role in the pathogenesis of IVDH associated pain has not been yet investigated.

Aims of this study are to analyse circulating and in situ levels of NGF in dogs suffering from IVDD and its association with clinically assessed pain. Results from an initial analysis of 10-20 cervical vs thoracolumbar samples vs control will be used to identify suitability of currently available canine NGF markers and to complete a power calculation to determine the total number of samples to analyse.

Results from this preliminary study may support additional research on spinal pain and lay the basis for prospective trials on immunomodulatory treatment targeting NGF specific receptors for IVDH associated pain in dogs.

Techniques to be used:
Dogs with confirmed IVDH and surgically treated, as a standard of care, at the Small Animal referral Hospital of Langford Vets – University of Bristol will be included in the study.
Pain will be assessed at admission to the hospital and post operatively by a simple standard clinical score as previously published (Fadda et al 2013).
Circulating levels of NGF will be determined on serum sample collected before surgery for pre-operative health check using an immunosorbent assay system - ELISA Test Kit.
Epidural material (consisting of extruded IVD, epidural fat, and hemorrhage) collected during surgery will be processed for histology as previously published (Fadda et al. 2013). Histological sections will be stained with hematoxylin and eosin (H&E) and immunostained for NGF marker. Results from a semiquantitative histopathological and immunohistochemical analysis on these

sections and will be compared between cervical and thoracolumbar IVDH cases and controls and correlated with severity of pain.
Samples for the control group will be collected from carcasses of dogs with no clinical signs of IVDH, donated by Owners for research purposes upon their informed consent and as per current Langfordvets – BVS guidelines.

3 Key references:

Bitterli, T., Schmid, D., Ettinger, L., Krupkova, O., Bach, F.C., Tryfonidou, M.A., Meij, B.P., Pozzi, A., Steffen, F., Wuertz-Kozak, K., Smolders, L.A., 2024. Targeted screening of inflammatory mediators in spontaneous degenerative disc disease in dogs reveals an upregulation of the tumor necrosis superfamily. JOR Spine 7, 1–19. https://doi.org/10.1002/jsp2.1292

Brisson, B.A., 2010. Intervertebral disc disease in dogs. Vet. Clin. North Am. - Small Anim. Pract. 40, 829–858. https://doi.org/10.1016/j.cvsm.2010.06.001

Fadda, A., Oevermann, A., Vandevelde, M., Doherr, M.G., Forterre, F., Henke, D., 2013. Clinical and Pathological Analysis of Epidural Inflammation in Intervertebral Disk Extrusion in Dogs. J. Vet. Intern. Med. 27, 924–934. https://doi.org/10.1111/jvim.12095

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

07: Project title: Matrix, memory and multimorbidity – do changes in hyaluronan homeostasis matter?

Primary supervisor: Dr Karen Mifsud

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

School / Faculty: Bristol Veterinary School

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

Hyaluronan (HA) is an important extracellular matrix (ECM) glycosaminoglycan expressed throughout the body. The presence and maintenance of HA in the extracellular environment has been shown to be important for a number of physiological functions in various tissues such as the brain, heart, kidney and joints. An interesting feature of HA is that its function depends on its molecular weight, with short chains of HA reported as exerting stimulatory actions such as inducing proliferation, inflammation and angiogenesis whereas longer forms are more stabilising, facilitating adaption of networks, cellular maturation and conferring anti-inflammatory actions. Interestingly, HA dysregulation is a common feature of many age-related disorders, such as arthritis in joints, kidney disease and cardiovascular disease.

Studies from my lab and others has shown a role for HA in cognition. Furthermore, pilot studies have shown an age-related decline in the expression of HAS2, a hyaluronan synthase responsible for the synthesis of high molecular weight HA in the rat hippocampus. This has led to a working hypothesis that ageing is affecting the distribution and size of HA in the hippocampus, a key area of the brain responsible for cognition and potentially responsible for development of age-related cognitive decline.

The overall aim of this project is therefore to characterise if and how the distribution and molecular weight of HA changes in the hippocampus due to ageing to generate data to support or reject the hypothesis above. This project will go on to assess the effect of ageing on HA dynamics in multiple tissues to determine if systemic modulation of HA, induced by ageing, could represent a potential underlying mechanism contributing to age-related multimorbidity, the development of multiple long-term health conditions in one individual.

Techniques to be used:

Experiments will be performed on biological samples collected from young or old individuals to compare the concentration, molecular weight and distribution of HA using a variety of lab-based methods (ELISA, IF, preparation of samples for SS-nanopore technology). Depending on progress and tissue availability there may also be the option to extend the study to investigate the expression of HA-related genes such as hyaluronan synthases (HAS1, 2, 3) and hyaluronidases (HYAL1, 2, 3) in relevant tissues.

3 Key references:

1. Zhang, Z., Tian, X., Lu, J. Y., Boit, K., Ablaeva, J., Zakusilo, F. T., Emmrich, S., Firsanov, D., Rydkina, E., Biashad, S. A., Lu, Q., Tyshkovskiy, A., Gladyshev, V. N., Horvath, S., Seluanov, A., & Gorbunova, V. (2023). Increased hyaluronan by naked mole-rat Has2 improves healthspan in mice. Nature, 621(7977), 196–205. https://doi.org/10.1038/s41586-023-06463-0

2. Rivas, F., Erxleben, D., Smith, I., Rahbar, E., DeAngelis, P. L., Cowman, M. K., & Hall, A. R. (2022). Methods for isolating and analyzing physiological hyaluronan: a review. American Journal of Physiology - Cell Physiology, 322(4), C674–C687. https://doi.org/10.1152/ajpcell.00019.2022
3. Sordo, L., Martini, A. C., Houston, E. F., Head, E., & Gunn-Moore, D. (2021). Neuropathology of Aging in Cats and its Similarities to Human Alzheimer's Disease. Frontiers in Aging, 2. https://doi.org/10.3389/fragi.2021.684607

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)?
HO licence? Not required
Other? Willingness to work with animal (rat, cat) samples (urine, blood, tissue).

08: Project title: Developing a next-generation in-vivo haematopoietic stem cell gene therapy for people with Friedreich's ataxia

Primary supervisor: Dr Kevin Kemp (email: kevin.kemp@bristol.ac.uk).

Secondary supervisor (for day-to-day support): Bruno Salomone Gonzalez de Castejon (email: bruno.salomone@bristol.ac.uk)

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

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

Friedreich's Ataxia (FA) is an incurable autosomal recessive multi-systemic disorder, typically presenting in late childhood. People with the condition experience progressive accumulation of neurological disability with impaired muscle coordination, weakness, difficulties with speech and swallowing, hearing, vision and sensation. The disorder also affects multiple other organs, with over half of FA patients also presenting with cardiomyopathy, and a third with diabetes. FA is caused by a genetic mutation in the *FXN* gene, which carries the genetic code for a life-essential mitochondrial protein called frataxin. This mutation leads to low levels of frataxin within cells, causing them to malfunction and die.

Studies have shown that transplantation of donor (allogeneic) haematopoietic stem cells (HSCs) offers the prospect of a disease-modifying treatment for people with FA. However, when used clinically, allogeneic transplantation is associated with risk of significant morbidity and mortality, in addition to challenges of finding an appropriate immunologic matched stem cell donor. To avoid the major limitations of allogeneic HSC transplantation, gene therapy approaches, involving ex-vivo genetic modification of autologous HSCs, are being developed. In current clinical practice, autologous HSC gene therapies rely on lentiviral vectors for efficient gene transfer. However, common ex-vivo approaches also suffer from the use of high-dose chemotherapy/irradiation conditioning regimens.

To mitigate the pitfalls associated with current HSC transplantation therapies and need for highly specialised clinical facilities, the aim of this project is to help develop an in-vivo HSC gene therapy approach for people with FA that offers the prospect of a universal, safe, and rapidly translatable treatment. Specifically, the student will construct and use next-generation helper-dependent adenoviral vectors (HDAd) to restore stable *FXN* gene expression in HSCs isolated from human blood samples; and investigate the downstream cellular effects of *FXN* restoration to HSCs and their immune cell progeny.

Techniques to be used:
Vector cloning; HDAd construction; haematopoietic stem cell isolation, culture, and differentiation; flow cytometry; fluorescence microscopy; protein expression analysis (ELISA/western blotting); PCR.

3 Key references:

1. Kemp KC, et al. Bone marrow transplantation stimulates neural repair in Friedreich's ataxia mice. Ann Neurol 83, 779-793 (2018).

2. Wang, H., et al., HDAd6/35++ - A new helper-dependent adenovirus vector platform for in vivo transduction of hematopoietic stem cells. Mol Ther Methods Clin Dev, 2023. 29: p. 213-226.

3. Koeppen AH. Friedreich's ataxia: pathology, pathogenesis, and molecular genetics. J Neurol Sci 303, 1-12 (2011).
Specific requirements for the project: Hepatitis B immunisation

09: Project title: Detecting affective state using novel machine learning-based analysis of behaviour in a mouse model of schizophrenia

Primary supervisor: Carole Fureix

Secondary supervisor (for day-to-day support): Michal Milczarek, Mike Ashby

School / Faculty: Bristol Veterinary School (CF) / School of Physiology, Pharmacology & Neuroscience (MM, MA)

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

Early-life experiences, genetic factors and adversity later in life interact to confer risk for developing, and worsening, neurodevelopmental and mood disorders, *e.g.* schizophrenia and depression. Comorbid depression and schizophrenia potentially share genetic and environmental risk factors, but their underlying mechanisms remain elusive, largely due to their heterogeneity in humans. By contrast, animal models of disease allow to precisely control genetic and environmental factors. Still, a key challenge in animal research is linking such manipulations with the ensuing phenotypes in a high-throughput, reproducible and translatable manner.

To that end, we have developed a behavioural scoring pipeline to monitor affective states of mice in their home-cage environment. Specifically, we can reliably manually detect (*i.e.* by human observer) instances when individuals are 'inactive but awake' (IBA), a measure closely linked to anhedonia, a clinical diagnostic symptom that can be common to depression and schizophrenia. Our first investigations also promisingly demonstrated potential for automated detection of IBA, though a functional toolkit remains to be fully developed.

Using visual and thermal imaging, our aims here are:

1. To quantify IBA from early in life in mice carrying a schizophrenia related GRIN2A mutation *versus* their wildtype littermates, allowing to identify if and when the behaviour differs due to genetic risk.

2. To further automate the process of quantifying IBA, by making a quantitative comparison of manually annotated data and machine-learning-based classifications.

Note: aim 1 is achievable using manual observation, hence can be completed independently from aim 2.

The project will contribute to the extension and refinement of the existing methodology to enable the assessment of genetically modified mouse disease models. It will also cement our between-schools collaboration *via* the generation of conference presentable / publishable data; contribute to future grant bids (e.g. UKRI Responsive Mode); and create multidisciplinary training and networking opportunities for the trainee.

Techniques to be used:

We will provide hands-on training for the student, capitalising on the expertise across the two Schools. The primary supervisor, Carole Fureix, will equip the student with a thorough understanding of animal experimental design and husbandry practice as well as instruct them in the implementation of behavioural sampling and annotation methods. With support from his line

manager (Mike Ashby), Michal Milczarek will introduce the student to the concept of colony management, train them in the use of multimodal video capture methodology and help develop analytic skills, including data handling, use of machine-learning algorithms and statistical testing. Furthermore, the student will be embedded into the wider MRC's National Mouse Genetics Network (of which Mike and Michal are members), giving them access to training and networking opportunities organised by the network. This will be supplemented by providing them access to online training and ECR-oriented resources (e.g. medical school short courses, national network ECR-supporting events, https://awrn.co.uk/category/awrn-news/).

The student will participate in generating research outcomes in the form of conference abstracts and presentations and will be encouraged to partake in public engagement events such as the Brain Awareness Week. This will outfit them not only with multiple research but also transferable skills valued in academia and industry.

3 Key references:

Fureix C, Trevarthen A, Finnegan E, Bučková K, Paul E, Mendl M (2022) Pharmacological validation of greater levels of in-cage waking inactivity in laboratory mice as a spontaneous depression-like symptom. Pharmacol Biochem Behav, 212: 173311, https://doi.org/10.1016/j.pbb.2021.173311

Herzog, L.E., Wang, L., Yu, E., Choi, S., Farsi, Z., Song, B., Pan, J.Q., Sheng, M., 2022. Mouse mutants in schizophrenia risk genes GRIN2A and AKAP11 show EEG abnormalities in common with schizophrenia patients. bioRxiv 2022.04.05.487037. https://doi.org/10.1101/2022.04.05.487037

Mathis, A., Mamidanna, P., Cury, K.M., Abe, T., Murthy, V.N., Mathis, M.W., Bethge, M., 2018. DeepLabCut: markerless pose estimation of user-defined body parts with deep learning. Nat Neurosci 21, 1281–1289. https://doi.org/10.1038/s41593-018-0209-y

Specific requirements for the project:

All experiments will be conducted under the existing PPL, P354E9EF0. An HO PIL will not be required for the trainee, since such home-cage behavioural observations are non-procedural and the student will not engage with the animals directly.

Allowed bench fees should enable covering the full research costs – any unexpected costs will be supported by Carole Fureix's new lecturer start-up research funds and/or existing Ashby MURIDAE Cluster funds.

10: Project title: Visible light activated photocatalytic antimicrobial coatings to combat nosocomial infections

Primary supervisor: Prof Bo Su

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

School / Faculty: Dental School/Health Sciences (Dorothy Hodgkin Building)

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]. Rather, bacterial pathogens are inactivated through a contact-killing mechanism, whereby the generated reactive oxygen species (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 photocatalytic antimicrobial coatings that possess antimicrobial and anti-biofilm activity under visible light (sunlight and artificial light), enabling effective removal of microbes and any other bio-contamination to reduce the transmission of bacterial infections primarily via touch surfaces in hospitals, e.g., door handles.

In this project, the photocatalytic effect and antimicrobial activity of coatings based on graphite carbon nitride (g-C_3N_4)/TiO_2 will be investigated. Our recent study shows that the heterojunctions of g-C_3N_4 nanosheets with TiO_2 nanoparticles have significantly enhanced photocatalytic activity under visible light compared to doped or undoped TiO_2 nanoparticles [2]. The g-C_3N_4/TiO_2 powders with an optimal ratio will be synthesised using our established protocol [3]. The coatings of g-C_3N_4/TiO_2 in a preceramic polymer will be deposited on various substrates by spraying or dip coating followed by crosslinking. The microstructure, photocatalytic activity and antimicrobial performance of the coatings will be characterised using scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FT-IR), UV-vis spectroscopy, and microbiology assays.

Techniques to be used:
Powder synthesis, spraying and dip coating, high-speed mixing, UV-vis spectroscopy, Fourier transform infrared spectroscopy, scanning electron microscopy, antimicrobial assays

Key references:

1. M. Schutte-Smith, E. Erasmus, R. Mogale, N. Marogoa, A. Jayiya, H. G. Visser, *J. Coat. Technol. Res.,* 20 (2023) 789–817
2. N.A. Ahmad Fauzi, A.J. Ireland, M. Sherriff, H. M. H. N. Bandara, B. Su, *Dental Materials*, 38 (2022) 147-157
3. F. da Silva, B. Su, *Ceramic International,* 49 (2023) 13265-13270

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

HO licence? No

11: Project title: Interactions between *Salmonella enterica* and the microbiota

Primary supervisor: Professor Paul Wigley

Secondary supervisor (for day-to-day support):Dr Tristan Cogan

School / Faculty: Bristol Veterinary School

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

Salmonella enterica can infect all warm-blooded hosts. A key part of this process is the ability of Salmonella to colonise the intestinal tract. During colonising there is a complex interaction with the resident microflora which can act to inhibit colonisation which can be exploited to prevent colonisation in the chicken which is a key reservoir for human foodborne infection (Pottenger et al, 2023). Infection with *Salmonella* causes considerable inflammation in most hosts which contributes to pathology and gastroenteritis. Recently, it has been proposed that inflammation within the gut offers *Salmonella* an advantage over anaerobic bacteria in the microbiome by raising local oxygen levels (Rogers et al 2021). We also know that key pathogen factors associated with driving inflammation such as the SPI1 encoded T3SS are needed for gut colonisation of the chicken (Jones et al 2007).

In this project we propose to treat *Salmonella* Typhimurium with cell-free supernatant of chicken intestinal content (the material we use for microbiome transplants) containing the metabolites from the microflora under both aerobic and anaerobic conditioins. We will use RNAseq-based approaches to identify transcriptional changes in Salmonella followed by targeted expression analysis of selected genes (e.g. over time, across strains) by RT-qPCR for cost efficacy. We will also assess phenotypic changes to *Salmonella* related to infection through the use of cell-based models of chicken epithelium and macrophages. These will include motility, cell attachment, cell invasion and the capacity to persist intracellularly. Dependent on progress we can being to determine host responses in the cell-models-notably production of inflammatory signals such a chemokines and pro-inflammatory cytokines.

Techniques to be used:

Basic bacteriology, cell-based infection models, cell culture, RNAseq, qPCR

3 Key references:

S Pottenger, A Watts, A Wedley, S Jopson, AC Darby, P Wigley, *Timing and delivery route effects of cecal microbiome transplants on Salmonella Typhimurium infections in chickens: potential for in-hatchery delivery of microbial interventions* Animal Microbiome. *2023,* **5** (1), 1-17

Rogers, A.W.L., R.M. Tsolis, and A.J. Baumler, *Salmonella versus the Microbiome.* Microbiol Mol Biol Rev, 2021. **85**(1)

Jones, M.A., et al., *The Salmonella pathogenicity island 1 and Salmonella pathogenicity island 2 type III secretion systems play a major role in pathogenesis of systemic disease and gastrointestinal tract colonization of Salmonella enterica serovar Typhimurium in the chicken.* Avian Pathol, 2007. **36**(3): p. 199-203.

Specific requirements for the project: None, but based at Langford.

Immunisations (e.g. Hepatitis B)?

HO licence?

Other

12: Project title:
The role of viral genomes on viral fitness and pathogenesis of HIV-1

Primary supervisor: Dr Jamie Mann

Secondary supervisor (for day-to-day support): Dr Katja Klein

School / Faculty: Bristol Veterinary School

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

RNA viruses represent one of the most important groups of zoonotic disease transmission, and a continued challenge for global disease control. RNA viruses are strong inducers of host innate immunity, usually because their genomes contain or generate immunogenic replication intermediates. To evade immune surveillance and detection, RNA viruses modify their genomic composition by suppressing the numbers of immunostimulatory regions (nucleotide motifs) present. While this was thought to be the case for human immunodeficiency virus-1 (HIV-1), our data, combining bioinformatic approaches on well characterised clinical data sets, as well as in vitro studies, demonstrated that HIV-1 has an enrichment for immunostimulatory motifs within its transmitted/founder virus population. By understanding why HIV-1 has genomes that are more likely to trigger immune responses, we will be able to understand HIV transmission and replication processes in much greater detail. Ultimately this work is expected to lead to the identification of novel vaccine and therapeutic candidates.

To begin to understand the role that viral genomes play in transmission and replication processes, a student will be embedded within the vibrant HIV/RNA virus research community at Bristol Veterinary School. Under the supervision of Dr Mann (project lead), the student will be mentored and trained in a range of lab-based approaches, including molecular cloning, RNA-sensing assays and tissue culture. Depending on the progress of the project, the opportunity exists for the student to explore the impact of wildtype and recoded viral genomes on transmissions processes using mucosal explant assays and deep gene sequencing. At the end of this project, the student will have a diverse knowledge on viral transmission biology and will be encouraged to pursue their own ideas and be creative. This will allow the student to take ownership of the project and play a significant role in shaping its direction and outcomes.

