

Research Areas within Bioscience for an Integrated Understanding of Health / AY 2023 -2024

Supervisor: Dr Della David (della.david@babraham.ac.uk or dd601@cam.ac.uk)

Website: <https://www.babraham.ac.uk/our-research/signalling/della-david>

Department / UPI: Babraham Institute

Research area:

The David lab investigates protein aggregation during ageing in *C. elegans*.

Our goal is to discover molecular mechanisms that promote healthy ageing and alleviate age-related diseases such as neurodegeneration. We and others have identified several hundred proteins that accumulate in solid aggregates during normal ageing in both invertebrates and mammals. Our research in the nematode *Caenorhabditis elegans* reveals that age-dependent protein aggregation is toxic and accelerates functional decline. Moreover, age-dependent protein aggregates trigger Alzheimer's disease-associated protein aggregation.

By studying age-dependent protein aggregation, we are identifying novel regulatory mechanisms that maintain protein stability with age, both inside and outside the cell. We aim to uncover strategies to rejuvenate aged tissues by restoring protein function and eliminating proteotoxicity.

Key techniques: *C. elegans* including functional assays and RNAi screens, biochemical characterisation of protein aggregates, fluorescence and confocal microscopy, proteomics.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Oliver Florey (oliver.florey@babraham.ac.uk)

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Department / UPI: Babraham Institute

Research area:

Lysosomes are critical organelles involved in a wide variety of processes, including degradation and recycling of cellular waste, nutrient signalling and metabolic homeostasis. Dysregulation of lysosomes is at the core of many disease pathologies. The Florey lab studies the mechanisms regulating lysosome function, with a focus on their interplay with different autophagy pathways. This has important implications in how cells respond to stress, such as infection. We employ fluorescent and electron microscopy, mass spectrometry and biochemical techniques to gain a greater understanding of lysosome biology.

BBSRC DTP secondary strategic theme: Understanding the rules of life

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Supervisor: Dr Jon Houseley (jon.houseley@babraham.ac.uk)

Website: <https://www.babraham.ac.uk/our-research/epigenetics/jon-houseley>

Department / UPI: Babraham Institute

Research area:

We are interested in mechanisms by which adaptive mutations form and the ways in which cells adapt to change. We have a major focus on the mechanisms of ageing, both why ageing occurs and how cells respond to age-linked change.

Key areas: DNA replication, extrachromosomal DNA, epigenetics, ageing, yeast

Key techniques: Sequencing (DNA and RNA) including developing new methods, ageing yeast biology, tissue culture

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Helen Mott (hrm28@cam.ac.uk)

Website: <https://www.bioc.cam.ac.uk/research/mott>

Department / UPI: Biochemistry

Research area:

Small G proteins are molecular switches that direct multiple pathways within cells, including cell growth, actin cytoskeleton rearrangements, vesicle trafficking and nuclear transport, via downstream effector pathways. They are inactive when bound to GDP, but in response to upstream signals GDP is exchanged for GTP, which switches the protein on. We particularly work on members of the Ras and Rho subfamilies, which are often deregulated in cancer. Work in our lab is focussed on a molecular understanding of the interactions between small G proteins of the Ras superfamily and their binding partners. These include regulator and effector proteins, and also the membranes to which the G proteins are attached via a lipid modification. We use a range of biophysical techniques and biochemical assays to study these interactions, in combination with structural biology (often, but not limited to, NMR). We are also using NMR to investigate how G proteins interact with the membrane to which they are attached. We are interested in understanding how the different lipid modifications affect these interactions and their consequences for binding of G proteins to their effectors and their regulation and potential for clustering. Our lab are also studying effectors for small G proteins that include large intrinsically disordered regions and the role of these in G protein signalling.

BBSRC DTP secondary strategic theme: Understanding the rules of life

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Supervisor: Prof Folma Buss (fb207@cam.ac.uk)

Website: <https://www.cimr.cam.ac.uk/staff/professor-folma-buss>

Department / UPI: Cambridge Institute for Medical Research

Research area:

Intracellular motility is driven by motor proteins that use energy derived from ATP hydrolysis to regulate the steady state organisation of cellular compartments and control intracellular transport along cytoskeletal tracks. Research in our lab is focused on the cellular function of myosin motors that generate force and move cargo along actin tracks. We follow the activity of myosin motors in living cells using high resolution microscopy but also use a wide variety of biochemical and biophysical techniques on isolated motors to study their characteristic behaviour in vitro. In addition, we employ a variety of cellular, molecular and biochemical approaches to determine how a motor recognizes and selects its cargo and how motor activity and cargo attachment are coordinated. Using in situ proximity labelling and functional proteomics for example we have mapped the interactome of several mammalian myosins. Finally, we are using a combination of computational modelling and virtual screening to identify specific inhibitors for not only for mammalian but also myosins from lower eukaryotic pathogens, as myosin motor proteins are attractive targets for small molecule inhibitors and to date several allosteric effectors for mammalian myosins have been identified.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Janet Deane (jed55@cam.ac.uk)

Website: <https://www.cimr.cam.ac.uk/staff/dr-janet-deane>

Department / UPI: Cambridge Institute for Medical Research

Research area:

The lipids that comprise biological membranes are potent bioactive molecules with important roles in protein trafficking, signalling and cell adhesion. My lab investigates the molecular mechanisms by which altered sphingolipid metabolism results in neurological disease. To study this we use a wide range of experimental techniques including genetic modification of iPSCs to generate cell-based models of neuronal disease, quantitative proteomics and high-resolution molecular structures. Our work explores how specific sphingolipids interact with proteins in the membrane to alter cell signalling and cause disease.

BBSRC DTP secondary strategic theme: Understanding the rules of life

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Supervisor: Dr David Gershlick (dg553@cam.ac.uk)

Website: www.gershlicklab.com

Department / UPI: Cambridge Institute for Medical Research

Research area:

Mutations in Amyloid Precursor Protein (APP) are causal to Alzheimer's disease. With multiple therapeutic strategies failing in the clinic, there is a drastic need for fundamental breakthroughs in our understanding of this process. We have developed novel CRISPR systems, with state-of-the-art super-resolution imaging approaches to understand how APP functions in live cells. We have simultaneously identified a host of novel interactors of APP that we have evidence are essential for the proper functioning of APP. These are totally unexplored and in combination with modern gene editing techniques through CRISPR represent an exciting opportunity to make a breakthrough in our understanding of APP functioning, with potential avenues for therapeutic applications.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof Stefan Marciniak (stm20@cam.ac.uk)

Website: <http://www.med.cam.ac.uk/marciniak/>

Department / UPI: Cambridge Institute for Medical Research

Research area:

Serpin family members serve a variety of functions in diverse tissues. Age-related diseases caused by serpin mutations (serpinopathies) involve polymerisation of mutant protein in the endoplasmic reticulum (ER) but the cellular consequences of this remain obscure. The Marciniak lab has recently discovered that serpin polymers form a solid matrix in the ER that entraps resident chaperones (<https://www.science.org/doi/10.1126/sciadv.abm2094>). Ongoing work aims to elucidate the biophysical consequences of such protein accumulation within the ER and how this alters protein folding and trafficking.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof David Rubinsztein (dcr1000@cam.ac.uk)

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Department / UPI: Cambridge Institute for Medical Research

Research area:

Autophagy

BBSRC DTP secondary strategic theme: Understanding the rules of life

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Supervisor: Prof Melinda Duer (mjd13@cam.ac.uk)

Website: <https://www.ch.cam.ac.uk/person/mjd13>

Department / UPI: Chemistry

Research area:

Structure and function of the extracellular matrix. The extracellular matrix is essential for life. It provides the requisite mechanical properties for structural tissues, like skin, bone, tendon etc, and the 3D scaffold that supports cells in all tissues. Crucially, cell differentiation is in large part driven by the molecular structure, 3D architecture and mechanical properties of the extracellular matrix. Changes in composition, structure and mechanics of the extracellular matrix occur throughout development and in ageing and correlate with changes in cell differentiation, adhesion and migration. However, the molecular mechanisms by which the extracellular matrix influences cell function are far from understood. This is a reflection of the chemical complexity of the extracellular matrix and the challenges of determining its structure and dynamics. We employ a wide variety of interdisciplinary biophysical methods, integrated with cell biology to drive new insights into the roles of the extracellular matrix in life. Recent projects include understanding the molecular mechanism of bone calcification, the changes in bone mineral composition with ageing and the role of osteoblast metabolites in bone mineral structure; the non-enzymatic chemistry of sugars with extracellular matrix proteins and its effects on collagen fibril structure and cell adhesion/ signalling. NMR spectroscopy is a central method in our work, and we have recently installed a state-of-the-art 600 MHz NMR spectrometer (dual solid/ solution state) through ERC funding. The Chemistry Dept has excellent on-site electron (SEM, TEM) and confocal microscopy, and the Duer labs include excellent cell biology facilities.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof david Klenerman (dk10012@cam.ac.uk)

Website: <https://www.ch.cam.ac.uk/person/dk10012>

Department / UPI: Chemistry

Research area:

Single molecule imaging of the adaptive and innate immune response in live cells to understand the molecular basis of the response. The work will focus on the triggering of T cells in response to cancer cells, adaptive immunity, and the inflammatory response mediated by Toll-like receptors (innate immune response).

