

Research Areas within Understanding the Rules of Life / AY 2023 -2024

Supervisor: Prof Raymond Goldstein (R.E.Goldstein@damtp.cam.ac.uk)

Website: www.damtp.cam.ac.uk/user/gold

Department / UPI: Applied Mathematics and Theoretical Physics (DAMTP)

Research area:

Physics of multicellularity; developmental biology; tissue folding; physical ecology; theory and experiment

Supervisor: Dr Maria Christophorou (maria.christophorou@babraham.ac.uk)

Website: <https://www.babraham.ac.uk/our-research/epigenetics/maria-christophorou>

Department / UPI: Babraham Institute

Research area:

The Christophorou lab study protein regulation through post-translational modification, and how this mediates the translation of environmental signals (such as developmental cues, injury or cellular stresses) into the epigenetic changes that determine cell fate. Our main focus is on a particular class of protein modifying enzymes, the peptidylarginine deiminases (PADIs), which carry out protein citrullination. Citrullination has been traditionally studied for this role in immunity and the impact of its deregulation in disease development (autoimmunity, neurodegeneration and cancer). Our work has shown that it mediates the establishment of pluripotency during mammalian development and the reprogramming of somatic cells into induced pluripotent stem (iPS) cells. We employ diverse a complementary biochemical, cell biological and in vivo approaches to understand the molecular mechanisms that govern PADI activity and how PADIs regulate cell and organismal biology. Our work contributes to the understanding of healthy embryonic development and may have implications for regenerative medicine.

PhD students joining our lab will have the opportunity to choose from projects in different biological disciplines (cell signalling, epigenetics, developmental biology) or work at the intersection between these. They will be guided to develop their research interest and plan their own research programme, while being trained in all aspects of scientific research, presentation and dissemination within a supportive and inclusive team.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Ian McGough (ian.mcgough@babraham.ac.uk)

Website: <https://www.babraham.ac.uk/our-research/signalling/ian-mcgough>

Department / UPI: Babraham Institute

Research area:

The lab aims to identify the molecular mechanisms needed to maintain tissue health and identify why these molecular mechanisms stop operating effectively during the ageing process. Ageing tissues experience a progressive decline in homeostatic and regenerative capacities. This has been attributed to degenerative changes in tissue-specific stem cells, including alterations in intercellular signalling pathways and a breakdown in protein homeostasis. The lab uses *Drosophila*

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melanogaster to investigate how protein homeostasis and intercellular signalling are accurately maintained in the intestinal stem cell niche and why signalling and proteostasis dysfunction occurs with age. To answer these questions the lab uses a combination of proteomics, RNA sequencing methodologies, molecular biology and genetics.

Like mammalian stem cells, a loss of proteostatic capacity in aged *Drosophila* intestinal stem cells (ISCs) leads to overactivation of stress signalling pathways, the mis-differentiation of ISCs and a decline in tissue homeostasis. This conservation, a short lifespan and an unparalleled ease of genetic manipulation makes *Drosophila* an excellent system to investigate what drives the loss of proteostasis in aged stem cells.

Ageing tissues also experience an alteration in signalling pathways that are crucial regulators of stem cell dynamics. This can lead to an over proliferation of stem cells, leading to stem cell exhaustion, and/or an imbalance in the differentiated cell types found within the tissue. The lab investigates how morphogen signalling pathways, such as Wnt and Hedgehog, are accurately regulated in the stem cell niche and how signalling dynamics are altered during the ageing process.

Supervisor: Dr Teresa Rayon (teresa.rayon@babraham.ac.uk)

Website: www.rayonlab.org

Department / UPI: Babraham Institute

Research area:

Control of developmental tempo in mammals

How processes are temporally controlled is a fundamental question in biology. The tempo in determines the rate of development of the whole organism, its size, and ultimately the length of time that embryogenesis takes (Ebisuya and Briscoe, Development 2018). Therefore, understanding the rules that determine how cells and organisms can precisely initiate and terminate processes at specified times and how do they modulate the rate at which they tick will help us explain when processes go awry, for example in tissue overgrowth or deficits.

We have developed comparative stem cell differentiation models to spinal cord motor neurons from mouse and human embryonic stem cells to investigate the molecular mechanisms that control developmental tempo. We found that mouse proteins are degraded twice as fast as human proteins, mirroring the differences in developmental tempo. In silico, decreasing the degradation rate of key transcription factors explained the slower temporal progression in human compared to mouse (Rayon et al., Science 2020). Now, the Rayon lab is exploring the following questions: (1) does protein turnover control developmental tempo in vivo?; (2) What are the mechanisms that control biological timing?; (3) Can we modulate developmental tempo within a species?

Our long-term goal is to modulate biological timing in a precise and tuneable manner. We look for applicants that are curious about evolution, developmental biology, and embryonic stem cells. A background on cell or molecular biology, as well as skills in bioinformatics or computational approaches would be useful, but ample opportunities for training will be provided.

BBSRC DTP secondary strategic theme: Transformative technologies

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Supervisor: Dr Peter Rugg-Gunn (peter.rugg-gunn@babraham.ac.uk)

Website: <https://www.babraham.ac.uk/our-research/epigenetics/peter-rugg-gunn>

Department / UPI: Babraham Institute

Research area:

Human Developmental Epigenetics

We are interested in understanding how the epigenome is established during human development and stem cell differentiation, and how epigenetic information changes over the life course of a person.

To research these topics, we use different types of stem cell (primarily human pluripotent stem cells), stem cell-based embryo models (blastoids and gastruloids), and donated human embryos, in combination with a variety of molecular and genetic approaches to investigate their epigenomes. At present, we are focused on understanding the control of developmental gene regulation, and the timing and origins of embryo lineages. Projects are available on these topics.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Sophie Trefely (Sophie.Trefely@babraham.ac.uk)

Website: <https://www.babraham.ac.uk/our-research/epigenetics/sophie-trefely>

Department / UPI: Babraham Institute

Research area:

The Trefely Lab studies metabolic pathways and metabolite signals linking diet to the epigenome.

We are particularly interested in the roles of metabolites as signalling molecules in highly metabolically responsive tissues, such as fat tissue, and how they can be targeted in metabolic diseases that occur in ageing including type 2 diabetes and obesity.

