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UKRI Medical Research Council

Fundamental Mechanisms of Disease

Project Booklet 2024-25

Professor Nazif Alic

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Theme: Fundamental Mechanisms of Disease

Research overview

Age is the main risk factor for diseases that plague contemporary societies. The impact of ageing can be altered by activity of neuroendocrine pathways, such as the signalling pathways triggered by release of adrenalin and noradrenalin. This project is focused on understanding the role of adrenergic signalling in age-related disease, specifically in metabolic and gut health.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

We will use the fruit fly Drosophila melanogaster. The fruit fly has a short lifespan and exquisite genetic tools, allowing us to probe into mechanistic links between ageing and disease (for example how gene regulation alters ageing, reference 1). The fruit fly as a signalling system equivalent to the mammalian adrenergic system, that uses octopamine and tyramine as the signalling molecules (reference 2). In this project, we will examine the effects of tyramine biogenesis on gut and metabolic health throughout a flie's lifespan, specifically comparing the effects of neuronally synthetised tyramine and tyramine made as an endocrine/paracrine factor. This is made possible by the availability of genetic reagents allowing manipulation of specific groups of neurons, or specific endocrine tissues, in vivo in the context of the whole animal. The rotation project is designed so it can yield results within the given timeframe but can also be naturally extended to a full PhD project.

Relevant publications 1

https://doi.org/10.1016/j.tig.2020.02.003

Relevant publications 2

https://doi.org/10.1146/annurev.ento.50.071803.130404

Dr Marc Amoyel

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Theme: Fundamental Mechanisms of Disease

Research overview

The Amoyel lab seeks to understand how stem cells interact with their environment to choose to self-renew or differentiate. Stem cells are crucial to maintaining adult tissues and failure to respond appropriately to signals from their local environment or adapt to systemic conditions such as nutrition can cause tissue dysfunction.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Within organisms, organs communicate with each other to maintain tissue homeostasis and adapt to environmental conditions such as changes in nutrition. Failure to adapt can result in metabolic diseases such as diabetes, or result in tissue degradation. Central metabolic organs such as the liver coordinate this adaptation, yet we know little of how these organs communicate. In this project, we will determine how central metabolic organs maintain stem cell homeostasis in distant tissues by secreting metabolites. We will use genetic tools to determine which specific metabolic pathways are active in central metabolic organs, and their importance to distant tissues. As the project develops, we will explore how the metabolites are used in the stem cells that receive them, and what cellular functions they support in these cells. We will use newly-developed fluorescent reporters to visualise metabolite levels in vivo, combined with genetic and pharmacological manipulations. Finally, we will determine how this process changes in physiologically relevant contexts such as changes in diet or ageing. Altogether, the project will provide a comprehensive view of the ways in which stem cell metabolism is supported by inter-organ communication, and how this is coordinated with the physiology of the whole organism to allow the organism to adapt to varying environmental conditions.

Relevant publications 1

Cell-cycle exit and stem cell differentiation are coupled through regulation of mitochondrial activity in the Drosophila testis. Sainz de la Maza D, Hof-Michel S, Phillimore L, Bökel C, Amoyel M. Cell Rep. 2022 May 10;39(6):110774. doi: 10.1016/j.celrep.2022.110774

Relevant publications 2

Local and Physiological Control of Germline Stem Cell Lineages in Drosophila melanogaster. Drummond-Barbosa D. Genetics. 2019 Sep;213(1):9-26. doi: 10.1534/genetics.119.300234

Professor Aida Andres

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Theme: Fundamental Mechanisms of Disease

Research overview

All traits, including disease, are shaped by evolution. Analysing genomes, we aim to understand how adaptation to the environment has influenced phenotypic diversity in modern populations. We investigate local adaptation as a source of important population differences, and how host adaptation in primates reduced the pathogenicity zoonotic SIV/HIV and malaria.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Human populations are genetically and phenotypically highly homogeneous, but they differ in important phenotypic traits. Arguably the most important of those are the traits that influence health, as their underlying genetic bases contribute to health disparities among human groups. Population disparities are a critical and growing problem, and we are dedicated to understanding their origin to help address them. Population differences can accumulate by chance, but our work shows that important differences in disease risk were generated by local adaptation—the genetic adaptation of each population to their local environment. Previously beneficial alleles may have deleterious side effects or they may become detrimental in modern societies, contributing to disease risk in populations where they are frequent. The high-coverage genomes of several early modern humans generated by our collaborators in Germany will allow us to investigate these processes in unprecedented detail. We aim to establish the connection between past adaptation and current health disparities. The rotation will investigate several health-related phenotypes, selected with the student. Combining data sources (GWAS, 1000KGs) and methodologies (genomics, evolutionary genetics, functional genomics) we will identify phenotypic traits whose genetic bases differ among populations due to local adaptation, and investigate the functional consequences of relevant genetic variants. The student will learn to manage genomic datasets, perform evolutionary analyses, and predict the functional consequences of genetic variants. For the PhD project, they will extend this work to hundreds of phenotypes and ancient genomes to determine which past human adaptations contribute to modern health disparities

Relevant publications 1

The genomics of human local adaptation. JS Rees, S Castellano, AM Andrés. Trends in Genetics 36 (6), 415-428. 2020.

Relevant publications 2

Human local adaptation of the TRPM8 cold receptor along a latitudinal cline FM Key, MA Abdul-Aziz, R Mundry, BM Peter, A Sekar, M D'Amato, ... PLoS genetics 14 (5), e1007298. 2018.

Professor Maryse Bailly

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Theme: Fundamental Mechanisms of Disease

Research overview

Our lab uses primary human cell from donors in 3D cultures and complex multicellular engineered tissues to understand the mechanisms regulating postnatal eye growth, and how these processes may be manipulated to prevent and treat myopia and the associated devastating sub-retinal tissue alterations that can lead to blindness.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The eye is close to its final size at birth, but its vision power is not fully developed and it continues to grow slowly until adolescence. These final stages of adjusted eye growth are critical to achieve perfect vision. When myopia develops, the normal growth pattern is altered: the eyes grow faster and for longer, becoming elongated, and eventually stretching and damaging the sclera (stiff white shell of the eye) and the choroid (vascular-rich tissue layer in between the sclera and the retina), the two tissue layers that give the eye its shape and provide mechanical and metabolic support to the neural retina. We have developed a lab model to study human choroid-sclera interactions and found that choroid cells produce factors that activate paediatric scleral fibroblasts, and that this activation is prevented when choroid cells are exposed to dopamine, the major light-induced “stop” signal for eye growth. We have identified candidate cytokines secreted by the dopamine-treated choroid cells, which could mediate the suppression of the scleral cell activation following dopamine treatment. These include PTX3, a protein previously linked to myopia in transcriptional data sets and GWAS studies. The student will use a combination of siRNA technology, contraction and motility assays in 3D models and engineered tissues to confirm a role for PTX3 as a mediator of the dopamine-mediated regulation of eye growth. PhD project: building on the rotation project results the PhD project will identify the molecular mechanisms by which PTX3 regulates scleral fibroblast activity

Relevant publications 1

MPhil Thesis: https://discovery.ucl.ac.uk/id/eprint/10163952/2/MPhil%20Thesis%20-%20Yuyi%20Ren%2018031931.pdf

Relevant publications 2

Metlapally R, Wildsoet CF. Scleral Mechanisms Underlying Ocular Growth and Myopia. Prog Mol Biol Transl Sci. 2015;134:241-248.

Dr/Dr Arantza/John Barrios/Labbadia

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Theme: Fundamental Mechanisms of Disease

Research overview

Protein aggregation is a hallmark of age-associated neurodegenerative diseases, such as Huntington's, Alzheimer's and Parkinson's. Recently, we have identified striking sex differences in the ability to suppress protein aggregation and toxicity within neurons. This opens new avenues to understand the mechanisms underlying different incidences of neurodegeneration in males and females.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Age-related neurodegenerative diseases are a common and devastating set of disorders. Despite this, the fundamental mechanisms behind neurodegenerative disease, and how these differ across males and females, remains unknown. We will use a combination of genetics, molecular biology, microscopy, proteomics and behavioural assays to elucidate the mechanisms underlying sex differences in susceptibility to protein aggregation. We will do this in the genetic model organism Caenorhabditis elegans, which has proven instrumental in identifying conserved protein quality control mechanisms, with relevance to human neurodegenerative disease. The PhD project will consist of the following 3 aims, any one of which can be undertaken as a rotation project. Aim 1. Identify sex-specific differences in neuronal protein quality control We will use fluorescence-based reporter systems and RT-qPCR to monitor and compare the activity of core constitutive and inducible protein folding and degradation pathways in males and hermaphrodites. Aim 2. Identify the role that N-terminal acetylation plays on protein control. N-terminal acetylation (by Nat proteins) has recently been identified as an important, but poorly understood, regulator of protein aggregation and toxicity in models of neurodegenerative disease. To understand this relationship, we will investigate how loss of NatC impacts protein quality control pathways across different tissues in both sexes. Aim 3. Identify the acetylated targets of NatC. We will use an intersectional approach combining bioinformatics and proteomics to identify proteins that are acetylated by NatC during translation. Following, this we will employ high-throughput genetic screening to identify NatC target proteins that contribute to sex-specific differences in neuronal protein quality control.

Relevant publications 1

Labbadia, J. & Morimoto, R. I. The Biology of Proteostasis in Aging and Disease. Annu. Rev. Biochem. 84, 1–30 (2015).

Relevant publications 2

Bae, E.-J. & Lee, S.-J. CRISPR-based identification of N-terminal acetylation in synucleinopathies. Trends Neurosci. 47, 324–325 (2024).

Professor Clare Bennett

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Theme: Fundamental Mechanisms of Disease

Research overview

The skin is our major immune and sensory barrier to the outside world. These finally balanced functions are regulated by macrophages, maintaining a neuro-immune axis in the skin. This project will investigate how macrophages protect our sensory nerves in the skin, and how treatments for cancer upset this balance.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

This project builds on our new data showing that differentiation of Langerhans cells (LCs), the macrophages of the skin epidermis, is associated with production of lipid mediators. We propose that these lipids are essential for LC-nerve cross-talk. The rotation project would begin to test this hypothesis: Explore expression of lipoxins/other lipid mediator pathways in LCs Use microscopy to define spatial macrophage-nerve interactions in the skin, overlaid with expression of lipoxins. Exploit in vitro cultures to test signalling requirements for lipoxin production. The students will use bioinformatics with data from the Bennett lab to define the most important lipid mediator pathways expressed by LCs. These will be tested by RT-PCR and flow cytometry. To begin to investigate how these lipids might be important in macrophage-nerve interactions students will use microscopy to image macrophage-nerve co-localisation, and pinpoint expression of lipoxygenase products (eg Alox5). In vitro cultures will be used in parallel to begin to define the signals that activate lipoxin expression by LCs. This rotation would contribute to the first chapter of the thesis. The students will also shadow other lab members to develop techniques such as tissue processing and flow cytometry that will be central to the project. The full PhD will use lipidomics to define the lipids produced by macrophages in the skin and how these lipid mediators are required for neuro-immune crosstalk. We would then investigate how this balance is altered by skin toxicities driven by cancer treatments (immune pathology, radiotherapy, chemotherapy).