BBSRC DTP secondary strategic theme: Transformative technologies

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Supervisor: Prof David Spring (spring@ch.cam.ac.uk)

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Department / UPI: Chemistry

Research area:

Next Generation Biotherapeutics. Our research interests use organic synthesis to make small molecules, which can be utilised to understand and exploit biological systems. We work on various approaches, including fragment based ligand discovery, peptides, peptide-conjugates and antibody-conjugates. We also have expertise in antibacterial discovery and development. More detail is contained on our webpages.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Clemence Blouet (csb69@medschl.cam.ac.uk)

Website: <https://www.mrl.ims.cam.ac.uk/research/principal-investigators/clemence-blouet/>

Department / UPI: Clinical Biochemistry

Research area:

We are able to offer a project in the study of the central control of energy and glucose homeostasis. The brain is a key regulator of the integrated regulation of homeostatic functions. We are specifically interested in how the brain senses signals of energy and nutrient availability and integrates these signals to control appetite, metabolism and endocrine functions.

Recent findings from the lab indicate that myelin in the hypothalamus is highly plastic and this plasticity is regulated by nutrients and metabolic hormones. This level of myelin plasticity seems to be very unique to the hypothalamus. Understanding the underpinning mechanisms may transform our understanding of myelin biology, its role in adult brain plasticity and the contribution of these mechanisms to energy and glucose homeostasis.

In the hypothalamus, myelin plasticity might represent a mechanism through which hypothalamic circuits become more efficient in specific physiological contexts. Intriguingly, our data suggest that myelin plasticity is important for long-term homeostatic regulations. In this project, we propose to survey the physiological relevance of hypothalamic myelin plasticity, test the effect of a variety of physiological stimuli relevant to homeostatic controls, and characterise the role of myelin plasticity in the long-term regulation of homeostats.

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Supervisor: Dr Florian Merkle (fm436@medschl.cam.ac.uk)

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Department / UPI: Clinical Biochemistry

Research area:

Our team is interested in metabolic diseases such as obesity and diabetes, how these diseases arise and can be treated, and how are connected to neurodegenerative disease. Since obesity is under strong genetic control and is largely due to the differential activity of certain appetite-regulating cell populations in the brain (specifically the hypothalamus), we are interested in studying how hypothalamic neurons behave in health and disease. To this end, we differentiate human pluripotent stem cells (hPSCs) into relevant hypothalamic cell populations to study how they respond to drugs and hormones, and how these responses change in cells carrying obesity-associated mutations. We also use animal models to probe how diet and drugs can alter the course of neurodegenerative disease. We are greatly interested in this topic given the rising rates of both metabolic and neurodegenerative disease, and hope our fundamental research can empower others to develop better treatments.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Prof Michael Coleman (mc469@cam.ac.uk)

Website: <https://colemanlab.brc.cam.ac.uk>

Department / UPI: Clinical Neurosciences

Research area:

Environmental risk factors for axon degeneration disorders.

The Coleman Group studies mechanisms of axon degeneration and their roles in human disease. We work with companies generating drugs to block axon degeneration, identifying human disorders in which these drugs are most likely to be effective. Our interests include Alzheimer's disease, Parkinson's disease, motor neuron disease, multiple sclerosis, glaucoma and peripheral neuropathies.

Lifelong survival of human axons is a major challenge. Our axons can be up to a meter long, some support over a million synapses and most do not regenerate. Animal studies show that many risk factors for axon survival, including some toxins, viruses, diabetes and injury, activate a well-characterised and fully preventable mechanism known as programmed axon death (Coleman and Hoke (2020) Nat Rev Neurosci). We began the molecular understanding of programmed axon death (Mack et al, Nat Neurosci 2001) and made many further contributions

<https://colemanlab.brc.cam.ac.uk/blog/20-years-wlds-gene>

A number of specific environmental risk factors are now known to activate programmed axon death. Examples include a disused rodenticide (Loreto et al, eLife 2021; <https://colemanlab.brc.cam.ac.uk/blog/old-rodenticide-drives-cutting-edge-research-save-axons-researchers>) and Zika virus (Crawford et al, Front Mol Neurosci 2022), both associated with axonal disorders in humans. We now aim to identify other environmental activators in collaboration with virologists and organic chemists in Cambridge, Glasgow and AstraZeneca.

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The student will gain extensive experience in molecular biology, cell culture, microscopy and enzyme and metabolite analysis, and benefit from our highly supportive team culture where valuing and developing our colleagues is a high priority.

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Supervisor: Dr Nick Cunniffe (ngc26@cam.ac.uk)

Website: <https://www.neuroscience.cam.ac.uk/directory/profile.php?ngc26>

Department / UPI: Clinical Neurosciences

Research area:

Multiple sclerosis affects over 125,000 people in the United Kingdom and is the leading non-traumatic cause of disability in young adults. The most urgent need for people with MS are treatments which slow, stop or reverse disability progression. Many believe that the most effective way to prevent progression is through remyelination: repairing the primary defect (demyelination) and thus protecting the underlying nerve fibre from degeneration.

Our clinical remyelination research in Cambridge is at the forefront of the international effort to find treatments capable of promoting remyelination in people with multiple sclerosis. We are at the exciting stage where the discovery of druggable pathways through our research in the Cambridge Centre for Myelin Repair (CCMR) is leading to clinical trials, in which we can observe nerve repair (remyelination) occurring in humans. Additionally, by using a host of different measures - imaging, electrophysiology, and serum biomarkers - our research is defining the optimal ways to precisely capture and track remyelination and neuroaxonal injury in people living with MS. We are also increasingly recognising the potential impact of demographic and lifestyle factors that impact endogenous remyelination, and are studying this in our research.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Rita Horvath (rh732@medschl.cam.ac.uk)

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Department / UPI: Clinical Neurosciences

Research area:

Identifying novel genes and developing treatments for children with inherited neuromuscular diseases

Inherited neuromuscular disorders are disabling, progressive, often fatal conditions, representing an enormous unmet medical need with devastating impacts on affected families, the healthcare system, and the economy. There are no cures and the limited therapies available treat symptoms without addressing the underlying disease.

Next-generation sequencing has facilitated a molecular diagnosis for many inherited neurological disorders, such as mitochondrial diseases and other neuromuscular diseases, which are the focus of this research. The development of targeted therapies requires detailed laboratory investigation of molecular and mutational mechanisms, and a systematic evaluation of well-chosen agents as well as gene and transcript directed strategies using standardized experimental systems. Our research is focusing on understanding the molecular pathogenesis of childhood onset inherited

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neuromuscular diseases, such as mitochondrial disease and other neuromuscular diseases to develop targeted therapies.

Using a translational approach, we aim to

1. understand the clinical course of patients in relation to the underlying disease mechanism
2. delineate the mutational and molecular mechanisms of the molecular defect in the appropriate cell types by developing model systems such as induced neuronal progenitor cells (in vitro) and zebrafish (in vivo)
3. improve the treatment options for patients by developing novel therapies that are directed at these mechanisms, including directly at the genetic mutation or resulting transcript.