Metabolites can have multiple functions depending on where they are located within the cell. In the nucleus, specific metabolites form epigenetic tags that control gene expression. The abundance of several metabolites have been linked to corresponding epigenetic tags that are required for functional reprogramming of gene expression. Despite metabolites being critical for the epigenetic regulation, how specific metabolites occur within the nucleus and their role in establishing and maintaining cell identity is unclear. We use powerful techniques for metabolomic analysis by liquid-chromatography-high resolution mass spectrometry (LC-HRMS) to analyse metabolism combined with a variety of biochemical and genetic approaches. Our methods for subcellular analysis have revealed distinct regulation of metabolism within the nucleus, which cannot be inferred from typical methods that use whole cell analysis. These approaches allow us to answer questions about regulation of metabolism specifically within the nucleus and how this supports epigenetic mechanisms required for establishing and maintaining cell identity.

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Supervisor: Dr Martin Turner (martin.turner@babraham.ac.uk)

Website: <https://www.babraham.ac.uk/our-research/immunology/martin-turner>

Department / UPI: Babraham Institute

Research area:

The Turner group aims to characterise fundamental mechanisms controlling lymphocyte development and function throughout the life-course. These include understanding the roles of RNA binding proteins in lymphocyte development and activation. We seek to explain how these are integrated with signal transduction pathways, microRNA and transcription factor networks; an important step towards a systems level understanding of immunity. Genetically modified mice in which the functions of signalling pathways and RNA-binding proteins can be controlled by conditional mutagenesis are one important research tool required for this understanding. Additionally, we are developing tools for measuring gene expression in rare cell populations. We also use genome wide approaches to study RNA turnover, mRNA translation and to identify the targets of RNA binding proteins. Our approach trains individuals who can combine bioinformatics, molecular, cellular and in vivo skills to tackle biological questions.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Philipp Voigt (philipp.voigt@babraham.ac.uk)

Website: <https://www.babraham.ac.uk/our-research/epigenetics/philipp-voigt>

Department / UPI: Babraham Institute

Research area:

We are interested in understanding the molecular mechanisms that control the accurate and timely expression of genes during development. Factors that regulate chromatin states play key roles in these processes. We aim to understand how posttranslational histone modifications ('marks') contribute to setting up chromatin states that support either gene activation or repression. In particular, we are interested in the so-called bivalent domains, a peculiar combination of active and repressive histone marks found at developmentally regulated genes. Bivalent domains are thought to maintain genes in a poised state in stem cells, ready for activation upon signals that cause the cells to differentiate. However, the underlying mechanisms and requirement of bivalency for proper development remain unclear. Understanding how chromatin states regulate developmental gene expression will not only shine light on the fundamental mechanisms of transcription, chromatin, and their connections to signalling processes, but also provide insight into development and ageing. The lab is applying a range of approaches to address these questions, combining chromatin biochemistry with proteomic, genomic, cell-biological, imaging-based, and systems biology-inspired techniques.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

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Supervisor: Dr Heidi Welch (heidi.welch@babraham.ac.uk)

Website: <http://www.babraham.ac.uk/our-research/signalling/heidi-welch>

Department / UPI: Babraham Institute

Research area:

Our lab is part of the Signalling Programme at the Babraham Institute.

We study the signalling mechanisms that control Rac GTPases, a protein family which regulates the actin cytoskeleton, oxygen radical production, gene expression, and other important cellular processes. Mostly, we study Rac-GEFs, the proteins that activate Rac. We discovered P-Rex family Rac-GEFs, and we have been studying the mechanisms of regulation and functional roles of these proteins.

We found that P-Rex Rac-GEFs control the morphology, adhesion, migration and tissue recruitment of leukocytes and platelets. We showed that they are important for host defence against bacterial infections, for the morphology and plasticity of neurons that control motor coordinations, and for the migration of melanocytes during development. We participated in studies which showed that deregulated P-Rex expression or activity contributes to cancer growth and metastasis. We defined the key signalling mechanisms that regulate the subcellular localisation and catalytic activity of P-Rex Rac-GEFs.

Currently, we are investigating functional roles of P-Rex Rac-GEFs in receptor trafficking and glucose homeostasis. We are beginning to define adaptor functions of P-Rex proteins in these processes and in neutrophils. We are also studying the roles of other Rac-GEFs in neutrophil-mediated defence against bacterial infections, and we developed tools to monitor the activity of these proteins in live cells. We also have an interest in the signalling mechanisms that lead to the decline in neutrophil function with ageing, and we are working on ways to inhibit Rac-GEF activity.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Alexander Borodavka (ab2677@cam.ac.uk)

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Department / UPI: Biochemistry

Research area:

Infectious Biology, Virology, Biophysics, RNA Biology, Biomolecular Condensates

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Supervisor: Prof Kathryn Lilley (k.s.lilley@bioc.cam.ac.uk)

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

Department / UPI: Biochemistry

Research area:

RNA biology

Multi omics

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Technology development to understand the expansion of function of molecules through post transcriptional and post translational modification

Projects on offer focus upon understanding the relationship between post transcriptional modification of RNA (both mRNA and noncoding RNA) is the relocalisation of RNA upon cellular stress and how this is orchestrated by the proteome. In particular we are keen to dissect core mechanisms from those that are stress type specific.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Eyal Maori (em514@cam.ac.uk)

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

Department / UPI: Biochemistry

Research area:

RNA transmission between organisms.

The Maori Group is broadly interested in the RNA interconnections of infection, immunity and genome dynamics. We are studying how RNA flows between individuals, and how it promotes social immunity and epigenetic communication between honeybees and other closely interacting organisms.

To achieve these goals, we combine RNA biochemistry techniques and imaging with high-throughput sequencing to define how beneficial RNA moves between cells, tissues and organisms.

Our research aims to provide knowledge and tools that will enable studying the biology of RNA transmission in other systems, including humans, in diverse biological aspects; hence, will ultimately contribute to the development of RNA-based applications to promote sustainability, health and disease control.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Darerca Owen (do202@cam.ac.uk)

Website: <https://www.bioc.cam.ac.uk/research/owen>, [@Mott_stuff](https://www.bioc.cam.ac.uk/mottowen)

Department / UPI: Biochemistry

Research area:

We are interested in understanding small G protein (Ras superfamily) controlled intracellular signalling pathways. We focus on the Rho family of small G proteins and particularly the Cdc42 effector tyrosine kinase, ACK. ACK is an oncogene in its own right and we are focussed on elucidating Cdc42-ACK signalling networks in cells to understand how ACK functions in normal physiology and how this is subverted in disease. We are investigating multiple downstream targets of Cdc42-ACK to determine the molecular details of its functional cellular network. ACK has far reaching effects in cells. It has multiple nuclear functions, regulating transcriptional networks and ribosomal activity, it modulates PI3Kinase signalling at multiple nodes, regulates receptor endocytosis and trafficking, and controls cell migration via regulation of actin

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polymerization. Understanding these networks is crucial to both understanding fundamental cellular processes and to designing strategies to manipulate them.