Techniques to be used:
Tissue culture, Molecular biology (genome recoding and pseudovirus engineering), RNA-sensing assays.

3 Key references:

Klein K, Nickel G, Nankya I, Kyeyune F, Demers K, Ndashimye E, Kwok C, Chen PL, Rwambuya S, Poon A, Munjoma M, Chipato T, Byamugisha J, Mugyenyi P, Salata RA, Morrison CS, Arts EJ. Higher sequence diversity in the vaginal tract than in blood at early HIV-1 infection. PLoS Pathog. 2018 Jan 18;14(1):e1006754. doi: 10.1371/journal.ppat.1006754. PMID: 29346424; PMCID: PMC5773221.

Klein K, Nankya I, Nickel G, Ratcliff AN, Meadows AAJ, Hathaway N, Bailey JA, Stieh DJ, Cheeseman HM, Carias AM, Lobritz MA, Mann JFS, Gao Y, Hope TJ, Shattock RJ, Arts EJ. Deep Gene Sequence Cluster Analyses of Multi-Virus-Infected Mucosal Tissue Reveal Enhanced Transmission of Acute HIV-1. J Virol. 2021 Jan 13;95(3):e01737-20. doi: 10.1128/JVI.01737-20. PMID: 33177204; PMCID: PMC7925087.

Joseph SB, Swanstrom R, Kashuba AD, Cohen MS. Bottlenecks in HIV-1 transmission: insights from the study of founder viruses. Nat Rev Microbiol. 2015 Jul;13(7):414-25. doi: 10.1038/nrmicro3471. Epub 2015 Jun 8. PMID: 26052661; PMCID: PMC4793885.
Specific requirements for the project: Immunisations (e.g. Hepatitis B)? HO licence? Other?

13: Project title:
Development of a self-amplifying RNA vaccine against HIV-1

Primary supervisor: Dr Jamie Mann

Secondary supervisor (for day-to-day support): Dr Katja Klein

School / Faculty: Bristol Veterinary School

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

It is acknowledged that an efficacious anti-HIV vaccine remains the best hope for eliminating the HIV-1 epidemic. However, the failure to produce effective vaccine immunogens and the inability of conventional delivery strategies to elicit the desired immune responses remains a central theme and has ultimately led to a significant roadblock in HIV vaccine development. Using several innovative technologies pioneered in our lab, and through close collaborations with scientists at international research institutions such as Western University (Canada), we have engineered >15 novel immunogens that display neutralisation sensitive epitopes on HIV-1. The aim being for the administered vaccine immunogens to trigger anti-viral neutralising antibody responses that are focused on this epitope. The opportunity now exists for an ambitious student to join our team and make a meaningful impact on global health by advancing our research in this area.

The student undertaking this project, will be embedded within a multidisciplinary research team at the forefront of HIV vaccine development. The recent COVID-19 pandemic has shown mRNA technology to be an effective technology at protecting populations against respiratory infections. Here, rather than using mRNA technology, the student will use a next generation self-amplifying (sa) RNA technology as a more promising and potent vaccine approach. Upon cloning the various immunogens into the saRNA vector, the student will then conduct studies to demonstrate that the vaccines express the desired immunogens and that they are recognised by well characterised anti-HIV antibodies.

The students involved in this project will have exposure to state-of-the-art vaccine engineering techniques and will gain invaluable insights from leaders in the field of HIV-1 vaccine development. They will receive continuous mentoring and training throughout the project, with encouragement to infuse their own ideas and creativity. This involvement allows students to play a significant role in shaping the direction and outcomes of the project.

Techniques to be used:
Western blot, saRNA vaccine production, tissue culture, pseudovirus neutralisation assays.

3 Key references:
Gao Y, McKay PF, Mann JFS. Advances in HIV-1 Vaccine Development. Viruses. 2018 Apr 1;10(4):167. doi: 10.3390/v10040167. PMID: 29614779; PMCID: PMC5923461.

Gao Y, Wijewardhana C, Mann JFS. Virus-Like Particle, Liposome, and Polymeric Particle-Based Vaccines against HIV-1. Front Immunol. 2018 Feb 28;9:345. doi: 10.3389/fimmu.2018.00345. PMID: 29541072; PMCID: PMC5835502.

Bloom, K., van den Berg, F. & Arbuthnot, P. Self-amplifying RNA vaccines for infectious diseases. Gene Ther 28, 117–129 (2021). https://doi.org/10.1038/s41434-020-00204-y

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

14: Project title: Comparative Analysis of the Microbiome in Pet Rabbits: Understanding Ceacal Dysbiosis Through 16S rRNA Sequencing

Primary supervisor: Sion Bayliss

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

School / Faculty: Bristol Veterinary School

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

Background: Ceacal dysbiosis represents significant health challenges in pet rabbits, leading to discomfort, morbidity, and even mortality. This condition is caused by an imbalance in the microbial population of the cecum, an essential part of the rabbit's digestive system where fermentation of fibrous materials occurs. Unlike their wild counterparts and those used in laboratory research, pet rabbits have been relatively understudied in terms of their microbiome's role in ceacal dysbiosis and other associated conditions. While extensive research has been conducted on the microbiomes of wild (Funosas et al. 2021) and farmed (Cotozzolo et al. 2020), and laboratory animals (Hu et al. 2021), the specific microbial communities within pet rabbits experiencing chronic and acute gastric stasis remain poorly characterised.

Project Aims: This project aims to establish if there are differences in the microbial communities present in the health pet rabbits and those suffering from cecal dysbiosis via the sequencing of faecal samples collected non-invasively. To achieve this, the student will perform 16S gene sequencing, this gene is present in all bacteria and can be used to differentiate between bacterial genera present in the microbiome. This approach will be used to differentiate between healthy and diseased microbiome constituents and to identify microbiomes dynamics in and around bouts of ceacal dysbiosis.

Outcomes: This project aims to elucidate the complex microbial environment of pet rabbits, focusing on those with a history of gastrointestinal issues. By identifying the specific microbiome constituents associated with healthy and dysbiotic states, this research could pave the way for novel preventative and therapeutic strategies. Ultimately, this project seeks to contribute to the broader understanding of pet rabbit health, emphasizing the need for targeted research in this underserved population. The findings could have significant implications for dietary recommendations, probiotic treatments, and overall management practices for pet rabbits, potentially reducing the incidence of these debilitating conditions.

Techniques to be used:
- Bacterial Culture and DNA Extraction
- Oxford Nanopore Gene/Genome Sequencing
- Microbial Community Analysis

3 Key references:

Cotozzolo, Elisa, Paola Cremonesi, Giulio Curone, Laura Menchetti, Federica Riva, Filippo Biscarini,

Maria Laura Marongiu, et al. 2020. “Characterization of Bacterial Microbiota Composition along the Gastrointestinal Tract in Rabbits.” Animals : An Open Access Journal from MDPI 11 (1). https://doi.org/10.3390/ani11010031.

Funosas, Gerard, Xavier Triadó-Margarit, Francisca Castro, Rafael Villafuerte, Miguel Delibes-Mateos, Carlos Rouco, and Emilio O. Casamayor. 2021. “Individual Fate and Gut Microbiome Composition in the European Wild Rabbit (Oryctolagus Cuniculus).” Scientific Reports 11 (1): 766.

Hu, Xiaofen, Fei Wang, Shanshan Yang, Xu Yuan, Tingyu Yang, Yunxiao Zhou, and Yong Li. 2021. “Rabbit Microbiota across the Whole Body Revealed by 16S rRNA Gene Amplicon Sequencing.” BMC Microbiology 21 (1): 312.

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? No
HO licence? No
Other? This would require a routine application for a University Investigation Number (UIN) with is the ethical review process for non-regulated research involving animals. This is internal system which is governed by the Animal Welfare and ethical Review Body (AWERB).

15: Project title: Development of an integrated multidisciplinary, adaptive approach on bacterial diseases with a view to address global health security threats in different farm ecosystems.

Primary supervisor: Benedetta Amato

Secondary supervisor (for day-to-day support): Daniel Enriquez Hidalgo

School / Faculty: Veterinary School

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

Soil provides the basic structure for the development of the ecosystem where humans and animals live. Soil microbiota, including different pathogenic and non-pathogenic microorganisms, are responsible for the health and maintenance of the ecosystem, creating the greatest biodiversity in the world. The interactions of the microorganisms harboured in the soil are complex. In most undisturbed ecosystems, these organisms are regulated by complex ecological mechanisms such as mutual beneficial relationships such as symbiosis, competition and predator–prey systems. Most soilborne/dwelling microorganisms do not pose a risk to human or animal health, but, some of the microorganisms that cause human disease can be naturally present in the soil/environment or be excreted by farm animals such cattle and wildlife and harboured in the soil. Furthermore, many of them have vectors that live in or spend part of their life cycle in soil. However, there is a lack of understanding about the role played directly or indirectly by those vectors in the maintenance and persistence of certain diseases and pathogens as well as the impact of the agricultural land management on the soil health, biodiversity and pathogen survival, particularly considering different key evolving factors as land use and degradation, changing climate and pandemic development.

This project aims to

1- Collect and analyse data of different farm management systems in order to identify possible natural or anthropogenic factors that may influence the presence and persistency in the soil and vectors (earthworms) of pathogenic microorganisms;
2- Assess and monitor the presence of pathogenic bacteria in soil from different farming systems and faeces from farm ruminants and wildlife;
3- Assess the presence and viability of pathogenic bacteria in earthworms.

Techniques to be used: Histology and special stains, bacterial culture, immunohistochemistry, immunocytochemistry, RT-PCR.

3 Key references:

1-Keesing F, Belden LK, Daszak P, Dobson A, Harvell CD, Holt RD, Hudson P, Jolles A, Jones KE, Mitchell CE, Myers SS, Bogich T, Ostfeld RS. Impacts of biodiversity on the emergence and transmission of infectious diseases. Nature. 2010 Dec 2;468(7324):647-52. doi: 10.1038/nature09575. PMID: 21124449; PMCID: PMC7094913.

2-Steffan JJ, Derby JA, Brevik EC. Soil pathogens that may potentially cause pandemics, including severe acute respiratory syndrome (SARS) coronaviruses. Curr Opin Environ Sci Health. 2020 Oct;17:35-40. doi: 10.1016/j.coesh.2020.08.005. Epub 2020 Sep 8. PMID: 33521411; PMCID: PMC7836926.

3- Barbier E, Chantemesse B, Rochelet M, Fayolle L, Bollache L, Boschiroli ML, Hartmann A. Rapid dissemination of Mycobacterium bovis from cattle dung to soil by the earthworm Lumbricus

terrestris. Vet Microbiol. 2016 Apr 15;186:1-7. doi: 10.1016/j.vetmic.2016.01.025. Epub 2016 Feb 16. PMID: 27016750.
Specific requirements for the project: None Immunisations (e.g. Hepatitis B)? HO licence? Other?

16: Investigating the immunotherapeutic and chemotherapeutic implications of RASAL2 in triple-negative breast cancer

Primary supervisor: Dr Nobue Itasaki

Secondary supervisor (for day-to-day support): Dr Siang Boon Koh

School / Faculty: Veterinary School/Faculty of Health Sciences; School of Cellular and Molecular Medicine/Faculty of Life Sciences

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

Triple-negative breast cancer (TNBC), defined by the lack of oestrogen and progesterone receptors expression and human epidermal growth factor receptor 2 (HER2) amplification, has long been notorious for its poor prognosis due to its insusceptibility to hormone and HER2-targeted therapies. In exploring non-hormonal chemotherapy approach, it was found that the high level expression of RASAL2, a RAS-GTPase-activating protein (RAS-GAP), in TNBC accounts for the drug resistance against platinum-based chemotherapy[1]. Therefore, other aspects of therapeutic approaches such as immunotherapy are desired in treating TNBC.

Previously, RASAL2 has been reported to influence TNF-α response in prostate cancer, suggesting its potential immunomodulatory capacity[2]. Through transcriptional profiling and protein expression analyses, we have recently discovered that overexpression of RASAL2 downregulates MHC class I molecules and interferon-γ gene signatures in TNBC. Therefore, we hypothesise that RASAL2's RAS-GAP activity may influence intrinsic immune signalling pathways downstream of interferon and/or cytokine receptors, thereby potentiating immune resistance against CD8+ T-cell responses. Despite the crucial clinical significance of RASAL2 in TNBC, its oncogenic effects in the interaction with T-cells and potential in instigating other hallmarks of cancer remain underexplored.

To address this, we will first establish matrigel-based 3D culture systems to better recapitulate the cell-cell contact and immune milieu of advanced TNBC[3]. Subsequently, RASAL2-overexpressing TNBC cells will be cocultured with T- and NK-cells to assess their tumour killing activities by employing ATP-based cell viability assay and time-lapse microscopy. Finally, the candidate immune-related genes and intrinsic immune signalling pathways by which RASAL2 modulates in response to immune cells (e.g. CD8+ T-cells, NK-cells, monocytes) will be characterised through expression assays and validated using knockdown experiments.

Collectively, these experiments will for the first time define the immunomodulatory role of RASAL2 in conferring immune resistance in TNBC, thus suggesting novel immunotherapeutic and chemotherapeutic approaches to target this highly refractory subset of TNBC.

Techniques to be used:

- *In vitro* 3D co-culture of RASAL2-overexpressing TNBC cells with T-/NK-cells
- Time-lapse microscopy
- XTT cell viability assay
- mRNA and protein expression characterisation (e.g. western blotting and RT-qPCR) of RASAL2-overexpressing TNBC cells
- Knockdown of RASAL2 and its target genes by siRNA transfection

3 Key references: [1] Koh SB, Ross K, Isakoff SJ, Melkonjan N, He L, Matissek KJ, et al. RASAL2 Confers Collateral MEK/EGFR Dependency in Chemoresistant Triple-Negative Breast Cancer. Clin Cancer Res. 2021 Sep 1;27(17):4883-4897. doi: 10.1158/1078-0432.CCR-21-0714. [2] Tailor K, Paul J, Ghosh S, Kumari N, Kwabi-Addo B. RASAL2 suppresses the proliferative and invasive ability of PC3 prostate cancer cells. Oncotarget. 2021 Dec 21;12(26):2489-2499. doi: 10.18632/oncotarget.28158. [3] Abe-Fukasawa N, Otsuka K, Aihara A, Itasaki N, Nishino T. Novel 3D Liquid Cell Culture Method for Anchorage-independent Cell Growth, Cell Imaging and Automated Drug Screening. Sci Rep. 2018 Feb 26;8(1):3627. doi: 10.1038/s41598-018-21950-5.
Specific requirements for the project: Immunisations (e.g. Hepatitis B)? No HO licence? N/A Other? No

17: Project title: 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'. 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 using CRISPR mutation and siRNA knock-down approaches in stem cells that reduced *SNRPB* expression *in vitro* interferes with osteogenesis and chondrogenesis, and causes inhibition of Wnt signalling and enhancement of BMP signalling, two pathways required for bone development [2]. This was recapitulated 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. Keeling, H., E.J. Williams, and N. Itasaki, *Consideration of the thoracic phenotype of cerebro-costo-mandibular syndrome.* Clin Anat, 2023: p. e-published ahead of print.
2. Knill, C., et al., *Defects of the spliceosomal gene SNRPB affect osteo- and chondro-differentiation.* FEBS J, 2023.
3. Turner, B.R.H. and N. Itasaki, *Local modulation of the Wnt/beta-catenin and bone morphogenic protein (BMP) pathways recapitulates rib defects analogous to cerebro-costo-mandibular syndrome.* J Anat, 2020. **236**(5): p. 931-945.

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

18: Project title: GelMA-polydopamine bioinks for vascularized bone tissue engineering

Primary supervisor: Dr. James Armstrong

Secondary supervisor (for day-to-day support): Dr. Farnaz Ghorbani

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

Summary of project:

Bone defects can arise from traumatic injury, tumour resection, or infection. Recent developments in biofabrication have demonstrated the potential to engineer patient-matched engineered tissues for the regeneration of bone defects. The Armstrong Group (www.TheArmstrongGroup.co.uk) is developing a number of biomaterial-based strategies for bone repair, including the use of multi-material bioprinting for vascularized bone tissue engineering. In this interdisciplinary project, the MRes student will formulate osteoblast-laden hydrogel bioinks comprising gelatin methacryloyl (GelMA) and polydopamine (PDA), polymeric materials that have been widely used to support bone growth. The exact formulation will be optimized to achieve the appropriate balance between shear-thinning, viscoelastic behaviour, and network density, parameters that are crucial for the bioink printability, shape fidelity, and cell viability. Optimal bioink compositions will then be put through extrusion tests, to measure the bioink printability, as well as *in vitro* tissue engineering to evaluate the support of the biomaterial for osteoblast proliferation and biomineralization. This study will yield important results for the field of bone biofabrication that will lay the groundwork for the development of new tissue engineering strategies for bone repair.

Objectives:

1. To define the specifications and requirements for the bioink.
2. To synthesize and characterize PDA nanospheres and GelMA.
3. To optimize the rheology of the GelMA-PDA bioink formulations.
4. To evaluate selected bioinks using extrusion tests and bone tissue engineering.

Techniques to be used:

Biomaterial synthesis (PDA, GelMA); chemical characterization (Fourier-transform infrared spectroscopy); bioink formulation; rheology and mechanical testing, extrusion printing; osteoblast cell culture; bone tissue engineering, cell staining and microscopy; cell viability and proliferation assays; biomineralization assays; immunostaining; RT-qPCR (*latter techniques depend on progress*).

3 Key references:

[1] L. Ouyang, J.P.K. Armstrong, Q. Chen, Y. Lin, M.M. Stevens, Void-Free 3D Bioprinting for In Situ Endothelialization and Microfluidic Perfusion, Adv. Funct. Mater. 30 (2020). https://doi.org/10.1002/adfm.201908349.

[2] F. Ghorbani, A. Zamanian, A. Behnamghader, M.D. Joupari, A facile method to synthesize mussel-inspired polydopamine nanospheres as an active template for in situ formation of biomimetic hydroxyapatite, Mater. Sci. Eng. C. 94 (2019). https://doi.org/10.1016/j.msec.2018.10.010.

[3] X. Sun, J. Yang, J. Ma, T. Wang, X. Zhao, D. Zhu, W. Jin, K. Zhang, X. Sun, Y. Shen, N. Xie, F. Yang, X. Shang, S. Li, X. Zhou, C. He, D. Zhang, J. Wang, Three-dimensional bioprinted BMSCs-laden highly adhesive artificial periosteum containing gelatin-dopamine and graphene oxide nanosheets promoting bone defect repair, Biofabrication. 15 (2023) 025010. https://doi.org/10.1088/1758-5090/acb73e.

Specific requirements for the project: None

Immunisations (e.g. Hepatitis B)?

HO licence? Other?

19: Project title: Characterizing the wound healing response of granular biomaterials

Primary supervisor: **Dr James Armstrong, Prof Chrissy Hammond**

Secondary supervisor (for day-to-day support): **Zhipeng Deng, Joanna Moss and/or Qiao Tong**

School / Faculty: **Bristol Medical School, Faculty of Health Sciences (JA, ZD)**
School of Physiology, Pharmacology & Neuroscience, Faculty of Life Sciences (CH)

Summary of project:

The Armstrong Group is developing and testing a suite of innovative wound-healing biomaterials. These "granular hydrogels" can be injected into wound sites to provide a microporous environment that allows invasion of endogenous cells for tissue regeneration. We have recently developed a new generation of granular hydrogels that have shown substantially enhanced mechanical and biological performance *in vitro*. This MRes project will be the first step towards clinical translation: assessing the regenerative response *in vivo* using zebrafish larvae models.