We use a combination of exome sequencing, genome sequencing, and other omics technologies to identify novel disease genes and disease mechanisms. By functional evaluation in vitro (induced neuronal progenitor cells) and in vivo (zebrafish) we confirm pathogenicity and uncover molecular mechanisms of disease. To address the mutational mechanisms, we use gene transfer, splice modulation, allele silencing and CRISPR/cas systems.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Will McEwan (wm305@cam.ac.uk)

Website: <https://mcewan-lab.com/>

Department / UPI: Clinical Neurosciences

Research area:

Antibodies have proven to be exceptionally powerful tools for therapeutic targeting in a broad range of diseases. However, they are limited to the extracellular environment, meaning they cannot engage the majority of proteins. Our group is interested in antibodies in the intracellular environment, where they can promote selective protein degradation (TRIMAway) via the cytosolic antibody receptor TRIM21. This strategy holds promise as a means of eliciting the degradation of cellular proteins, but the circumstances where antibodies enter cells are limited and poorly defined. This project will characterise the ability of antibodies to enter cells and elucidate the molecular mechanisms of TRIM21 activity.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Flavia Mancini (fm456@cam.ac.uk)

Website: www.noxlab.org

Department / UPI: Engineering

Research area:

Our research group includes a mix of information engineers, computer scientists, computational and cognitive neuroscientists. We are united by a shared passion for the development and application of computational methods to understand brain function and improve human health. We have a specific focus on biological learning in conditions of adversity, which underscores people's resilience to persistent stress, pain and other forms of suffering.

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Our research is divided into two main streams:

1. a basic science stream, which aims to understand the link between perception/action and neural activity by using a mix of computational, behavioural and neuroimaging methods. Our current research is focused on computational and neural mechanisms of statistical learning and their relevance to pain and mental health.
2. A translational research stream, which applies computational methods for precision medicine and digital healthcare. This is to improve the identification of people at risk of developing chronic pain, fatigue and mental health problems.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Henrik Salje (hs743@cam.ac.uk)

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Department / UPI: Genetics

Research area:

We are a computational group that works on understanding fundamental processes that lead to viral evolution and changing patterns of infection risk at individual and population scales. We use dengue virus, a vector borne disease found throughout tropical and subtropical regions, as our main model system. We work with detailed datasets that have characterised the genetic and antigenic evolution of the virus in real world settings over the past 50 years. We use mathematical models to identify how changes in the genome lead to shifts in the ability of infected individuals to mount an effective immune response. Separately, we consider how immunity to viruses such as dengue virus evolve over the life course by working with cohorts that have been following individuals since birth. This work provides is essential to battling the ongoing threats of viruses, including through vaccines.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Elisa Laurenti (e1422@cam.ac.uk)

Website: <https://www.stemcells.cam.ac.uk/people/pi/laurenti>

Department / UPI: Haematology / Wellcome - MRC Cambridge Stem Cell Institute

Research area:

Our laboratory studies the rules by which human haematopoietic stem cells govern blood formation at all stages of human life. We are particularly interested in understanding how blood formation is established in the embryo, the molecular mechanisms by which all blood cell types are specified, and how ageing impact haematopoietic stem cell function and increases disease risk. We use integrative single cell approaches, combining single cell -omics with single cell functional assays and clonal tracking. We may offer both wet or dry lab projects.

BBSRC DTP secondary strategic theme: Understanding the rules of life

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Supervisor: Prof Fiona Gribble (fmg23@cam.ac.uk)

Website: <https://www.mrl.ims.cam.ac.uk/research/principal-investigators/fiona-gribble/>

Department / UPI: Institute of Metabolic Science

Research area:

Hormones from the gut are central to the control of appetite and insulin release. Drugs based on the gut hormone glucagon-like peptide-1 (GLP-1) have proved highly successful for treating type 2 diabetes, and also suppress food intake. In collaboration with Frank Reimann, our group researches how gut hormones are released and their actions on target tissues. We hope this will lead to the development of new drugs or diets that treat diabetes and obesity by targeting gut hormone release.

The release of gut hormones such as GLP-1 and PYY after a meal conveys signals to the brain to stop eating, to the pancreas to produce insulin and to the gut to coordinate digestion. We are particularly interested in establishing how gut hormones are released after food ingestion, and how the gut endocrine system is affected after gastric bypass surgery.

Our research encompasses a range of experimental approaches, from physiological studies in humans to analysis of single cells in vitro. We use optical and electrophysiological recording techniques to monitor stimulus detection and vesicle release from endocrine cells in primary intestinal cultures, intestinal organoids and immortalized cell lines. To identify living gut endocrine cells, we have generated transgenic models in which hormone producing cells, or cellular targets of gut hormones, are labelled by cell-specific fluorescent markers and reporters of cytoplasmic signalling pathways. The mechanisms by which cells detect stimuli are identified by combining methods such as live cell imaging, electrophysiology, transcriptomics and measurements of hormone secretion using immunoassays and LC-MS.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof Frank Reimann (fr222@cam.ac.uk)

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Department / UPI: Institute of metabolic Science

Research area:

We recently showed that infusion of InsI5 into the ventromedial hypothalamus (VMH) of mice increased intake of highly palatable foods, such as high fat diet or Ensure milk shake, whilst not affecting chow intake. The receptor for InsI5, Relaxin/insulin-like family peptide receptor 4 (Rxfp4) is known to be Gi-coupled and using a newly developed Rxfp4-Cre mouse we showed that chemogenetic inhibition (Di-DREADD) had similar selective orexigenic effects, whilst chemogenetic activation (Dq-DREADD) reduced palatable food intake and the willingness of mice to work for Ensure in operant chambers. Viral mapping of the VMH-Rxfp4 neuronal connections showed reciprocal connectivity with hypothalamic nuclei implicated in homeostatic feeding control and projections to nuclei implicated in hedonic feeding control. We now want to better understand the activity of VMH-Rxfp4 neurons during behaviour and how they communicate with other established feeding modulating signals, such as the POMC-system. Using in vivo fibre photometry the student will monitor VMH-Rxfp4 neuronal activity in mice performing feeding

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related tasks in operant chambers. In collaboration with experienced post-docs in the group the student will develop this technique and will have the opportunity to employ chemogenetic and/or optogenetic stimulation in vivo after stereotactic AAV delivery into the VMH and to work with ex vivo hypothalamic slice preparations to monitor electrophysiological and/or second messenger (Ca²⁺/cAMP) activity.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Laura Dearden (ld454@medschl.cam.ac.uk)

Website: <https://www.mrl.ims.cam.ac.uk/about-us/our-people/early-career-investigators/laura-dearden/>

Department / UPI: Institute of Metabolic Science / Clinical Biochemistry

Research area:

We research how the environment a baby experiences in early life alters development of the pathways in their hypothalamus that control energy homeostasis. We achieve this primarily by using a mouse model of maternal obesity and working with a variety of in vivo and ex vivo techniques to study neurodevelopment, as well as long term studies of feeding behaviour in the offspring of obese mothers. We also have a particular interest in how some of these effects are mediated by changes to circulating miRNAs in both the mother and the baby.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof Susan Ozanne (seo10@cam.ac.uk)

Website: <https://www.mrl.ims.cam.ac.uk/research/principal-investigators/susan-ozanne/>

Department / UPI: Institute of Metabolic Science / Clinical Biochemistry

Research area:

It is well established that the environment in which we develop in utero, impacts on our long-term health. This has been termed the Development Origins of Health and Disease. One important early environmental factor known to have such programming effects is nutrition. Initial focus was directed towards the detrimental effects of low birth weight and early under-nutrition. In light of the growing epidemic of obesity, including in women of child-bearing age, more focus is now being directed towards the detrimental effects of early over-nutrition. Both fetal under-nutrition and fetal over-nutrition appear to have the same phenotypic consequences in terms of metabolic disease risk. It is yet to be established if they mediate their effects through the same mechanistic pathways. Many rodent models have been established to mimic the human situation and allowing studies across the life course. We use these as tools to establish underlying molecular mechanisms (such as the role of programmed changes in miRNAs) and to explore suitable intervention strategies. These findings therefore can have potential impact on the health of women and their children.

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Supervisor: Dr Maria Duque-Correa (mad75@cam.ac.uk)

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<https://www.stemcells.cam.ac.uk/people/affiliates/dr-maria-duque-correa>

Department / UPI: Medicine / Wellcome - MRC Cambridge Stem Cell Institute

Research area:

Trichuriasis is a major neglected tropical disease, affecting 500 million people worldwide, and caused by infection with whipworms. Whipworms are large parasites that live inside the gut lining. Whipworms remain in their host for years by interacting with the gut lining and surrounding cells to manipulate gut structure and immune responses. How the parasite mediates these interactions is not understood. The Duque-Correa lab aims to determine how whipworms invade, colonise and persist in the gut. Using a new model Dr Duque-Correa developed based on “mini-guts”, the first to mimic whipworm infections in a lab dish, together with microscopy and sequencing, her lab is characterising: 1) the molecular and cellular changes that happen in the whipworm and the gut lining and surrounding cells when the parasite enters and colonises the gut and; 2) the interactions that allow the parasite to persist and the gut lining to repair during chronic infections. This knowledge will open new avenues to eradicate whipworm infections and control gut inflammatory diseases.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Bob Carlyon (bob.carlyon@mrc-cbu.cam.ac.uk)

Website: <https://www.mrc-cbu.cam.ac.uk/people/bob.carlyon/>

Department / UPI: MRC Cognition and Brain Sciences Unit

Research area:

Cochlear implants (CIs) restore hearing to deaf people by electrically stimulating the auditory nerve. Although many CI listeners understand speech well, the variation in outcomes is large and some patients struggle even in quiet backgrounds. Furthermore, new methods of programming CIs also vary in their effectiveness, with some patients showing a substantial benefit while others show no benefit or even perform worse with the new method.