A parallel focus in the lab, applies our knowledge of signalling pathways and our structural and biophysical analysis of many of the protein complexes we study, to design inhibitors. We are particularly interested in developing peptide biologics and often work in collaboration with industrial partners. These moieties act as valuable probes to dissect pathway and protein functions but can also be developed as early-stage therapeutic molecules. Importantly we want to understand their mechanism of action and define rules to help us design more effective probes and therapeutics.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Prof Luca Pellegrini (lp212@cam.ac.uk)

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

Department / UPI: Biochemistry

Research area:

The aim of our research is to explain the molecular mechanisms that cells use to maintain an error-free genome and to duplicate our genetic information before cell division. We aim to achieve this by using modern Biophysical and Biochemical techniques, such as cryoEM and single-particle fluorescence, as well as conventional Biochemical assays. The successful outcome of our experiments provides a high-resolution representation of the dynamic macromolecular processes that are responsible for maintaining genomic stability in the cell. In addition to their fundamental biological importance, these studies have a broad clinical and medical relevance as pathologies such as cancer are caused by defects in the molecular mechanisms responsible for the accurate repair and replication of our DNA.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Katherine Stott (ks123@cam.ac.uk)

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

Department / UPI: Biochemistry

Research area:

We investigate molecular recognition by disordered proteins, exploring their role in different biological contexts from signalling hubs to condensates. Our overall aim is to establish a biochemical and biophysical toolkit to study these complex multivalent systems. We use a broad methodology, including a range of biophysical methods and NMR spectroscopy.

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Supervisor: Prof Ross Waller (r fw26@cam.ac.uk)

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Department / UPI: Biochemistry

Research area:

Apicomplexans are eukaryotic intracellular parasites that cause diseases in humans and animals such as malaria, toxoplasmosis, coccidiosis and cryptosporidiosis. These organisms diverged from the animal lineage more than a billion years ago and, therefore, possess many divergent molecular and cellular traits. On the other hand, since adopting parasitism as their lifestyles, apicomplexans have been coevolving with their animal intracellular habitats for hundreds of millions of years. This coevolution has resulted in highly complex and intimate molecular relationships with their animal hosts. In the Waller lab we are investigating the adaptations of parasitism in apicomplexans. In particular, we are seeking answers to questions of the molecular basis of parasite invasion of hosts, their interactions with host cells after invasion, the biogenesis of some of their unique organelles, and how these processes have evolved from the last common ancestor of apicomplexans and during the diversification of this highly successful lineage. We employ a combination of experimental cell biology using the genetically tractable *Toxoplasma gondii* as a model, systems biology methodologies, and evolutionary analysis to address these questions. Our broader goals are to determine the universal principles of how cells behave and evolve, to appreciate the diversity of these processes, and to understand the mechanisms of successful parasitism displayed by apicomplexans.

Supervisor: Prof Julian Rayner (jcr1003@cam.ac.uk)

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Department / UPI: Cambridge Institute for Medical Research

Research area:

Apicomplexan parasites are an extraordinarily successful group of eukaryotic organisms that have adapted to live inside vertebrate hosts, where their parasitic lifecycle results in significant human and animal diseases including malaria. Key to their ability to invade and feed on host cells are a number of unique and highly specialised membrane-bound organelles which perform a range of essential functions from internalising and digesting host proteins, to secreting parasite proteins involved in host cell invasion.

We currently understand little about how these organelles are created and how proteins are trafficked between them, in part because much of the work on membrane trafficking and organelle biology has focussed on model eukaryotes, not these highly specialised parasites which diverged very early in the tree of life. New tools, including high throughput experimental genetics, spatial proteomics and live cell microscopy, are offering the opportunity to deliver new insights into apicomplexan cell biology.

Working with malaria parasites, which invade human red blood cells and digest their haemoglobin in order to grow and multiply, we use these tools to understand how proteins are trafficked out of the parasite and into the red blood cell, how specialised invasive organelles are built and maintained, and how haemoglobin is internalised and digested.

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Our approach is interdisciplinary, bringing together Cambridge labs with different areas of expertise, and addressing fundamental questions of how eukaryotic life is organised, as well as specific questions of malaria parasite biology.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Prof Michael Weekes (mpw1001@cam.ac.uk)

Website: <https://www.cimr.cam.ac.uk/staff/professor-michael-weekes>

Department / UPI: Cambridge institute for Medical Research

Research area:

Antiviral restriction factors (ARF) are a critical element of cellular innate immunity, representing the first barrier to viral infection that can determine outcome. Our aim is to identify and characterise novel antiviral restriction factors (ARF), and novel aspects of cellular machinery that sense and signal viral infection.

To do this, we employ a number of human pathogens, in particular Human Cytomegalovirus (HCMV), Monkeypox virus (MPXV) and its vaccine, Modified Vaccinia Ankara (MVA). Our systematic proteomic analyses determine which cellular factors each pathogen targets for destruction, since we have shown these to be enriched in novel ARFs. For example, we recently developed a multiplexed proteomic technique that enables identification and characterisation of proteins degraded in the proteasome or lysosome very early during human cytomegalovirus infection (Nightingale et al, Cell Host & Microbe 2018). We identified a shortlist of 35 proteins that are degraded with high confidence, and showed that one of these, helicase-like transcription factor can restrict HCMV. Application to MVA infection indicated further candidates, and identified novel mechanisms of vaccine action (Albarnaz et al, in review, preprint on Research Square). Furthermore, additional proteomic screens can identify the viral factor(s) responsible for targeting each ARF, and indicate mechanism (Nobre et al eLife 2019). Ongoing work in the lab aims to determine which degraded proteins can restrict diverse viruses and the mechanisms of restriction and the mechanism of virally mediated protein degradation.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Sebastian Ahnert (sea31@cam.ac.uk)

Website: <http://www.tcm.phy.cam.ac.uk/~sea31/#publications>

Department / UPI: Chemical Engineering and Biotechnology

Research area:

We use computational and theoretical methods to investigate how structural and functional complexity arises in biological evolution. In particular we study genotype-phenotype maps on a large-scale, mostly in the context of self-assembly (protein complexes) and folding (RNA and proteins). We are interested in measuring robustness and evolvability of phenotypes, and in understanding the role of neutral evolution. On a more applied level we want to understand the structural impact of mutations, and the potential for predicting evolutionary outcomes from large-scale genotype-phenotype mapping. Such approaches could have important implications for the prediction of virus strains as well as tumour progression.