Relevant publications 1

Appios et al (2023) Convergent evolution of monocyte differentiation in adult skin instructs Langerhans cell identity BioRxiv doi: https://doi.org/10.1101/2023.11.13.566862

Relevant publications 2

Ferrer et al (2019) A wave of monocytes is recruited to replenish the long-term Langerhans cell network after immune injury. Science Immunology PMID: 31444235

Dr Ashleigh Boyd

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Theme: Fundamental Mechanisms of Disease

Research overview

We investigate stem cell biology and immunology applications in cell therapy and tissue engineering, using induced pluripotent stem cells (iPSCs) to generate disease models as drug testing platforms, and other stem cells including haematopoietic stem cells (HSCs), we strive to better understand disease and develop future cell replacement/regenerative medicine therapies.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Our kidneys are vital for filtering blood, controlling blood pressure, and hormone production. Chronic Kidney Disease (CKD) affects 10% of people globally, developing most commonly due to diabetes where it presents as Diabetic Nephropathy (DN), the leading cause of End-Stage Renal Disease (ESRD). DN is marked by renal fibrosis, albuminuria, and reduced glomerular filtration, with structural damage including glomerulosclerosis and tubulointerstitial fibrosis. Current treatments like dialysis and transplantation have limitations, necessitating new therapies. Existing pre-clinical drug screening using animal models and 2D cell cultures are inadequate due to interspecies differences and lack of relevancy. Here we propose to develop a 3D human renal fibrosis model using human induced pluripotent stem cells (hiPSCs) - somatic cells 'reprogrammed' to pluripotency by introduction of stem cell factors - to generate kidney organoids, mimicking kidney function with extracellular matrix (ECM) support. Unlike primary cell cultures, iPSC-derived organoids maintain stability and display relevant drug responses, making them suitable for drug screening. During their rotation the student will learn hiPSC culture and tissue decellularization, to generate hiPSC-renal organoids incorporating human renal ECM. Assays will include immunofluorescence imaging, flow cytometry, mechanical testing and gene expression analyses. The PhD project will establish organoid culture conditions which recapitulate pro-fibrotic changes observed in DN, test clinically relevant small molecules in ameliorating the induced fibrotic signature and evaluate the transcriptomic landscape of healthy and 'diseased' renal organoids by RNA sequencing to better understand DN disease pathogenesis and its impact on renal organoid structure and function.

Relevant publications 1

Decellularization of Mouse Kidneys to Generate an Extracellular Matrix Gel for Human Induced Pluripotent Stem Cell Derived Renal Organoids; 22 Mar 2023; Organoids 2(1):66-78; MDPI AG; Nag S. and A.S. Boyd

Relevant publications 2

Microfluidic devices towards personalized health and wellbeing; 1 Aug 2019; Journal of Chemical Technology and Biotechnology; Wiley-Blackwell; Marques MP, Boyd A, Polizzi K, Szita N

Professor Jeremy Brown

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Theme: Fundamental Mechanisms of Disease

Research overview

My laboratory investigates the pathogenesis and prevention of bacterial pneumonia funded by MRC and Wellcome Investigator grants. We have active projects on S. pneumoniae investigating strain variations in virulence, novel vaccine approaches, and immunity in a human infection challenge model, and a project developing an antibody therapy for A. baumannii.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The student will take advantage of recent developments within UCL Respiratory in single cell RNA (scRNA) and human lung slice models to investigate in detail Streptococcus pneumoniae interactions with host cell subsets during the development of pneumonia. The research questions to be addressed are (1) which specific lung cells do S. pneumoniae interact with when establishing infection; (2) how do these cells respond to S. pneumoniae; and (3) do these parameters vary between invasive serotype 1 strains compared to less invasive serotypes. By combining human lung slice and tissue culture infection models with established flow cytometry techniques and recently developed scRNA analyses of host cells the student will be able to characterise S. pneumoniae / lung interactions in much greater detail than has previously been possible. The project will run in parallel and be supported by our Wellcome funded programme investigating the virulence of S. pneumoniae serotype 1 strains. This funds two postdocs in the Brown laboratory, plus two more with our partner Prof Wren at the London School of Hygiene and Tropical Medicine, providing very strong academic and practical support for the student. The project can readily evolve into a PhD project in several directions depending on the data obtained, any specific questions arising from data obtained from the wider Wellcome project, and the student's own areas of interest. The student will be part of the wider UCL Respiratory research department consisting of 80+ investigators and based in recently refurbished laboratories on the first floor of the Rayne building.

Relevant publications 1

A Randomized Controlled Clinical Trial of Nasal Immunization with Live Virulence Attenuated Streptococcus pneumoniae Strains Using Human Infection Challenge. Hill H, et al .Am J Respir Crit Care Med. 2023 Oct 15;208(8):868-878

Relevant publications 2

Durmort C et al. Deletion of the Zinc Transporter Lipoprotein AdcAII Causes Hyperencapsulation of Streptococcus pneumoniae Associated with Distinct Alleles of the Type I Restriction-Modification System. mBio. 2020 Mar 31;11(2):e00445-20

Associate Professor Amanda-Jaye Carr

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Theme: Fundamental Mechanisms of Disease

Research overview

Our research uses induced pluripotent stem cells from patients to understand and develop treatments for macular disease. We focus on degenerative and inherited forms of macular disease, modelling pathological mechanisms by generating cells affected by disease, including the retinal pigment epithelium and immune cells.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The retinal pigment epithelium (RPE) is key cell involved in the development of age-related macular degeneration (AMD), the leading causes of sight loss in the western world. The RPE is a support cell which maintains the health and function of the neural retina. Age and AMD immune associated risk genetics impact on the function and survival of the RPE, ultimately leading to photoreceptor cell degeneration and vision loss. During the 3-month rotation project, the student will create a new cell model system to investigate the effects of RPE cell loss. The student will culture induced pluripotent stem-derived RPE from patients and healthy controls, and subject them to a scratch wound. RPE wound responses will be recorded using cytokine assays and high throughput live cell imaging techniques, employing live cell dyes to assess epithelial cell division and fibrosis. In the long term, this project will be a starting point to examine the effects RPE wounding on the immune system, with a focus on macrophage cells. The student will examine interactions between the IPSC-RPE and IPSC-macrophages in co-culture experiments to assess the effects of RPE wounding in patient and control derived cells. Ultimately, we aim to understand how RPE loss affects the immune response in healthy ageing and disease, and whether an abnormal immune response to RPE wounding contributes to the development and progression of AMD.

Relevant publications 1

A.-J. F. Carr, M. J. K. Smart, C. M. Ramsden, M. B. Powner, L. da Cruz, and P. J. Coffey, “Development of human embryonic stem cell therapies for age-related macular degeneration,” Trends Neurosci., vol. 36, no. 7, pp. 385–395, 2013.

Relevant publications 2

L. J. Bailey-Steinitz, Y. H. Shih, M. J. Radek, and P. J. Coff, “An in vitro model of chronic wounding and its implication for age-related macular degeneration,” PLoS One, vol. 15, no. 7 July, pp. 1–22, 2020

Professor Guillaume Charras

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Theme: Fundamental Mechanisms of Disease

Research overview

My lab focuses on understanding the interplay between cytoskeletal organization, intercellular adhesion and the mechanics of cells and tissues. In our research, we combine techniques from physics and engineering with molecular cell biology, microscopy, optogenetics, and image analysis to study questions relevant to cell and developmental biology.

Rotation project (including a brief outline of how this will develop into a PHD project)

Epithelia line all of our organs, forming a barrier between the internal and external environments. They are attached to a basement membrane (BM) that is a dense, planar and thin extracellular matrix. As epithelia are continuously subjected to mechanical stresses, the BM likely contributes to the overall mechanical resilience of the tissue and may play a role in ensuring rapid healing when cells within the epithelium are compromised. Mutations in BM components and the structures linking epithelial cells to the BM lead to many severe genetic diseases (e.g. epidermolysis bullosa). Yet, we now very little about the BM mechanical properties and its role in healing epithelial wounds. The 3 month rotation project will aim to: -Determine the time course of BM synthesis -Design and 3D print a simple device to generate suspended epithelial monolayers -Conduct mechanical tests to characterize the contribution of the BM to tissue mechanics Students will first grow epithelial cells on dextran hydrogels moulded within 3D printed devices. They will then perform immunostaining and confocal microscopy at fixed time points to determine when each BM component is secreted and BM structural organisation. Next, the students will digest the dextran hydrogel to generate suspended epithelial monolayers. They will characterise the mechanical contributions of the BM to tissue mechanics using particle image velocimetry. They will compare mechanical readouts before and after digestion of BM components. Further goals will involve characterizing mechanics with AFM, determining the impact of mutations, and investigating the role of BM in healing small wounds.

Relevant publications 1

"Rupture strength of living cell monolayers". Duque J, Bonfanti A, Fouchard J, Baldauf L, Azenha S, Ferber E, Harris A, Barriga E, Kabla A, and Charras G. Nature Materials (2024 - accepted). https://www.biorxiv.org/content/10.1101/2023.01.05.522736v2

Relevant publications 2

Kelkar M, …, Salbreux G, Charras G. “Spindle reorientation in response to mechanical stress is an emergent property of the spindle positioning mechanisms”. PNAS, 119:e2121868119, (2022).

Professor Umber Cheema

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Theme: Fundamental Mechanisms of Disease

Research overview

Tissue engineering the tumour micro-environment provides an understanding of the parameters driving cancer metastasis. We aim to develop biomimetic, patient-specific 3D cancer models to understand (i) the crosstalk between cancer cells and surrounding stromal cells using spatial transcriptomics; (ii) cancer invasion into healthy stromal tissue; (iii) matrix remodelling by cancer.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Cancer invasion and metastasis is directed in part by underlying genetics and in part by the tumour microenvironment. The complex milieu of the tumour microenvironment includes the surrounding cells in the healthy stromal tissue as well as the biophysical and biochemical facets of the microenvironment. A tumour generally starts growth within healthy stromal tissue and over time invades this tissue and can directly interact with healthy cells to transform them into cancer-associated cells. The presence of cancer associated fibroblasts (CAFs) have been implicated in particularly aggressive cancers. This project aims to interrogate the crosstalk between cancer cells and CAFs in 3D engineered models of colorectal cancer, termed tumouroids. These models are generated by culturing a tumour mass compartment within a healthy stromal compartment and studying the boundary between the tumour and stroma. This model has shown that the incorporation of patient CAFs results in increased invasion of cancer into the healthy stroma tissue compartment, and a specific matrix remodelling pattern associated with invasion. This project aims to grow matched patient specific cancer and CAFs in 3D engineered tumouroids. Different tissue engineering strategies will be employed for this, including organoid culture. For later work, we anticipate spatial transcriptomics will be employed to understand the mechanisms behind cancer-CAF crosstalk driving invasion within these complex tumouroids models. Targeted therapy, including ultrasound therapy and proton beam therapy, will then be used and the mechanism of action and of resistance to therapy will be interrogated.