In this project, the student will fabricate, functionalize, and characterize gelatin-based granular hydrogels (using established protocols developed by Zhipeng Deng). These will then be injected into the wound site of zebrafish larvae with skin and muscle injury or into bony regions following genetic ablation of osteoblasts, with the subsequent tissue regeneration characterized over 2-3 days. We will characterise the responses of multiple cell types (*e.g.*, neutrophils, macrophages, myoblasts, fibroblasts, endothelial cells and osteoblasts) using transgenic fish lines carrying fluorescent reporters labelling cells of interest (all established in the Hammond lab), using bioimaging (*e.g.*, stereo, confocal, light sheet microscopy). We will test how cells interact with and migrate through the hydrogels and measure regenerative processes (e.g., skin wound closure, bone formation). We will study three groups: our latest generation granular hydrogels *vs* conventional granular hydrogels *vs* no biomaterial controls. This will provide key insight into the regenerative capacity of our biomaterial for soft-tissue wound healing.

Techniques to be used:

- Granular hydrogel fabrication and functionalization
- Biomaterial assays to characterize granular hydrogel
- Zebrafish in vivo imaging

3 key references:

1. Granular hydrogels for endogenous tissue repair - ScienceDirect
2. Sticking Together: Injectable Granular Hydrogels with Increased Functionality via Dynamic Covalent Inter-Particle Crosslinking - PubMed (nih.gov)
3. https://pubmed.ncbi.nlm.nih.gov/33668680/

Specific requirements for the project:

Immunisations (e.g. Hepatitis B)? No
HO licence? No
Other? No

20: Project title: 3D printing high-density collagen towards vascular bone tissue engineering

Primary supervisor: **Dr James Armstrong**

Secondary supervisor (for day-to-day support): **Norah-Jane Prendergast, Dr Camila Tovani**

School / Faculty: **Bristol Medical School, Health Sciences (JA, NJP); Sorbonne University (CT)**

Summary of project:

The bone extracellular matrix is composed of high-density type I collagen fibrils mineralized with hydroxyapatite.[1] Although bone has an impressive capacity for self-healing, large defects (>1 cm) commonly require surgical intervention with tissue grafts or biomaterial implants. Given its natural matrix role, type I collagen has been widely explored as a regenerative biomaterial for bone repair. Much of the previous work has focused on low-concentration collagen biomaterials, however, these lack the biological and mechanical characteristics that enable natural bone function.[1] The team led by Dr. Nadine Nassif at Sorbonne University has developed an innovative method to pack collagen molecules into dense microparticles, which enables it to be extruded at unprecedentedly high concentrations.[2] This approach enabled the fabrication of collagen structures at bone-like densities, which provides high mechanical performance and guided biomineralization (Figure 1).

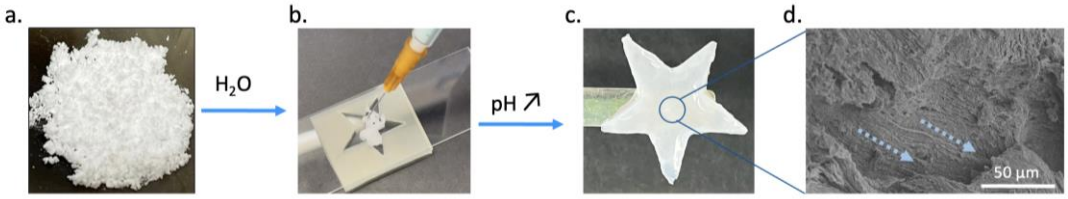


Figure 1. (a) Collagen/calcium phosphate particles powder, (b) injectable high-concentration collagen/calcium phosphate mixture, (c) 3D bone-like scaffold, (d) scanning electron microscopy showing bone-like assembly (blue arrows) and density of mineralized collagen fibrils.

This interdisciplary project will develop this biomaterial into a suitable bioink for 3D printing, which would open up new possibilities for patient-specific tissue grafting. The student would undertake a short placement at Sorbonne University, guided by Dr Camila Tovani, in which they would learn to prepare and handle collagen biomaterials. Returning to Bristol, the student would then work with Norah-Jane Prendergast and other experts in the Armstrong Group to formulate the material into printable bioinks and optimize the 3D printing parameters to yield stable, high-fidelity structures.[3] Finally, the student will perform a biological assessment of the printed structures using endothelial cells to inform future studies in vascularized bone tissue engineering. This collaborative endeavour, at the forefront of biomaterials and biofabrication science, will provide the student with unique training across a number of key techniques (see below).

Techniques to be used:
- Type I collagen extraction, purification and characterization (e.g., rheometry, electron microscopy)
- 3D printing tests
- Sterile cell culture of HUVEC cells
- Cell staining and confocal fluorescence microscopy.

3 Key references:

1. Wang et al. *Nature materials* (2012).
2. Lama et al. Small (2019).
3. Ouyang *et al. Science Advances* (2020).

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

HO licence? No Other? No

21: Project title: Exploring the angiogenesis-related function of newly discovered cardiac pericyte markers.

Primary supervisor: **Dr Elisa Avolio – Research Fellow**

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

School / Faculty: Bristol Medical School - THS

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

Cardiac pericytes (PCs) are the second most abundant cell population of the heart after cardiomyocytes. They wrap around the coronary microvasculature where they contribute to preserving vascular and cardiac homeostasis (**REF1-2**). Due to their properties, PCs might play a key role in orchestrating the heart reparative response after ischemia. However, a limitation in studying these cells is represented by the lack of specific markers distinguishing PCs from other similar mural cells (vascular smooth muscle cells) and cardiac stromal cells (**REF1-2**).
We recently demonstrated that cardiac PCs can be differentiated into contractile cells with superior angiogenic activity to aid the revascularisation of the heart after ischemia (**REF 3**). To induce cell differentiation, we treated PCs with a selective inhibitor of the MEK kinase (PD0325901) for 10 days (**REF 3**). To better understand the mechanisms of PC differentiation, we performed bulk RNA-Sequencing analysis of basal PCs and differentiated PCs (DPCs). Through this analysis, we extrapolated a list of transcripts uniquely expressed by either PCs or DPCs. We therefore identified a novel marker expressed by PCs: cell adhesion molecule 3 (CADM3), which is important to preserve cell-cell junctions and control vascular permeability; and two novel markers expressed solely by DPCs: aquaporin 1 (AQP1), which facilitates endothelial cell (EC) migration by a mechanism involving water transport across angiogenic lamellipodia, and cellular retinoic acid binding protein 2 (CRABP2), which controls angiogenesis through modulation of RA transport from the cytosol to nuclear RA receptors (**REF 3**). Although the function of these markers is known in other cell populations, we still don't know why cardiac PCs express these markers and whether they contribute to the superior DPC angiogenic activity. Therefore, this project will aim to explore the functional role of these newly discovered PC and DPC markers.

Techniques to be used:

- In vitro culture and expansion of human primary cardiac PCs previously extracted from patients' myocardial biopsies, and of commercial coronary artery ECs (CAECs).
- Cardiac PC differentiation using the MEK inhibitor PD0325901.
- Immunocytochemistry staining of cardiac PCs to check the expression of PC and differentiation markers.
- Transient gene silencing using siRNA pools to knock-down the expression of CADM3, AQP1, and CRABP2 genes in cardiac PCs and DPCs to perform functional assays.
- RNA extraction, reverse transcription, and real-time qPCR to confirm gene silencing.
- Protein extraction for western blotting to confirm protein knock-down in PCs.
- Matrigel angiogenesis assay (co-culture of PCs and CAECs).
- Permeability assay using Electric Cell-substrate Impedance Sensing (ECIS) with co-cultures of PCs and CAECs.
- Wound healing migration assay with PCs.

3 Key references:

(REF 1) Avolio E, Campagnolo P, Katare R, Madeddu P. *The role of cardiac pericytes in health and disease: therapeutic targets for myocardial infarction*. Nature Rev Cardiol. 2023 Aug 4. doi: 10.1038/s41569-023-00913-y. Review.
(REF 2) Avolio E, Madeddu P. *Discovering cardiac pericyte biology: From physiopathological mechanisms to potential therapeutic applications in ischemic heart disease*. Vascul Pharmacol. 2016 Nov;86:53-63. doi: 10.1016/j.vph.2016.05.009. Review
(REF 3) Avolio E, Katare R, et al. *Cardiac pericyte reprogramming by MEK inhibition promotes arteriologenesis and angiogenesis of the ischemic heart*. J Clin Invest. 2022 May 16;132(10):e152308. doi: 10.1172/JCI152308

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? **Yes**, as the project includes manipulation of primary pericytes extracted from patients' cardiac samples.
HO licence? No
Other?

22: Project title: Electrophysiological properties of cardiac pericytes in health and disease

Primary supervisor: Svetlana Mastitskaya

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

School / Faculty: THS and PPN

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

Pericytes are contractile cells wrapped around capillaries, playing an important role in supporting vascular wall integrity and angiogenesis. There is substantial evidence for capillary pericytes acting as metabolic sentinels in the brain, sensing local depletions of metabolic reserves and responding through electrical signaling to increase blood flow to the affected region and replenish the local energy supply, thereby protecting neuronal health and function. The same role is suspected for cardiac pericytes as well. Additionally, pericytes express receptors for various neurotransmitters and vasoactive substances, positioning them ideally to regulate blood flow at the capillary level in response to the metabolic demands of the tissue and neural and hormonal stimuli.

This project will investigate signaling mechanisms in cultured cardiac pericytes in response to autonomic neurotransmitters (e.g., NA, ACh, NPY), vasoconstrictors, and vasodilators, and how these are affected in pathological conditions such as hyperglycaemia or hypoxia. The contractile responses of pericytes are dependent on intracellular Ca dynamics, which will be studied using Ca imaging with epifluorescence or confocal microscopy. The relaxation of pericytes, in turn, is dependent on the activity of ATP-sensitive potassium channels, which regulate their membrane potential. These processes will be studied using patch-clamping techniques. Characterizing the properties of cardiac pericytes and their alterations in *in vitro* models of disease allows for an understanding of how these cells respond to pathological changes associated with conditions like diabetes and ischaemia. This knowledge can guide the development of pharmacological interventions targeting pericytes to modulate blood flow and tissue perfusion, potentially mitigating the progression or complications of such pathological conditions.

Techniques to be used:
Cell culture, immunostaining, Western blot, Ca imaging, patch-clamping.

3 Key references:

1) Avolio, E., Campagnolo, P., Katare, R. *et al.* The role of cardiac pericytes in health and disease: therapeutic targets for myocardial infarction. *Nat Rev Cardiol* **21**, 106–118 (2024). *doi*: 10.1038/*s41569-023-00913-y.*
2) Longden TA, Zhao G, Hariharan A, Lederer WJ. Pericytes and the Control of Blood Flow in Brain and Heart. Annu Rev Physiol. 2023 Feb 10;85:137-164. doi: 10.1146/annurev-physiol-031522-034807.
3) Lee LL, Khakoo AY, Chintalgattu V. Cardiac pericytes function as key vasoactive cells to regulate homeostasis and disease. *FEBS Open Bio*. 2021;11(1):207-225. doi:10.1002/2211-5463.13021.

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

23: Project title: The effects of autonomic neurotransmitters on cardiac pericyte function

Primary supervisor: Svetlana Mastitskaya

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

School / Faculty: THS

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

Pericytes are contractile cells with processes wrapped around capillaries. They contract or relax in response to neurotransmitters and vasoactive agents and thus regulate capillary diameter. In the brain, pericytes contribute to neurovascular coupling. There is also increasing experimental evidence that cardiac pericytes actively regulate coronary blood flow (Zhao et al., 2020). This becomes especially important in pathology - in heart ischaemia, pericytes constrict and die in rigor, which causes no-reflow phenomenon and further damage to the myocardium (O'Farrell et al., 2017). Neurotransmitters released in the tissue during ischaemia may contribute to this constriction. It is known that in the brain, noradrenaline causes pericyte constriction. Sympathetic overactivity is a known feature of myocardial ischaemia. At the same time, parasympathetic (vagal) activity is reduced in the acute phase of myocardial infarction, and reduced cardiac vagal tone is associated with mortality. Stimulation of the vagus nerve is known to preserve the failing heart and improve exercise capacity (Machhada et al., 2020). The cardioprotective effects of vagus nerve stimulation are at least in part mediated via modulation of cardiac pericyte contractility.

This project aims to study the effects of sympathetic (NA, NPY) and parasympathetic (ACh) neurotransmitters on cardiac pericyte contractility in physiological and ischaemic conditions. The findings of this study will help to understand the autonomic regulation of cardiac pericytes and may inform the therapeutic approaches to improving the outcomes of myocardial infarction. Experiments will be performed on isolated mouse heart tissue using widefield and confocal microscopy. The capillary diameter will be measured at pericyte locations upon application of vasoactive substances and in conditions of tissue ischaemia.

Techniques to be used:
Live tissue imaging, immunostaining, Ca imaging.

3 Key references:

1) Machhada A et al. Optogenetic stimulation of vagal efferent activity preserves left ventricular function in experimental heart failure (2020) *JACC Basic Transl Sci* 5(8); doi: 10.1016/j.jacbts.2020.06.002.
2) Zhao G et al. ATP- and voltage-dependent electro-metabolic signaling regulates blood flow in heart (2020) *PNAS* 117(13); doi: 10.1073/pnas.1922095117.
3) O'Farrell F et al. Capillary pericytes mediate coronary no-reflow after myocardial ischaemia (2017) *eLife* 6; doi: 10.7554/eLife.29280.

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

24: Project title: Investigating the extracellular matrix protein agrin and its potential of inducing cardiac repair

Primary supervisor: Maria Giulia Bigotti/Danielle Paul

Secondary supervisor (for day-to-day support): Maria Giulia Bigotti/Danielle Paul

School / Faculty: Faculty of Health and Life Sciences (Schools of THS and PPN)

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

Background

Heart failure is a leading cause of morbidity and mortality worldwide. After cardiac injury, the mammalian adult heart has a very limited capacity to regenerate fully functional muscle, due to the inability of differentiated cardiomyocytes (CMs) to efficiently proliferate. This has been directly linked to the extracellular matrix (ECM) surrounding and connecting CMs, as its increasing rigidity during heart maturation has a crucial impact over their proliferative capacity. Recent studies using mouse models have demonstrated how the ECM protein agrin promotes heart regeneration through CMs de-differentiation and proliferation (1). In maturing CMs, this proteoglycan acts as an inducer of a specific regenerative pathway by binding the ECM receptor α-dystroglycan (α-DG) at the cell membrane of CMs. During heart development, agrin gets progressively downregulated (1, 2) and ultimately replaced by other ECM proteins, eventually leading to loss of proliferation/ regenerative capacity in mature CMs. Crucially, administration of exogenous agrin to both murine and piglet models of myocardial infarction has been demonstrated to reactivate cardiomyocyte proliferation and promote cardiac repair (1), which makes this protein a promising target for development into a cardioprotective therapeutic agent.

Aims

The mechanism behind the agrin-driven regenerative program is poorly defined, also due to a lack of available structural information on this complex proteoglycan (3). We aim at filling this knowledge gap by focusing on the minimal C-terminal fragment of agrin necessary for the interaction with α-DG, and thus primarily responsible for the switching-on and off of the proliferation program, that we have cloned and overproduced in recombinant form (rAgrin).

Techniques to be used:

- *rAgrin high-resolution 3D structure by Cryo-Electron Microscopy (cryo-EM):*

after 'in-house' sample preparation (rAgrin expression in E.coli and purification, Cryo-EM grids preparation) Cryo-EM data will be collected at the Uni Bristol Cryo-EM Facility. Image data will be processed and analysed also employing AI generated new tools to automate the dataset handling workflow. Deep learning-based structure prediction methods such as alphafold2 will be used to augment experimentally derived data.

-*Structural investigation of the rAgrin-α-DG interaction:*

if successful, this Cryo-EM analysis will be expanded to the rAgrin-α-DG complex. α-DG from rabbit muscle tissue will be purified to homogeneity, and its binding capacity to rAgrin will be measured by solid-phase binding essays. The rAgrin- α-DG complex will then be analysed by Cryo-EM as described for rAgrin alone.

3 Key references:

1. Bassat E, Mutlak YE, Genzelinakh A, et al. The extracellular matrix protein agrin promotes heart regeneration in mice. *Nature*. 2017;547(7662):179-184. doi:10.1038/nature22978.
2. Skeffington KL, Jones FP, Suleiman MS, Caputo M, Brancaccio A, Bigotti MG.(2022). Determination of Agrin and Related Proteins Levels as a Function of Age in Human Hearts. *Front Cardiovasc Med*. 2022;9:813904. doi:10.3389/fcvm.2022.813904.
3. Bigotti MG, Skeffington KL, Jones FP, Caputo M, Brancaccio A. (2020). Agrin-Mediated Cardiac Regeneration: Some Open Questions. *Front Bioeng Biotechnol*. 2020;8:594. doi:10.3389/fbioe.2020.00594.

Specific requirements for the project: none
Immunisations (e.g. Hepatitis B)?
HO licence?
Other?

25: Project title: Biodistribution profiling of a gene therapy targeting the glomerular endothelium.

Primary supervisor: Aldara Martin Alonso (secondary: Becky Foster, Simon Satchell)

Secondary supervisor (for day-to-day support): Aldara Martin Alonso

School / Faculty: Bristol Medical School (THS)

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

The glomerular filtration barrier in the kidneys filter water and small solutes from the blood, whilst retaining macromolecules. The glomerular endothelium, lining the blood vessels, is the first barrier in direct contact with blood and is a key player in the glomerular filtration barrier function. In addition, glomerular endothelial cells (GEnCs) produce a poly-anionic gel, named endothelial glycocalyx, that is of critical importance to blood vessel function. Dysfunction of the glomerular endothelial cells (GEnCs) is important in different glomerular diseases. Crucially, they are implicated in the development of diabetic kidney disease (DKD).

Gene therapy is a promising therapeutic tool due to its cell-specificity, stability, and safety profile. However, GEnC-specific gene therapies have not been possible due to the lack of known GEnC-specific markers, until now. We are currently developing an adeno-associated virus (AAV)-based gene therapy using our novel promoter that will allow specific targeting to GEnCs (AAV-GEnC), 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.

The main aim of this project is to support the analysis of a study that aims to evaluate the distribution of the AAV-GEnC in different organs and cell types. This is a key step to evaluate the therapeutic potential as well as safety of this gene therapy system.
The supervisor would have completed this study and collected the tissue samples. The student will contribute to the assessment of the AAV-GEnC biodistribution in different tissues (e.g., kidney, liver, heart, retina) using a range of techniques to quantify gene and protein expression and/or activity (RTqPCR, Western blot, immunostaining, enzyme activity assays). Different reagents (e.g., antibodies) and conditions might be optimised at this step.

Techniques to be used:
Immunohistochemistry/immunofluorescence, BCA assay, SDS-PAGE, Western blot, RNA extraction, reverse transcription, 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
- Wu JC, Sundaresan G, Iyer M, Gambhir SS. Noninvasive optical imaging of firefly luciferase reporter gene expression in skeletal muscles of living mice. *Mol Ther*. 2001; 4:297-306. doi: 10.1006/mthe.2001.0460.
- Remes A, Basha DI, Puehler T, Borowski C, Hille S, Kummer L, Wagner AH, Hecker M, Soethoff J, Lutter G, Frank D, Arif R, Frey N, Zaradzki M, Müller OJ. Alginate hydrogel polymers enable efficient delivery of a vascular-targeted AAV vector into aortic tissue. *Mol Ther Methods Clin Dev*. 2021; 24;21:83-93. doi: 10.1016/j.omtm.2021.02.017.