We use a combination of behavioural and electrophysiological methods to understand and overcome the limitations on hearing by CI users and to extend the benefits of CIs to a wider population. Many of our experiments bypass the limitations of the commercial CI and use research software and hardware to present novel patterns of electrical stimulation. In addition to potential long-term clinical benefit this approach, by directly stimulating the auditor nerve without the involvement of cochlear mechanics, provides new insights into the basic processes of human hearing.

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Supervisor: Prof Tamar Makin (tamar.makin@mrc-cbu.cam.ac.uk)

Website: <https://www.mrc-cbu.cam.ac.uk/people/tamar.makin/> and <https://plasticity-lab.com/>

Department / UPI: MRC Cognition and Brain Sciences Unit

Research area:

Our main interest is in understanding the key drivers and limitations of reorganisation in the adult human brain. Our primary model for this work is studying differently abled individuals.

We aim to develop a mechanistic understanding of the neural basis of hand function and dysfunction, and understand how we could use technology to increase hand functionality in able and disabled individuals at all ages.

In particular, we want to know what happens to the cortical territories of the hand following arm amputation, and understand how the brain best supports the acquisition of new skills necessary for patients to adapt to their disability, including prosthetic limb usage and augmentative technology such as the Third Thumb. We are also interested in further understanding why amputees experience vivid sensations of their missing hand many decades after amputation. To understand these processes better, we combine experimental models, performed on healthy participants, and related clinical populations (e.g. individuals with congenital hand loss, stroke survivors). Our research seeks to define the boundaries of plasticity - our brain's ability to adapt how it processes inputs based on changed experience.

There are projects that revolve around the main research themes of the lab available for short- and long-term project. These projects will be developed together with the individual students to fit their skills and interests. Please check out our lab's website for our ongoing research: www.plasticity-lab.com.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Camilla Nord (camilla.nord@mrc-cbu.cam.ac.uk)

Website: <https://www.mrc-cbu.cam.ac.uk/people/camilla.nord/>

Department / UPI: MRC Cognition and Brain Sciences Unit

Research area:

Our group focuses on the cognitive neuroscience of mental health and disorders, in particular, the interplay and influence between mental and physical health. PhD projects would fall under the general research area of body-brain interactions in mental health conditions, a topic which can be explored using approaches including neuroimaging (fMRI), brain stimulation (TMS, tUS), computational modelling, and pharmacology. The general aim of this work is to answer: what are the biological processes driving mental (ill-)health? Could we use neuroscience to better map mechanisms onto new or existing treatments, potentially tailoring treatments for individual patients?

BBSRC DTP secondary strategic theme: Transformative technologies

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Supervisor: Dr Amy Orben (amy.orben@mrc-cbu.cam.ac.uk)

Website: <https://orben.group/>

Department / UPI: MRC Cognition and Brain Sciences Unit

Research area:

Adolescent mental health has declined substantially in the last decade (Sadler et. al, 2018), stretching health services and making the area a medical research priority (MRC, 2019, Wellcome Trust, 2020). Concurrently, widespread digital innovation has radically altered child and adolescent behaviour (91% of 12-15 year-olds now own a smartphone; Ofcom, 2021). This has spurred pervasive concern that digitalisation and social media use might be decreasing adolescent mental health and well-being (Chief Medical Officer, 2019). The Digital Mental Health Group's research addresses these concerns by studying the relationship between social media use and adolescent mental health and well-being in large-scale samples. Their work has engendered substantial health and policy impact, informing advice given by entities such as the UK Chief Medical Officers and the US Surgeon General.

Current research in the group examines the mechanisms linking social media use to mental health in adolescence. One area of interest is our application of formal computational models to social media data in order to study whether reward sensitivity and habits drive behaviours. We also use touch-based data from phone screens to try to identify when an individual user starts using their phone habitually. We augment this with longitudinal and cross-sectional data-driven research on social media and its links to mental health across clinical groups and in community samples, always trying to supplement questionnaire data with data collected from phones or social media platforms. Finally, we additionally work with partners such as UNICEF to examine the impact of technology use on mental health in the Global South.

Supervisor: Dr James Thaventhiran (jedt2@cam.ac.uk)

Website: <https://www.mrc-tox.cam.ac.uk/research/thaventhiran-project>

Department / UPI: MRC Toxicology Unit

Research area:

The clonal response of lymphocytes, adaptive immunity, dictates the response to environmental challenges that occur over the life-span. These responses can be regulatory or inflammatory. Immunotherapy works by targeting beneficial adaptive immune responses; however, this is inherently risky for the host as misdirected adaptive immune reactions often lead to life-threatening toxicity. Variations in the genotype, prior environmental exposures and immunotherapy formulation might all contribute to whether a good or bad outcome occurs. The Thaventhiran group uses a combination of human and mouse studies to investigate this. We determine the genotype/phenotype associations of people exposed to immunotherapy to determine the genetic and environmental factors that affect adaptive immune responses. We use animal models to test hypotheses suggested by these human studies to confirm causality.

Currently, we focus on the antigen-specific adaptive immune responses driven by the mRNA lipid nanoparticle (mRNA-LNP) vaccines (e.g. Pfizer and Moderna COVID-19 vaccines) and the antigen-non-specific adaptive immune responses promoted by immune checkpoint blockade treatments

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used in cancer immunotherapy. We use cutting-edge technologies such as combined single-cell RNA sequencing and immune repertoire sequencing to track the immune response across time and in different tissues determining how this varies. A current project is offered towards discovering optimal nucleotide sequences and peptide adjuvants for mRNA-LNP vaccines for uses such as personalised cancer vaccines. Alternative projects could also be considered based on the laboratory's interests and experience (see PubMed and preprint servers Medrxiv).

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Colin Crump (cmc56@cam.ac.uk)

Website: <https://www.path.cam.ac.uk/research/virology-division/crump-group>

Department / UPI: Pathology

Research area:

Our laboratory studies cellular mechanisms utilised and modified by viruses during their replication, in particular viruses from important families of human and veterinary pathogens including herpesviruses, polyomaviruses, and bunyaviruses.

Herpesviruses are large and complex enveloped dsDNA viruses that are ubiquitous pathogens of vertebrates and establish life-long latent infections in their hosts. Herpesviruses are associated with many serious diseases including life-threatening conditions in immuno-compromised patients. Herpesviruses encode several multi-functional proteins that cause dramatic modifications of host cells enabling the evasion of antiviral responses and efficient production of new virions.

Polyomaviruses are small non-enveloped dsDNA viruses that are ubiquitous pathogens in humans and can establish life-long persistent infections with regular asymptomatic virus shedding. While polyomavirus infections are generally benign, they can cause serious disease in immuno-compromised patients including haemorrhagic cystitis, polyomavirus-associated nephropathy, Merkel cell carcinoma, and progressive multifocal leukoencephalopathy.

Bunyaviruses are enveloped segmented negative-strand RNA viruses that are commonly transmitted by arthropods and includes many neglected tropical disease pathogens such as Rift Valley fever virus, Crimean-Congo haemorrhagic fever virus, and Oropouche virus. In collaboration with colleagues in Brazil we are investigating virus-cell interactions of Oropouche virus, an arbovirus that is widespread in South America.

We are particularly interested in identifying and studying the cellular mechanisms that are essential for virus infection or are potent antiviral effectors, using state-of-the-art microscopy imaging, proteomics and genetic screening techniques. Gaining deeper understanding of these virus-host interactions will enable the development of improved antiviral therapies, and viral vectors for vaccines and gene therapies.