Relevant publications 1

• Micalet, A. Upadhyay, A. Javanmardi, Y. Gabriela de Brito, C.Moeendarbary, E. Cheema, U. Patient Specific Colorectal Cancer-Associated Fibroblasts Modulate Tumour Microenvironment Mechanics. 2024. iScience

Relevant publications 2

• Pape, JM. Magdeldin, T. Stamati, K. Nyga, A. Loizidou, M. Emberton, M. Cheema, U. (2020). 'Cancer-associated fibroblasts mediate cancer progression and remodel the tumouroid stroma.' Br J Cancer. 123: 1178–1190.

Dr Rachael Dickman

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Theme: Fundamental Mechanisms of Disease

Research overview

Our research aims to develop new regenerative medicines for treatment of nervous system injury and disease. To do this, we are investigating whether peptides are able to mimic the pharmacological action of growth factors to promote regeneration of damaged tissues.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

This project will be conducted in collaboration with Prof. James Phillips (UCL School of Pharmacy) and will involve chemistry, in vitro models, microscopy, image analysis, computational modelling, and structural biology. Prior work in the Dickman and Phillips labs has established that peptides mimicking the structure and function of native growth factors have potential in nervous system regeneration. As part of this work, we have developed a workflow for the design, synthesis and in vitro testing of novel peptides. The aim of the rotation project is to: (i) build on our previous work by assessing the mechanism of action of novel peptides; (ii) begin the design of the next generation of peptides. During the rotation project the student will gain experience in both labs and learn techniques that will be used throughout the PhD project. Initially, we will chemically synthesise one of our novel peptides, purify it and characterise it using mass spectrometry and NMR. Secondly, we will assess the activity and mechanism of the peptide in comparison to the native growth factor using in vitro assays with neurons and glial cells. Thirdly, we will use the results from in vitro testing combined with computational tools to optimise the peptide design to achieve better receptor activation. The PhD will build on the foundation laid in the rotation project, with the overall aim of designing new peptides with improved activity as potential therapies for nervous system injury and disease. If time allows, the designed peptides can be assessed using in vivo models.

Relevant publications 1

E. Atkinson, R. Dickman, Growth factors and their peptide mimetics for treatment of traumatic brain injury, Bioorg. Med. Chem., 2023, 90, 117368.

Relevant publications 2

G. Q. Gong, B. Bilanges et al., A small-molecule PI3Kα activator for cardioprotection and neuroregeneration, Nature, 2023, 618, 159-168.

Professor Ariberto Fassati

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Theme: Fundamental Mechanisms of Disease

Research overview

We demonstrated that the canine venereal transmissible (CTVT) is a naturally transmissible allograft. CTVT evades allorecognition during transmission but is rejected by the immune system when the drug vincristine is administered. This extreme bi-modal phenotype may provide key insights into preventing transplant rejection and triggering the rejection of human cancers.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

To understand how a cancer allograft can evade allogeneic rejection, we have passaged a mouse melanoma in progressively immunologically mismatched mouse strains and obtained an allo-transplantable cancer model. Tumour and host cells from each passage have been analysed by multiparameter flow cytometry and RNAseq to study how the tumour has evolved the ability to escape allogeneic rejection. Surprisingly, we found that cancer immune-evasion is linked to a state of sterile inflammation, which upregulates immune-modulatory molecules on the tumour surface. Furthermore, two key innate immune sensors are implicated in the induction of inflammation in the tumour cells. We aim to gain more mechanistic insight into the pathways that trigger the inflammatory signal in the tumour cells. To this end, the objective of the rotation project is to knock out by CRISPR/Cas9 KO one of the two innate immune sensors and study the effect on the inflammatory signature in the tumour cells. This will be done by multiparameter flow cytometry to examine surface expression specific immunomodulatory markers, and by RT-qPCR to measure expression of candidate genes such as non-classical MHC-I molecules and other immune-suppressive genes. Eventually, the KO cells that show a reduced inflammatory phenotype will be transplanted into immunologically mismatched mice to test if the tumour is rejected whereas the parental tumour cells are not.

Relevant publications 1

https://pubmed.ncbi.nlm.nih.gov/29634949/

Relevant publications 2

https://pubmed.ncbi.nlm.nih.gov/24458646/

Professor Patrizia Ferretti

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Theme: Fundamental Mechanisms of Disease

Research overview

therapeutic interventions using reprogrammed patient-derived cells which can be differentiated in all tissue types affected by the mutated gene and a range of cellular/molecular techniques. The main focus is on diseases affecting skeletal growth and cognitive development.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Autosomal dominant mutations in PDE4D (cAMP-specific-phosphodiesterase-4D) and PRKAR1A (type-1A-regulatory subunit of protein-kinase-A, PKA), both components of the cAMP/PKA signalling pathway, underly two types of the rare disease, acrodysostosis (ACRDYS), ACRDYS2 and ACRDYS1, respectively. They share many distinctive features, including facial hypoplasia, brachydactyly, and obesity, but present important differences including hormonal stimulation resistance of growth plate chondrocytes and reduced height (predominantly ACRDYS1), and mental retardation (predominantly ACRDYS2). The mechanisms underlying these differences are not well understood and there is no targeted care for these patients. The overall aim of the study is to use human embryonic/foetal brain and skeletal tissues and human cell models of ACRDYS to understand how mutations in genes along the same signalling pathway, the cAMP/PKA pathway, lead to converging and diverging phenotypes in ACRDYS1 and ACRDYS2. This will guide development of novel tissue/patient-specific therapeutic approaches and can be also relevant to other diseases affecting cAMP/PKA signalling. The rotation will involve becoming familiar with growth/differentiation of human stem/progenitor cells from healthy and ACRDYS patients, establish a 3-dimensional bone growth plate model to mimic normal and defective skeletal growth, and assess PDE4D and PRKAR1A expression changes during differentiation using a range of techniques (e.g. immunostaining, western blotting and RT-qPCR). The project will progress with investigating different hypotheses underlying the disease mechanism(s) leading to skeletal and neural defects and differences in disease presentation, and with identifying downstream pathway(s) that could provide suitable therapeutic targets using both growth plate and neural models, that will be used to assess possible pharmacological interventions.

Relevant publications 1

1. O.F.W. Gardner, T. Bai, G.S. Baillie, P. Ferretti, Phosphodiesterase 4D activity in acrodysostosis-associated neural pathology: too much or too little?, Brain Commun 6(4) (2024) fcae225.

Relevant publications 2

2. Lange, J., Gillham, O., Alkharji, R., Eaton, S., Ferrari, G., Madej, M, Flower M, Tedesco FS, Muntoni F, Ferretti, P. (2022). Dystrophin deficiency affects human astrocyte properties and response to damage. Glia. 70:466-490 doi: 10.1002/glia.24116

Dr Lazaros Foukas

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Theme: Fundamental Mechanisms of Disease

Research overview

Dysregulation of metabolic pathways underpins multiple age-related pathologies ranging from neurodegeneration to cancer. The lab studies the mechanisms of metabolic decline associated with ageing which often leads to chronic age-related diseases such as obesity, type-2 diabetes and cardiovascular disease. It is now well recognised that chronic inflammation underlies these diseases.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Genetic studies have been instrumental in uncovering the genetic basis of human diseases. However, genetic studies produce tens or hundreds of candidate genes and the mechanistic interpretation of the role of these genes in the development of disease is a bottleneck in understanding the mechanism of pathogenesis and thus in developing effective therapies. The project aims to exploit the power of cell-based models in functionally testing the cellular effects of perturbations of human genes identified through a combination of modern genome, transcriptome and proteome studies as implicated in metabolic diseases. The rotation project will use metabolic (adipocyte, hepatocyte) and/or immune cell culture models in which the expression levels of candidate disease genes will be altered by RNAi-mediated knockdown or cDNA overexpression to assess their impact on cellular metabolic function. The project will use various cell biological techniques including virally-mediated gene delivery, measurement of inflammatory cell signalling pathway activation, analysis of mitochondrial content and function, glucose and lipid metabolism. The data from the rotation project will form the groundwork for a PhD project which would expand the study using genome editing technology such as Crispr/Cas, pharmacological inhibition, and modelling in vertebrate species (fish, mice) to probe the roles of additional genes and pathways potentially contributing to the development of metabolic pathologies. This work has the potential to identify novel therapeutic targets for the prevention/treatment of chronic age-related metabolic diseases such obesity and associate type 2-diabetes, non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease.

Relevant publications 1

Araiz C, Yan A, Bettedi L, Samuelson I, Virtue S, McGavigan AK, Dani C, Vidal-Puig A, Foukas LC. (2019) Enhanced β-adrenergic signalling underlies an age-dependent beneficial metabolic effect of PI3K p110α inactivation in adipose tissue. Nat Commun.10(1):1546. doi: 10.1038/s41467-019-09514-1.

Relevant publications 2

Lau W, Andrew T, Maniatis N. (2017) High-Resolution Genetic Maps Identify Multiple Type 2 Diabetes Loci at Regulatory Hotspots in African Americans and Europeans. Am J Hum Genet.100(5):803-816. doi: 10.1016/j.ajhg.2017.04.007.

Dr Gabriel Galea

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Theme: Fundamental Mechanisms of Disease

Research overview

Severe malformations of the brain and spinal cord, such as spina bifida, continue to affect 1:1,000 births. We study the causes of these malformations using advanced microscopy (Maniou et al PNAS 2021), mouse (Galea et al Nat Commun 2021) and human iPSC models (Ampartzidis et al Dev Biol 2023).

Rotation project **(including a brief outline of how this will develop into a PHD project)**

We recently developed the first mouse model of a rare human malformation of the spinal cord often described as 'closed' spina bifida (Maniou et al Development 2023). Unexpectedly, we discovered that it is not caused by the same embryonic defects responsible for the more common 'open' spina bifida. That means the preventative treatment we have for open spina bifida – folic acid supplementation - may not be effective for this closed form. However, we also found that a different pathway – retinoic acid signalling – is abnormal in embryos with closed spina bifida. Over the next year, we will be carrying out treatment trials to establish whether folic acid or retinoic acid prevent closed spina bifida, and test alternative potential treatments. During a rotation project, you would contribute to phenotypic characterisation of embryos from treated and untreated litters, perform immunofluorescent analysis of the developing spinal cord in embryos with closed spina bifida, and quantitatively analyse neuron progenitor cells in treated and untreated embryos. If treatments we test prove effective at preventing or reducing the severity of open spina bifida, you could study the mechanisms by which this is achieved during a full PhD project. If none of our hypothesises treatments prove effective, you could identify and test alternatives, for example using organotypic slice cultures to assay multiple agents simultaneously. Depending on your interests, these studies could be extended to CRISPR-edited or patient-derived iPSC models. Throughout, you will work in a supportive, interdisciplinary group committed to your personal and professional development.