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Supervisor: Dr Graham Christie (gc301@cam.ac.uk)

Website: <https://www.ceb.cam.ac.uk/research/groups/rg-molecular-microbiology>

Department / UPI: Chemical Engineering and Biotechnology

Research area:

1. Molecular and structural microbiology, with a focus on spore forming bacteria i.e. how spores are formed and how they germinate.
2. Biotechnology applications involving bacterial spores i.e., spores as bio-catalyst, spores as vectors for drug delivery etc.
3. Sensors i.e., developing sensors for the detection of bacterial spores; using spores as biosensor components.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Prof Michele Vendruscolo (mv245@cam.ac.uk)

Website: <http://www-vendruscolo.ch.cam.ac.uk/>

Department / UPI: Chemistry

Research area:

We are investigating the role of protein liquid-liquid phase separation in neurodegenerative diseases. We would like to understand whether the dysregulation of the formation of membraneless organelles results in cytotoxic processes.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Jelle van den Ameele (jv361@cam.ac.uk)

Website: <https://www.mrc-mbu.cam.ac.uk/research-groups/van-den-ameele-group>

Department / UPI: Clinical Neurosciences

Research area:

The broad goal of our lab is to better understand tissue-specific presentation of mitochondrial and neurodegenerative diseases. We mainly study how mitochondrial dysfunction and mutations in the mitochondrial genome affect neural stem cell behaviour in *Drosophila* and mouse. The questions we address are:

- (1) how mitochondrial dysfunction affects normal and pathological cell fate decisions in the developing brain. We previously showed that neural stem cells in the brain rely heavily on mitochondria and now study how their metabolism interacts with cells in the stem cell niche.
- (2) how transcription of the nuclear genome is regulated when a cell is confronted with mitochondrial dysfunction. We employ and develop DamID-based in vivo chromatin profiling technology to study metabolism of chromatin modifications.

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(3) how mutations in the mitochondrial genome evolve over time, during brain development and aging. We use in situ hybridisation-based methods and single-cell CRISPR screening to identify novel regulators of mitochondrial DNA.

In order to study these questions in an in vivo context, in (stem) cells surrounded by their appropriate tissue environment, our primary model system is the fruit fly, *Drosophila melanogaster*. In addition, we actively translate our findings and the technology we develop into mammalian model systems, in particular the mouse embryonic cortex.

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Supervisor: Prof Patrick Chinnery (pfc25@cam.ac.uk)

Website: <https://www.mrc-mbu.cam.ac.uk/research-groups/chinnery-group>

Department / UPI: Clinical Neurosciences / MRC Mitochondrial Biology Unit

Research area:

We use high throughput single cell techniques to understand how mitochondria communicate with the cell nucleus during development and with ageing in health and disease.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Bakshi Bakshi (sb2330@cam.ac.uk)

Website: <https://www.bakshilab.net/>

Department / UPI: Engineering

Research area:

While antibiotic resistance is spreading at an alarming rate, the speed of antibiotic discovery has slowed down. To tackle the resistance of pathogens towards currently available antibiotics, we urgently need new antibiotics or alternative antimicrobials. We will offer projects in the following two research area to address this need Reverse engineering antibiotic production in bacteria and Benchmarking phage infection steps for engineering phage therapy.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Prof Máté Lengyel (m.lengyel@eng.cam.ac.uk)

Website: <http://lengyellab.org>

Department / UPI: Engineering

Research area:

The brain has a remarkable capacity to learn continuously about the environment and to use this knowledge flexibly to make predictions and guide its future decisions. Our group studies learning and memory from computational, algorithmic/representational and neurobiological viewpoints. We also maintain an active interest in the possible computational functions of neural oscillations, particularly those present in the hippocampus and neocortex.

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Computationally and algorithmically, we use ideas from Bayesian approaches to statistical inference and reinforcement learning to characterize the goals and mechanisms of learning in terms of normative principles and behavioral results. We also perform dynamical systems analyses of reduced biophysical models to understand the mapping of these mechanisms into cellular and network models.

We collaborate very closely with experimental neuroscience groups, doing in vitro intracellular recordings, multi-unit recordings in behaving animals, and human psychophysical and fMRI experiments.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Prof Timothy O'Leary (tso24@cam.ac.uk)

Website: <http://www.eng.cam.ac.uk/profiles/tso24>

Department / UPI: Engineering

Research area:

Our work studies how behaviours and actions in the immediate future are represented in the brain at the neural population level, how this representation evolves in time, and how the brain uses internal feedback to retain robust function. We collaborate with experimental groups in Harvard and Cambridge who measure activity in neural populations during behaviour, then use ideas from neural network theory to model the formation and evolution of cell assemblies in neural circuits. We then use the same basic ideas to make practical decoding algorithms that can 'read out' an animals' behavioural state in simple navigation tasks.

Using these decoders, we design and analyse brain-machine interface experiments in which animals control their movement in virtual environments using signals extracted directly from the cortex. Intriguingly, these cortical representations evolve over a timescale of days to weeks, even in fixed tasks, posing a challenge for robust decoding as well as for theories of learning, memory retention and the neural control of behaviour. A range of projects related to this research are available in data analysis, computational modelling, machine learning and theoretical neuroscience.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Felipe Karam Teixeira (fk319@cam.ac.uk)

Website: <https://www.gen.cam.ac.uk/directory/felipe-karam-teixeira>

Department / UPI: Genetics

Research area:

Mechanisms controlling and protecting germline development

Our lab studies the germline, the immortal cell lineage that provides the continuity of life. Using *Drosophila* as a model, we combine developmental, genetics, microscopy, and genomic analysis (small RNA-seq, RNA-seq, Ribo-seq) to build a systematic and unbiased understanding of diverse aspects governing germline biology in vivo. We are interested in dissecting the mechanisms protecting the germline genome against selfish DNA modules such as transposons (Teixeira et al,

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2017; Gebert et al, 2020), as well as in using germline stem cells as a model for understanding stem cell self-renewal, growth, and differentiation in vivo (Sanchez et al, 2016; Gui et al, 2021).

1) Mechanisms safeguarding genome integrity:

Accumulation of unrepaired damage can lead to infertility and tumour development. A major threat to the germline genome is provided by selfish DNA modules known as transposons – mobile units that aim to increase in copy number. We aim to understand, at the single-cell level, how germ cells assess, control, and respond to transposon activity during development. Current projects involve developmental, microscopy, single-cell and NGS approaches.