BBSRC DTP secondary strategic theme: Understanding the rules of life

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Supervisor: Dr Anton Enright (aje39@cam.ac.uk)

Website: <https://www.path.cam.ac.uk/research/cellular-and-molecular-pathology-division/enright-group>

Department / UPI: Pathology

Research area:

We work on small RNAs such as microRNAs and piwiRNAs and also on large-scale analysis of gene-expression and how small RNAs influence the lifecycle of messenger RNAs. We are both a computational and experimental laboratory and can offer wet, dry and hybrid projects according to a students desired balance. We are currently focused on developing new laboratory and computational techniques for detection of RNA methylation to study how the epitranscriptome influences the lifecycle of mRNAs and their impact on disease. No computational experience is required we have trained many molecular biologists over the years to be competent computational biologists.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof Stephen Graham (scg34@cam.ac.uk)

Website: <http://www.atomicvirology.path.cam.ac.uk/>

Department / UPI: Pathology

Research area:

We seek to understand how herpesviruses modify the environment of infected cells to promote virus replication while evading host immune responses. Herpesviruses are highly prevalent pathogens that cause significant human and veterinary disease. Herpesviruses are characterised by establishing latent infections for the lifetime of the host, with occasional reactivation to cause clinical symptoms (e.g. cold sores). Over millennia of co-evolution with their hosts these viruses have evolved intricate and sophisticated mechanisms to control the intracellular environment of infected cells. There is increasing evidence linking herpesvirus infection with neurodegenerative conditions like multiple sclerosis and Alzheimer's disease in humans, but we know very little about the molecular consequences of life-long latent neuronal infection. Our lab harnesses cell biology, molecular virology and biochemistry techniques including cell-based infection assays, fluorescence microscopy, proteomics, protein biochemistry and structural biology to probe the molecular consequences of herpesvirus infection. We are particularly interested in the use of pluripotent stem cell technologies to understand how herpesviruses spread efficiently to neurons and the molecular interactions that promote infection within the brain. Our work provides the foundational knowledge required to develop new vaccines and antiviral therapies to prevent and treat human and veterinary herpesvirus infections. Our studies will help unlock the potential of herpesviruses as oncolytic agents and gene delivery vectors.

BBSRC DTP secondary strategic theme: Bioscience for sustainable agriculture and food

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Supervisor: Dr Catherine Merrick (cjm48@cam.ac.uk)

Website: <https://www.path.cam.ac.uk/directory/catherine-merrick>

Department / UPI: Pathology

Research area:

I study the protozoan parasite Plasmodium, which causes malaria in humans and many other animals. Research interests are centred around DNA biology, particularly the molecular mechanisms underlying DNA replication and cell cycle control in this early-diverging eukaryote, which replicates by an unusual non-binary-fission method called schizogony.

I am also interested in the roles that G-quadruplex DNA and RNA structures may play in the parasite - for example, in silencing and promoting the recombination of a family of key virulence genes called var genes, whose variant expression is under epigenetic control. In fact, we have discovered that G-quadruplexes and their helicases have more general roles in genome stability/evolution in the malaria parasite, as well as influencing gene expression at the RNA level.

Finally, I have a long-standing interest in epigenetics, particularly in the regulation of subtelomeric chromatin and virulence gene expression, and in how epigenetic pathways may be used for host-parasite signalling.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Rahul Roychoudhuri (rr257@cam.ac.uk)

Website: <http://roychoudhurilab.org/>

Department / UPI: Pathology

Research area:

Stemness and maintenance of CD4+ regulatory T cell (Treg) responses in homeostasis, inflammation and ageing

CD4+ Regulatory T (Treg) cells are rare immune cells with powerful immunoregulatory functions. Loss of Treg cells results in lethal inflammation, while defects in their function are associated with autoimmunity and allergy. Treg cells also suppress immune responses in cancer. There is intense scientific and translational interest in exploiting the powerful functions of Treg cells but efforts to do so have thus far been disappointing - harnessing Treg cells to treat disease remains a major outstanding challenge for the field. A majority of Treg cells develop in early life, but maintenance of Treg responses is required throughout life to prevent lethal inflammation. Maintenance of Treg responses is also critical to efficacy of Treg-targeted therapies, including Treg cell therapy and tolerogenic vaccines.

While much is now known about how Treg cells develop, we lack a framework for understanding how Treg responses are maintained. In many tissues, cellular populations are maintained by quiescent stem cells which self-renew while giving rise to shorter-lived progeny. We have recently found that a critical characteristic of stem cells – quiescence – is required for Treg cells to be maintained over long periods of time.

This research will test the hypothesis that long-lived Treg responses are hierarchically organised, with quiescent self-renewing progenitor cells giving rise to shorter-lived functionally active

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progeny. It will define molecular mechanisms by which quiescent cells are maintained and how these can be manipulated to improve therapy.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Jeanne Salje (jss53@cam.ac.uk)

Website: <https://www.path.cam.ac.uk/directory/dr-jeanne-salje>

Department / UPI: Pathology / Cambridge Institute for Medical Research

Research area:

The Salje lab studies obligate intracellular bacteria and how they have evolved to live inside eukaryotic cells without being destroyed by them. This unusual group of organisms are a powerful system for studying both fundamental questions of bacterial physiology and interactions between bacterial and eukaryotic cells.

This PhD project focuses on one of the most important structures in a bacterial cell: the peptidoglycan cell wall. This large, cross-linked polymer is essential in most bacterial species and a target of several classes of antibiotics. We recently discovered that a small group of bacteria have lost one of the major enzymes normally used to polymerise peptidoglycan (class A PBPs) whilst retaining other genes in the peptidoglycan biosynthesis pathway. The species that lack this gene were almost all closely associated with eukaryotic hosts, suggesting that it enables them to evade immune defences. We were able to show experimentally that they build an unusual cell wall that is less abundant and robust than normal peptidoglycan. We term these “peptidoglycan-intermediate bacteria”. This finding opens many exciting questions, as we try to understand how and why these peptidoglycan-intermediate bacteria build their cell walls.

This PhD project will be based in the highly collaborative and inter-disciplinary Salje lab. Approaches will include bioinformatics and cutting-edge fluorescence and electron microscopy techniques, as well as classical microbiology/cell biology approaches. Whilst the project is based around a defined central question, there will be a lot of scope for an energetic and creative student to generate ideas and new avenues of exploration.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Matthew Harper (mth29@cam.ac.uk)

Website: <https://www.phar.cam.ac.uk/research/harper>

Department / UPI: Pharmacology

Research area:

Haemostasis is essential to survival. Without effective haemostasis, blood vessel injury might cause fatal haemorrhage. Haemostasis involves crosstalk between platelets and the coagulation cascade, each activating and enhancing the other. The Harper lab focused on understanding this crosstalk. In particular, we study how platelet procoagulant activity is controlled. Platelet procoagulant activity involves surface exposure of phosphatidylserine (PS), rapid platelet 'ballooning', and release of extracellular vesicles from the plasma membrane. By unravelling the molecular regulation of these processes, we aim to understand how procoagulant platelets control coagulation and haemostasis.

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Supervisor: Prof Graham Ladds (grl30@cam.ac.uk)

Website: <https://www.phar.cam.ac.uk/research/Ladds>

Department / UPI: Pharmacology

Research area:

The adenosine A1 receptor (A1R), like many G protein-coupled receptors, GPCRs, is potentially a high value drug target for conditions, such as type 2 diabetes mellitus, pain, epilepsy and cerebral ischemia, and while drugs for these conditions exist, nevertheless there remain clear unmet clinical needs in these areas. However, the A1R has been classified as undruggable because of serious side effects intrinsically linked to the target.

The problem arises because the A1R activates multiple G proteins. In the CNS, A1Rs inhibit synaptic transmission, induce neuronal hyperpolarization and cause sedation, while in the cardiorespiratory system A1Rs slow the heart (bradycardia) and contribute to reducing blood pressure (hypotension), and depressed respiration (dyspnea). Recently the Ladds group, with others has identified a compound BnOCPA, which has totally shifted the paradigm as it only activates the G protein *G_o* (the CNS effects), through which it confers pain relief in vivo. It does not activate *G_α* so there are no cardiovascular side effects. BnOCPA now allows us to propose a rational approach to designing G protein selective A1R agonists.