Relevant publications 1

Maniou et al Development 2023

Relevant publications 2

Galea et al Nat Commun 2021

Professor Ivan Gout

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Theme: Fundamental Mechanisms of Disease

Research overview

We have recently pioneered a new field of research on protein CoAlation and antioxidant function of CoA in cellular response to oxidative and metabolic stress. Our research is currently focused on molecular dissection of the CoAlation/deCoAlation cycle and investigating the neuroprotective function of CoA in pathologies associated with oxidative stress.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Accumulating evidence shows that dysregulation of energy metabolism and oxidative stress are associated with neurodegeneration leading to energy crisis and neuronal cell death. CoA and CoA thioesters are critical for cellular metabolism and the regulation of gene expression. The newly discovered antioxidant function of CoA involves covalent modification of cellular proteins by CoA, termed CoAlation. This rotation project is an integral part of our research on investigating neuroprotective function of CoA. The rational for this project originates from our and other findings, which show that in-born mutations in genes involved in CoA biosynthesis result in neurodegeneration. We also found that protein CoAlation is significantly increased in the post-mortem brains of neurodegenerative pathologies, raising a fundamentally important question: what is the molecular mechanism of CoA neuroprotection? The rotation project will focus on advancing our ongoing studies aimed at exploring the role of CoAlation in regulating peroxiredoxin 6 (PRDX6) peroxidase activity in health and neurodegeneration. PRDX6 is known as a membrane-repair protein which protects cells from lipid peroxidation and ferroptosis. The student will gain hands-on experience in diverse methodologies, including mammalian and bacterial cell biology, molecular cloning, expression and purification of recombinant proteins, mass-spectrometry and various biochemical assays. On this project, we have established collaborative interactions with Dr. M. Skehel (Head of Proteomics, The Francis Crick Institute), Prof. T. Lashley (UCL Institute of Neurology) and Prof. B. Paul (Neuroscience, Johns Hopkins University). The knowledge and results generated during this rotation will form a backbone for a research chapter on a PhD project.

Relevant publications 1

Filonenko. V., Gout, I. (2023) Discovery and functional characterisation of protein CoAlation and the antioxidant function of coenzyme A. BBA Adv. 3:100075. doi: 10.1016/j.bbadva.2023. Read our recent research publications and reviews on this emerging topic of research.

Relevant publications 2

Lashley, T,….. Skehel, M., Gout, I. (2021) Extensive Anti-CoA Immunostaining in Alzheimer's Disease and Covalent Modification of Tau by a Key Cellular Metabolite Coenzyme A. Front. Cell. Neurosci., 15, 739425.

Professor Garrett Hellenthal

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Research overview

Genomes of present-day people reflect composites of ancestral groups that intermixed in the past, each subjected to unique environmental pressures. This project will leverage 100,000s of mixed ancestry genomes, including from understudied African/Asian groups and unpublished data, to pinpoint genetic loci essential for the health and survival of modern humans.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

We have access to >300,000 UK Biobank genomes, >4,000 African genomes, and unpublished genomes from >10,000 Japanese and >300 Papuans. The PhD will quantify how the intermixing of disparate groups has spread locally-adapted genetic variants, and their impact on human health today. To initiate this work, the rotation project – developed with the PI and student – can involve (e.g.): (1) Reconstructing genomes of the first farmers in Japan, to determine genetic and health consequences of the hunter-gatherer to agricultural transition. (2) Pinpointing adaptive variants brought by Anglo-Saxon migrants to the UK, and their influence on health today. (3) Elucidating the genetic adaptation history of Ethiopia using >2,000 present-day Ethiopians and 4,500 year old ancient DNA (aDNA) from Ethiopia. (4) Mapping survival pressures onto the migrations of Bantu-speaking peoples throughout the African continent, starting at ~2500BC. (5) Quantifying the impact of archaic (e.g. Neanderthal) DNA on humans.

Relevant publications 1

Quinn et al 2024, “Population structure and migration in the Eastern Highlands of Papua New Guinea, a region impacted by the kuru epidemic”, AJHG 111(4):668-679.

Relevant publications 2

Mendoza-Revilla et al 2022, "Disentangling Signatures of Selection Before and After European Colonization in Latin Americans", Mol Biol Evol 39(4):msac076.

Professor Adrian Isaacs

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Research overview

My laboratory focuses on understanding the cellular and molecular causes of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), with a particular focus on the CHMP2B and C9orf72 genes. We utilise iPSC-neurons as well as fly and mouse models to understand disease mechanisms and develop therapeutic approaches.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are devastating neurodegenerative diseases with no cure. This rotation and PhD will build on very exciting new data from the lab which shows that specific lipids are neuroprotective in FTD/ALS. You will utilise cutting-edge lipidomics, iPSC-neuron maintenance and transduction, immunofluorescence staining, confocal microscopy and automated image analysis as well as biochemical assays to investigate how these lipids provide their protective effects.

Relevant publications 1

Neuronal polyunsaturated fatty acids are protective in FTD/ALS. A Giblin, AJ Cammack et al. bioRxiv 2024.01.16.575677; doi: https://doi.org/10.1101/2024.01.16.575677

Relevant publications 2

C9orf72-mediated ALS and FTD: multiple pathways to disease. Balendra R, Isaacs AM. Nat Rev Neurol. 2018 Sep;14(9):544-558. doi: 10.1038/s41582-018-0047-2.

Professor Dan Jagger

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Theme: Fundamental Mechanisms of Disease

Research overview

My lab studies the function of sensory and non-sensory tissues of the inner ear in health and disease. We ask collaborative questions on the neurobiology of syndromic (multi-system) and non-syndromic (ear-specific) hearing loss and balance disorders, towards therapies for patients.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Alport Syndrome, characterised by kidney disease and deafness, is caused by reduced type IV collagen networks in basement membranes. This project will map these proteins within the inner ear to localise potential lesion sites in sensory and non-sensory tissues, and so identify cellular targets for therapies. The main aim of this project is to examine type IV collagen α3α4α5 networks in the cochlea and vestibular organs, focusing on basement membrane-dependent tissues such as the blood vessels and ion transporting epithelia that are essential for normal hearing and balance. The project will examine how and where the novel collagens contribute to inner ear function during early development and throughout the life-course. In the 3-month rotation you will learn: 1. Inner ear dissection. 2. Immunofluorescence. 3. Confocal and super-resolution imaging techniques. The results of this rotation will contribute to a chapter of your final PhD thesis. This three-month project will form the foundation for an exciting multidisciplinary PhD project investigating the cellular basis of hearing loss in Alport Syndrome. The wider project will benefit from a network of national and international collaborations and will use models of X-linked and autosomal recessive disease. The outcomes of the research will help in the design of specific therapies to slow or prevent sensory dysfunction in this disease. We work with a highly organised and motivated patient support group, providing you with excellent opportunities for public outreach and real-world impact for your research.

Relevant publications 1

Laraba L, et al (2023). Inhibition of YAP/TAZ-driven TEAD activity prevents growth of NF2-null schwannoma and meningioma. Brain v146, p1697-1713.

Relevant publications 2

Bryant D, et al (2022). The timing of auditory sensory deficits in Norrie disease has implications for therapeutic intervention. Journal of Clinical Investigation Insights v7(3), e148586.

Professor James Jepson

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Theme: Fundamental Mechanisms of Disease

Research overview

We use the fruit fly, Drosophila, as a model to understand the patho-mechanisms of involuntary movement disorders such as dystonia, and identify novel drug treatments for these debilitating diseases. Our research utilises state-of-the-art genetics (e.g CRISPR-Cas gene editing, spatio-temporal gene manipulations), in-depth behavioural recordings, transcriptomics, calcium imaging, and confocal microscopy.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Dystonia is the third most common movement disorder. It is characterized by co-contractions of antagonistic muscles, causing painful, debilitating, and in some cases, lethal involuntary movements. Inherited mutations causing dystonia provide a means to study dystonia pathogenesis at both the molecular and neural circuit levels. More broadly, such mutations provide an entry-point to study the genetic basis of movement. We have generated a tractable Drosophila model of the most common form of inherited dystonia, caused by loss-of-function mutations in a molecular motor called TorsinA (Torsin in Drosophila). Strikingly, using jGCaMP8-based calcium imaging, we have found that Torsin knockout flies exhibit antagonistic muscle co-contractions, similarly to human patients. We have also performed suppressor screens that have identified potential drugs capable of rescuing motor defects in these flies; and RNA sequencing to identify transcriptional changes caused by loss of Torsin. The rotation will follow on from these exciting and unpublished works. Depending on the student's interests, we aim to 1. Use recent connectomic data to understand how altered neuronal development in Torsin knockout flies might lead to aberrant muscle co-contractions; 2. Identify cellular pathways downstream of Torsin that drive motor circuit dysfunction, or which can restore normal circuit activity in Torsin knockout flies; 3. Define new pharmacological suppressors of antagonistic muscle co-contractions in Torsin knockout flies, which may represent new (and urgently needed) drug treatments. Preliminary data garnered during the rotation will provide an excellent foundation for a broader PhD project focusing on these goals.

Relevant publications 1

Lowe et al., (2024) Modulation of a critical period for motor development in Drosophila by BK potassium channels. Current Biology in press. https://doi.org/10.1016/j.cub.2024.06.069

Relevant publications 2

Kratschmer et al., (2021) Impaired pre-motor circuit activity and movement in a Drosophila model of KCNMA1-linked dyskinesia. Movement Disorders 36: 1158-1169. doi: 10.1002/mds.28479

Professor Liz Jury

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Theme: Fundamental Mechanisms of Disease

Research overview

Normal immune responses are critical to survival, but hyperinflammatory responses are harmful, and can lead to cytokine storm, multi-organ failure and death (mortality between ~50-80%). Secondary haemophagocytic lymphohistiocytosis (sHLH) is a prototypic hyperinflammatory syndrome caused by malignancies, rheumatological conditions, and infections but the underlying immunopathogenesis remains unknown and under-investigated.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Project Title: Investigating the pathogenic processes underlying the hyperinflammatory response associated with secondary haemophagocytic lymphohistiocytosis (sHLH). Supervisors: Prof Liz Jury and Dr Jessica Manson, within the newly established sHLH research team comprising consultants, senior research fellows and PhD students/research assistants. Objective: To improve patient outcomes, we need to develop a strong evidence base. This has been lacking to date because of a lack of concentration of expertise. The UCLH HLH Service was set up to address this and we have seen 41 patients in 2023-4, compared to approximately 2-4 patients/year prior to the establishment of this service. Patient samples are recruited to a biobank and matched clinical database (recruitment of 5-10 patients/month ongoing). We plan to harness this unique resource to improve our understanding of hyperinflammatory responses. This project will use immunological and proteomic analysis to characterise hyperinflammation phenotypes and heterogeneity for improved understanding of this aberrant immune response. We want to characterise the inflammatory response in patients with sHLH during the acute phase of the disease while patients are in intensive care. Aims: 1: Use multiparameter spectral flow cytometry to immune-phenotype already available patient and control samples from the only UK-HLH sample Biobank (Jury lab). 2. Interrogate flow cytometry data using unsupervised dimensionality reduction and clustering analysis to define known and novel immune subsets. 3. Relate immune-phenotype data to available clinical and blood proteomic data to identify disease endotypes. Outcome: The results from this project will provide a base for future in vitro mechanistic experiments aimed at understanding hyperinflammation.