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

26: Project title: 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 Nesreen Hamad and 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.

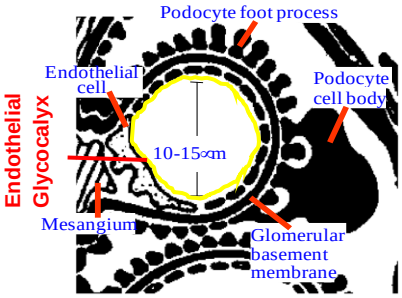


Fig 1. Cross section through a glomerular capillary

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 $EXT1^{fl/fl}$ 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.

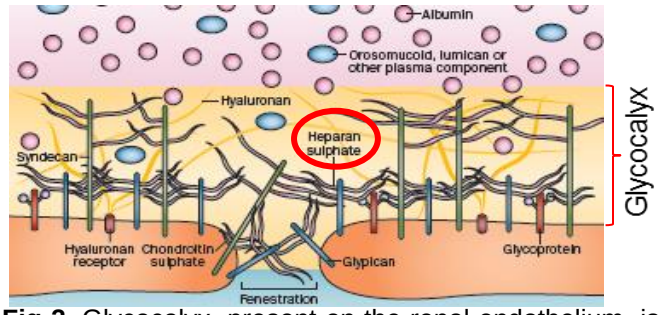


Fig 2. Glycocalyx, present on the renal endothelium, is a negatively charged gel composed of different components. Amongst them is the glycosaminoglycan heparan sulphate.[2]

We hypothesise that **HS is a key component of the GEnC glycocalyx and represents a potential therapeutic target in disease states.**

Aim 1. To confirm the importance of HS in the GEnC glycocalyx by specifically deleting HS in GEnC using a transgenic mouse model. Detailed analysis of these mice will reveal effects on glomerular function and compensatory changes in glycocalyx.

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 EXT1$^{fl/fl,}$ mice will be injected with streptozotocin to induce Type 1 diabetes

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

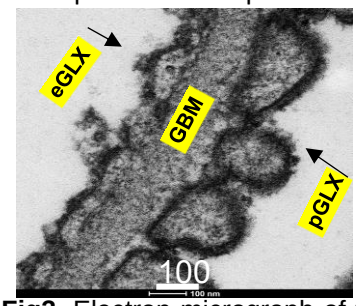


Fig3. Electron micrograph of the glomerular capillary wall shows endothelial glycocalyx (eGLX) on the luminal side of the vessel, glomerular basement membrane (GBM) and podocyte glycocalyx (pGLX)

***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.

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.

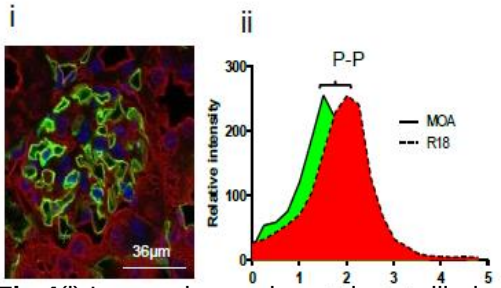


Fig 4(i) Image shows glomerular capillaries labelled red (R18) and the luminal endothelial glycocalyx labelled green (MOA). (ii) Peak to Peak (P-P), an index of glycocalyx thickness,will be determined from an average of 3 lines in a loop, 3 loops in a glomerulus, 3 glomeruli in a mouse and n=4 mice in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

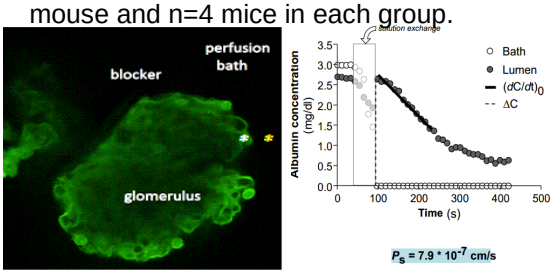


Fig 5. A single glomerulus isolated from a mouse, perfused with Alexa 488-labelled BSA. Single capillary loops (*) were identified. The diffusive albumin solute permeability (P_S^{alb}) for that capillary lumen was calculated from the decay in capillary lumen fluorescence intensity.

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
Other?

27: Project title:
Characterisation of the IL-23 pathway in models of uveitis

Primary supervisor: Dave Copland

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

School / Faculty: Ophthalmology, Translational Health Sciences

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

Acute anterior uveitis is a frequent ocular co-morbidity strongly associated with the Spondyloarthropathies (SpA), a group of chronic inflammatory diseases affecting the joints, skin, and gut of patients. Pathology at these different anatomical sites is driven by local resident interleukin (IL)-23 responsive lymphoid cells. We have identified a novel population of ocular T cells defined by CD3+CD4-CD8-TCRγδ+IL-23R+ expression resides within the anterior uvea of the mouse eye. We also have corroborative evidence that a similar IL-23R+ population exists in the human uvea which, by analogy with disease at other sites, are likely to drive uveitis.

The model we have established to interrogate these cells involves intravitreal administration of an adeno-associated viral (AAV) vector engineered to over-express IL-23 in the mouse eye. Localised ocular cytokine expression demonstrates that the resident IL-23R+ IL-17A producing cells are both necessary and sufficient to drive uveitis in response to IL-23. We have characterised this population in the anterior uvea using flow cytometry in naïve and virus injected eyes of C57BL/6 wildtype and C57BL/6 IL23R$^{GFP/+}$ mice. However, due to the pigmentation of the eye we have generated a C57BL/6(Cg)-Tyrc-2J/J IL23R$^{GFP/+}$ non-pigmented (albino) line, which will be used for whole tissue imaging. This will enable us to determine the spatial localization of these cells within the anterior uveal tissues.

In addition to characterising the spatial localization of these cells in the adult murine eye, work in human foetal eyes suggests the presence of this population during development. Therefore, using the C57BL/6 IL23R$^{GFP/+}$ mouse strain, the project will also evaluate eyes at developmental stages for phenotypic characterisation by flow cytometry and microscopy.

Understanding how these T cells interact with the tissue and contribute to Uveitis will deliver targets for therapeutic modulation, that could be used to inhibit inflammation and prevent disease relapse and restore normal regulation of the ocular environment.

Techniques to be used:

This project will involve working with mouse models of AAV-mediated inflammation. In vivo imaging (fundus and optical coherence tomography), murine eye dissection, flow cytometry, confocal fluorescence and LightSheet microscopy.

3 Key references:

Sherlock, J. P., Joyce-Shaikh, B., Turner, S. P., Chao, C.-C., Sathe, M., Grein, J., et al. (2012). IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4-CD8- entheseal resident T cells. Nature Medicine, 18(7), 1069–1076.

Reinhardt, A., Yevsa, T., Worbs, T., Lienenklaus, S., Sandrock, I., Oberdörfer, L., Korn, T., Weiss, S., Förster, R. and Prinz, I. (2016), Interleukin-23–Dependent γ/δ T Cells Produce Interleukin-17 and Accumulate in the Enthesis, Aortic Valve, and Ciliary Body in Mice. Arthritis & Rheumatology, 68: 2476-2486.

Jesus Gil-Pulido, Núria Amézaga, Ivana Jorgacevic, Helga D Manthey, Melanie Rösch, Theresa Brand, Peter Cidlinsky, Sarah Schäfer, Andreas Beilhack, Antoine-Emmanuel Saliba, Kristina Lorenz, Louis Boon, Immo Prinz, Ari Waisman, Thomas Korn, Clément Cochain, Alma Zernecke, Interleukin-23 receptor expressing γδ T cells locally promote early atherosclerotic lesion formation and plaque necrosis in mice, *Cardiovascular Research*, Volume 118, Issue 14, October 2022, Pages 2932–2945

Specific requirements for the project:

No specific requirements but this project provides an opportunity for the student to observe in vivo (mouse) research.

28: Project title: Creating patient-specific retinal organoids from human induced pluripotent stem cells for in vitro simulation of uveitis

Primary supervisor: Dr Panayiotis Maghsoudlou

Secondary supervisor (for day-to-day support): Prof Andrew Dick

School / Faculty: THS

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

Uveitis, although uncommon, is a notable cause of visual impairment and blindness. Uveitis encompasses a range of conditions driven by both innate autoinflammatory and adaptive autoimmune CD4 T-cell responses. The study of its immune-mediated pathways has been limited by the lack of humanised tissue constructs and in vitro platforms for testing new therapeutic targets. Laboratory studies examining the behaviour of retinal cells from affected individuals will shed light on mechanisms and identify potential treatments.

Through the application of induced pluripotent stem-cell technology, mature human retinal pigment epithelium, microglia, and photoreceptors, as well as immune cells, can be generated in the lab using a single blood sample from patients . These genetically identical organoids serve as in vitro models that can be manipulated to replicate the inflamed eye. We have recently shown that the pro-inflammatory state of retinal organoids derived from patients with Birdshot Chorioretinopathy, a type of uveitis, is maintained.

The development of an in vitro retinal organoid platform will provide insights into the immune responses in uveitis. We hypothesise that the pro-inflammatory phenotype observed in Birdshot will also be preserved in HLA-B27 and Behçet's organoids. This platform will facilitate the identification and evaluation of novel, condition-specific therapeutic agents.

Aims and objectives

The PhD aims to develop an in vitro organoid platform to understand the innate immune and T cell responses in uveitis and response of the tissue (retinal cells). The goal is ultimately to facilitate the development of specific treatments for the variety of uveitic conditions.

The objectives are:

- To generate retinal organoids using blood samples from patients with specific uveitic conditions, including HLA-B27-associated uveitis, Birdshot Chorioretinopathy, and Behçet's Disease.
- To characterise this novel in vitro disease model and explore the interaction between the patient's retina and immune system, using methods such as patient-specific T-cell co-culture.
- To trial this new system for the development and evaluation of novel therapeutic agents targeting specific uveitic conditions, while also assessing patient-specific responses.

Techniques to be used:

- Differentiation and Maintenance,
- Flow Cytometry: For cell sorting and analysis,

- RT-PCR: For gene expression studies,
- Immunocytochemistry/Immunofluorescence: For protein localisation,
- Confocal Microscopy and Image Analysis,
- Western Blotting: For protein expression,
- RNA Sequencing: For transcriptome analysis
- T-Cell Proliferation Assays: For functional studies

3 Key references:

1. Tsirouki, T. et al. A Focus on the Epidemiology of Uveitis. Ocul Immunol Inflamm 26, 2–16 (2018).
2.Gonzalez-Cordero, A. et al. Photoreceptor precursors derived from three-dimensional embryonic stem cell cultures integrate and mature within adult degenerate retina. Nat Biotechnol 31, 741–747 (2013).
3.Reichman, S. et al. From confluent human iPS cells to self-forming neural retina and retinal pigmented epithelium. Proc Natl Acad Sci U S A 111, 8518–8523 (2014).

Specific requirements for the project:
N/A

29: Project title: Pleural fluid biomarkers- predicting treatment response in pleural infection

Primary supervisor: David Arnold

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

School / Faculty: Academic Respiratory Unit (Bristol Medical School: Translational Health Sciences)

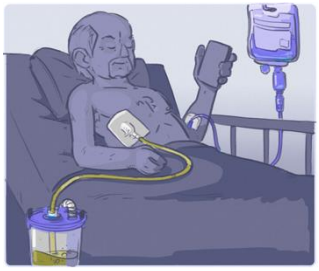
Summary of project (<300 words / ~ half-page):

Introduction

When people get chest infections, fluid can sometimes build up around the lung. In about 1 in 10 cases, this "pleural fluid" itself becomes infected and needs drainage. This is called pleural infection. Pleural infection is a serious condition, affecting over 10,000 people per year in the UK (1).

The clinical spectrum of pleural effusions related to infection is wide. From simple parapneumonic effusions that settle with conservative management, through to grossly septated fibropurulent collections where chest tube drainage, intrapleural fibrinolytics or thoracic surgery are required for resolution (2).

In current practice, a chest tube is inserted based on the pleural fluid pH. Once a chest tube is inserted (see figure) the infected fluid is drained out over the next few days to weeks. However, little is known about how the characteristics of the pleural fluid change over this time and whether this can be used to predict the need for 'rescue therapies' such as interpleural fibrinolytics or thoracic surgery (3).



Methods

As part of a previous clinical study we have collected serial pleural fluid from patients with pleural infection. This current project will involve testing these existing samples for some routine pleural fluid biomarkers (pH, protein, LDH, glucose) and some novel markers (suPAR and PAI-1), and their correlation with clinical outcomes.

Based on the results there would be the opportunity to prospectively assess any promising biomarkers in an actively recruiting observational study based at North Bristol NHS trust.

This project is supported by the NIHR Pleural Translational Research Collaboration.

Techniques to be used:

Enzyme-linked immunosorbent assay (ELISA)
Basic statistical analysis
Recruiting to clinical studies

3 Key references:

(1) Epidemiology of pleural empyema in English hospitals and the impact of influenza.
Arnold DT, et al. Eur Respir J. 2020 Dec 17:2003546.
(2) Pleural infection: past, present, and future directions. Corcoran JP, et al. Lancet Respir Med. 2015 Jul;3(7):563-77.
(3) Intrapleural use of tissue plasminogen activator and DNase in pleural infection. Rahman NM, et al. N Engl J Med. 2011 Aug 11;365(6):518-26. doi: 10.1056/NEJMoa1012740. PMID: 21830966.

Specific requirements for the project: NIHR Good Clinical Practice certificate Honorary Contract at North Bristol NHS trust with proof of vaccination to allow for recruitment to clinical studies in a hospital setting.

30: Project title: Outcomes of tricuspid valve surgery – insights from a large audit database analysis

Primary supervisors: Professor Gianni Angelini, BHF Professor of Cardiac Surgery

Secondary supervisor (for day-to-day support): Mr Jeremy Chan, ACF, ST3, Adult Cardiac Surgery

School / Faculty:

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

Isolated tricuspid valve surgery is rarely performed, and the available data suggests this is associated with a high mortality risk and morbidity. There are only a few extensive retrospective studies originating mainly from the USA but no large UK or European studies. The proposed project will review the outcomes and trends of isolated tricuspid valve surgery in the UK by undertaking a retrospective analysis of the UK National Institute for Cardiovascular Outcomes Research (NICOR) analysis-ready dataset of over 600000 patients. No data collection will be involved, and the focus will be hands-on big data analysis. This is a unique opportunity to be a co-author in a publication and national oral presentation (SCTS). The Bristol Academic Cardiac Surgery Unit is currently leading research in database analysis and using state-of-the-art machine learning techniques to predict heart surgery outcomes.

You will also gain valuable skills in writing a scientific paper and performing a statistical analysis independently using the R software (no prior experience required) under dedicated supervision. We will focus on the efficiency of summarising data, using logistic regression models to understand the effect of various covariates/predictors on a binary outcome and analysis of trends. There will also be opportunities to get you involved in future projects.

Techniques to be used:

- One-to-one supervision of undertaking a fundamental analysis in R of a large dataset
- Teaching on structuring and writing a scientific paper.

Zack C, Fender E, Chandrashekar P, et al. National Trends and Outcomes in Isolated Tricuspid Valve Surgery. J Am Coll Cardiol. 2017 Dec, 70 (24) 2953–2960. https://doi.org/10.1016/j.jacc.2017.10.039

Kawsara A, Alqahtani F, Nkomo VT, Eleid MF, Pislaru SV, Rihal CS, Nishimura RA, Schaff HV, Crestanello JA, Alkhouli M. Determinants of Morbidity and Mortality Associated With Isolated Tricuspid Valve Surgery. J Am Heart Assoc. 2021 Jan 19;10(2):e018417. doi: 10.1161/JAHA.120.018417. Epub 2021 Jan 5. PMID: 33399012; PMCID: PMC7955319.

Julien Dreyfus, Michele Flagiello, Baptiste Bazire, Florian Eggenspieler, Florence Viau, Elisabeth Riant, Yannick Mbaki, Yohann Bohbot, Damien Eyharts, Thomas Senage, Henri Dubrulle, Martin Nicol, Fabien Doguet, Virginia Nguyen, Augustin Coisne, Thierry Le Tourneau, Yoan Lavie-Badie, Christophe Tribouilloy, Erwan Donal, Jacques Tomasi, Gilbert Habib, Christine Selton-Suty, Richard Raffoul, Bernard Iung, Jean-François Obadia, David Messika-Zeitoun, Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes, European Heart Journal,

Volume 41, Issue 45, 1 December 2020, Pages 4304–4317, https://doi.org/10.1093/eurheartj/ehaa643
Specific requirements for the project: Immunisations (e.g. Hepatitis B)? No HO licence? No Other? No

31: Project title: Short and long-term outcomes of on-pump versus on-pump coronary artery bypass grafting: an institutional experience

Primary supervisors: Professor Gianni Angelini, BHF Professor of Cardiac Surgery Adult Cardiac Surgery

Secondary supervisor (for day-to-day support): Mr Jeremy Chan, ACF, ST3, Adult Cardiac Surgery

School / Faculty:

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

Despite a significant body of evidence consisting of randomized controlled trials and extensive retrospective analyses, the outcomes of off-pump coronary versus on-pump coronary bypass grafting remain a matter of hot debate amongst heart surgeons. This exciting project aims to undertake an extensive retrospective analysis of several thousand coronary artery bypass operations performed at the Bristol Royal Infirmary. This will involve you in undertaking a step-by-step analysis of the National Institute for Cardiovascular Outcomes Research (NICOR) local data extract linked with long-term survival. No data collection will be involved, and the focus will be hands-on analysis and the opportunity to be a co-author in a publication and national oral presentation. (SCTS). You will also gain valuable skills in writing a scientific paper and performing a statistical analysis independently using the R software (no prior experience required) under dedicated supervision. We will focus on the efficiency of summarising data, using logistic regression models to understand the effect of various covariates/predictors on a binary outcome and how to perform survival analyses. Apart from learning valuable and transferable analysis skills, you will have the opportunity to work in a world-renowned academic cardiac surgery centre with a long tradition and history of pioneering off-pump coronary artery bypass techniques. There will also be opportunities to get involved in future projects.

Techniques to be used:

- One-to-one supervision of undertaking a basic analysis in R of a large dataset
- Teaching on structuring and writing a scientific paper.

3 Key references:

Angelini GD, Taylor FC, Reeves BC, Ascione R. Early and midterm outcome after off-pump and on-pump surgery in Beating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2): a pooled analysis of two randomized controlled trials. Lancet. 2002 Apr 6;359(9313):1194-9. doi: 10.1016/S0140-6736(02)08216-8. PMID: 11955537.

Fudulu D, Benedetto U, Pecchinenda GG, Chivasso P, Bruno VD, Rapetto F, Bryan A, Angelini GD. Current outcomes of off-pump versus on-pump coronary artery bypass grafting: evidence from randomized controlled trials. J Thorac Dis. 2016 Nov;8(Suppl 10):S758-S771. doi: 10.21037/jtd.2016.10.80. PMID: 27942394; PMCID: PMC5124584.

Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Straka Z, Piegas LS, Avezum A, Akar AR, Lanas Zanetti F, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Tao L, Olavegogeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Gao P, Pettit S, Yusuf S; CORONARY Investigators. Five-Year Outcomes after Off-Pump or On-Pump Coronary-Artery

Bypass Grafting. N Engl J Med. 2016 Dec 15;375(24):2359-2368. doi: 10.1056/NEJMoa1601564. Epub 2016 Oct 23. PMID: 27771985.
Specific requirements for the project: Immunizations (e.g. Hepatitis B)? No HO licence? No Other? No

32: Project title:
Impact of cuddling during cooling therapy and intensive care on the cooling process and the cerebral oxygenation

Primary supervisor: Dr Ela Chakkarapani

Secondary supervisor (for day-to-day support): Ms Sara Rapuc

School / Faculty: Bristol Medical School / Health sciences

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

In the UK, approximately 800 newborns receive whole-body cooling therapy annually for hypoxic ischaemic encephalopathy (HIE) induced by birth asphyxia.[1] Although it's common for parents to hold their babies during intensive care, parents of babies undergoing HIE cooling therapy typically cannot, due to concerns about affecting the cooling treatment. We developed the CoolCuddle technique to allow cuddling during cooling therapy and intensive care. Our study found that, on a population level, CoolCuddle doesn't affect cardiorespiratory physiology or cerebral oxygenation significantly, but it does cause a slight increase in rectal temperature, probably due to heat exchange between parent and the infant during cuddling.[2] This heat exchange could have been minimised by the cooling machine's servocontrol mechanism cycling the cooling mattress temperature to maintain consistent rectal temperature. The cycling of the cooling mattress temperature could affect the body surface temperature, vascular calibre and brain perfusion or oxygenation.[3]

Therefore, there are some uncertainties including, 1) How does cuddling impact the servocontrol mechanism? 2) Are babies exposed to extreme mattress temperatures during cuddling to maintain stable rectal temperature? 3) How does cycling mattress temperature affect cerebral oxygenation and oxygen extraction by the brain?

We aim to address these using the pre-existing data on 27 infants who underwent 72 CoolCuddle episodes, each lasting up to two hours. We will examine the swings in the mattress temperatures during cuddling versus before cuddling, and its association with regional cerebral oxygenation and brain tissue oxygen extraction, measured using near-infrared spectroscopy. The MRes student will conduct a literature review, analyse existing data under supervision, and prepare an abstract and manuscript for publication.

Techniques to be used:
Data visualisation
Literature review
Data analysis

3 Key references:

1. Shipley, L., Gale, C. & Sharkey, D. Trends in the Incidence and Management of HypoxicIschaemic Encephalopathy in the Therapeutic Hypothermia Era: A National Population Study. *Archives of disease in childhood* **106**, 529-534 (2021).
2. Odd, D. et al. Physiological Responses to Cuddling Babies with Hypoxic-Ischaemic Encephalopathy During Therapeutic Hypothermia: An Observational Study. *BMJ Paediatr Open* **5** (2021).
3. Sutin, J. et al. Association of Cerebral Metabolic Rate Following Therapeutic Hypothermia with 18-Month Neurodevelopmental Outcomes after Neonatal Hypoxic Ischemic Encephalopathy. *EBioMedicine* **94**, 104673 (2023).

Specific requirements for the project: None

33: Project title: Is there evidence of a Barker effect in the diagnosis of brain tumours?

Primary supervisor:
Dr Denize Atan, Associate Professor, University of Bristol

Secondary supervisor (for day-to-day support):
Professor Beth Stuart, Medical Statistician, Queen Mary University of London
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 cause raised intracranial pressure, which can present with headache and/or papilloedema (optic nerve swelling at the back of his eyes). Unless diagnosed early, many people with brain tumours will die or suffer long-term disabilities, like 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 papilloedema. 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 papilloedema. Because of this, we think more patients with brain tumours are diagnosed earlier and more frequently than 5 years ago.

Aims
1. To measure the incidence of brain tumours and the proportion diagnosed by eye specialists compared with other specialists in England before and after 2016.

2. To calculate the time to diagnosis, survival, and outcomes of people with brain tumours diagnosed by eye specialists versus other routes-to-diagnosis.

Techniques to be used:

NHS Digital routinely collects data on everyone diagnosed with benign and malignant brain tumours in England. We have National Research Ethics Committee approval to access NHS Digital 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 and using interrupted time series analysis. We will determine the change in:
(i) Adjusted odds ratios for the number of brain tumours diagnosed via hospital eye services compared with other hospital specialities
(i) Time to diagnosis
(ii) WHO tumour grade at diagnosis
(iii) Cancer stage at diagnosis
(iv) Time between diagnosis and treatment
(v) 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.
2. Elliss-Brookes L, et al. Routes to diagnosis for cancer. B J Cancer 2012.
3. 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

34: Project title:
Sensory processing and emotional regulation in children cooled for neonatal hypoxic ischaemic encephalopathy

Primary supervisor: Dr Ela Chakkarapani

Secondary supervisor (for day-to-day support): Ms Sara Rapuc

School / Faculty: Bristol Medical School / Health sciences

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

Worldwide, each year, around 1.2 million newborn babies develop neonatal hypoxic-ischaemic encephalopathy (HIE) secondary to birth asphyxia and HIE is the 12th leading cause of disability adjusted life years. To reduce the death and disability, newborn infants with HIE undergo whole-body cooling therapy in high-income countries. Although cooling therapy reduced mortality and severe motor disability, we showed that these children have lower IQ scores and difficulties with attention, communication and behaviour.[1] Some of these children are not ready for school due to impaired executive function, fine motor skills and language.[2] Additionally, school readiness and academic attainment is impacted by social-emotional development driven by emotional regulation and sensory processing.[3] Currently we do not know whether pre-school children cooled for HIE have difficulties with emotional regulation or sensory processing and whether these difficulties could be identified using the developmental assessments at 24 months of age. Addressing the emotional or sensory dysregulation early will boost the school readiness and academic attainment of children cooled for HIE.

We have a cohort of 50 children cooled for HIE, who will be between 4-6 years of age from January 2024, and have their global development assessed at 2 years of age using Bayley scales of infant and Toddler development. As part of their routine follow up, parents will be completing Emotion regulation checklist and short sensory profile-2 questionnaires either over telephone or using paper form and return to us in prepaid addressed envelopes. Ethics approval is underway to use routinely collected data for research. Outcomes will be emotional regulation global score, lability and negativity, sensory processing total raw score. We will compare the mean (SD) scores of outcomes with the published normative scores and the association with developmental scores at 2 years. The MRes student will be conducting the data collection and analysis under supervision.

Techniques to be used:

1. Completing validated questionnaires, Emotion Regulation Checklist and Sensory Profile-2 questionnaire over phone
2. Receiving training on scoring the questionnaires
3. Data analysis

3 Key references:

1. Lee-Kelland, R. et al. School-Age Outcomes of Children without Cerebral Palsy Cooled for Neonatal Hypoxic-Ischaemic Encephalopathy in 2008-2010. *Archives of disease in childhood* **105**, 8-13 (2020).
2 Edmonds, C. J., Cianfaglione, R., Cornforth, C. & Vollmer, B. Children with Neonatal Hypoxic Ischaemic Encephalopathy (Hie) Treated with Therapeutic Hypothermia Are Not as School Ready as Their Peers. *Acta Paediatr* **110**, 2756-2765 (2021).
3 Clarke, A. M., Morreale, S., Field, C., Hussein, Y. & Bary, M. M. *What Works in Enhancing Social and Emotional Skills Development During Childhood and Adolescence?*, (2015).

Specific requirements for the project:

None

35: Project title: Does being born with a cleft increase risk to neurodevelopmental and psychiatric disorders? An investigation using Mendelian randomization.

Primary supervisor: Dr Evie Stergiakouli

Secondary supervisor (for day-to-day support): Dr Rachel Blakey

School / Faculty: BRMS

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

Cleft of the lip and/or palate (CL/P) is one of the most common congenital anomalies requiring corrective surgery within the first year of life. Children born with CL/P have 3.2 admissions and spend 13.2 days in hospital in the first two years of life. Despite treatment to repair the cleft in infancy, being born with a cleft frequently results in multiple adverse outcomes across the lifespan, including potentially poor educational, vocational, social, mental and physical health outcomes. We have previously shown, using data from a large cohort of children born with cleft, the Cleft Collective, that children born with CL/P have higher levels of behavioural problems than children in the general population at 5 and 10 years (1). However, we do not know whether there is genetic correlation between cleft neurodevelopmental disorders and psychiatric disorders or whether factors associated to the cleft phenotype cause psychiatric disorders in children born with cleft. Causally informative analyses, such as Mendelian randomization, use genetic data as instrumental variables for exposures of interest. These analyses can help overcome the problems of measurement error, bias and confounding and identify causal risk factors for mental health problems in cleft.

We have previously used Mendelian randomization to show that being born with cleft does not cause children to underperform at school (2).

AIMS & OBJECTIVES: In this project, we will explore the links between cleft and neurodevelopmental and psychiatric disorders (ADHD, autism spectrum disorder (ASD), anxiety, depression, schizophrenia).

A. We will use two-sample Mendelian randomization (3) to investigate any causal links between genetic liability to cleft of the lip and/or palate, and ADHD, ASD, anxiety, depression, schizophrenia bidirectionally
B. Apply sensitivity analyses including weighted median, weighted mode, MR-Egger regression, MR-PRESSO and colocalization analyses to assess and adjust for pleiotropy
C. We will perform Linkage Disequilibrium (LD)-score regression (4) to estimate any genetic correlation between cleft of the lip and/or palate, and ADHD, ASD, anxiety, depression, schizophrenia

Techniques to be used:

Mendelian randomization (MR) including 2-sample MR using large genetic whole-genome data, advanced genetic epidemiological analyses including MR sensitivity analyses and genetic correlation analyses

3 Key references:

1. Berman et al. Prevalence and Factors Associated with Behavioural Problems in 5-year-old Children Born with Cleft Lip and/or Palate from the Cleft Collective. Cleft Palate Craniofac J. 2024 Jan;61(1):40-51. doi: 10.1177/10556656221119684. Epub 2022 Sep 9. PMID: 36083151; PMCID: PMC10676624.
2. Dardani et al. Is genetic liability to ADHD and ASD causally linked to educational attainment?, International Journal of Epidemiology, 2021;, dyab107, https://doi.org/10.1093/ije/dyab107
3. Davey Smith, G. & Hemani, G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum. Mol. Genet.* 23, R89–R98 (2014)

Specific requirements for the project: None
Immunisations (e.g. Hepatitis B)?
HO licence?
Other?

36: Project title: An assessment of the predictors of post-concussion syndrome and the effect of socio-economic group in children aged 1-17 years who have experienced traumatic brain injury

Primary supervisor: Rebecca Wilson

Secondary supervisor (for day-to-day support): Kate Birnie / Theresa Redaniel

School / Faculty: Population Health Sciences

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

Traumatic brain injuries can cause long-term adversities for patients, including post-concussion syndrome (PCS), where symptoms (including cognitive, physical, and behavioural problems) can last for several months. Approximately 33% children with concussion experience PCS. It is important to identify risk factors for developing PCS. One potential factor associated with risk of PCS is socioeconomic position.

Using primary care data, this project will explore whether socioeconomic group is associated with developing post-concussion syndrome after a traumatic brain injury in children aged 1-17 years as the primary objective. The secondary objective will explore whether this effect is modified by child's age or sex.

Techniques to be used:

Univariable analysis including measures of previous concussion and post-concussion syndrome and multivariable logistic regression including potential confounders. Multiple imputation will be used to manage missing data.

3 Key references:

Ijaz, S., Scott, L., Dawson, S., Wilson, R., Jackson, J., Birnie, K., Redaniel, M. T., Savović, J., Wright, I., Lyttle, M. D., & Mytton, J. (2023). Factors related to adverse long-term outcomes after mild traumatic brain injury in children: a scoping review. Arch Dis Child, 108, 492–497. https://doi.org/10.1136/archdischild-2022-325202

Zemek, R., Barrowman, N., Freedman, S. B., Gravel, J., Gagnon, I., McGahern, C., Aglipay, M., Sangha, G., Boutis, K., Beer, D., Craig, W., Burns, E., Farion, K. J., Mikrogianakis, A., Barlow, K., Dubrovsky, A. S., Meeuwisse, W., Gioia, G., Meehan, W. P., … Moore, J. (2016). Clinical risk score for persistent postconcussion symptomsamong children with acute concussion in the ED. JAMA - Journal of the American Medical Association, 315(10), 1014–1025. https://doi.org/10.1001/jama.2016.1203

Watson, J., Nicholson, B. D., Hamilton, W., & Price, S. (2017). Identifying clinical features in primary care electronic health record studies: methods for codelist development. BMJ Open, 7(11), e019637. https://doi.org/10.1136/BMJOPEN-2017-019637

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

37: Project title: Evaluating the potential impact of Targeted Lung Health Checks on reducing emergency presentations with lung cancer

Primary supervisor: Anna Bibby

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

School / Faculty: Academic Respiratory Unit (Bristol Medical School: Translational Health Sciences)

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

Lung cancer kills more people than any other cancer, despite cure being possible if tumours are detected when small and localised. Screening high-risk individuals for lung cancer using low dose CT scans detects more tumours at a treatable stage, with an associated reduction in lung cancer deaths. As a result, NHS England is rolling out a national lung cancer screening programme called Targeted Lung Health Checks.

The causal relationship between lung cancer and tobacco results in disproportionate disease prevalence in socioeconomically disadvantaged communities where tobacco use is more commonplace. Typically, these higher risk populations encounter more challenges in accessing healthcare, including financial constraints, competing demands on time (e.g. zero-hours contracts) and language and literacy barriers. Targeted Lung Health Checks aim to overcome these barriers by providing screening in community locations (e.g. supermarket carparks), with extended opening hours, and interpreters where required. The goal is to increase access to the service for people who need it the most.

Outside of Targeted Lung Health Checks, people with lung cancer present either to their GP with symptoms or as an emergency to ED. Higher risk populations tend to favour the emergency pathway. Unfortunately, the clinical outcomes for emergency presentations are dramatically worse, with tumours often diagnosed at a higher stage, with fewer treatment options available, and shorter overall survival as a result.

This project will use a large clinical dataset from North Bristol NHS Trust to explore the characteristics of people diagnosed via the emergency pathway to determine how many would have been eligible for a Targeted Lung Health Check, and could therefore have been diagnosed earlier. Interrogation of primary care records will determine healthcare utilisation in the years prior to lung cancer diagnosis to determine whether there were missed opportunities to identify symptoms or whether this represents an underserved population that struggle to access routine health care. Ultimately the aim is to evaluate whether Targeted Lung Health Checks have the potential to reduce emergency presentations amongst high risk populations, saving lives and reducing health inequalities.

Techniques to be used:

Clinical data collection, handling and cleaning

Basic epidemiology including descriptive statistics, regression analysis and time-to-event analysis
3 Key references: (1) https://view-health-screening-recommendations.service.gov.uk/lung-cancer/ (2) https://www.nhs.uk/conditions/lung-health-checks/ (3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6310353/
Specific requirements for the project: Some basic statistical understanding (with further training available) Computer literacy

39: Project title: Cost-consequence analysis of a domestic abuse perpetrator programme (REPROVIDE)

Primary supervisor: Estela Capelas Barbosa

Secondary supervisor (for day-to-day support): Helen Cramer / Karen Morgan

School / Faculty: Population Health Sciences / Bristol Medical School

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

REPROVIDE is a randomised controlled trial looking at the effectiveness and cost-effectiveness of a 23-week group domestic abuse perpetrator programme. There are additional individual sessions based on need, and a monthly Relapse Prevention Group (RPG) for an additional 6 months. The programmes are run by RESPECT accredited teams (https://www.respect.org.uk/) in five sites in England and Wales.

While individual level quality-of-life outcomes will be collected (EQ-5D-5L; SF-12 and ICECAP-A), it is expected that there will be potential consequences of the intervention that may result in benefits for participants, that are not quality-of-life outcomes. To better understand these potential consequences, the student will join the research team to extract information about any potential consequences from a sample the practitioner's case notes from each site. More specifically, consequences will be defined from an emerging analytical coding framework, and the scale and scoring of potential consequences will take place independently by two members of the team. The researchers will aim to come to a consensus about the type and size of the consequences, including what the size of the consequences may be on a larger scale. For sites with fewer participants, the research team will sample more case notes.

A cost-consequence analysis is a form of economic evaluation that has been previously defined as:

> *"a form of health economic evaluation study in which all direct and indirect costs and a catalogue of different outcomes of all alternatives are listed separately. No specific preference for one costing approach or one outcome measure (as is the case for cost-effectiveness analysis or cost–utility analysis) is made. […] The reader or the decision maker has to form their own opinion concerning the relative importance of costs and outcomes.*" (Kirch, 2008, p. 30)

This project offers the student the opportunity to learning how to carry out costing techniques in a wide variety of (statutory and non-statutory) settings and apply qualitative skills into a form of economic evaluation.

Techniques to be used:
Micro-costing
Qualitative evaluation of consequences
Cost-consequence analysis

3 Key references: KIRCH, W. 2008. *Encyclopedia of Public Health: Volume 1: A-H Volume 2: I-Z*, Springer Science & Business Media. MORRIS, S., DEVLIN, N., PARKIN, D. & SPENCER, A. 2012. *Economic analysis in healthcare*, John Wiley & Sons. POTTER, S., DAVIES, C., DAVIES, G., RICE, C. & HOLLINGWORTH, W. 2020. The use of micro-costing in economic analyses of surgical interventions: a systematic review. *Health Economics Review,* 10**,** 1-11.
Specific requirements for the project: Enhanced DBS (to access case notes of participants who are a vulnerable group due to exposure to domestic violence).

39: Project title: Descriptive analyses within UK LLC of self-reported COVID-19 diagnoses: including comorbidities, risk factors and geographical region.

Primary supervisor: Emma Turner

Secondary supervisor (for day-to-day support):
UK LLC team members including Rich Thomas, Andy Boyd

School / Faculty: Bristol Medical School Population Health Sciences

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

UK Longitudinal Linkage Collaboration (UK LLC) is a national trusted research environment for longitudinal research holding records for over 280,000 individuals from 24 Longitudinal Population Studies (LPS). UK LLC is a unique resource hosting de-identified data from inter-disciplinary LPS systematically linked to participants health, administrative and environmental records enabling inclusive and cross-sector research in a secure analysis environment.

Previous work carried out within the UK LLC (linked data from 8 LPS) found that some people were more likely to receive a GP diagnosis of 'Long COVID-19' (signs, symptoms and conditions that continue or develop after acute COVID-19 infection – Centre for Disease Control (CDC) definition) than others. The factors included age, ethnicity, deprivation levels and certain health conditions. [1]
Research carried out in the Clinical Practice Research Datalink (CPRD) reported a wide range of sociodemographic and clinical factors associated with long COVID-19 [2] including female sex, belonging to an ethnic minority, socioeconomic deprivation, smoking, obesity, and a range of co-morbidities.
Regional variations in diagnosis across the UK have been reported, including differences in COVID-19 mortality across geography [3].

The wide geographical distribution, diverse populations and detailed data collection within the LPS hosted by UK LLC will enable the factors above to be analysed.

The specific aims are to:

i) Produce detailed descriptive analysis of self-reported COVID-19 diagnosis.
ii) Consider the impact of any differences observed across groups, for example geographical variation.

Techniques to be used:
Review existing literature. Design and conduct appropriate statistical analysis producing descriptive statistics. Interpret the results in the context of literature and contribute as co-author to publication of results.