Our strategy is based on the observation that BnOCPA is a novel bitopic ligand that spans both the orthosteric and an allosteric binding sites. We will therefore study combinations of orthosteric and allosteric modulators to find combinations that alter the bias of the A1R. The nature of the interactions will also be determined through mutagenesis and chemical modification BnOCPA. These results will feed into the design of novel BnOCPA analogues with rationally designed G protein selectivity.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Delphine Larrieu (dl437@cam.ac.uk)

Website: <https://www.larrieulab.com/>

Department / UPI: Pharmacology

Research area:

Characterisation of new genes that can restore cellular dysfunction in ageing

The nuclear envelope is a crucial cellular structure for maintaining cellular homeostasis, by preventing uncontrolled exchange of proteins between the nucleus and the cytoplasm, by acting as an anchoring platform for tethering chromatin, and by transmitting mechanical forces between the cytoplasm and the nucleus.

The importance of the nuclear envelope is highlighted by the catastrophic diseases caused when it is dysfunctional. These include cancers, muscular diseases, neurodegenerative syndromes and premature ageing syndromes (progeria). Importantly, nuclear envelope dysfunction also occurs in normal ageing but the mechanisms driving this remain unknown.

In the lab, we have implemented cutting-edge whole-genome CRISPR-Cas9 approaches to identify new players regulating nuclear envelope function in ageing. This led to the identification of 43 new genes that when deleted, can restore nuclear envelope defects in ageing cells. However, the

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function of these genes in the context of ageing remains unknown. Current projects in the lab are investigating the mechanisms behind this rescue by generating cellular models in which candidate genes are knocked out by CRISPR-Cas9 and studying the cellular phenotypes, the integrity of the nuclear envelope and the response of cells to mechanical stress. This work will therefore reveal new pathways underlying nuclear envelope dysfunction, shedding fresh light on mechanisms driving physiological ageing.

Supervisor: Dr Clare Buckley (ceb85@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/clare-buckley>

Department / UPI: Physiology, Development and Neuroscience

Research area:

My group's primary goal is to uncover how apical-basal polarity level sculpts the development of the CNS. Our current research investigates how apical-basal polarity, signalling and morphogenesis interrelate during secondary neural tube opening and later cell differentiation. We use high resolution imaging, CRISPR and optogenetics approaches in vivo, within the developing zebrafish neural tube. This enables us to image the behaviour of cells before, during and after a precise manipulation in polarity or signalling deep within the brain of a vertebrate organism. In addition, we use in vitro multicellular mouse embryonic stem cell (mESC) culture to compare the fundamental mechanisms of de novo polarisation in a non-neural epithelial context. We aim to understand how single cells respond to and affect their neighbours to build whole organs and to directly test what role apical-basal polarity dysregulation plays in the initiation of disease. Through this work, we hope to unravel parallel mechanisms of epithelial tube development and disease. We are currently particularly interested in understanding the links between cell-cell adhesion, actomyosin contractility and cellular mechanics in relation to polarity initiation and morphogenesis of epithelial tubes. We are also interested in determining the effects of aberrant PI3K signalling on cellular behaviour and epithelial tube morphogenesis.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Angeleen Fleming (af425@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/angeleen-fleming>

Department / UPI: Physiology, Development and Neuroscience

Research area:

The role of protein clearance pathways in health and disease; the role of proteostasis in the developing and ageing brain and CNS

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Supervisor: Dr James Fraser (jaf21@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/james-fraser>

Department / UPI: Physiology, Development and Neuroscience

Research area:

My group uses computer modelling of skeletal muscle fibres alongside electrophysiological research and clinical collaborations to understand normal and abnormal excitability. This includes understanding the causes and consequences of excitability changes in exercise, as well as working towards the improved diagnosis and treatment of abnormal excitability in conditions such as myotonia congenita. Projects do not require any initial knowledge of coding or mathematics, but will introduce you to the powerful synergies between computer modelling and experimental work.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof Dino Giussani (dag26@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/dino-giussani>

Department / UPI: Physiology, Development and Neuroscience

Research area:

The Giussani Lab is interested in how adverse pregnancy can trigger embryonic origins of heart disease in the adult offspring. Current research programmes focus on pregnancy complicated by maternal obesity, fetal growth restriction, chronic hypoxia, excess glucocorticoid exposure, inflammation, and oxidative stress. We work with animal models including sheep, rats, mice, and chicken embryos. In each species, we adopt an integrative approach, combining experiments in vivo with those at the isolated organ, cellular, mitochondrial, molecular, and epigenetic levels. We are at an exciting phase of our work, which is intervention. Therefore, we are doing research with conventional and mitochondria-targeted antioxidants and agomirs. Our strength is cardiovascular phenotyping.

Key references

1. Giussani. Circulation 144(17):1429-1443, 2021.
2. Botting et al. Science Advances6(34): eabb1929, 2020

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof David Keays (dak55@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/staff/keays> & <https://keayslab.org/>

Department / UPI: Physiology, Development and Neuroscience

Research area:

Neurodevelopmental Disorders and the Microtubule Cytoskeleton.

The construction of the vertebrate brain is dependent on a complex cascade of biological processes that include mitotic division, relocation of migrating neurons, and the extension of dendritic and axonal processes. To gain insight into the molecules that mediate these cellular

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events the Keays laboratory employs novel transgenic mouse mutants, iPSCs, coupled with human genetic studies. This work has highlighted the importance of the microtubule cytoskeleton and microtubule associated proteins (MAPs) in the building of the human brain. At present the lab focuses on various members of the tubulin gene family (e.g. TUBB2A, TUBB2B, TUBB5) as well as a family of uncharacterised microtubule associated serine threonine kinases (MAST1-4), which are associated with a spectrum of disease states (e.g. epilepsy, autism, polymicrogyria, microcephaly). Our goal is to gain insight into the molecular and cellular mechanisms that cause the disease, catalysing the development of rational therapeutic interventions.

Supervisor: Dr Golnar Kolahgar (gk262@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/golnar-kolahgar>

Department / UPI: Physiology, Development and Neuroscience

Research area:

The Kolahgar lab investigates fundamental mechanisms regulating intestinal tissue maintenance and regeneration. The intestinal epithelium constantly regenerates from stem cells, which adjust their behaviour to the changing physiological conditions the gut is exposed to. For example, stem cell proliferation rates can transiently increase to speed up regeneration after tissue loss or in response to the diet, before reverting to steady-state levels once correct tissue size is reached. This plasticity is essential for intestinal function, as lack of regeneration causes tissue atrophy whereas unrestricted stem cell proliferation promotes cancer.

Our aim is to identify novel conserved factors regulating gut plasticity. We work with the intestine of the fruit fly *Drosophila* due to the ease with which it can be genetically manipulated and imaged with sophisticated microscopy, its rapid lifecycle and because it is cost-effective.

Importantly, this organism shares more than 70% of its DNA with human disease genes, meaning that our basic research has the potential to uncover new insights into intestinal maintenance and degenerative diseases.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof Andrew Murray (ajm267@cam.ac.uk)

Website: www.pdn.cam.ac.uk/directory/andrew-murray

Department / UPI: Physiology, Development and Neuroscience

Research area:

Our research concerns integrated mitochondrial physiology in health and disease. We are interested in how factors such as diet, environment and genetics influence mitochondrial respiratory function, and the implications this has for function at the level of the cell, tissue, organ and organism. A major focus of our work lies in understanding the impact that tissue hypoxia (low oxygen levels) has on mitochondrial respiration, and the metabolic response to hypoxia. Hypoxia can result from impairments in systemic oxygen delivery, and is a defining feature of life at high altitude. In populations resident at high altitude for many thousands of years, there has been the selection of physiological features, underpinned by gene variants, that support the capacity to live, work and reproduce in low oxygen conditions. Projects in our group include the investigation of some of these selected gene variants and their functional consequences, and studies into the

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metabolic phenotypes of high altitude populations. This work could shed new light on mechanisms that might support physiological function in other contexts where hypoxia occurs.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Luca Peruzzotti-Jametti (lp429@cam.ac.uk)

Website: <http://bit.ly/Peruzzotti-Jametti>

Department / UPI: Physiology, Development and Neuroscience

Research area:

Research in our group is focused on the understanding of inflammation in central nervous system (CNS) diseases. Over the past years, our research in regenerative neuroimmunology led to novel experimental advanced therapeutics with neural stem cells, acellular therapeutics (e.g., extracellular vesicles), and small molecules for the treatment of ischemic stroke, spinal cord injury, and progressive multiple sclerosis (MS).

Our most recent work is focusing on immunometabolism and mitochondria to find novel ways to modulate chronic inflammation and favour CNS regeneration. To this aim, we apply unique tools to model metabolic/mitochondrial dysfunctions in vitro (using human cells and gene editing techniques) and in vivo (with animal disease models), as well as cutting edge techniques to detect metabolic changes in rodent/human cells and tissues.