Relevant publications 1

Hutchinson M, Tattersall RS, and Manson JJ. Haemophagocytic lymphohisticytosis-an underrecognized hyperinflammatory syndrome. Rheumatology (Oxford). 2019;58(Suppl 6):vi23-vi30

Relevant publications 2

Robinson GA, Peng J, Dönnes P, Coelewij L, Naja M, Radziszewska A, et al. Disease-associated and patient-specific immune cell signatures in juvenile-onset systemic lupus erythematosus: patient stratification using a machine-learning approach. Lancet Rheumatol. 2020;2(8):e485-e96

Professor David Long

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Theme: Fundamental Mechanisms of Disease

Research overview

I have a strong kidney translational research mission which aims to understand mechanisms which underlie kidney disease in children and adults with the goal of translating these findings for patient benefit. To do this, my group combines experimental models of kidney disease and patient samples with innovative technologies including three-dimensional imaging, mathematical modelling, gene editing, stem cell technology and novel therapeutic approaches.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Current work supported by a Wellcome Trust Investigator Award in Science examines how specialised tubes called lymphatic vessels, which clear away excess fluid, immune cells and debris, grow, work and 'talk' to other cells in growing or diseased organs. Defects in lymphatics are linked to common and major diseases including heart attacks, obesity, dementia, cancer, and kidney disease. In this rotation project the student will use sophisticated technologies, capable of three-dimensional imaging and reading genes at cellular detail to explore how lymphatics change structurally and molecularly in kidney disease (diabetic nephropathy, cystic kidneys and glomerulonephritis). The student will learn methodologies in three-dimensional imaging (confocal and light sheet microscopy) and its analysis alongside assessment of single cell sequencing data. Moving forward the student will use this data to develop a PhD project using tools to manipulate lymphatics and their molecular communication in the laboratory either using animal models of kidney disease, 3-dimensional organoids, or gene therapy technologies. This will allow us to determine whether lymphatic based treatments could be used as a therapy for patients with kidney disease.

Relevant publications 1

Jafree et al Elife (2019) 8:e48183

Relevant publications 2

Jafree et al bioRxiv 2022.10.28.514222

Associate Professor Jens Madsen

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Research overview

Dr Madsen's research area is mainly focused on the role of innate immune proteins in health and disease in the airways, particular preterm infants and chronic airway diseases such as asthma and chronic pulmonary disease (COPD): https://iris.ucl.ac.uk/iris/browse/profile?upi=JMADS35 Feel free to send me an email if you have any questions or would like to hear more about other potential projects.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

While bronchial asthma affects about 300 million people worldwide, asthma incidence and severity are higher in women than in men, and highest in women between the 4th and 6th decade. During childhood, boys have nearly twice the risk of developing asthma over girls. During adulthood there is a shift to a female predominance, which affects mainly non-atopic asthma. In the elderly, the gender-related differences decrease (1, 2). The bronchial epithelium has a primary function to act as a defensive barrier that aids in the maintenance of normal airway function. Bronchial epithelial cells form the interface between the external environment and the internal milieu, making the bronchial epithelium a major target of inhaled insults. When exposed to allergens or viruses, bronchial epithelial cells produce inflammatory cytokines, which contribute to the innate inflammatory responses. The particular profile of cytokine production may provide important information regarding the nature of an immunotoxic response such as hypersensitivity, the TH1 vs. TH2 response. The project: investigate if sex hormones have an influence on the inflammatory response in airway epithelial cells. Techniques: Cell culture of airway epithelial cells with sex hormones and stimulation with pollen or airway virus. Measure the change in expression of cytokines at the mRNA and using quantitative real-time polymerase chain reaction (qRT-PCR) and perhaps also at the protein level using enzyme-linked immunosorbent assay (ELISA), respectively. Potential PhD project: This project is part of a bigger project trying to make patient specific air-liquid interphase (ALI) primary-like cell cultures using inducible pluripotent stem cells (iPCS) to identify allergens/triggers and thereby also inform what a specific treatment potentially could be.

Relevant publications 1

2) Prudente de Carvalho Baldaçara et al. Association between asthma and female sex hormones. 2017. Sao Paulo Med J. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9969728/

Relevant publications 2

3) Cervantes et al. Role of Hormones in the Pregnancy and Sex-Specific Outcomes to Infections with Respiratory Viruses. 2022. Immunol Rev. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9189035/

Dr Roope Mannikko

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Theme: Fundamental Mechanisms of Disease

Research overview

My research interest is ion channels and channelopathies: how do ion channels work and contribute to physiology, how does channel function change in disease and how does that lead to disease?

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Rotation project involves functional analysis of ion channel variants found in patients associated with neurological disease. You will learn patch clamp and other electrophysiological methods. The channels are expressed in heterologous expression systems. The project, if interested, may involve a component of genetic analysis to identify novel variants that you would then proceed to characterize. Alternatively, you may characterize a novel mechanism of molecular dysfunction across voltage gated sodium channels. We've found a novel pathogenic mechanism in skeletal muscle sodium channel NaV1.4 (unpublished). Related variants are found in other NaV1 isoforms, where they are likely to cause similar channel dysfunction, and ultimately neurological or cardiac disease. UCL neurogenetics continuously identifies novel variants in novel channel genes and these findings may provide further opportunities. Full PhD, in addition to molecular analysis, involves characterization of mouse model(s) of channelopathies or alternatively of iPSC models derived from patients with rare channel variants. Preliminary characterization of a mouse model carrying a gain-of-function variant in KCNH5 suggests very severe phenotype in mice. Very little is known of normal function of KCNH5 in brain and even less of its role in neurological disease. We have also got access to cells from patients with KCNA6 variants that can be differentiated in collaborator lab. Again, very little is known of normal function of KCNA6 in brain and even less of its role in neurological disease. The project benefits of collaborations at the Institutes of Neurology and Child Health.

Relevant publications 1

De novo KCNA6 variants with attenuated KV1.6 channel deactivation in patients with epilepsy.

Relevant publications 2

Spider toxin inhibits gating pore currents underlying periodic paralysis.

Professor Yanlan Mao

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Research overview

In the Mao lab, we are interested in how mechanical forces control tissue growth, homeostasis and repair. We use an interdisciplinary approach, combining in vivo genetics, advanced imaging, AI based image analysis, biophysics and computational modelling, in different epithelia, to uncover general principles of tissue size and shape control.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Biomechanical regulation of tissue repair and regeneration Tissue repair and regeneration after wounding is a fundamental problem of vast medical importance. Over 30% of premature deaths are due to wound healing defects. Previous studies have largely focused on the biochemical control of tissue regeneration. However, there is increasing evidence that the mechanical environment of the tissue also plays a role in the regeneration process. During this project you will use an interdisciplinary approach to understand how tissue mechanical forces can contribute to regeneration, and importantly, how the tissue senses when to stop healing, to prevent scarring and cancer development. In this rotation, you will utilize novel techniques in organoid culture to 3D live-image the regeneration process using mammalian organoids, such as the liver. You will use machine-learning techniques to analyse the 3D cell shape changes in your time-lapse movies. There will be opportunities to learn computer programming if you are keen to do so. This can be expanded into a PhD project to investigate how different cell types in multicellular organoids impact on the mechanical properties of tissues, and the molecular pathways responsible for this. You will use novel hydrogels to dissect the mechanical role of the tissue microenvironment and the cross talk with signalling pathways to investigate how they impact on tissue repair. You will have access to diseased organoids, e.g. from human fibrotic liver patients. This clinical link will allow direct translation of our discoveries to design novel therapies to improve wound healing and improve patient health.

Relevant publications 1

https://www.nature.com/articles/s41567-019-0618-1?proof=t

Relevant publications 2

https://www.nature.com/articles/s41563-020-0783-8

Professor Simon Mead

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Research overview

The Group investigates the question: why do people get prion diseases such as Creutzfeldt-Jakob disease (CJD)? We are interested in the discovery of genetic and/or epigenetic risk factors that might help us understand the mechanisms of human prion disease and new targets for drug treatments. Having recently discovered some risk factors, we are now interested in understanding mechanisms using cellular and in vivo models.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Prion disease susceptibility and disease modification is known to be controlled by genetic factors. Recently we identified STX6 and GAL3ST1 as risk factors for CJD. Our main aim now is to understand how these risk factors work. Sphingolipids are a major class of membrane lipids. The class structure is typically based on an 18-carbon amine alcohol, often conjugated with a fatty acid and a sugar residue to make a cerebroside. Cerebrosides in vertebrates may be sulphated by the cerebroside sulfotransferase enzyme to make sulfatide, a dominant component of the myelin sheath in the nervous system. Abnormal metabolism of sulfatide is directly implicated in neurological disease as mutations in the enzyme that degrades sulfatide are associated with metachromic leukodystrophy (MLD), a rare lysosomal storage disorder caused by the accumulation of sulfatide. Very early in the clinical course, severe sulfatide deficiency has also been repeatedly documented in Alzheimer's disease (brain or CSF) and Parkinson's disease. Importantly, the UCL Institute of Prion Diseases (IoPD) has discovered that a common amino acid variant (V29M) of the sole enzyme involved in the synthesis of sulfatide (cerebroside sulfotransferase (CST) enzyme (GAL3ST1 gene)) confers a strongly increased risk of the most common prion disease sporadic Creutzfeldt-Jakob disease (sCJD). Genetic association implies a causal association between sulfatide metabolism and neurodegeneration. We will establish an assay for sulfatides, to measure sulfatide and other sphingolipid metabolite concentrations in biofluids and tissues of patients with prion and other neurodegenerative disorders, determine a direction of effect of the V29M polymorphism of CST on enzyme activity in model systems, and to test hypotheses about the effects of modification of this pathway on propagation of prions and other proteopathic seeds in cellular and animal models (knockout of CST already exists). We have evidence that the protective polymorphism at this enzyme acts to reduce expression, making CST a potentially tractable therapeutic target. In a 3 month rotation project we might pilot assays to test the effects of sulfatide on prion replication in cellular or cell free amplification assays, or a biophysical interaction between sulfatides (or premetabolites) and prion protein.