3 Key references:
[1] Kuppel, Boyd, Macleod, Chaturvedi, Williams (preprint) The long COVID evidence gap: comparing self-reporting and clinical coding of long COVID using longitudinal study data linked to healthcare records.
https://www.medrxiv.org/content/10.1101/2023.02.10.23285717v1

[2] Subramanian, et al Symptoms and risk factors for long COVID in non-hospitalized adults Nature Medicine 2022 https://doi.org/10.1038/s41591-022-01909-w

[3] Office for National Statistics. 2021. Analysis of geographic concentrations of COVID-19 mortality over time, England and Wales: deaths occurring between 22 February and 28 August 2020. Analysis looking at clusters of deaths involving COVID-19 across time and areas in England and Wales. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/analysisofgeographicconcentrationsofcovid19mortalityovertimeenglandandwales/deathsoccurringbetween22februaryand28august2020

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? No
HO licence? No
Other? Previous experience of using a statistical software package could be beneficial, but support can be provided. The individual will need to obtain Accredited Researcher Status (ARS) with ONS to be able to access these data within UK LLC TRE. https://www.ons.gov.uk/aboutus/whatwedo/statistics/requestingstatistics/secureresearchservice/becomeanaccreditedresearcher

40: Epidemiology of respiratory tract and other fever-associated infections in children presenting in community and hospital populations in the UK between 2018-2023

Primary supervisor: *Katharine Looker*

Secondary supervisor (for day-to-day support): *Eleanor Walsh*

School / Faculty: **Population Health Sciences - Bristol Medical School**

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

Background: Respiratory tract infections (RTIs) in children and young people are common in both primary care and hospital settings[1,2]. Fever is common as a presenting symptom in children and can be without apparent cause or identifiable infection[3]. Yet infections and fever at presentation to healthcare differ by age and disease severity between clinical settings. A review of current evidence would be a unique way of quantifying these differences in infections diagnosed in children and young people presenting to healthcare and the community.

Research objectives: Review of studies of the characteristics of children who present with RTIs with or without associated fever in primary care and secondary care and national surveillance data in the UK before and during the COVID-19 era. To investigate potential differences in

i) baseline exposure characteristics (e.g., age, gender, co-morbidities) and
ii) outcomes (e.g. diagnoses, no. of consultations/duration of hospital stay, prescriptions).

Techniques to be used:

- Appropriate search strategies (e.g., MeSH terms, citations) and publication databases to identify relevant scientific outputs
- Calculate pooled estimates using meta-analysis/meta-regression, where appropriate
- Interpret and critically appraise summarised descriptions considering current literature, context and methodologies.

Software: R or Stata; Endnote

3 Key references:

1. Whitburn S, Costelloe C, Montgomery AA, et al. The frequency distribution of presenting symptoms in children aged six months to six years to primary care. *Prim Health Care Res Dev* 2011;12(2):123-34. doi: 10.1017/s146342361000040x [published Online First: 2011/04/05]
2. Macfarlane J, Holmes W, Gard P, et al. Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *Thorax* 2001;56(2):109-14. doi: 10.1136/thorax.56.2.109
3. Bleeker SE, Moons KG, Derksen-Lubsen G, et al. Predicting serious bacterial infection in young children with fever without apparent source. *Acta Paediatr*

2001;90(11):1226-32. doi: 10.1080/080352501317130236 [published Online First: 2002/01/26]
Specific requirements for the project: *None* Immunisations (e.g. Hepatitis B)? HO licence? Other?

41:Project title: Prognosis of dermatitis herpetiformis patients and predictive factors.

Primary supervisor: Penny Whiting

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

School / Faculty: Medical school, population health sciences

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

Dermatitis herpetiformis (DH) is a skin manifestation of coeliac disease and affects about 13% of coeliac patients. Coeliac disease is an immune-mediated enteropathy against dietary gluten present in wheat, rye and barley and affects 1 in 100 people worldwide. DH has a varied clinical presentation and causes severe itching. Patients may present with a rash or scratching lesions alone. A lifelong gluten free diet is essential to treat DH, but because resolution of DH rash can take months or longer on dietary treatment alone, DH patients with severe skin symptoms are additionally treated with dapsone medication to control the rash more quickly. Patients with DH have an increased risk of other autoimmune conditions such as type 1 diabetes and autoimmune thyroid disease. In addition, the risk of developing non-Hodgkin lymphoma is increased (1).

Studies have shown that DH incidence has been declining over the years (1,2) and it has been suggested that this is due to better case finding of coeliac disease, resulting in patients starting a gluten free diet sooner which prevents the development of DH. Better adherence to the diet has been shown to reduce the risk of long-term complications such as lymphomas.

This project aims to describe DH incidence over time and the risk of developing related conditions, such as lymphomas and other immune mediated conditions. We aim to investigate whether prognosis of patients with DH has changed over the last 30 years and to identify risk factors for developing secondary conditions.

Methods:

1) A review of the literature to identify risk factors related to DH prognosis
2) An analysis of routinely collected primary care data in the UK (CPRD):
    a. Describe how DH incidence has changed over time and how this relates to coeliac disease incidence.
    b. Describe how outcomes of DH patients have changed over time (for instance, a measure for DH severity is the need for and length of dapsone treatment, a measure for DH outcomes is the development of related conditions).
    c. Explore risk factors of DH and whether they predict DH outcomes.

Techniques to be used:

- Evidence synthesis methods, including developing a systematic search and standardized data extraction forms, abstract and full texts screening, synthesis of relevant evidence.
- Descriptive statistical analyses, Incidence analyses, Prediction modelling using R or Stata.

3 Key references:

1. K. Hervonen, M. Vornanen, H. Kautiainen, P. Collin, T. Reunala, Lymphoma in patients with dermatitis herpetiformis and their first-degree relatives, British Journal of Dermatology, Volume 152, Issue 1, 1 January 2005, Pages 82–86, https://doi.org/10.1111/j.1365-2133.2005.06345.x
2. West, Joe PhD1, 2; Fleming, Kate M PhD1; Tata, Laila J PhD1; Card, Timothy R PhD1, 2; Crooks, Colin J PhD1. Incidence and Prevalence of Celiac Disease and Dermatitis Herpetiformis in the UK Over Two Decades: Population-Based Study. American Journal of Gastroenterology 109(5):p 757-768, May 2014. | DOI: 10.1038/ajg.2014.55
3. Albadri Z, Al Bayati D, Häbel H, Jerkovic Gulin S, Grönhagen C, Seifert O. Incidence of Dermatitis Herpetiformis in Sweden 2005 to 2018: A Nationwide Retrospective Cohort Study. Acta Derm Venereol. 2023 Nov 16;103:adv13210. doi: 10.2340/actadv.v103.13210. PMID: 37971253; PMCID: PMC10666066.

Specific requirements for the project:

- Ideally experience with either R or Stata

42: Project title: Evaluate the variation and trends in testing to monitor patients with long-term conditions in UK primary care.

Primary supervisor: Penny Whiting

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

School / Faculty: Medical school, population health sciences

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

Over the past few decades, there has been a notable increase in the rates of laboratory testing within UK GP practices, with significant geographical variation. We recently conducted a study which described the variation and trends in testing rates for monitoring hypertension, Type 2 diabetes, and Chronic Kidney Disease (CKD). We found that testing rates have largely plateaued in recent years, although considerable variation persists among GP practices.

Our analyses suggested a potential lack in testing for HbA1c and microalbuminuria levels, and potential over-testing for lipids, Full Blood Count (FBC), liver function, and thyroid function when compared to guideline recommendations. However, this analysis included data from June 2013 and May 2018 and did not include the pandemic.

We propose a follow-up analyses to evaluate the variation and trends of the same monitoring tests and describe what happened during and in the aftermath of the pandemic.

Techniques to be used:

- This is a longitudinal observational study using prospectively collected routine administrative information about patients registered with UK GP practices
- Descriptive statistics in R or Sata
- Calculating age and sex standard testing rates

3 Key references:

4. Timothy Jones, Rita Patel, Martha M C Elwenspoek, Jessica C Watson, Ed Mann, Katharine Alsop and Penny F Whiting. BJGP Open 2023; 7 (1): BJGPO.2022.0139. DOI: https://doi.org/10.3399/BJGPO.2022.0139
5. Busby J, Schroeder K, Woltersdorf W, et al. (2013) Temporal growth and geographic variation in the use of laboratory tests by NHS general practices: using routine data to identify research priorities. Br J Gen Pract 63 (609):e256–e266, doi:10.3399/bjgp13X665224.
6. O'Sullivan JW, Stevens S, Hobbs FDR, et al. (2018) Temporal trends in use of tests in UK primary care, 2000-15: retrospective analysis of 250 million tests. BMJ 363 doi:10.1136/bmj.k4666. k4666.

Specific requirements for the project:

- Ideally experience with either R or Stata

43: Project title:
Evaluating the effect of the STROBE-MR extension on the reporting quality and reproducibility of Mendelian randomisation studies.

Primary supervisor: Rebecca Richmond

Secondary supervisor (for day-to-day support): Benjamin Woolf, Matthew Lee

School / Faculty: Population Health Sciences / Bristol Medical School

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

Mendelian randomization (MR) is a statistical method which uses genetic variants as instrumental variables that, under specific assumptions, can be used to investigate the causal relationship between an exposure and outcome. As the availability of large and deeply phenotyped population studies has increased, so too has the application of MR. This is particularly true for two-sample MR, in which summary level data are used for both the exposure and outcome.

In previous work, we found a large proportion of the Mendelian randomization literature to be poorly reported (1). The STROBE-MR checklist was subsequently introduced as a guideline to improve reporting of studies using Mendelian randomization (2). A core fundamental of open science is the ability to reproduce analyses and report guidelines aim to aid in this regard. However, whether two-sample MR studies are reproducible given their reported methods has not been addressed. Likewise, the effect that issuing the STROBE-MR guidelines has had on reporting quality in MR studies requires evaluation.

This project will investigate whether studies of varying reporting quality can be reproduced and if the publication of the STROBE-MR guidelines and/or adoption by journals has improved reproducibility and reporting quality among studies.

The project will involve:

1. Sampling studies published in 2023 which cited the STROBE-MR guidelines and used TwoSampleMR or MR-Base.
2. Evaluating the reporting quality of these studies using the tools we developed for our previous review (1).
3. Contrasting the quality of reporting in our pre-STROBE-MR review with reporting quality in the post-STROBE-MR studies in the random sample.
4. Attempting to replicate one poorly reported, one adequately reported, and one well reported study before and after the publishing of STROBE-MR
5. Considering if there are useful changes which should be made to the STROBE-MR checklist – e.g. simplifications or additions

Techniques to be used:
Systematic reviewing
Meta-data analysis and visualisation in R
Understanding of Mendelian randomization methodology

3 Key references:

1. Woolf, B., Di Cara, N., Moreno-Stokoe, C., Skrivankova, V., Drax, K., Higgins, J. P., ... & Richmond, R. C. (2022). Investigating the transparency of reporting in two-sample summary data Mendelian randomization studies using the MR-Base platform. *International Journal of Epidemiology*, *51*(6), 1943-1956.

2. Skrivankova, V. W., Richmond, R. C., Woolf, B. A., Yarmolinsky, J., Davies, N. M., Swanson, S. A., ... & Richards, J. B. (2021). Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: the STROBE-MR statement. *Jama*, *326*(16), 1614-1621.

3. Skrivankova, V. W., Richmond, R. C., Woolf, B. A., Davies, N. M., Swanson, S. A., VanderWeele, T. J., ... & Richards, J. B. (2021). Strengthening the reporting of observational studies in epidemiology using mendelian randomisation (STROBE-MR): explanation and elaboration. *bmj*, *375*.

Specific requirements for the project:

Immunisations (e.g. Hepatitis B)?

HO licence?

Other?

None

44: Project title: Investigating sleep issues in individuals affected by KBG syndrome

Primary supervisor: Dr Karen Low

Secondary supervisor (for day-to-day support): Georgia Treneman-Evans

School / Faculty: PHS, Medical School – Centre for Academic Child Health

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

KBG syndrome is a rare neurodevelopmental disorder caused by alterations in the ANKRD11 gene. This condition is rare affecting approximately 500 families worldwide but is one of the commonest genetic neurodevelopmental disorders. Parents/carers and affected individuals report significant problems around sleep which significantly impacts the individuals behaviour and wellbeing and also impacts family life. Most of the evidence regarding sleep disturbance is anecdotal with very patchy reporting in the literature alongside minimal detail. It is essential to understand the scale of sleep problems in order to then undertake research into best strategies to help. Conducting this survey will utilise a published sleep measure to enable families, clinicians and researchers to have a clearer picture of the scale and nature of sleep issues in KBG syndrome. The information may help to determine possible strategies for treatments and also to help inform next steps for research into what interventions work best in this condition.

The project encompasses a full research cycle including application for university ethical approval, development of all study materials, building a REDCAP survey, recruitment and then subsequent analysis. The study will be international and will require collaboration with international experts. We are currently undertaking a similar study and so the student will have a clear template to follow in all aspects.

Dependent on results, we anticipate that this will lead to publication and presentation at a conference.

It may be possible within the funding allocation for the student to spend a short time period with our collaborators Dr Allan Bayat and Dr Francesca Furia in Denmark –please note this is not guaranteed and details to be determined. The student will undertake most of the project as part of the CACH team which will also enable a chance to network within a well established paediatric research network.

Techniques to be used:

Scoping literature review; co production of questionnaire with PPI group/KBG foundation; REDCAP questionnaire development; qualitative text analysis of survey and descriptive statistics along with analysis of survey according to the validated measure analysis guidelines.

3 key references:

1. Low KJ, Ashraf T, Canham N,Clayton-Smith J, …, Hills A, Holder S, Irving M, Joss S, Kivuva E, Lachlan K, Magee A, McConnell V, McEntagart M, Metcalfe K, Montgomery T, Newbury-Ecob R, Stewart F, Turnpenny P, Vogt J,Fitzpatrick D, Williams M, DDD Study ,Smithson S. Clinical and Genetics aspects of KBG Syndrome. American Journal of Medical Genetics. 2016. 170(11):2835-2846

2. Agar G et al. Mol Autism. 2021; 12: 18. Sleep disorders in rare genetic syndromes: a meta-analysis of prevalence and profile doi: 10.1186/s13229-021-00426-w

3. GeneReviews: KBG Syndrome https://www.ncbi.nlm.nih.gov/books/NBK487886/

Specific requirements for the project:
Immunisations (e.g. Hepatitis B)? Interest in rare disease research
HO licence?
Other?

45: Project title: Public attitudes to xenotransplantation: preparing for policy change

Primary supervisors: Associate Professor Pippa Bailey and Ms Bonnie Venter

Secondary supervisor (for day-to-day support): Associate Professor Pippa Bailey

School / Faculty: Bristol Medical School: Population Health Sciences

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

Background

Xenotransplantation is the transplantation of organs or tissues from animals to humans. There is no legislation which regulates whole-organ xenotransplantation research in the UK. Following recent world-first pig-to-human heart and kidney transplants in the USA which received world-wide media coverage, whole-organ xenotransplantation is now a reality, albeit still in a research capacity. No xenotransplant research is being undertaken in the UK due in part to the lack of UK regulatory policy. UK public opinion regarding xenotransplantation is unknown.

UK regulatory policy is urgently required. Ascertainment of public perceptions is essential prior to the development of new policy. An understanding of public opinion allows identification of concerns regarding xenotransplant to be addressed before policy implementation. It allows unexpected harms to be identified and action taken to prevent them. Public views towards xenotransplantation in the UK are unknown: previous research is extremely limited. A 2021 UK study investigated attitudes to xenotransplantation amongst 1550 school students. 33.2% reported a hypothetical preference for a transplant from a human donor, 22.3% for a laboratory-grown organ, 1.6% a preference for a pig organ, with 26.3% uncertain.

Aims

The study will assess UK public attitudes towards xenotransplantation, including:

- Objections
- Positive perspectives
- Ethical, moral and scientific uncertainties
- Misinformation
- Topics that require further investigation in qualitative research, including animal welfare and impact on human organ donation.

Methods

The student will conduct an inductive qualitative content analysis of public comments on online news articles from national media outlets between 01/2021 and 1/2024. They will search the major UK news outlets that have unrestricted access and allow public comments. A full-text review of articles will be undertaken and article characteristics extracted, describing article type (e.g., article/opinion piece), tone (e.g., for/against/impartial), and perspectives presented (e.g., clinicians/patients/politicians). Comments and responses linked to the articles will be extracted and imported into NVivo

software. Comments identified as from outside the UK will be analysed separately. Usernames will be connected to comments for analysis but removed at publication. This approach provides insight into the views of the diverse public, including those of people who choose not to take part in research.
Techniques to be used: Inductive qualitative content analysis
3 Key references: 1. Haddow G. 'Dirty pigs' and the xenotransplantation paradox. Med Humanit. 2021;47(417-24). 2. Hsieh H, Shannon S. Three approaches to qualitative content analysis. Qual Health Res. 2005;15(9):1277-88. 3. Martínez-Alarcón L, Ríos A, Pons J, González M, Ramis G, Ramírez P, et al. Attitudes toward islet cell and tissue xenotransplantation among kidney and liver patients on the transplant waiting list. Transplant Proc. 2010;42(8):3098-101.
Specific requirements for the project: Immunisations (e.g. Hepatitis B)? HO licence? Other?

46: Project title: Impact of COVID-19 on parental wellbeing and child development in a cleft population

Primary supervisor: Amy Davies

Secondary supervisor (for day-to-day support): Sarah Lewis and Evie Stergiakouli

School / Faculty: Bristol Dental School

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

Approximately 1 in 700 children in the UK are born with an orofacial cleft (OFC). Children born with OFC have a 20-year care pathway, undergo multiple child- and adulthood surgeries and have an increased health burden which may be intensified further by additional comorbidities. Some children born with OFC experience developmental delays and recent evidence has found elevated levels of behavioural problems in children born with OFC compared to the general population. Further evidence has also suggested that parents of children born with OFC may experience social and emotional challenges.

The COVID-19 pandemic has resulted in delays and reduced services within cleft care. In addition, many children will have missed time from school and/or childcare and will have been faced with limited social interaction outside of the family unit during the pandemic. The pandemic will have likely caused further burdens for children born with OFC and their families which could impact parental wellbeing and child development.

Using data from the Cleft Collective cohort study, a national longitudinal prospective cohort of children born with OFC and their families, the following aims and objectives will be addressed:

Aim 1: Determine whether there is a difference in parental wellbeing in parents of children born with OFC pre and post pandemic.

Objective 1a: Describe measures of parental wellbeing and potential confounding variables by pre and post pandemic sub-groups.
Objective 1b: Compare parental wellbeing between pre and post pandemic sub-groups.

Aim 2: Determine whether there is a difference in child development in children born with OFC pre and post pandemic.

Objective 2a: Describe measures of childhood development and potential confounding variables by pre and post pandemic sub-groups.
Objective 2b: Compare childhood development between pre and post pandemic sub-groups.

Techniques to be used:

- Descriptive statistics to be undertaken on all outcomes and confounders by exposure group (pre and post pandemic).
- Pre and post pandemic comparisons to be made by Odds Ratios for categorical outcomes and t-tests (where normally distributed) or Mann Whitney U (where distribution is skewed) for numerical outcomes.
- Binary and ordinal logistic regression to be performed for categorical outcomes and multivariable linear regression models to be performed for numeric outcomes to enable the adjustment of confounders.

3 Key references:

Berman S, Sharp GC, Lewis SJ, et al. Prevalence and Factors Associated with Behavioral Problems in 5-Year-Old Children Born with Cleft Lip and/or Palate from the Cleft Collective. The Cleft Palate Craniofacial Journal. 2024;61(1):40-51. doi:10.1177/10556656221119684

Costa B, McWilliams D, Blighe S, et al. Isolation, Uncertainty and Treatment Delays: Parents' Experiences of Having a Baby with Cleft Lip/Palate During the Covid-19 Pandemic. The Cleft Palate Craniofacial Journal. 2023;60(1):82-92. doi:10.1177/10556656211055006

Nidey N, Moreno Uribe LM, Marazita MM, Wehby GL. Psychosocial well-being of parents of children with oral clefts. Child Care Health Dev. 2016 Jan;42(1):42-50. doi: 10.1111/cch.12276. Epub 2015 Aug 25. PMID: 26302988; PMCID: PMC4758188.