2) Regulation of stem cell differentiation:

Accumulating evidence indicate that regulation of protein synthesis and metabolism plays critical roles during development, tissue homeostasis, and tumorigenesis. Yet, the study of spatiotemporal regulation of cellular activities controlling stem cells has been mostly restricted to transcriptional-based mechanisms. Using genetics, microscopy, genomics, and metabolomics, we aim to build a refined molecular understanding of how protein synthesis and metabolism govern germline stem cell biology in vivo.

Supervisor: Prof Cahir O'Kane (c.okane@gen.cam.ac.uk)

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Department / UPI: Genetics

Research area:

Human axons can extend as long as 1m from the cell body and comprise a large fraction of cytoplasmic volume. This architecture requires a lot of engineering, and failure of this engineering can lead to axon degeneration or axonopathy conditions. One of these is hereditary spastic paraplegia (HSP; affecting primarily upper motor axons in the spinal cord). Many of the causative mutations for HSP affect proteins that model the shape of endoplasmic reticulum (ER), suggesting that integrity of ER is required for continued axon maintenance. ER is unique among organelles by its physical continuity, which makes it a channel for regional or long-distance communication, and earning it the term "a neuron within a neuron".

We use *Drosophila* to explore how ER is assembled across the enormous sub cellular distances of axons, and the role of axonal ER in neuronal function and physiology. Our approaches include *Drosophila* genetics and targeted expression, live confocal microscopy, fluorescence recovery after photobleaching, EM reconstruction, and collaborations on single molecule imaging. We see a continuous and remarkably dynamic ER network along the length of *Drosophila* motor axons. We have generated larvae mutant for a number of HSP gene, and find a number of phenotypes including partial loss of ER, and sporadic visible gaps in the ER network (Yalcin et al, eLife, 2017, <https://elifesciences.org/articles/23882>) and impaired ER continuity (atlastin, unpublished). One of our current interests is in understanding whether the exceptionally narrow diameter of ER tubules in axons could impair diffusion along the tubule lumen, and whether movement of molecules within the tubule is directional relative to the polarity of the axon. The availability of mutants that we have generated, that affect parameters such as tubule diameter, or continuity, provides us with a toolbox to explore these ideas.

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Understanding the consequences of axonal ER specialisms such as continuity or narrow diameter promises not only a better understanding of ER, but of how this fascinating and under-explored organelle contribute to the maintenance and survival of axons.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Ben Steventon (bjs57@cam.ac.uk)

Website: <https://steventonlab.wordpress.com/>

Department / UPI: Genetics

Research area:

The central question that motivates work in our lab is how cells can organise themselves into complex structures during early embryo development. We study the process of self-organisation in a range of experimental systems that include zebrafish and chick embryos, as well as embryonic organoids produced from mouse embryonic stem cells. Our lab uses a combination of experimental embryology and advanced quantitative imaging and molecular biology techniques. We have multiple collaborators from the physical sciences to generate mathematical models of the biology we study. This combination of approaches enables us to uncover novel principles of development.

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Supervisor: Dr Ritwick Sawarkar (rs2099@cam.ac.uk)

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<https://www.gen.cam.ac.uk/research-groups/research-groups/sawarkar-group>

Department / UPI: Genetics / MRC Toxicology Unit

Research area:

The role of biomolecular condensation in cell-size control

Biomolecular condensation is an emerging area in Cell Biology that underlies formation of membrane-less organelles performing specific tasks. Interdisciplinary methods are required to identify how components of condensates, such as RNA and proteins, form specific and functional assemblies. Proteins with unstructured domains or intrinsically disordered regions drive condensation, in most instances along with polymeric RNA. The formation and dissolution of most condensates in our cells is under strict signaling control - the dysregulation of which leads to human pathologies such as neurodegeneration.

Our lab recently discovered a novel Stress-Induced nuclear granule (SING) that regulates transcription under stressful conditions in human cells. Surprisingly, deletion of intrinsically disordered domains of proteins that drive SING leads to an increased cell size, linking biomolecular condensation to one of the most fundamental properties of a living cell - its size. How the loss of biomolecular condensation affects cell size is unknown. The project will identify the sequence of events that causally link condensation to cell size. We aim to uncover rules of life controlling the fundamental property of our cells, namely cell size.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

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Supervisor: Prof Julie Ahringer (ja219@cam.ac.uk)

Website: <https://www.ahringer.group.gurdon.cam.ac.uk/>

Department / UPI: Gurdon Institute

Research area:

1. Functional analysis of new heterochromatin regulators

The organization and packaging of the genome within the nucleus is crucial for its function. Constitutive heterochromatin is a poorly understood component of inactive chromatin that covers 20-50% of animal genomes. Heterochromatin loss disrupts chromatin organization, activates repetitive elements, alters gene expression, and causes genome instability, and heterochromatin dysfunction is associated with human disease, including cancer. Our understanding of how constitutive heterochromatin forms and functions is extremely limited, especially in animals.

We previously identified a network of *C. elegans* heterochromatin factors that genetically interact and co-localise with H3K9me2 at repetitive elements and other genomic regions (McMurchy et al, 2017). To identify and functionally dissect novel components of constitutive heterochromatin, we built a comprehensive network through RNAi genetic interaction screening in seven heterochromatin mutant strains. The screens revealed 289 enhancers including components of ribosome biogenesis, ubiquitylation, SUMOylation, RNA splicing and chromatin remodelling pathways, and 86 suppressors, many of which are associated with active transcription. Most hits have a human orthologue and interact with more than one mutant strain, highlighting the conservation and high interconnectivity of the network.

This project will characterise novel genes identified the screen to understand their roles in heterochromatin formation and function. This will involve diverse techniques including CRISPR, super-resolution microscopy, high-throughput sequencing assays, and computational analyses

2. There are also projects that use single-cell analyses to investigate the transcriptional and chromatin regulatory events underlying developmental decisions.

Supervisor: Dr Iva Tchasovnikarova (it257@cam.ac.uk)

Website: <https://www.tchasovnikarova-lab.org/>

Department / UPI: Gurdon Institute / Biochemistry

Research area:

Epigenetic modifications of DNA, RNA and histones are important regulators of all DNA-templated processes, including transcription, DNA repair and replication. Disruption of these epigenetic pathways is therefore commonly observed in a variety of human conditions, such as developmental disorders and cancer. The reversible nature of these disruptions has made epigenetic regulators attractive targets for therapeutic manipulation. However, a detailed understanding of the fundamental biology underlying these epigenetic mechanisms is still needed to delineate the optimal targets for future therapeutic manipulation.