Relevant publications 1

https://www.sciencedirect.com/science/article/pii/S1474442220302738?via%3Dihub

Relevant publications 2

https://www.sciencedirect.com/science/article/pii/S0969996120302485?via%3Dihub

Associate Professor Philip Pearce

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Theme: Fundamental Mechanisms of Disease

Research overview

We will use mathematical modelling to identify treatment strategies for diseases of the blood, by characterising how red blood cell (RBC) properties affect blood rheology. We will apply the modelling in the context of sickle cell disease, in which deoxygenation perturbs RBC properties, increasing blood viscosity and occluding blood vessels.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

In sickle cell disease (SCD), red blood cells (RBCs) stiffen in deoxygenated conditions, which can increase effective blood viscosity and eventually cause complete occlusion of blood vessels. Mathematical modelling is a useful tool in the development of genetic and pharmacological treatment strategies: models can be applied to identify and, eventually, control the biophysical processes that lead to vessel occlusion. In this project, based on recent measurements identifying significant heterogeneity in RBC properties in SCD blood samples, we will quantitatively characterise the factors that contribute to clogging in suspensions of deformable and stiffened cells. In the rotation project, the student will run cell-based simulations based on our existing code framework, to investigate dynamics in mixtures of rigid and healthy red blood cells in simple pipe flows representing microvessels. The student will predict how the proportion of stiffened RBCs affects overall blood viscosity; the model will be iteratively compared and refined against experiments performed on SCD blood in microfluidic devices by our collaborators David Wood (University of Minnesota) and John Higgins (Harvard Medical School). In the PhD project, the student will investigate how RBC dynamics are perturbed in whole vascular networks, by running simulations in more complex geometries. We will use our simulations to predict how treatments that change the proportion of stiffened RBCs affect cell distribution and blood occlusion in physiological networks. We will thereby predict optimised interventions such as drug treatments, gene-editing and blood transfusions that preclude blood occlusion. We will test model predictions against experiments performed by our collaborators.

Relevant publications 1

Feature tracking microfluidic analysis reveals differential roles of viscosity and friction in sickle cell blood. H. M. Szafraniec, J.M. Valdez, E. Iffrig, W. A. Lam, J.M. Higgins, P. Pearce and D.K. Wood. Lab on a Chip 8 (2022): 1565. PMID: 35315465 PMCID: PMC9004467 DOI: 10.1039/d1lc01133b

Relevant publications 2

Physical and geometric determinants of transport in feto-placental microvascular networks. A. Erlich, P. Pearce, R. Plitman Mayo, O.E. Jensen and I.L. Chernyavsky. Science Advances 5.4 (2019): eaav6326. PMID: 31001587 PMCID: PMC6469945 DOI: 10.1126/sciadv.aav6326

Professor/Dr Paola and Martin Pedarzani and Stocker

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Theme: Fundamental Mechanisms of Disease

Research overview

The overall scope of our research is to elucidate how neurons in the brain receive, integrate and transform signals in health and disease. We are interested in understanding how ion channels shape and regulate the electrical response patterns and excitability of neurons and in the design of new drugs to target them.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

In early infantile epileptic encephalopathy (EIEE), seizures and epileptiform electroencephalographic abnormalities contribute to progressive cerebral dysfunction. This condition is severely invalidating, has a poor prognosis and a poor responsivity to pharmacological control of seizures. The majority of EIEE cases are associated with structural brain abnormalities. However, underlying genetic mutations in genes involved in metabolic functions and synaptic transmission have also been reported in EIEE. Additionally, mutations in genes encoding for ion channels that regulate neuronal excitability and signalling have been proposed to contribute to EIEE, but it is unclear how the severe and progressive impact on brain functions and the lack of responsivity to pharmacological treatment originate and evolve. Next generation sequencing focusing on a panel of 36 genes linked to infantile epileptic encephalopathy revealed mutations in three genes of an EIEE patient. The proteins mutated are all involved in the transport of potassium and sodium ions across the plasma membrane: a neuronal voltage-gated sodium channel, a potassium channel belonging to a family linked to benign epilepsy of childhood, and a sodium/potassium ATP-ase. By using a combination of electrophysiology, molecular biology and pharmacology, we will study how the mutations found in this EIEE patient affect the function of the channels and pump. We will then reconstitute these mutant proteins in a neuronal system and study their interaction and synergistic impact on neuronal excitability and function. This system will be further used to explore potential pharmacological approaches to control the epileptic phenotype generated by this complex channelopathy.

Relevant publications 1

Tedoldi A., Ludwig P., Fulgenzi G., Takeshima H., Pedarzani P. and Stocker M. Calcium-induced calcium release and type 3 ryanodine receptors modulate the slow afterhyperpolarising current, sIAHP, and its potentiation in hippocampal pyramidal neurons. PLoS One 15(6): e0230465 (2020).

Relevant publications 2

Sampedro Castañeda M., Tonini R. , Richards C.D., Stocker M. and Pedarzani P. Benzamil inhibits neuronal and heterologously expressed small conductance Ca2+-activated K+ channels. Neuropharmacology 158: 107738 (2019).

Professor Stephen Perkins

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Theme: Fundamental Mechanisms of Disease

Research overview

Protein three-dimensional structures are invaluable for elucidating the functional effect of disease-causing genetic variants. We analyse variants for the complement (inflammation) and coagulation (haemophilia) proteins (https://www.complement-db.org/; https://www.factorix.org/). Our web sites are published in leading journals. We wish to enhance our websites further, including developing improved predictive methods for analysing variants.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Title: Development of interactive databases for the evolutionarily-related coagulation and complement proteins. Background: Dysregulation of the coagulation proteins leads to rare diseases such as haemophilia A and B, where we have created widely-used genetic variant web databases for the F7, F8, F9, F10 and F11 genes. Dysregulation of the complement system is associated with two severe rare renal diseases as well as age-related macular degeneration (the most common cause of blindness in the Western world), for which we have a complement database. The aim of this rotation project is to create a new coagulation database, most probably for Protein S or Protein C. Experimental: For Protein S or Protein C, which are closely related to FVII, FIX and FX, the student will perform literature and web searches for genetic variants. These variants will be uploaded into a myPHPadmin database at UCL. We will then create the web site using HTML programming to adapt one of our existing websites into a new one, and compare the variants with those in FVII, FIX and FX for the first time – for publication. Training will be provided on how an interactive database is set up based on transferable skills using mySQL and HTML programming. A detailed understanding of these variants will help us understand the molecular mechanism of these diseases. Such a project leads into the PhD project itself where we will undertake more ambitious variants analyses using more advanced techniques such as molecular dynamics analyses to establish how the variants cause disease.

Relevant publications 1

Xu, Z., Spencer, H. J., Harris, V. A., and Perkins, S. J. (2023) An updated interactive database for 1692 genetic variants in coagulation Factor IX provides detailed insights into haemophilia B. J. Thromb. Haemost. 21, 1164-1176. https://doi.org/10.1016/j.jtha.2023.02.005

Relevant publications 2

Efthymiou, C., Print, E. H. T., Simmons, A., and Perkins, S. J. (2023) Analysis of 363 genetic variants in F5 via an interactive web database reveals new insights into FV deficiency and FV Leiden. Thromb. Haemost. Open, 7, e30-e41. https://doi.org/10.1055/a-1987-5978

Professor Robert Pitceathly

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Theme: Fundamental Mechanisms of Disease

Research overview

My laboratory focuses on three major research themes that crosscut mitochondrial biology and translational science. These include: 1) Understanding the role of mitochondria in health and disease; 2) Generating effective therapies for neurodegenerative and mitochondrial diseases; 3) Establishing the global prevalence and genetic architecture of mitochondrial diseases

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Frontotemporal dementia (FTD) is the second most prevalent cause of young-onset dementia after Alzheimer's disease. Mutations in the GRN gene, which encodes progranulin (PGRN), contribute to 5-20% of familial FTD cases and 1-5% of sporadic cases. There has been recent progress in characterising the neuropathology in FTD-GRN; however, the underlying mechanism of disease pathogenesis is unknown. Neurons have a high metabolic rate, with the brain consuming up to 20% of the total body's energy. To meet this extensive energy requirement, neurons rely on glucose metabolism and mitochondrial oxidative phosphorylation. Mitochondria act as sophisticated energy sensors, modulating their morphology and activity according to cellular energy demands. Emerging evidence suggests that mitochondria play a crucial role in GRN-related FTD. However, their impact on FTD disease pathogenesis is unknown. The potential rotation projects will focus on understanding: 1) the contribution of impaired mitochondrial bioenergetics to FTD pathogenesis. 2) the selective vulnerability of specific groups of cells in the central nervous system to mitochondrial impairment. 3) the mechanistic link between GRN deficiency and impaired mitochondrial bioenergetics. These projects have the potential to develop into a full PhD in neurodegeneration under the co-supervision of Professor Rob Pitceathly and Dr Micol Falabella. The student will benefit from iPSCs, patient-derived brains, fibroblasts, and blood samples. The PhD candidate will undergo specialised training in mitochondrial biology and single-cell analysis. Additionally, they will develop skills in RNA-scope and brain histological approaches and receive comprehensive training in cellular and molecular biology techniques.

Relevant publications 1

Falabella, M., Minczuk, M., Hanna, M. G., Viscomi, C. & Pitceathly, R. D. S. Gene therapy for primary mitochondrial diseases: experimental advances and clinical challenges. Nat. Rev. Neurol. 18, 689–698 (2022).

Relevant publications 2

Falabella M, Vernon HJ, Hanna MG, Claypool SM, Pitceathly RDS “Cardiolipin, mitochondria and neurological disease” Trends Endocrinol Metab. 2021 Apr;32(4):224-237. doi: 10.1016/j.tem.2021.01.006. Epub 2021 Feb 24. PMID: 33640250

Associate Professor Darren Player

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Theme: Fundamental Mechanisms of Disease

Research overview

Skeletal muscle tissue engineering, with a focus on pre-clinical model development for the study of basic mechanisms of disease and scalable models for surgical implantation.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

3D Bioprinting for the development of scalable tissue engineered skeletal muscle. This project will focus on developing the biomaterial and bioprinting parameters required for the successful generation of functional skeletal muscle in vitro. The rotation project will establish the mechanical and biological properties of customisable biomaterials, which will be examined using a range of materials characterisation techniques and biological assays. The rotation project will develop into the main PhD project through the integration with a perfused system (working in collaboration with Bi/ond), whereby it will be possible to establish a high throughput screening tool for therapeutic intervention development for neuromuscular disease. Skeletal muscle ageing will be used as an exemplar to test a novel intervention (based on the human skeletal muscle map), using an established model previously used in the laboratory. The goal of this research is to establish and validate a pre-clinical model of skeletal muscle, which can be used to develop novel interventions for neuromuscular disease.