Our multi-disciplinary approach is setting the stage for a new series of interventions that target cell metabolism in immune cells, as the next opportunity to promote the healing of the persistently inflamed CNS.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof Stefano Pluchino (spp24@cam.ac.uk)

Website: <https://scholar.google.co.uk/citations?user=nhLL1cwAAAAJ&hl=en>

Department / UPI: Physiology, Development and Neuroscience

Research area:

We aim to elucidate how the immune system, in particular its cells called myeloid cells, affects brain structure and function under normal healthy conditions and in disease.

Our objective is to find how myeloid cells communicate with the central nervous system and affect tissue healing and functional recovery by stimulating mechanisms of brain plasticity mechanisms such as the generation of new nerve cells and the reduction of scar formation. To this aim, we use state-of-the-art transcriptomics, proteomics, and molecular approaches to study murine and human disease models of inflammation and neurodegeneration.

BBSRC DTP secondary strategic theme: Transformative technologies

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Supervisor: Prof Angela Roberts (acr4@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/angela-roberts>

Department / UPI: Physiology, Development and Neuroscience

Research area:

The functional organisation of the prefrontal cortex during development and in adulthood in relation to its role in the regulation of positive and negative emotion in a non-human primate, the common marmoset.

The range of techniques include pathway intervention studies using viral mediated vectors, multi-modal neuroimaging, cardiovascular measurements using wireless technology and complex behavioural analyses. The focus will be on developing an understanding of the neurocognitive circuits that regulate emotional responsivity to reward and threat.

Supervisor: Dr Elena Scarpa (es697@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/staff/scarpa>

Department / UPI: Physiology, Development and Neuroscience

Research area:

Investigating In Vivo Compressive Forces: Cell Division, Nuclear Integrity, Cancer Initiation.

When dividing or migrating in tissues, cells push against other cells around them or squeeze through tight spaces. In vitro studies have shown that cells that are physically compressed experience mechanical stress. This can lead to DNA damage because of deformation of the nucleus or to errors in chromosome segregation during mitosis. Physical confinement can also cause heritable changes in the genome of cancer cells.

However, the effects of compressive forces have not yet been investigated in a physiological in vivo setting, since migrating cells in mammalian tissues are inaccessible to imaging, and because of the difficulty in manipulating the physical properties of tissues in vivo. We are overcoming these challenges by using the Zebrafish. Zebrafish embryos are translucent, enabling us to visualise migrating cells in an intact animal amenable to mechanical manipulations.

We investigate a population of embryonic multipotent stem cells, neural crest cells(NCCs). In the trunk of the Zebrafish embryo, they migrate through narrow spaces, in between other tissues, before differentiating into Schwann cells or neurons. This confined migration is highly conserved across vertebrates, including humans. We observe that NCCs experience significant nuclear deformation during migration and that they make errors when dividing.

These findings are important for human health, because trunk NCCs can initiate neuroblastoma, a common solid tumour in children. Neuroblastoma still has only 50% survival rate and 98% of cases are linked to chromosomal abnormalities. It is unknown why neuroblastomas suffer genomic errors. One possibility, supported by recent clinical findings, is that this might be a consequence of in vivo mechanical stress.

BBSRC DTP secondary strategic theme: Understanding the rules of life

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Supervisor: Prof Amanda Sferruzzi-Perri (ans48@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/amanda-sferruzzi-perri>

Department / UPI: Physiology, Development and Neuroscience

Research area:

The lab is focused on understanding the importance of genetic factors (e.g. imprinted genes and metabolic signalling pathways) and parental environments (e.g. nutrient restriction, stress, heat strain, obesity, advanced age and hypoxia) on the maternal, placental and fetal inter-relationships that govern pregnancy success and life-long cardio-metabolic health. A PhD project could be thus be designed specifically related to these lab focal points and combine physiological experimentation, pre-clinical mouse models, novel transgenic approaches, human biobanks, and a range of techniques that provide integrated information of changes occurring at the molecular, cellular, tissue and whole body physiological levels.

Supervisor: Dr Erica Watson (edw23@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/watson-erica>

Department / UPI: Physiology, Development and Neuroscience

Research area:

The overarching research goal of the Watson lab is to understand the multigenerational effects of abnormal folate metabolism on development. We aim to tease apart how metabolic disruption affects the germ cell epigenome and whether these epigenetic factors are inherited to influence fetal-placental development in the direct offspring and over multiple generations. Projects in the lab will use a novel (and rare) mouse model of abnormal folate metabolism (Mtrr^{Δgt} mice) that displays transgenerational epigenetic inheritance of congenital malformations including neural tube defects and congenital heart defects. We employ mouse genetics, embryo manipulation, molecular and histological phenotyping of fetoplacental development, germ cell analysis, transcriptomics, and epigenomics. Ultimately, we aim to use the knowledge collected in mice to better understand the mechanism of folate metabolism during human development as well as how non-communicable diseases and congenital malformations of an unknown cause are inherited in humans.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Eleanor Raffan (er311@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/eleanor-raffan>

Department / UPI: Physiology, Development and Neuroscience / Institute of Metabolic Science

Research area:

Why are some individuals prone to obesity and yet others stay lean in an obesogenic environment? Obesity is highly heritable as are related metabolic traits. We study obesity genetics 'in the round' starting from genetic discovery studies using GWAS and other epidemiological approaches working with 'big data'. Capitalising on my background as a vet, we often start with canine genetics - dogs are an excellent animal model for genetic studies because selective

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breeding means their genetics are particularly conducive to the studies we do. Recent work is extending into horse and production animal genetics.

To follow up genetic findings, we use cellular experiments to understand the consequences of mutations on metabolism at a molecular level, focussing on neuronal development, cell signalling and adipocyte biology. And in pet dogs volunteered by their owners we study energy expenditure and eating behaviour to understand the whole-body physiological consequences of mutations of interest. Eleanor is a vet and we also have a clinically focussed research stream looking at the management of obesity in pet dogs and cats.

I am happy to design PhD projects to suit the interests of each student. In the lab currently graduate students are working on clinical projects, cell biology, physiology and statistical genomics. There is the opportunity to have a true multidisciplinary training in the group and I am happy to talk to potential students about what you want from your PhD research.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof Paul Bays (pmb20@cam.ac.uk)

Website: <https://bayslab.org>

Department / UPI: Psychology

Research area:

Working memory is a core cognitive system that underpins most complex behaviour, from learning new motor skills to reasoning and decision-making. Given the global aging of the world's population, it is of growing importance to understand the mechanisms underlying the deterioration of working memory in later life. Recent years have seen rapid advances in our ability to delineate different causes of working memory errors in healthy young people and relate them to aspects of neural population coding. We seek to explain impairments in a range of working memory abilities assessed in healthy aging, Alzheimers and non-Alzheimers dementia, based on a neurocomputational model of binding incorporating conjunctive codes. The results could reveal new diagnostic criteria to guide interventions aimed at extending effective memory capacity across the lifespan.

Supervisor: Prof Sarah-Jayne Blakemore (sjblakemore@psychol.cam.ac.uk)

Website: <https://www.psychol.cam.ac.uk/staff/professor-sarah-jayne-blakemore>

Department / UPI: Psychology

Research area:

Neurocognitive development and mental health in human adolescence

Adolescence, defined as 10-24 years in humans, is considered a sensitive period of brain development and social cognitive maturation. This period of life is also characterised by a vulnerability to mental health problems, which often first appear before the age of 24. This project aims to explore potential risk and resilience factors that can influence neurocognitive development and mental health during adolescence and early adulthood. The project involves investigating how external lifestyle factors, such as the peer environment, sleep and social media use, can impact on brain development, learning, social cognition and mental health. The project

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will involve behavioural studies of adolescents and young adults, as well as neuroimaging studies. Understanding the factors that influence development and mental health is a critical step in developing strategies that aim to protect the mental health of young people.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof Nicola Clayton (nsc22@cam.ac.uk)

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Department / UPI: Psychology

Research area:

My Comparative Cognition Laboratory uses natural behaviours of corvids (members of the crow family that includes the jays, rooks, ravens and crows) to study complex cognition, focusing on two aspects of sustainable food that are critical to the lives of animals, namely (1) the capacity to cache food for the future, rely on memory to recover these hidden stashes of food at a later date and keep track of who is watching when in order to protect those stashes from being stolen from onlookers; and (2) the ability to share food with their mates during courtship, which can be used to explore the extent to which these birds can take into account what their partner wants, even when in conflict with their own needs and desires. We also study cephalopods, especially cuttlefish, to investigate diverse intelligences shaped by different bodies and distantly related minds, questioning which selection pressures have been essential for the evolution of cognition in ourselves and other species with whom we share the planet.