The overarching goal of the Tchasovnikarova lab is to apply novel genetic approaches to mechanistically dissect epigenetic pathways. We aim to (1) understand the molecular mechanisms utilised by chromatin regulators to exert their function in healthy human cells, and (2) examine how these mechanisms are altered in human disorders. We take advantage of existing high-

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throughput genetic technologies, such as CRISPR/Cas9 genetic screens, to discover novel factors involved in chromatin pathways, which we then characterise using a combination of genetic and biochemical approaches. We are also particularly interested in developing novel genetic methods to study epigenetic pathways in human cells.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Sumru Bayin (nsb44@cam.ac.uk)

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

Department / UPI: Gurdon Institute / Physiology, Development and Neuroscience

Research area:

There is an unmet need for repair following injury in humans, particularly in the brain where endogenous stem cell activity is minimal. An understanding of neural progenitor diversity and flexibility in their fate choices is crucial for understanding how complex organs like the brain are generated or undergo repair. The neonatal mouse cerebellum is a powerful model system to uncover regenerative responses due to its high regenerative potential.

We have previously shown that the cerebellum can recover from the loss of at least two types of neurons via distinct regenerative mechanisms (Wojcinski, 2017; Bayin, 2018; Bayin, 2021). In one case, a subpopulation of the nestin-expressing progenitors (NEPs) that normally generate astroglia undergoes adaptive reprogramming and replenishes the lost neurons. However, the molecular and cellular mechanisms that regulate neonatal cerebellar development and adaptive reprogramming of NEPs upon injury are unknown.

Interestingly, the regenerative potential of the cerebellum decreases once development ends, despite the presence of NEP-like cells in the adult cerebellum that respond to cerebellar injury by increasing their numbers. However, neuron production is blocked. We hypothesize that the lack of regeneration is due to a lack of pro-regenerative developmental signals in the adult brain in addition to epigenetic silencing of stem cell differentiation programs and inhibitory cellular mechanisms as development is completed.

Our lab is interested in answering two overarching questions:

- 1) What are the cellular and molecular mechanisms that enable regeneration in the neonates and inhibit in the adult?
- 2) Can we facilitate regeneration in the brain?

Supervisor: Dr Emma Rawlins (elr21@cam.ac.uk)

Website: <https://www.gurdon.cam.ac.uk/people/emma-rawlins/>

Department / UPI: Gurdon Institute / Physiology, Development and Neuroscience

Research area:

The developmental cues which regulate lung branching, epithelial and mesenchymal differentiation and maturation have been investigated in the mouse lung. How many of the morphogenetic events and signals are conserved in human lung embryonic development? Can we develop improved models of in vitro human lung development that will facilitate drug screening

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and disease modelling? And gain insights into lung regeneration? Can we learn from the effects of human genetic diversity to understand lung development and disease? The Rawlins lab uses human lung organoid models, CRISPR tools and imaging and single cell approaches to answer fundamental questions about cell fate decisions and coordinated morphogenesis to improve our understanding of human lung development.

Nikolić MZ, Caritg O, Jeng Q, Johnson J, Sun D, Howell, KJ, Brady JL, Laresgoiti U, Allen G, Butler R, Zilbauer M, Giangreco A, Rawlins EL (2017) Human embryonic lung epithelial tips are multipotent progenitors that can be expanded in vitro as long-term self-renewing organoids. *Elife*. 2017 Jun 30;6. pii: e26575. doi: 10.7554/eLife.26575. PMCID: PMC5555721.

Sun D, Evans LD, Perrone F, Sokleva V, Lim K, Rezakhani S, Lutolf M, Zilbauer M, Rawlins EL (2021) A functional genetic toolbox for human tissue-derived organoids. *eLife* DOI: 10.7554/eLife.67886

Sun D, Batlle OL, van den Aamele J, Thomas C, He P, Lim K, Tang W, Xu C, Meyer KB, Teichmann SA, Marioni J, Jackson SP, Brand AH, Rawlins EL. An organoid CRISPRi screen revealed that SOX9 primes human fetal lung tip progenitors to receive WNT and RTK signals. *EMBOJ*
<https://doi.org/10.15252/emj.2022111338>

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Prof Giles Yeo (gshy2@cam.ac.uk)

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

Department / UPI: Institute of Metabolic Science / Clinical Biochemistry

Research area:

We aim to identify new molecules and pathways that play a role in the brain control of energy homeostasis, and thus reveal new potential therapeutic targets to tackle obesity. One of the approaches we have taken is to map the normal weight human hypothalamic functional architecture underlying appetitive control using both single nucleus RNA sequencing (NucSeq) and single molecule fluorescent in situ hybridization (smFISH).

We are now embarking on extending these studies to the overweight and underweight human hypothalamus.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Prof Tim Dalgleish (tim.dalgleish@mrc-cbu.cam.ac.uk)

Website: <http://www.mrc-cbu.cam.ac.uk/people/tim.dalgleish/>

Department / UPI: MRC Cognition and Brain Sciences Unit

Research area:

A promising approach in management of anxiety disorders is self-distancing . In this procedure, the person imagines a scene that induces anxiety, then increasingly “pulls back” to imagine themselves further and further away. This kind of change in an imagined spatial context may depend on the brain’s default mode network (DMN), and more widely, we have evidence that the DMN is involved in large changes of mental focus.

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Based on supportive pilot data, we should like to test the role of broad DMN involvement in escape from a mental focus on threatening mental contents.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Prof Rik Henson (rik.henson@mrc-cbu.cam.ac.uk)

Website: <http://www.mrc-cbu.cam.ac.uk/people/rik.henson/personal/>

Department / UPI: MRC Cognition and Brain Sciences Unit

Research area:

Cognitive neuroscience of human long-term memory, ageing and dementia.

Memory problems are some of the first complaints as we grow older, and can be particularly debilitating following brain injury or neurodegenerative disease. This programme investigates the cognitive neuroscience of human long-term memory and its disorders using novel psychological tasks, combined with neuroimaging and neuropsychological assessment of patients, in addition to computational modelling, multivariate analyses of large cohorts and advanced methods development.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Sarah Aitken (sa696@cam.ac.uk)

Website: <https://www.mrc-tox.cam.ac.uk/research/research-groups/aitken-group>

Department / UPI: MRC Toxicology Unit

Research area:

The Aitken lab at the MRC Toxicology Unit is a diverse team of researchers spanning multiple scientific disciplines, including cancer biology, genomics, digital pathology, mathematical modelling, and bioinformatics.