Relevant publications 1

https://www.frontiersin.org/articles/10.3389/fcell.2021.760260/full

Relevant publications 2

https://journals.sagepub.com/doi/full/10.1177/2041731420985205

Associate Professor Richard Poole

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Theme: Fundamental Mechanisms of Disease

Research overview

Our research reveals fundamental principles of neural development. One current aim is to uncover the cellular and molecular mechanisms that regulate sex-specific neural precursor divisions and differentiation, which should subsequently provide the basis for novel personalised sex-specific therapies for brain tumours.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

SEXUALLY DIMORPHIC REGULATION OF QUIESCENT NEURAL PRECURSOR ASYMMETRIC CELL DIVISIONS: One key hallmark of tumorigenesis is misregulation of the cell cycle. Importantly, sex differences are evident in the rates of a number of human cancers, most notably brain tumours, specifically gliomas, which occur three times more frequently in males than females. This has been linked to cell intrinsic sexually dimorphic differences in the regulation of the cell cycle in neural precursors, yet how genetic sex influences the cell cycle is not at all understood. We have identified a class of differentiated glia that act as neural progenitors during the juvenile-to-adult transition of C. elegans, in a sexually dimorphic male-specific manner, enabling us to address sex specific regulation of glial cell division in a genetically tractable system at single-cell resolution. We have discovered that the cell cycle exists in two different states in males vs hermaphrodites – with a key negative regulator of the cell cycle fzr-1/Cdh1 preventing division in hermaphrodites. Excitingly we have discovered that fzr-1 co-regulates both cell division and asymmetric cell fate decisions, linking the cell cycle to neurogenesis in these glial cells. We also have preliminary data suggesting the sex-determination pathway (and a key transcription factor tra-1/GLI) likely regulates the expression of fzr-1/Cdh1 and at least one other unidentified cell cycle component. The main aim of this rotation will be to quantify fzr-1/Cdh1 expression levels (in males vs hermaphrodites) using smFISH and to determine if tra-1/GLI directly regulates fzr-1/Cdh1 using CRISPR-based promoter analysis. A subsequent PhD project will delve more deeply into these genetic mechanisms.

Relevant publications 1

Sammut, M., et al. (2015). Glia-derived neurons are required for sex-specific learning in C. elegans. Nature 526, 385 390. https://doi.org/10.1038/nature15700

Relevant publications 2

Molina-García, L. et al. (2020). Direct glia-to-neuron transdifferentiation gives rise to a pair of male-specific neurons that ensure nimble male mating. Elife 9, e48361. https://doi.org/10.7554/elife.48361

Professor Andres Ramos

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Research overview

m6A methylation provides an essential layer of mRNA regulation in neuronal development and disease. The project investigates how a set of important neuronal regulators, the FMRP, IMP1 and Syncrip proteins, recognise m6A sites and regulate translation in the brain - by coupling structure to a quantitative biology approach in neurons.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

m6A is the most common internal modification of mRNA and is prevalent in the brain, where regulates essential aspects of cell differentiation and function. In turn, the dysregulation of m6A regulatory pathways is linked to severe neuronal pathologies. The dynamic m6a code is transduced by protein 'readers' that recognise sites of methylation on the target mRNAs, and regulate mRNA metabolism and translation. Our group studies a diverse group of non-canonical m6A readers, that perform roles essential to neuronal differentiation and function. Some of the key questions we ask are how the readers recognise the m6A methylation of the target mRNAs and regulate their translation, and how the action of individual readers on the same RNA is integrated at the molecular level. As part of the rotation project, the student will use computational tools, structural biology and biophysical methods to explore the inter-play of the readers on the target mRNAs in a quantitative fashion. They will build mechanistic models(1,2) that explain how changes in the concentrations of the reader proteins, in development and in disease states, regulates these interactions. The models will then be developed during the PhD project, in vitro (using a range of biophysical tools) and in neurons(2), using high resolution microscopy and transcriptome-wide analysis methods(1) such as iCLIP/miCLIP and proteomics.

Relevant publications 1

Nicastro G*, Abis G*, Klein P, Esteban-Serna S, Gallagher C, Chaves-Arquero B, Cai Y, Figueiredo AM, Martin SR, Patani R, Taylor IA, Ramos A. (2023) Direct m6A recognition by IMP1 underlays an alternative model of target selection for non-canonical methyl-readers. Nucleic Acids Res. 51:8774-8786.

Relevant publications 2

Klein P, Petrić Howe M, Harley J, Crook H, Esteban Serna S, Roumeliotis TI, Choudhary JS, Chakrabarti AM, Luisier R, Patani R, Ramos A (2024) m6a methylation orchestrates IMP1 regulation of microtubules during human neuronal differentiation. Nature communications.15(1):4819.

Dr Matthew Reeves

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Theme: Fundamental Mechanisms of Disease

Research overview

Human cytomegalovirus (HCMV) establishes lifelong latent infections of the host which can cause disease in immune-suppressed. As a lab we investigate the host mechanisms that support latency, how the virus manipulates the host cell environment to survive, and key immune responses for control of HCMV all with a view to therapeutic intervention by pharmacological or immunological means.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Over 50% of the world population are infected with human cytomegalovirus for life. However, during latency HCMV is not silent. Instead, HCMV expresses a subset of genes which alter cell biology essential for latency. We hypothesise that strategies that manipulate biological processes regulated by latent viral functions provides opportunity to target and eliminate the latent virus – which is a leading cause of disease in transplant patients. One host pathway we have recently identified important is the LRP1/TGF/Beta catenin signalling which silences viral lytic gene expression in latency likely protecting the virus from T cell immune-surveillance. Importantly, we observe HCMV up-regulates LRP1 in latently infected cells. The rotation project will focus on investigating the role of LRP1/TGF/Beta catenin signalling in HCMV latency using orthogonal pharmacological approaches directed against components of LRP1/TGF/Beta catenin signalling to manipulate and visualise aberrant viral gene expression during latency thus learning core molecular virology techniques. It is expected that the PhD project would then address the mechanism by which HCMV manipulates the LRP1/TGF/Beta catenin pathway with a focus on a virally encoded deSUMOylase, LUNA, we have shown previously to target a component of innate immunity and now show binds to LRP1. Ultimately, we will test whether we can use pharmacological approaches to exposes latent cells to immune cell targeting and clearance by promoting aberrant viral lytic gene expression. To investigate mechanism a combination of genetic (CRISPR/inducible shRNA/engineered iPS cells/recombinant viruses) and pharmacological approaches will be used in combination with bespoke immune assays for T cell function.

Relevant publications 1

Poole E.L., Lau J.C.H., Murray, M.J., Kew V.G., Stamminger T., Sinclair J.H. & Reeves M.B. (2018) A virally dependent de-sumoylase activity is required for HCMV reactivation from latency Cell Reports 24(3):594-606

Relevant publications 2

Griffiths P.D. & Reeves M.B. (2021) Pathogenesis of human cytomegalovirus in the immune-compromised Nat. Rev. Micro. 19:759-773

Professor Christiana Ruhrberg

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Theme: Fundamental Mechanisms of Disease

Research overview

The Ruhrberg lab defines molecular mechanisms that underlie blood vessel growth and dysfunction in the brain, retina, heart and lung.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Chromosomal and hormonal sex differences impact normal organ function and affect the prevalence, severity and outcome of cardiovascular diseases. Recent studies showed that such sex differences are abundant in endothelial cells, the main building block of all blood vessels. Being tasked with controlling nutrient transport from blood to tissues, these cells have to minimise their own nutrient consumption to support cells in the organs they supply. In this project, the student will learn cell/molecular biological and 'omics' techniques to examine how obesogenic signals differentially affect the metabolic signature of male, female and transgender endothelial cells in an organ of their choice. Specifically, the student will examine how the endothelial cell metabolic signature is differentially influenced by sex chromosomes and hormones in health and under obesogenic conditions. Students have the option to study human endothelial cells and or endothelial cells from male and female mice as well as mice with male sex chromosomes but female hormones, mice with female sex chromosomes but male hormones. Understanding sex differences in endothelial nutrient trafficking will help identify molecular pathways affected by altered cardiometabolic diseases or which are altered by sex chromosome-hormone ratios to impact on cardiometabolic function.

Relevant publications 1

Brash, J.T., Diez-Pinel, G., Colletto, C. et al. The BulkECexplorer compiles endothelial bulk transcriptomes to predict functional versus leaky transcription. Nat Cardiovasc Res 3, 460–473 (2024). https://doi.org/10.1038/s44161-024-00436-w, with Editorial: Redmond, D., Rafii, S. Bulking up to shed light on leaky transcription in endothelium. Nat Cardiovasc Res 3, 412–413 (2024). https://doi.org/10.1038/s44161-024-00458-4

Relevant publications 2

Plein, A., Fantin, A., Denti, L., Pollard J. W., Ruhrberg, C. (2018). Erythro-myeloid progenitors contribute endothelial cells to developing vasculature. Nature, 562(7726):223-228; with Editorial: A dual origin for blood vessels (2018). Nature 562: 195-197.

Professor Joanne Santini

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Theme: Fundamental Mechanisms of Disease

Research overview

Neonatal sepsis is one of the leading causes of neonate death in LMICs. Hospital- acquired Klebsiella pneumoniae is the leading cause of sepsis. This project will use two approaches to prevent and treat sepsis using phages or phage enzymes as 1) prophylactics and 2) “cocktails” in combination with antibiotics for treatment.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The PhD project involves developing phage and phage enzymes for prophylactic and therapeutic use against Klebsiella pneumoniae, the leading cause of neonatal sepsis in low and middle income countries. We will use a collection of neonatal sepsis-causing K. pneumoniae strains from Malawi representing different capsule (KL) types. These strains have been sequenced, and their capsule types determined. In Malawi the predominant capsule types are KL2 and KL16. We have 65 phages that infect some of these KL types. The rotation project involves developing different skills including: 1) Phage isolation: a variety of samples will be used (e.g., sewage from the UK and Malawi). 2) Phage characterisation: this will involve sequencing/sequence annotation, electron microscopy to visualise phages, host-range determination etc. 3) Developing expression systems: for phage enzymes such as depolymerases (degrade bacterial capsule), which removes the “armour” of the bacteria. The PhD project will involve characterisation of the phages, establishment of phage “cocktails”, testing in combination with antibiotics, purification and characterisation of phage enzymes. Efficacy of the phages/enzymes will also be tested in milk (for prophylactic use) and in serum (for therapeutic use). Additionally, the immune response to the phages and enzymes will be assessed using tissue culture experiments. Pre-clinical trials testing efficacy of phage “cocktail” (or enzyme) will be done in vivo using Galleria mellonella as the model organism; this will also be done in combination with antibiotics. This project involves collaborations with Prof. Nicholas Feasey (St Andrews), Prof. David Goldblatt (Institute for Child Health) and Dr Kondwani Kawaza (Queen Elizabeth Central Hospital, Malawi).