My lab also investigates embodied cognition, namely the way in which our thinking processes are constrained by what we know about how our bodies work, for example the blind spots in seeing and road blocks in thinking revealed by magic effects, and how they are shaped by whether we have wings, tentacles, or fingers and thumbs. This work has implications for the Bioscience for an Integrated Understanding of Health, namely how the mind and body interact and how these interactions are shaped by our expectations of embodied cognition and constrained by evolutionary pressures. The use of magic techniques also opens up the possibility to explore Transformative Technologies.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Prof Zoe Kourtzi (zk240@cam.ac.uk)

Website: <https://www.abg.psychol.cam.ac.uk>

Department / UPI: Psychology

Research area:

Successful everyday behaviours—from finding objects in a cluttered scene, to recognizing a friend in the crowd and coordinating social interactions—critically depend on our ability to extract meaningful information from ambiguous sensory signals. Although these visual recognition processes may appear effortless, they pose significant computational demands on the brain that is faced with the challenge to robustly estimate the current state of the environment from sensory signals that are noisy and inherently uncertain. Learning and experience are known to improve our perceptual skills in (i) deciphering complex patterns of visual information and (ii) improving fine perceptual discriminations. Yet, despite the fundamental role of learning in guiding our

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decisions and actions, we know surprisingly little about how the brain learns to improve our judgments and support precise and flexible perceptual decisions. We combine recent advances in computational modelling and machine learning with ultra high-field brain imaging to interrogate the fine-scale adaptive computations in biological and artificial systems.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof Jon Simons (jss30@cam.ac.uk)

Website: <http://www.memlab.psychol.cam.ac.uk/>

Department / UPI: Psychology

Research area:

Making the most of our memory as we age

Improving healthy ageing across the lifecourse is one of the principal challenges facing society, and a key strategic priority for BBSRC. The ageing process is typically characterised by neural degeneration in a number of brain regions associated with cognitive abilities such as attention, planning, problem solving and processes that control how information is stored and retrieved from memory. However, the ageing brain may be more resilient than previously thought, with evidence that activity decreases in some areas may be accompanied by increased activation in other cortical regions. By capitalising on the cognitive abilities that are comparatively resistant to the ageing process, it may be possible for older adults to develop effective strategies that will allow them to make the most of their memories as they age. PhD students will have the opportunity to gain experience in a wide range of interdisciplinary cognitive neuroscience methods used in the Memory Laboratory, including behavioural studies, functional and structural neuroimaging (f/sMRI), electrophysiology (EEG/MEG), and brain stimulation (TMS/tDCS). The results of this project could be applied to explore memory-related cognitive training techniques with the potential to enhance remembering in older adults.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Mara Lawniczak (mara@sanger.ac.uk)

Website: <https://www.sanger.ac.uk/person/lawniczak-mara/>

Department / UPI: Sanger Institute

Research area:

We are carrying out large scale DNA based surveys of Anopheles diversity across Africa and insect diversity across the UK and are looking for PhD students interested in working on data interpretation. More information on these projects can be found at <https://www.sanger.ac.uk/collaboration/bioscan/> and <https://www.sanger.ac.uk/collaboration/the-anospp-project/>. In addition to the aims of the projects as described, we are also keen to study the population genomics of some of the species we encounter using linked or long read data.

BBSRC DTP secondary strategic theme: Bioscience for sustainable agriculture and food

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Supervisor: Dr Raheleh Rahbari (rr11@sanger.ac.uk)

Website: <https://www.sanger.ac.uk/person/rahbari-raheleh/>

Department / UPI: Sanger Institute

Research area:

Our research focuses on understanding mutations acquired during natural process of ageing, with an aim to provide insight into mutational processes that leads to ageing and disease transformation throughout life. We also aim to understand the role of selection in shaping different cell populations. Over the past few years, systematic sequencing of tumours has revolutionised our understanding of cancer evolution. This has revealed that most cancers carry elevated number of mutations accumulated through the lifetime of their cells. However, due to technical limitations, little is known about the pre-cancerous stage and how normal cells within our tissues accumulate mutations during ageing and in their progression towards cancer and/or other diseases. We investigate these early changes by studying somatic evolution in normal and precancerous tissues. In 2016 we published the first comprehensive description of how ageing affects the germline cells (Rahbari et al., 2016). We showed that due to ageing, germline cells accumulate mutations that are inherited to the offspring. Our study revealed that cellular processes, that are operative in cancer neoplasms, also exist in normal germline cells. In recent years, we have published an encyclopaedia of clonal structures, mutation rates and signatures across an extensive range of human normal somatic and germline cells (Moore et al., 2020). We described the extent of variation in clonal dynamics and mutation rates across somatic and germline cells. Our team develops novel multi-omics experimental and computational methods to further investigate the clonal dynamics and selection in normal tissues during ageing.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Dr Alexandre Almeida (aa2369@cam.ac.uk)

Website: <https://www.vet.cam.ac.uk/staff/dr-alexandre-almeida>

Department / UPI: Veterinary Medicine

Research area:

My research group leverages genomic and metagenomic approaches to investigate the human microbiome's role in health and disease. In particular, my group focuses on obtaining a deeper understanding of the function and diversity of the hidden, uncultured microbiome --- the thousands of bacterial and viral species living with us that remain virtually unknown. The PhD projects I am proposing all use cutting-edge bioinformatics and statistical methods (e.g., multivariable statistics and machine learning) to gain new biological insights from large-scale multi-omics data. The main topics include: i) uncovering the natural diversity, function, and ecology of opportunistic pathogens within the human gut microbiome; ii) modelling the multi-kingdom diversity of the human gut microbiome in health and disease; and iii) investigating the genomic evolution and host adaptation of the human gut microbiome. Students will be embedded in an excellent interdisciplinary environment that will allow them to obtain an in-depth training in microbiology, genomics, phylogenetics, computational biology and advanced statistics.

BBSRC DTP secondary strategic theme: Understanding the rules of life

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Supervisor: Dr Olivier Restif (or226@cam.ac.uk)

Website: <https://www.vet.cam.ac.uk/directory/or226@cam.ac.uk>

Department / UPI: Veterinary Medicine

Research area:

Dynamics of antimicrobial resistance (AMR) in livestock:

- analysis of metagenomic data to monitor AMR alleles in the pig microbiome
- models for covariation in susceptibility to multiple drugs
- models for horizontal transfer of AMR genes in bacterial communities

BBSRC DTP secondary strategic theme: Bioscience for sustainable agriculture and food

Supervisor: Prof Bertie Gottgens (bg200@cam.ac.uk)

Website: <https://www.stemcells.cam.ac.uk/people/pi/gottgens>

Department / UPI: Wellcome - MRC Cambridge Stem Cell Institute

Research area:

Blood stem cell research: From single cell genomics to quantitative Tissue Models

Putative PhD projects will utilize state of the art single cell genomics and data analysis methods to develop a systems level understanding of how blood stem cells can maintain a healthy blood system over the entire lifespan.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Supervisor: Prof Ragnhildur Karadottir (rk385@cam.ac.uk)

Website: <https://www.stemcells.cam.ac.uk/people/pi/karadottir>

Department / UPI: Wellcome - MRC Cambridge Stem Cell Institute

Research area:

Neuroscience, Myelin biology

The brain is responsive to an ever-changing environment, enabling the organism to learn and change behaviour accordingly.

Efforts to understand the underpinnings of this plasticity have almost exclusively focused on the functional and underlying structural changes that neurons undergo at neurochemical synapses. What has received comparatively little attention is the involvement of activity-dependent myelination in such plasticity and the functional output of circuits controlling behaviour.

The traditionally held view of myelin as a passive insulator of axons is changing to one of lifelong changes in myelin, modulated by neuronal activity and experience. Nascent evidence, and preliminary data from the lab implicate a functional role of myelin plasticity in strengthening circuit functions that underlie learning and behaviour.

A few projects are available in the lab that focus on myelin plasticity. We use behavioural tasks and transgenic mouse models along with in situ electrophysiology (whole-cell patch clamp) or in



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vivo photometry for mechanistic insights. Molecular and morphological insights are gained using histology, electron microscopy and confocal microscopy with artificial intelligence image analysis, and transcriptional studies.

BBSRC DTP secondary strategic theme: Understanding the rules of life