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

47: Project title: Female domestic abuse perpetrators: Behaviour change intervention adaptations and integrated support.

Primary supervisor: Helen Cramer

Secondary supervisors: Karen Morgan and Laura Bennett

School / Faculty: Centre for Academic Primary Care, Population Health Sciences, Bristol Medical School, University of Bristol,

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

Both women and men can experience Intimate Partner Violence (IPV), but frequency and severity are highest for women. Although in recent years, there has been greater focus on perpetrator work, , there has been relatively little attention paid to female perpetrators. Consequently, less is understood about them with a few notable exceptions [1,2].

Provision of behaviour-change interventions, often referred to as Domestic Abuse Perpetrator Programmes (DAPPs), tends to focus on male perpetrators in heterosexual relationships. Although some services offer support to female perpetrators, provision appears limited. Many DAPPs are accredited by Respect, a national, membership-based, domestic abuse organisation, which sets standards and provides training.[3] A necessary condition of accreditation is providing integrated survivor-support, which helps ensure appropriate safeguarding measures are put in place and that the victim/survivor has support from a specialist worker.

This project will establish currently available behaviour-change provision for female IPV perpetrators in England and Wales, and examine what support is provided to their victims/survivors. This will involve:

- conducting a literature review of evidence;
- mapping what behaviour-change interventions are available to female perpetrators and how these are delivered;
- conducting interviews with up to 10 service providers working with female perpetrators. This will be to:
    - better understand who is accessing the programmes and why;
    - similarities and differences between interventions for male and female perpetrators;
    - to understand how DAPPs need to be adapted for mixed groups including female perpetrators
    - to understand how support is provided to victims/survivors of female perpetrators.

The supervisors are working on two linked studies which will facilitate access to potential interview participants:

- REPROVIDE: a randomised controlled trial to determine the (cost-)effectiveness of group DAPPs for men

(https://www.bristol.ac.uk/primaryhealthcare/researchthemes/reprovide/domestic-abuse-group-programme-for-men/)

- The role of survivor-support services integrated within DAPPs (ISS-DAPP) which looks at the provision of survivor-support in the context of DAPPs (https://issdapp.blogs.bristol.ac.uk/).

Techniques to be used:

- Literature review of existing evidence of women using abusive behaviours in same-sex and heterosexual relationships
- Mapping of interventions currently available for female DVA perpetrators in England and Wales
- Semi-structured interviews (5-10) with perpetrator intervention providers to determine the demand for interventions for female perpetrators, how such interventions are delivered, who is accessing them, and the key similarities and differences between interventions for male perpetrators and those for females.
- Interviews to be transcribed, anonymised and analysed thematically.
- The student will obtain Research Ethics Approval through an application to the Faculty Research Ethics Committee

3 Key references:

[1] Barton-Crosby, J & Hudson, N. (2021). Female perpetrators of IPV: Stakeholder Engagement Research. Home Office. Available at https://natcen.ac.uk/sites/default/files/2022-12/NatCen_Female-IPV-perpetrators-report.pdf

[2] Laskey, P. (2016) Systematic review of female perpetrators of intimate partner violence and their treatment. Journal of Applied Psychology and Social Science, 2 (1). pp. 62-88.

[3] Respect (2022) *The Respect Standard*, 4th edition. London: Respect. https://hubble-live-assets.s3.amazonaws.com/respect/file_asset/file/1458/Respect_Standard_4th_edition_2022.pdf

Specific requirements for the project:

None

Some skills in qualitative research methods and literature reviewing would be an advantage

48: Project title: Can the usual research measures of programme integrity and fidelity apply to behaviour change groups for domestic abuse perpetrators?

Primary supervisor: Helen Cramer, co supervisor Karen Morgan

Secondary supervisor:

School / Faculty: Centre for Academic Primary Care, Population Health Sciences, Bristol Medical School, University of Bristol,

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

Despite calls for data on 'programme integrity' to inform the evaluations of domestic abuse perpetrator programmes (DAPPs), Kelly and Westmarland 2015), there is little consensus in the literature about what programme integrity actually means. Although levels of fidelity to the programme manual would be appropriate for some interventions (Carrol et al 2007), it a poor fit for DAPPs (Phillips 2015). UK Respect accredited DAPPs (https://www.respect.uk.net/pages/accreditation) encompass weekly groups for people who are abusive to their partners and ex partners as well as one-to-one support, partner support and information sharing. DAPPs do have manuals and policies to provide a secure and shared practice framework, but also draw on professional judgement and expertise to work flexibly and responsively with the material that men bring to group work. A group facilitator showing no flexibility and strict adherence to the manual would be as problematic as no adherence to the manual at all.

The REPROVIDE study (https://reprovideprogramme.blogs.bristol.ac.uk/) is testing the efficacy of DAPPs in 4 sites. Integrity work already undertaken includes: 1) Respect accreditation reports; 2) facilitators' adherence reports completed after each group session on core objectives and reasons for any divergence; and 3) observation reports for a sample (5%) of group recordings based on a template and covering delivery style and stance.

This work would involve: understanding the principles of fidelity and integrity in the wider field and specific challenges in DAPPs, reflecting, collating and combining the different data sources on fidelity and integrity into a more detailed analysis and helping to produce a coherent report.

There would also be an opportunity to present this work and discuss findings with representatives of Respect.

Techniques to be used:

- Conduct a literature review.
- Review summarised adherence data for each site
- Review accreditation reports for each site
- Review some videos of DAPP groups-in action to become familiar with the material
- Review and analyse observation reports including some research notes on 'live' observations of groups

Ethics approval for this work is already granted through the REPROVIDE trial's main ethics application. The MRES candidate would work closely with REPROVIDE team members and would not be expected to be knowledgeable about DAPPs or domestic abuse beforehand. This MRES might suit someone with an interest in domestic abuse/psychiatry/gender relations/criminology or someone interested in therapeutics, behaviour change and group dynamics.

'Integrity' 'implementation' 'fidelity' 'quality' all used interchangeably in programme integrity research. 'Fidelity' is the degree of exactness with which something is copied or reproduced; 'integrity' is the degree to which a programme is delivered as designed and planned.

3 Key references:

Carroll, C., Patterson, M., Wood, S. *et al.* A conceptual framework for implementation fidelity. *Implementation Sci* **2**, 40 (2007). https://doi.org/10.1186/1748-5908-2-40

Kelly, L. and Westmarland, N. (2015) *Domestic violence perpetrator programmes: steps towards change*, Project mirabal final report, London and Durham: London Metropolitan University and Durham University.
https://repository.londonmet.ac.uk/1458/1/ProjectMirabalfinalreport.pdf

Phillips, R. (2015) *British domestic violence perpetrator programmes: 'Programme integrity' within 'service integrity'*. Unpublished PhD thesis, London Metropolitan University.
https://repository.londonmet.ac.uk/940/1/PhillipsRuth_BritishDomesticViolencePerpetratorProgrammes.pdf

Specific requirements for the project:
None
This MRES might suit someone with an interest in domestic abuse/psychiatry/gender relations/criminology or someone interested in therapeutics, behaviour change and group dynamics.

49: Project title: Co-designing an art and wellbeing programme to help prevent anxiety and depression in schools

Primary supervisor: Dr Naomi Warne (Prudence Trust/Elizabeth Blackwell Institute Fellow)

Secondary supervisor (for day-to-day support): Liz Jestico (Research Associate)

School / Faculty: Bristol Medical School

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

Anxiety and depression are impairing mental health problems that commonly co-occur and often develop in adolescence. Most young people with anxiety and depression do not receive any treatment and, if they do, treatments are not always effective. It is important to *prevent* anxiety and depression to improve young people's lives.

Mental health prevention programmes run in schools could reduce mental illness in large numbers of young people. However, most current programmes are tied to research funding and not sustained long-term (Werner-Seidler et al., 2021). To make prevention programmes sustainable in schools, we need to co-develop programmes with school staff and students to ensure the programmes fit the needs of individuals and communities involved.

Visual art-based interventions, including art therapy and non-therapeutic engagement with the visual arts, can help young people express their feelings without the need for verbal communication. Importantly, visual art interventions reduce symptoms of anxiety and depression in young people and also show promise in preventing these symptoms (Easwaran et al., 2021).

In this project, the student will work with the Create for Confidence Team to develop an art and wellbeing programme aimed at preventing anxiety and depression in UK secondary schools. We will use co-production – a way of working with people from the community in equal partnership, engaging people at the earliest stages of design, development and evaluation.

The MRes student will support co-design workshops with young people, parents, school staff, art therapists and mental health professionals. There will also be opportunity to lead "think-aloud interviews" to encourage young people to share their thoughts about early iterations of the programme.

The MRes student can choose to qualitatively analyse transcripts of the workshops or interviews using thematic analysis or content analysis (Braun & Clarke, 2021).

Techniques to be used:
Co-production – working with young people and adults to co-design the art and wellbeing programme at face-to-face and online co-design workshops
Think-aloud interviews
Qualitative analysis of transcripts (thematic analysis or content analysis)

3 Key references:

Easwaran, K. *et al.* Why art matters for youth mental health: A youth led participatory insight analysis. *PsyArXiv* (2021) doi:10.31234/OSF.IO/AP476.

Werner-Seidler, et al. (2021) Clinical Psychology Review, 89. https://doi.org/10.1016/J.CPR.2021.102079

Braun, V., & Clarke, V. (2021). Can I use TA? Should I use TA? Should I not use TA? Comparing reflexive thematic analysis and other pattern-based qualitative analytic approaches. Counselling & Psychotherapy Research, 21(1), 37–47. https://doi.org/10.1002/capr.12360

Specific requirements for the project:

Immunisations (e.g. Hepatitis B)? No

HO licence? No

Other? Enhanced DBS check to work with children and vulnerable adults

50: Project title:
Mapping the current landscape of information provided to support informed decision-making for women with breast cancer in the UK

Primary supervisor: Professor Shelley Potter

Secondary supervisor (for day-to-day support): Professor Shelley Potter

School / Faculty: THS

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

Background

Breast cancer affects 55,000 women every year in the UK. Treatment for breast cancer is multimodal but usually involves surgery and a combination of systemic anticancer therapy, radiotherapy and/or endocrine therapy.

Treatment decision-making in breast cancer, however, is increasingly complex. Women often face a bewildering array of decisions regarding the sequencing of their treatments; options for oncoplastic surgery and if mastectomy is recommended, multiple possible breast reconstruction procedures. Not all women, however, are offered all treatment options. Reasons for this inequity are largely unknown, but are likely to reflect surgeon preference; local surgeon skill-mix and organisation of care.

The James Lind Priority Setting Process for breast cancer surgery which involved 200 patients and 100 healthcare professionals identified the need for research to support informed decision-making as a top 10 research priority (1). The priorities related to information in the top 10, however, were extremely broad and could not be directly translated into researchable questions. A subsequent research priority setting exercise specifically focusing on information and support for women undergoing breast cancer surgery was therefore undertaken with patients. The final workshop was held in March 2024 and the top research priority was identified as:

'How can we ensure that all patients with breast cancer are offered and given fair and balanced information about all appropriate types of breast cancer surgery? How can we best support patients to make decisions about what option is best for them?'

The first step in addressing this research priority is to explore the current landscape of information provision to support informed decision-making to determine if and how it needs to be improved.

Aims and objectives

The overall aim of this project is to map the current landscape of information provided to women with newly diagnosed breast cancer to support informed decision-making regarding their treatment options.

Specific objectives will be to explore:

i. The types of information provided to women by their surgical teams, additional resources used
ii. Women's views of the utility of these resources including what types of information not covered and how methods for sharing information
iii. Women's perceptions of the optimal ways of providing and sharing information to support informed decision-making

Methods

This is a mixed methods project involving the following components:

i. A patient survey to explore current practice across the UK
ii. Qualitative interviews with patients to explore views regarding information and support in more detail
iii. Content analysis of information resources provided by local trusts and charities

Techniques to be used:

Patient survey
Qualitative semi-stuctured interviews
Content analysis of patient information

3 Key references:

Potter et al (2023) Identifying research priorities in breast cancer surgery: a UK priority setting partnership with the James Lind Alliance. Breast Cancer Res Treat. 2023; 197(1): 39–49. doi: 10.1007/s10549-022-06756-4
Specific requirements for the project: Immunisations (e.g. Hepatitis B)? HO licence? Other?

51: Project title: Cognitive bias modification for eating disorders and body dissatisfaction

Primary supervisor: Dr Helen Bould

Secondary supervisor (for day-to-day support): Dr Charlotte Crisp

School / Faculty: Bristol Medical School, Centre for Academic Mental Health

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

Meta-analysis of studies using eye-tracking finds that individuals with eating disorders, and those with higher levels of body dissatisfaction (a risk factor for both subsequent eating disorders and depression) spend more time attending to bodies of lower weight, likely exacerbating their dissatisfaction. Attentional retraining to target this cognitive bias has the potential to prevent and treat eating disorders and depression. However, attempts to measure this bias using various attention measuring tasks other than eye-tracking have been unsuccessful, due to high levels of between-trial variability.

The project student would have the opportunity to join the team in refining an eye-tracking task to replicate existing studies measuring attentional bias to bodies of different sizes amongst individuals with varying levels of body dissatisfaction. The project student would then support the co-creation (with PPI involvement) of a bias modification task designed to retrain attentional biases away from smaller bodies. This would help to lay the groundwork for feasibility testing in those with high levels of body dissatisfaction and eating disorders.

This project forms part of a programme of work supported by the Bristol Biomedical Research Centre. The student will be supported to pre-register their experiments and share their data in line with Open Science principles. They will be supervised in writing University ethics applications and research protocols, learning skills in programming eye-tracking tasks using EyeLink 1000 Plus software, recruiting participants, developing analysis skills in either Stata or R, and writing up their work for publication and presentation at conferences.

Techniques to be used:

- Programming using EyeLink 1000 Plus eye-tracker software
- Recruitment and running of eye-tracking study
- Co-creation of a retraining task with PPI group
- Analysis of results using Stata or R
- Writing up results for publication

3 Key references:

House T, Graham K, Ellis B, Bould H, Attwood AS, Stephen ID, et al. Is body dissatisfaction related to an attentional bias towards low weight bodies in non-clinical samples of women? A systematic review and meta-analysis. Body Image. 2023;44:103-19.

Ralph-Nearman, C. et al A systematic and methodological review of attentional biases in eating disorders: Food, body, and perfectionism. *Brain behav* 2019 **9**, e01458

Stephen ID, Sturman D, Stevenson RJ, Mond J, Brooks KR. Visual attention mediates the relationship between body satisfaction and susceptibility to the body size adaptation effect. PLoS One. 2018;13(1):e0189855.

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

52: Project title: Use of imagery in kidney patient information materials

Primary supervisor: Dr Barnaby Hole (university of Bristol). External supervision will be provided by Dr Anna Winterbottom (University of Leeds).

Secondary supervisor (for day-to-day support): Dr Samantha Hayward (UoB)

School / Faculty: Population Health Sciences

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

Background

Chronic kidney disease is the progressive deterioration in people's kidney function, which can lead to kidney failure. Kidney health professionals and people with kidney disease make decisions together about treatments that will fit best into their everyday life. Treatments are used to slow down damage to the kidneys, prevent secondary problems from low kidney function, manage symptoms, and – if kidney failure develops – to replace kidney function. Treatments for kidney failure include kidney transplantation from a live, deceased, or altruistic donor; haemodialysis; continuous ambulatory peritoneal dialysis; automated peritoneal dialysis; and comprehensive conservative care. Each option has an associated treatment burden, requiring considerable adaptations to a person's daily routines.

Kidney units prepare people for changes to their kidney disease management as their illness worsens. Patient information leaflets are frequently used to supplement verbal information. These contain information to help people cope and adjust to their kidney disease, prepare them for treatments/surgery, provide service relevant information, and make treatment decisions. Patient information leaflets may be developed in-house – by individual kidney units, or by national patient charities [1]. Frequently, leaflets include photographs and illustrations of people undertaking treatment or daily activities, to supplement written text. To support people making treatment decisions, information should be presented in a balanced and unbiased way [2]. Using patient stories to supplement patient information is likely to bias people's decision making [3]. It is not known whether the use of images impacts in a similar way.

Aim

This project will explore how the use of imagery in patient information materials impacts on people's attitudes and perceptions of the suitability of treatments for kidney failure.

Objectives

To describe the use of imagery in kidney patient information available in in UK kidney units and via kidney patient charities (phase 1).

To explore people's attitudes and perception of images used within kidney patient information materials (phase 2&3).

Techniques to be used:

Phase 1 - An environmental scan to describe and collate images used within kidney patient information used to supplement decision making about treatment options.

Phase 2&3 – Patient and public involvement, focus group, and survey methodologies with a broad cross section of people living with kidney disease to explore the impact of these images on decision making.

3 Key references:

[1] Winterbottom AE., Mooney A., Russon L., et al. Critical Review of Leaflets About Conservative Management Used in UK Renal Services. Journal of Renal Care. 2020a 46(4), 250–257.

[2] Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, Holmes-Rovner M, Llewellyn-Thomas H, Lyddiatt A, Thomson R, Trevena L. Decision aids for people facing health treatment or screening decisions. Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD001431. DOI: 10.1002/14651858.CD001431.pub5. Accessed 18 December 2023.

[3] Witteman HO, Maki KG, Vaisson G, Finderup J, Lewis KB, Dahl Steffensen K, Beaudoin C, Comeau S, Volk RJ. Systematic Development of Patient Decision Aids: An Update from the IPDAS Collaboration. Med Decis Making. 2021 Oct;41(7):736-754. doi: 10.1177/0272989X211014163. Epub 2021 Jun 19.

Specific requirements for the project: None.
Immunisations (e.g. Hepatitis B)? Not required.
HO licence? No.
Other? Nil.

53: Project title: Changes in social and economic outcomes associated with exposure to intimate partner violence: a focused systematic review of longitudinal studies.

Primary supervisor: Natalia Lewis, nat.lewis@bristol.ac.uk

Secondary supervisor (for day-to-day support): Estela Capelas Barbosa, eb18912@bristol.ac.uk

School / Faculty: Bristol Medical School (PHS)

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

This project is for a student with interest in social determinants of health, quantitative methods, and evidence synthesis methods.
Intimate partner violence has a negative impact on social and economic outcomes. However, it has not been established how long those social and economic consequences last and how the duration varies with the type of violence. Duration of such effects is needed to cost the social and economic harms from violence.
Research objective: To quantify the average length of time for which social and economic outcomes are affected by intimate partner violence, by type of violence (sexual, physical, emotional, financial).
Methods: A focused systematic review of studies reported in peer reviewed literature that recruited adults, had multiple time points, a social and/or economic outcome(s) and where intimate partner violence was a predictor, independent variable, or inclusion criterion.
Support will be provided by supervisors and BMS subject librarian. Training on quantitative evidence synthesis is available via short course and guided self-learning.

Techniques to be used:

- Designing search strategy, searches of electronic databases, title and abstract and full text screening, data extraction, quality appraisal, quantitative evidence synthesis with or without meta-analysis.
- Rayyan platform for screening of title and abstracts and full text reports.
- STATA or R software for quantitative analysis.
- EndNote for managing references.