Relevant publications 1

Heinz et al. https://www.medrxiv.org/content/10.1101/2023.09.26.23296137v2.full.pdf

Relevant publications 2

Hallmaier-Wacker et al. 2022. http://dx.doi.org/10.1136/archdischild-2022-324047

Dr Maria Secrier

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Theme: Fundamental Mechanisms of Disease

Research overview

The Secrier lab pioneers research into the genetic and cellular mechanisms driving cancer development. We create innovative computational tools that integrate DNA/RNA-sequencing and imaging data. By leveraging cutting-edge AI techniques, we delve into the dynamic interactions between tumors and immune cells, aiming to predict therapeutic resistance and cancer relapse.

Rotation project (including a brief outline of how this will develop into a PHD project)

Risk factors such as acid reflux or smoking act as strong mutagens contributing to the development of oesophageal adenocarcinoma and its precursor stage, Barrett Oesophagus. The effects of these mutagens can be captured through detailed DNA and RNA-sequencing at different stages in the evolution of this cancer, unveiling cellular processes that enable cancer cells to adapt and thrive within the tissue niche. This adaptation is so successful that these cells are frequently resistant to any therapy, leading to dismal survival outcomes (<20% 5-year survival rates). What enables therapeutic resistance is unknown, but key to tailoring treatments successfully to patients. This rotation project will explore how cancer is initiated within the oesophageal tissue niche, and the contribution of inflammation to cancer progression. We will employ rich sequencing datasets of large patient cohorts (including single cell from precursor, primary and metastatic disease), clinical information and detailed spatial profiling of the tissue. This fully computational project will make use of cutting-edge AI and statistical modelling techniques inspired from graph theory and ecology to explore how cancer cells interact with immune and stromal cells in their environment and how mutagenic processes contribute to a chronic inflammation environment that encourages immune evasion and therapeutic resistance. These initial findings will feed into the PhD project, whose longer-term aims are to identify cellular vulnerabilities that can be exploited for therapeutic benefit. We will collaborate with the Fitzgerald lab (University of Cambridge) and other groups from the Oesophageal Molecular and Clinical Stratification Consortium to validate our findings experimentally.

Relevant publications 1

Abbas S, Pich O, Devonshire G, Zamani SA, Katz-Summercorn A, Killcoyne S, Cheah C, Nutzinger B, Grehan N, Lopez-Bigas N; OCCAMS Consortium; Fitzgerald RC, Secrier M. Mutational signature dynamics shaping the evolution of oesophageal adenocarcinoma. 2023. Nat Commun. 14(1):4239. PMID: 37454136.

Relevant publications 2

Withnell E, Secrier M. SpottedPy quantifies relationships between spatial transcriptomic hotspots and uncovers new environmental cues of epithelial-mesenchymal plasticity in cancer. bioRxiv 2023.12.20.572627; doi: https://doi.org/10.1101/2023.12.20.572627

Professor Benedict Seddon

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Theme: Fundamental Mechanisms of Disease

Research overview

My lab studies the genetic and cellular mechanisms controlling the development and function of T cells in the immune system. We use sophisticated mouse genetics, high dimensional spectral flow, transcriptomics, proteomics and mathematical modelling to analyse T cells in viral infection and cancer.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

T lymphocytes are cells of the adaptive immune system critical for normal immunity to infectious disease. Their antigen receptors allow them to specifically recognise and react against foreign invaders, clonally expanding and fighting off infection. The formation of long lived "memory" T cells following infection is the biological basis for immunological memory, and the key property of the adaptive immune system that vaccines attempt to exploit – with varying degrees of success. Our understand of the rules that govern the formation of long lived T cell memory remains poor, and is one of the great challenges for modern medicine. The are various models that attempt to explain how immunological memory forms such as development of memory stem cells during immune responses independently of effectors. However, it is unclear whether such mechanisms account for memory to different pathogens (viral vs bacterial), by different T cell lineages (CD4 vs CD8) and at different sites in the host (circulating memory vs tissue resident memory). This project will study the whole body immune responses of mice to bacterial (listeria) and viral (influenza) infection, using powerful genetic fate reporter mouse models (Ki67-CreERT Rosa26RYFP) developed uniquely from my lab, to precisely track and map the ontogeny of immunological memory. The project will utilise in vivo mouse models of infection, mouse genetics, single cell analysis by flow cytometry and RNAseq, and computational modelling techniques to analyse data and test candidate models, providing a broad interdisciplinary training to PhD students.

Relevant publications 1

The dynamics and longevity of circulating CD4+ memory T cells depend on cell age and not the chronological age of the host M. Elise Bullock, Thea Hogan, Cayman Williams, Sinead Morris, Maria Nowicka, Minahil Sharjeel, Christiaan van Dorp, Andrew J. Yates, Benedict Seddon. 2024. Plos Biology, in press. https://doi.org/10.1101/2023.10.16.562650

Relevant publications 2

Lukas, E., Hogan, T., Williams, C., Seddon, B. & Yates, A. J. Quantifying cellular dynamics in mice using a novel fluorescent division reporter system. Front. Immunol. 14, 1157705 (2023).

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Theme: Fundamental Mechanisms of Disease

Research overview

Multi-species microbial communities can perform useful functions (e.g. probiotics). For a microbial community to be useful, it must be "robust" – able to survive perturbations. This project will quantitatively examine community robustness against a variety of perturbations, using a combination of experiments and mathematical modelling.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

In the rotation project, we will study the robustness of an engineered yeast community "CoSMO" (Cooperation that is Synthetic and Mutually Obligatory) [1]. CoSMO comprises two cooperating S. cerevisiae strains, each overproducing and releasing an essential metabolite to support the growth of the partner strain. We have constructed a mathematical model that quantitatively explains two types of community robustness: robustness against drastic population reductions (mimicking antibiotic treatments), and robustness against gentle dilutions (mimicking daily stool passage) [2]. During evolution (serial passaging), robustness against drastic population reductions rapidly improved in all communities, while robustness against gentle dilutions improved in some communities but declined in others. This suggests that the two types of robustness are impacted by distinct evolutionary mechanisms: We will examine how individual mutations impact community robustness. We will isolate evolved clones from a strain, and pair them with either ancestral or evolved clones from the partner strain. We will then quantify community robustness, and test how evolutionary changes in strain phenotypes affect community robustness. This will set the stage for PhD work where we will ask questions such as: How might community robustness change during evolution? How might robustness against different perturbations be linked to each other? Can we steer the evolution of community robustness? The project offers an excellent opportunity for inter-disciplinary training.

Relevant publications 1

https://www.pnas.org/doi/10.1073/pnas.0610575104

Relevant publications 2

https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3000135

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Research overview

Migrating cells, including metastatic cancer cells, are constantly exposed to mechanical forces that result in rapid alterations in plasma membrane (PM) tension. This project will address how cells sense and respond to changes in membrane tension using inter-disciplinary approaches and develop innovative strategies to target membrane stress in cancer cells.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The plasma membrane (PM) must withstand rapid increases in tension upon exposure to mechanical forces, and disruptions in PM integrity are linked to numerous diseases and disorders. Consequently, cells have evolved robust systems to sense and respond to PM stress by adjusting the composition and biophysical properties of the PM bilayer. Yet when considering cell mechanics, tension within the membrane bilayer is often overlooked. This is because methods to monitor membrane stress (stretch) are limiting. This project will address how cells sense and respond to membrane stress using optogenetics and novel membrane nanoprobes to modulate and monitor membrane tension. The Stefan lab is uncovering unprecedented roles of contacts between the endoplasmic reticulum and plasma membrane, ER-PM contacts, in phosphoinositide (PI) kinase and target of rapamycin complex 2 (TORC2) signalling cascades that serve as master regulators of PM tension, homeostasis, and integrity. This PhD research project aims to determine: 1) how ER-PM crosstalk and PI kinase-TORC2 signalling pathways modulate PM tension, 2) how alterations in these pathways impact PM organisation and integrity using advanced nanoprobes and optical approaches, and 3) how modulating membrane tension impacts cancer cell migration and survival. The project will employ state-of-the-art imaging approaches (super resolution microscopy, FRET, FRAP, FLIM, CLEM), as well as biochemical, biophysical, structural, and computational approaches to study membrane mechanotransduction. We expect to uncover fundamentally important regulatory mechanisms for membrane homeostasis, to develop new technologies to modulate and monitor membrane tension, and to uncover new strategies to target membrane tension in cancer cells.

Relevant publications 1

https://www.molbiolcell.org/doi/10.1091/mbc.E21-11-0534-T

Relevant publications 2

https://www.life-science-alliance.org/content/5/8/e202201430

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Research overview

This project will kick-start research towards new therapies for Parkinson's Disease. We will start with novel small molecule binders of a new protein target, and optimise these using a combination of chemistry, protein science, biophysics, molecular modelling and cellular assays, depending on the background of the students.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The LRRK2 protein has been a high priority target for the treatment of Parkinson's Disease (PD) for many years, with mutations in this protein being the most common genetic risk factors. Given the societal impact of the disease, several potential small molecule therapeutics have entered clinical trials, in all cases targeting the protein's kinase domain. That all these molecules operate by the same mechanism presents a significant risk to the overall approach; indeed despite the very considerable efforts expended to date there are no available small-molecule therapeutics with this mechanism of action in part because of the complexity of ensuring kinase selectivity alongside other desirable compound attributes. There is an under-studied domain of LRRK2 featuring a so-called WD40 repeat (WDR) structure, a motif that has, in other therapeutic areas, been shown to be both disease-relevant and druggable. The LRRK2 WDR motif is key to the proper functioning of the protein and its removal blocks the neurotoxicity of several LRRK2 PD-associated mutations. One such risk-associated mutation (G2385R), the most common in Asian populations, occurs in the WDR domain. This project will start with the very first, recently-discovered small molecule binders of LRRK2-WDR, modify the structures of these molecules (either commercial or in-house chemistry), evaluate them in binding assays and assess their impact in relevant cellular models of the disease. Towards the overall aim of a new potential therapeutic, there will be rotation projects available in the areas of in silico model design, chemical synthesis, protein binding assay development and cell biology.

Relevant publications 1

https://www.biorxiv.org/content/10.1101/2024.07.18.603797v1

Relevant publications 2

The WD40 Domain is Required for LRRK2 Neurotoxicity, N. D. Jorgensen, Y. Peng, C. C.-Y. Ho, H. J. Rideout, D. Petrey, P. Liu and W. T. Dauer. PLoS ONE 2009, 4(12): e8463. DOI: 10.1371/journal.pone.0008463