The overall aim of our interdisciplinary research group is to investigate mechanisms of cellular damage, and to understand their consequences for human health and disease. We use experimental and computational approaches to study genomic, cellular, and tissue-level responses to injury, and aim to identify molecular mechanisms which are dysregulated in disease, including cancer.

Potential projects include:

- Molecular consequences of DNA damage
- Digital pathology and image analysis
- Use of 2D/3D in vitro models, and in vivo and human tissue samples

The candidate will gain experience with molecular biology, genomics, and computational approaches. Candidates are expected to have excellent communication, organisational, and problem-solving skills, as well as creativity, curiosity, and aptitude to work both independently and contribute intellectually to other projects developed in the laboratory.

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Relevant publications:

1. Anderson, et al ... SJ Aitken*, MS Taylor*. Strand-resolved mutagenicity of DNA damage and repair. bioRxiv. 2022; 2022.06.10.495644.
<https://www.biorxiv.org/content/10.1101/2022.06.10.495644v1>
2. SWK Ng, et al. Convergent somatic mutations in metabolism genes in chronic liver disease. Nature. 2021;598:473-478. <https://doi.org/10.1038/s41586-021-03974-6>
3. SJ Aitken, et al. Pervasive lesion segregation shapes cancer genome evolution. Nature. 2020;583:265-270. <https://doi.org/10.1038/s41586-020-2435-1>
4. SF Brunner, et al. Somatic mutations and clonal dynamics in healthy and cirrhotic human liver. Nature. 2019;574:538-542. <https://doi.org/10.1038/s41586-019-1670-9>
5. SJ Aitken**, X Ibarra-Sor-ia**, et al. CTCF maintains regulatory homeostasis of cancer pathways. Genome Biology. 2018;19:106. <https://doi.org/10.1186/s13059-018-1484-3>

*Corresponding author. **Equal contribution.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Prof Anne Willis (aew80@cam.ac.uk)

Website: <https://www.mrc-tox.cam.ac.uk/staff/anne-willis-obe>

Department / UPI: MRC Toxicology Unit

Research area:

Post-transcriptional control of gene expression in response to environmental stress caused by exposure to external agents, including those associated with climate change, with a focus on the role of RNA-binding proteins (both canonical eukaryotic initiation and elongation factors, and non-canonical RNA binding proteins that have "moonlighting" functions) regulatory RNA motifs and tRNAs.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Prof Francesco Colucci (fc287@cam.ac.uk)

Website: <https://www.obgyn.cam.ac.uk/staff/senior-staff/dr-francesco-colucci/>

Department / UPI: Obstetrics and Gynaecology

Research area:

Maternal Immune system and offspring health

Every day ~800 women die of pregnancy complications. According to the World Health Organisation, 10% of the global burden of disease is due to perinatal morbidity of mother and baby. This means that what happens in this critical time has far reaching ramifications on the health of both women and their children. The developmental origin of health and disease is indeed an established concept and birth weight is a predictor of cardiovascular and metabolic disease. Prenatal exposure to maternal immune activation predisposes to autism spectrum disorders and shapes offspring immunity. Maternal immunity also underlies the hypertensive disorder of pregnancy pre-eclampsia. Prenatal maternal infections shape offspring immunity. A better understanding of how the immune system contributes to these conditions could help to

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address them earlier and improve the health of women and their offspring. This is the ultimate aim of our research.

Tissue lymphocytes are integral to health and disease of every tissue. We focus on tissue lymphocytes in the womb, mainly uterine NK (uNK) cells, which orchestrate key vascular adaptations in the uterus that facilitate placentation and foetal growth. We have shown a pathway including the lymphocyte receptor NKG2A is key for optimal uterine lymphocyte functions in mice and in women it protects from pre-eclampsia. The complex immunological code of pregnancy has just started to be deciphered [Colucci, Science 2019]. A better understanding may inform new strategies to improve pregnancy outcomes and offspring health.

Supervisor: Dr Miguel Constanca (jmasmc2@cam.ac.uk)

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

Department / UPI: Obstetrics and Gynaecology / Institute of Metabolic Science

Research area:

We work on the research area of Developmental Epigenetics. Epigenetics refers to the study of heritable changes in gene expression that are dictated by 'chemical' tags that are added to the DNA and chromatin proteins as part of normal development. Epigenetics exerts major effects on cellular processes, from cell lineage specification and stem cell biology to cancer and aging. We are particularly interested in the study of epigenetic mechanisms that control growth and metabolic processes, and the role of epigenetics in coordinating the genomic responses to environmental exposures across the life course, including transgenerational effects.

Specific ongoing projects include investigations on: a) inter-organ communication during pregnancy (mother-placenta-fetal organs) as gatekeepers for optimal growth and metabolic health in later life; b) molecular mechanisms of epigenetic programming in early embryos and placenta, including the transmission of epigenetic information from gametes to offspring that may set-up programmed changes during development; c) the impact of epigenetic mechanisms on key metabolic organs and how they can cause metabolic disease.

To address our research questions, we use integrative developmental and physiology (epi)genetic approaches, which include environmental exposures (eg. nutrition) and omics platforms, that are applied to cellular models (human and mouse) and in vivo genetically engineered mouse models.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Andrew Blagborough (amb283@cam.ac.uk)

Website: <https://www.path.cam.ac.uk/directory/andrew-blagborough>

Department / UPI: Pathology

Research area:

Research activities within my lab involve performing research on the sexual stages of Plasmodium, with emphasis on gamete cell biology, fertilisation and the blockade of malarial transmission in the lab and the field. We have a particular interest in proteins expressed in the male and female plasmodial gametes, followed by examination by genetic/protein biochemical methods,

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translation to novel transmission blocking interventions (TBIs) candidates. Research can broadly be divided into three individual but complimentary streams, namely:

- 1) Fundamental characterisation of the cell biology of the sexual stages of Plasmodium, and biochemical examination of the processes of transmission.
- 2) Effective delivery of anti-malarial transmission blocking agents to induce maximal anti-malarial efficacy
- 3) Enhanced, field-relevant assessment of TBI efficacy.

Projects on any (or multiple) of these subjects can be offered after conversation with individual applicants to identify specific interests.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Michael Boemo (mb915@cam.ac.uk)

Website: <https://www.boemogroup.org/>

Department / UPI: Pathology

Research area:

The timely and accurate replication of DNA is critical for cell viability, but how DNA replication forks navigate a wide array of obstacles (including actively transcribed genes, DNA lesions, and repetitive sequences) to copy the genome is an important unsolved problem. This problem has remained elusive in part because of a lack of appropriate methods: Existing methods either measure how a population of cells replicate, which “averages out” rare but important behaviour, or they work with single-molecule resolution but have low throughput.