3 Key references:

1. Patton SC, Szabo YZ, Newton TL. Mental and Physical Health Changes Following an Abusive Intimate Relationship: A Systematic Review of Longitudinal Studies. Trauma Violence Abuse. 2022 Oct;23(4):1079-1092. doi: 10.1177/1524838020985554. Epub 2021 Jan 20. PMID: 33468040.
2. Page, M.J., McKenzie, J.E., Bossuyt, P.M. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 10, 89 (2021). https://doi.org/10.1186/s13643-021-01626-4
3. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160. doi: 10.1136/bmj.n160

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

54: Project title:
Investigating long-COVID in the UK: A review of research

Primary supervisor: *Katharine Looker*

Secondary supervisor (for day-to-day support): *Eleanor Walsh*

School / Faculty: **Population Health Sciences - Bristol Medical School**

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

Background: Since March 2020 there have been many research groups set up to investigate health and associated outcomes of the SARS-CoV-2 pandemic. Latterly, these studies have used longitudinal data to investigate long-COVID beyond the acute phase (>4 weeks). Prevalence estimates of long-COVID have been difficult to interpret due to heterogenous study designs[1]. Whilst the limitations of pooled estimates due to study heterogeneity have been acknowledged, the specifics of these study differences have yet to be described and directly compared. A direct comparison of study designs and populations would be useful to illustrate the similarities and differences in study characteristics to aid the interpretation of long-covid estimates in adults, children and young people.

Research objectives: Review to describe and compare the design characteristics of long-COVID studies to aid interpretation of long-COVID estimates across UK populations, for example:

- Characteristics of population (age, gender, location)
- Recruitment strategy & sample size
- Exposure and outcome measures (survey, biological samples, electronic health records)
- Long-COVID definitions
- Compare estimates of long-COVID by age across adults, children and young people.

Techniques to be used:

- Appropriate search strategies (e.g., MeSH terms, citations) and publication databases to identify relevant scientific outputs
- Summarise and describe study designs and methodologies appropriate for comparison
- Calculate pooled estimates using meta-analysis/meta-regression, where appropriate
- Interpret and critically appraise summarised descriptions considering current literature, context and methodologies.

Software: R or Stata; Endnote

3 Key references:

1. Chua PEY, Shah SU, Gui H, et al. Epidemiological and Clinical Characteristics of Non-Severe and Severe Pediatric and Adult COVID-19 Patients across Different Geographical Regions in the Early Phase of Pandemic: A Systematic Review and

Meta-Analysis of Observational Studies. *Journal of Investigative Medicine* 2021;69(7):1287-96. doi: 10.1136/jim-2021-001858
2. Lopez-Leon S, Wegman-Ostrosky T, Ayuzo del Valle NC, et al. Long-COVID in children and adolescents: a systematic review and meta-analyses. Scientific Reports 2022;12(1):9950. doi: 10.1038/s41598-022-13495-5
3. 4. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature 2021;594(7862):259-64. doi: 10.1038/s41586-021-03553-9

Specific requirements for the project: *None*
Immunisations (e.g. Hepatitis B)? HO licence? Other?

55: Project title:
A systematic review update of dressings for the prevention of surgical site infection

Primary supervisor: Dr Rhiannon Macefield

Secondary supervisor (for day-to-day support): Dr Kerry Avery

School / Faculty: Bristol Medical School

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

Over five million surgical procedures are performed annually in the UK. Most surgical incisions are closed with sutures or staples and covered by a dressing. Evidence for the benefits of dressings compared to 'no dressings' (i.e., leaving the wound exposed) is, however, limited and up to 25% of incisions develop a surgical site infection (SSI). SSI has significant morbidity, quality-of-life impact and cost.

Our NIHR-funded 'Bluebelle' study[1] found that topical skin adhesives (glue) – developed originally for wound *closure* – have an innovative application 'as-a-dressing' by providing a sealed, flexible, waterproof barrier that may prevent bacterial contamination. Glue as-a-dressing was emerging in practice at the time of our study (2015) but its benefit/harm for preventing SSI is uncertain. Our 2016 Cochrane review did not identify any randomised controlled trials (RCTs)[2].

Work undertaken withing our centre has shown that a trial randomising patients to receive a wound dressing, no dressing or glue-as-a-dressing is feasible and acceptable with economic value[1]. To take this work forward, an update systematic review to search for new existing evidence for no dressing and glue-as a dressing is now needed.

The project will involve an update of a systematic review following standard systematic review methodology[3]. The project will include bespoke on-the-job training in systematic review methodology, evidence based surgical practice and outcome assessment. The student will work within our team within the NIHR Bristol Biomedical Research Centre (BRC) Surgical and Orthopaedic Innovation theme, based in the Centre of Surgical Research, Bristol Medical School. Students will have the opportunity to attend team meetings which take place several times per month (online and in-person). This will provide an opportunity to learn about other projects within the Centre for Surgical Research and the Bristol BRC.

Techniques to be used:

A systematic review will be undertaken. Specific tasks include:

1. Searching of electronic bibliographic databases and registries for relevant studies.
2. Screening titles, abstracts and full-text articles to assess studies for eligibility according to pre-defined inclusion criteria.
3. Data extraction from included studies using a pre-designed and piloted data extraction form.

4. Performing quality and risk-of-bias assessments of included studies based on established criteria.
5. Syntheses and analysis of data.
6. Writing for scientific reports/papers.

3 Key references:

1. Reeves BC, Rooshenas L, Macefield RC, Woodward M, Welton NJ, Waterhouse BR, et al. Three wound-dressing strategies to reduce surgical site infection after abdominal surgery: the Bluebelle feasibility study and pilot RCT. Health Technology Assessment 2019;23:1-166. https://doi.org/10.3310/hta23390
2. Dumville JC, Gray TA, Walter CJ, Sharp CA, Page T, Macefield R, et al. Dressings for the prevention of surgical site infection. The Cochrane Database of Systematic Reviews 2016;12:Cd003091. https://doi.org/10.1002/14651858.CD003091.pub4
3. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

Specific requirements for the project:
None specific, experience of literature searching is desirable.

56: Project title:

Economic Evaluation of Hepatitis C Virus (HCV) Screening in Emergency Departments: A Systematic Review

Primary supervisor: Asra Asgharzadeh

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

School / Faculty: Population Health Science/Medical school

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

Introduction:
The global challenge of Hepatitis C Virus (HCV) remains a significant public health concern, necessitating timely diagnosis and access to healthcare services for effective intervention. Emergency Departments (EDs) serve as crucial entry points for various patient demographics, including those at risk of undiagnosed HCV infections. Incorporating HCV screening into routine ED practices has shown promise in improving diagnosis rates and facilitating early intervention. However, understanding the economic implications of implementing such screening programs is essential for informed resource allocation decisions.

Objectives:
This research project aims to conduct a systematic review to evaluate the economic aspects of HCV screening interventions in ED settings. Specific objectives include:

- Identifying relevant studies assessing the cost-effectiveness, cost-benefit, or cost-utility of HCV screening programs in EDs.
- Synthesizing evidence on the economic outcomes (e.g., costs, savings, quality-adjusted life years) associated with various HIV screening strategies.
- Analysing the methodological approaches and key findings of included studies to inform future economic evaluations and policy decisions.

By the conclusion of this research project, we aim to provide a thorough look at the economic evidence surrounding HCV screening in Emergency Departments. These findings will form the basis for ongoing health economic modelling of the BBV opt-out testing program in EDs. We'll share our results through peer-reviewed publications and conference presentations, helping to improve understanding in health economics and HCV elimination.

Techniques to be used:
Considering the significance of HCV screening as an integral component of opt-out testing in EDs in the UK, conducting a review would furnish timely evidence to bolster ongoing efforts aimed at expanding BBV opt-out screening across the UK healthcare system, thereby aligning with prevailing public health priorities.

The systematic review will adhere to established guidelines such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. The following steps will be undertaken:
- Systematic literature search across electronic databases (e.g., PubMed, Embase, Cochrane Library) for relevant studies published within a specified timeframe.
- Selection of studies based on predefined inclusion and exclusion criteria, with screening conducted by two independent reviewers.
- Data extraction using standardized forms to capture information on study characteristics, economic parameters, and outcomes.
- Quality assessment of included studies to evaluate the risk of bias and methodological rigor.
- Synthesis of findings through narrative synthesis and, if feasible, meta-analysis to quantify the economic impact of HIV screening in EDs.

3 Key references:

Noiriel N, Williams J. Early cost-utility analysis of hepatitis C virus testing for emergency department attendees in France. PLOS Global Public Health. 2023 Feb 23;3(2):e0001559.

Williams J, Vickerman P, Smout E, Page EE, Phyu K, Aldersley M, Nebbia G, Douthwaite S, Hunter L, Ruf M, Miners A. Universal testing for hepatitis B and hepatitis C in the emergency department: a cost-effectiveness and budget impact analysis of two urban hospitals in the United Kingdom. Cost Effectiveness and Resource Allocation. 2022 Nov 14;20(1):60.

Mendlowitz AB, Naimark D, Wong WW, Capraru C, Feld JJ, Isaranuwatchai W, Krahn M. The emergency department as a setting-specific opportunity for population-based hepatitis C screening: An economic evaluation. Liver International. 2020 Jun;40(6):1282-91.

Malaisamy M, Nagarajan K, Kirti T, Malkeet S, Venkatesan P, Senthilkumar S, Sananthya K, Rajendran K, Kavitha R, Vivekanandan S, Selvavinayagam TS. Economic evaluation of implementing a rapid point-of-care screening test for the identification of hepatitis C virus under National Viral Hepatitis Control Programme in Tamil Nadu, South India. Journal of Global Infectious Diseases. 2021 Jul 1;13(3):126-32.

Coward S, Leggett L, Kaplan GG, Clement F. Cost-effectiveness of screening for hepatitis C virus: a systematic review of economic evaluations. BMJ open. 2016 Sep 1;6(9):e011821.

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

57: Project title:

A Systematic review of Economic Evaluation of Immunoglobulin Therapies for primary immunodeficiency disease

Primary supervisor: Asra Asgharzadeh

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

School / Faculty: Population Health Science/Medical school

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

Background:

As instances of immunodeficiency disorders continue to rise, it becomes imperative to delve into the economic dimensions associated with these conditions. These genetic disorders impair the immune system's ability to combat infections. Immunoglobulin therapy, a treatment utilizing antibodies from donated blood plasma, is administered through techniques such as subcutaneous and intravenous methods. Subcutaneous administration, being a newer approach, is included in the comparison to shed light on its economic aspects and patient outcomes. The comparison between home-based subcutaneous immunoglobulin therapy and hospital-based intravenous immunoglobulin therapy not only illuminates cost-effectiveness but also provides valuable insights into patient outcomes, addressing a significant gap in the existing literature.

Objectives:

The primary goal of this project is to conduct a systematic review of economic evaluations pertaining to home-based subcutaneous immunoglobulin therapy (SCIG) versus hospital-based intravenous immunoglobulin therapy (IVIG). By synthesizing available evidence, the study aims to assess the cost-effectiveness, resource utilization, and patient-related outcomes associated with these two modalities of immunoglobulin therapy.

Techniques to be used:

Methods:

The study will employ systematic review methodologies, including comprehensive literature searches, data extraction, quality assessment, and synthesis of findings. Analyzing economic evaluations will provide a comprehensive overview of the comparative economic aspects of these two immunoglobulin therapy modalities. The following steps need to be undertaken in accordance with the PRISMA standard for this systematic review:

- Literature Searches: Comprehensive searches will be conducted across electronic databases such as PubMed, Embase, and the Cochrane Library, targeting relevant studies published within the last decade.

- Inclusion Criteria: The study will include research presenting economic evaluations that draw a comparison between home-based subcutaneous immunoglobulin therapy and hospital-based intravenous immunoglobulin therapy.

- Data Extraction: A thorough extraction of pertinent information will encompass study design, patient characteristics, intervention details, and economic outcomes.

- Quality Assessment: Recognized tools, such as the CHEERS checklist, will be employed to assess the methodological quality of the included studies.

- Synthesis: The study will perform data synthesis through narrative synthesis, aiming to draw meaningful comparisons and identify overarching trends in the economic evaluations of these two immunoglobulin therapy modalities.

***Specify that a one-page protocol must be submitted to PROSPERO before commencing the systematic review.

**Here are some suggested search terms for this systematic review on economic evaluations of immunoglobulin therapies for primary immunodeficiency diseases:

Population: "Primary immunodeficiency diseases", “PID”
Intervention: "Subcutaneous immunoglobulin therapy ", “SCIG”, “home-based immunoglobulin therapy",
Comparator: "Intravenous immunoglobulin therapy ", “IVIG”, "Hospital-based immunoglobulin therapy",
Study design: "Economic Evaluation”, “cost-effectiveness", “Cost minimisation”, “Cost benefit”, “Cost utilisation”, “Cost estimation”

3 Key references:

Alsina L, Montoro JB, Moral PM, Neth O, Pica MO, Sánchez-Ramón S, Presa M, Oyagüez I, Casado MÁ, González-Granado LI. Cost-minimization analysis of immunoglobulin treatment of primary immunodeficiency diseases in Spain. The European Journal of Health Economics. 2022 Apr 1:1-8.

Windegger TM, Nghiem S, Nguyen KH, Fung YL, Scuffham PA. Primary immunodeficiency disease: a cost-utility analysis comparing intravenous vs subcutaneous immunoglobulin replacement therapy in Australia. Blood Transfusion. 2020 Mar;18(2):96.

Shabaninejad H, Asgharzadeh A, Rezapour A, Rezaei N. Cost-effectiveness analysis of subcutaneous immunoglobulin replacement therapy in Iranian patients with primary immunodeficiencies. Medical Journal of the Islamic Republic of Iran. 2017;31:94.

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

58: Project title:

Eye tracking to diagnose neurodegenerative disease

Primary supervisor:

Dr Denize Atan, Associate Professor, University of Bristol

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

Matt Dunn, Lecturer, University of Cardiff

School / Faculty: Translational Health Sciences

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

Eye movements are controlled by centres in the brain in the cortex, brain stem, cerebellum and vestibular system. Consequently, many acquired brain disorders cause problems with eye movements, like stroke, myasthenia gravis, Parkinson's disease, Alzheimer's disease, and Multiple Sclerosis (MS).

Increasingly, eye movement recordings have become a sensitive, non-invasive, and reproducible method to detect eye movement abnormalities and diagnose underlying neurological diseases. Eye tracking could facilitate the diagnosis of patients presenting with eye movement abnormalities, reducing diagnostic uncertainty, and reducing the testing burden placed on patients by unnecessary, costly, and invasive tests. Furthermore, eye movement recordings might improve the diagnostic categorisation of patients selected to take part in clinical trials. Additionally, eye movement recordings provide an objective means to monitor clinical course and measure response to treatment. For example, eye tracking has been particularly useful in the diagnosis and monitoring of eye movement abnormalities in patients with MS. In treatment trials, Dalfampridine and Fampridine have been shown to improve the velocity of smooth pursuit eye movements and disability scores in patients with MS.

Aim

Our hypothesis is that patients with different neurodegenerative aetiologies will have different, potentially diagnostic, eye movement characteristics. The aim of the project is to characterise and quantify these differences in eye movements between patients and normal age- and sex-matched control subjects.

Techniques to be used:

Health Research Authority and National Research Ethics Committee approval for this study has already been obtained (IRAS 325200). Patients with a range of neurodegenerative diseases will be recruited from neurology outpatient clinics at University Hospitals Bristol & Weston NHS Foundation Trust (UHBW) and North Bristol NHS Trust (NBT). Age and sex matched health control subjects will be recruited from outpatient clinics at BEH.

The student will have access to two different technologies to measure eye movements:

1. The EyeLink1000 Eye Tracker (https://www.sr-research.com/eyelink-1000-plus/).

2. Bulbitech BulbiCam (https://bulbitech.com/) is a relatively new CE-certified device that combines eye tracking with a range of other ocular diagnostic tests. The Bulbitech company have agreed to loan us this device.

Participants will be invited to attend research clinic appointments in the neuro-ophthalmology clinic area at Bristol Eye Hospital where both devices are located. Anonymised patient data from eye tracking will be exported into Microsoft Excel for statistical analysis using SPSS to compare the sensitivity and specificity of eye movement parameters recorded by both devices in patients with varied neurodegenerative aetiologies. Differences in these eye movement parameters between patient groups and control subjects will be explored.

References

1. Leigh RJ, Zee DS. The Neurology of Eye Movements. New york University Press 1999.
2. Kanhai KMS, et al. Treatment of internuclear ophthalmoparesis in multiple sclerosis with fampridine: A randomized double-blind, placebo-controlled cross-over trial. *CNS Neurosci Ther* 2019;25(6):697-703
3. Serra A, Skelly MM, Jacobs JB, et al. Improvement of internuclear ophthalmoparesis in multiple sclerosis with dalfampridine. *Neurology* 2014;83(2):192-4

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

59: Project title: Investigating the eating behaviour and nutrition of patients with Idiopathic Intracranial Hypertension

Primary supervisor:
Dr Denize Atan, Associate Professor, 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. Our hypothesis is that IIH is exacerbated by nutritional deficiencies associated with the obesogenic diet.

Aim

The aim of this proposal is to investigate the eating behaviour and nutrition of IIH patients compared with healthy age-, sex- and BMI- matched controls.

Techniques to be used:

Patients with IIH will be identified and recruited from the clinics of five 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). Healthy age-, sex- and BMI- matched controls will be recruited by social media and from staff and students at the University of Bristol.

Analyses will include comparisons between IIH patients and controls in the following tests delivered online:

1. *Surveys:*
   - Eating Disorder Examination Questionnaire 6.0
   - Adult Eating Behaviour Questionnaire
   - Taste preference questionnaire
   - Visual functioning questionnaire + 10 item neuro-ophthalmology supplement
   - SF36 Quality of Life questionnaire
2. *Behavioural tasks:*
   - Food choice task

- Response inhibition task (Food-related No-go/Go task)

8. *Macronutrient and micronutrient intake:*
   - Dietary recall recorded by Intake 24 (https://intake24.co.uk/).

3 Key references:

4. Burkett JG, Ailani J. An Up to Date Review of Pseudotumor Cerebri Syndrome. *Curr Neurol Neurosci Rep* 2018; 18(6): 33.
5. 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.
6. 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

60: Project title: The Impact on Memory of Epilepsy – the TIME Study

Primary supervisor:
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Secondary supervisor (for day-to-day support):
Dr Kasia Sieradzan, Consultant Neurologist, Southmead Hospital, Bristol
Dr Kathryn Urankar, Consultant Neuropathologist, Southmead Hospital, Bristol

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 acts as the "gateway" to the hippocampus and has a specialised role in memory known as pattern separation. Pattern separation refers to the process of representing highly similar memories in a distinct way, allowing them to coexist with minimal interference. 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 pattern separation are known to correlate with age-related changes in the hippocampus, mild cognitive impairment, dementia and more recently, TLE. We have also found that there is an age-related decline in mossy cells in the human brain, which might explain why pattern separation problems become more common with age. Furthermore, young epilepsy patients have pathological changes in their brains that are more typical of older adults. Preliminary work by the research team has shown that pattern separation deficits in young epilepsy patients linearly correlate with the degree of hippocampal dentate gyrus volume loss on their MRI scans.

Our hypothesis is that people with TLE will be impaired in pattern separation because of the death of mossy cells in the hippocampal dentate gyrus from recurrent seizures.

Aims:
1. To compare memory function of people with TLE with healthy age and sex matched controls using a well validated behavioural test of pattern separation
3. To determine the relationship between performance on the pattern separation task and the number and density of mossy cells in the hippocampal dentate gyrus of people with TLE who have epilepsy surgery.

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 TLE patients and control subjects recruited to the study to perform a 10 to 15-minute online memory task, called the Mnemonic Similarity Task (developed by the Stark lab). For those TLE patients who 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 hippocampal dentate gyrus. The student will investigate the relationship between these pathological changes with the patients' pre-operative performance on the pattern separation task.

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