In a field comprised mainly of wet lab scientists, the Boemo Group is a computational biology laboratory specialising in software development, artificial intelligence, and mathematical modelling which gives us a unique approach and perspective.

A key area of our research is developing artificial intelligence software that measures the movement of replication forks from Oxford Nanopore sequencing data. This method provides a high-throughput, inexpensive, accurate, and automated way to measure replication fork movement.

We also compute at scale to develop whole-genome simulations of how DNA replication takes place in various organisms, including in human cells. Our research is highly collaborative with different laboratories around the world, and it is the ideal supportive environment in which to learn (or improve upon) software development, machine learning, and the analysis of big datasets while answering some of the most fundamental questions in genome stability.

BBSRC DTP secondary strategic theme: Transformative technologies

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Supervisor: Prof Ian Brierley (ib103@cam.ac.uk)

Website: <https://www.path.cam.ac.uk/directory/ian-brierley>

Department / UPI: Pathology

Research area:

My laboratory studies the regulation of gene expression in RNA viruses, focusing on the role of RNA structures and of RNA-protein complexes in the regulation of viral protein synthesis. Much of our recent work has been on coronaviruses and retroviruses. The research spans a fairly broad area, from RNA secondary structure analysis through to high resolution structure probing of protein-RNA complexes and ribosomes. We also are interested in looking at these translational control processes (like ribosome frameshifting and stop codon readthrough) in vitro and in infected cells, through ribosome profiling.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Betty Chung (bcy23@cam.ac.uk)

Website: <https://www.path.cam.ac.uk/research/microbiology-and-parasitology-division/chung-group>

Department / UPI: Pathology

Research area:

My group aims to understand how living organisms utilise novel protein synthesis regulatory mechanisms to counteract external stresses, especially during host:pathogen interaction (animal) and in response to temperature fluctuation (plants). Therefore we can offer a wide-range of projects (wet, dry or combined), whether it is in thermo-regulatory of protein synthesis in plants, non-canonical translational mechanisms in pathogens (viruses, bacteria and the unicellular parasite toxoplasma) or molecular immunology (i.e. molecular mechanisms utilised by macrophages to counteract infection). All within the remit of BBSRC.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Paolo D'Avino (ppd21@cam.ac.uk)

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

Department / UPI: Pathology

Research area:

Cell division is one of the most fundamental biological processes. It is essential for growth, development and reproduction in many organisms, including humans. Cell division faithfully partitions the genomic information between the two daughter cells and errors in this process have been implicated in many human diseases, including cancer. Thus, a thorough understanding of the regulation and mechanics of mitosis may lead to the development of novel anti-cancer therapies. As the genome is compacted into chromosomes during mitosis, cell division events are regulated mainly through reversible post-translational modifications (PTMs), such as ubiquitylation and phosphorylation. My research interests focus on the study of the mechanisms

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and signalling pathways that govern cell division in eukaryotic cells and their de-regulation in cancer cells, with particular emphasis on how kinases and phosphatases regulate its last phase, cytokinesis.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Julia Kenyon (jck33@cam.ac.uk)

Website: <https://www.path.cam.ac.uk/directory/dr-julia-kenyon>

Department / UPI: Pathology

Research area:

The roles of RNA structures in controlling viral lifecycles

RNA viruses pack as many functions as possible into small genomes, and have a variety of strategies to do this, such as using overlapping reading frames. As RNA itself can have structural and also catalytic roles, it is likely that, in addition to proteins, RNA viruses also use RNA structures to perform essential functions during the viral lifecycle. There is evidence for this in multiple RNA viruses (doi: 10.3390/v13112130). Until recently, however, it has not been possible to study in detail the individual RNA structures formed within a mixture of genomic and subgenomic viral RNAs.

Our lab studies the conserved RNA structures and structural interactions of various viruses of veterinary and zoonotic importance, including flaviviruses and lentiviruses. Flaviviruses include the important pathogens Zika, dengue and West Nile viruses. Lentiviruses include FIV (the feline equivalent of HIV). We study individual RNA structures and RNA-protein interactions using cutting-edge in vitro structural techniques we have developed: in-gel SHAPE (selective 2'OH acylation analysed by primer extension) and XL-SHAPE.

We also plan to use Nanopore sequencing technology combined with SHAPE to study the RNA structures formed by viruses inside cells. Alongside these structural experiments, we study how well the viruses can replicate when we mutate conserved RNA structures- and which of their lifecycle stages are affected.

Our aim is to understand the importance of RNA structures to viral lifecycles, and to identify potential drug targets for the development of antiviral drugs.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Prof Heike Laman (hl316@cam.ac.uk)

Website: <https://www.laman-lab.path.cam.ac.uk/>

Department / UPI: Pathology

Research area:

Our laboratory works on ubiquitin ligases, which are enzymes that post-translationally modify other proteins causing a change in stability, function or localisation. This process is important in fundamental cellular processes, like cell cycle and differentiation, and also in the response to infection and other stress responses. We study their function in normal cellular differentiation in a variety of cell types, ranging from blood and immune cells to spermatocytes and neurons, and also how their deregulation causes diseases like Parkinson's disease and cancer. The knowledge

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surrounding the selectivity of ubiquitin ligases in promoting the proteasomal-mediated destruction of their substrates is currently being exploited to create new molecules capable of targeted protein degradation. Our laboratory is working on ways to design novel biologics that can eliminate proteins by design.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Valeria Lulla (vl284@cam.ac.uk)

Website: <https://www.path.cam.ac.uk/directory/dr-valeria-lulla>

Department / UPI: Pathology

Research area:

Enteric viruses are a major cause of mortality and morbidity in the young, elderly, and immunocompromised. Understanding the dynamics of molecular mechanisms during RNA replication advances the development of accurate models and therapeutic approaches. The research theme of our lab rotates around gut-specific mechanisms of enteric virus infection. We use a range of molecular virology techniques and human gut epithelial organoid systems to understand the virus-host interplay and the molecular basis of virus tropism and virulence.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr David Bulmer (dcb53@cam.ac.uk)

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

Department / UPI: Pharmacology

Research area:

Mechanosensitivity is essential to the detection of changes in the luminal environment within the bowel and the regulation of its autonomic function. Recent work from my group implicates mechanosensitive GPCRs in these processes and the aim of this project will be to explore the role of these different receptors in the transduction of visceral pain by nociceptors using a range of electrophysiological and imaging approaches.

Supervisor: Prof Laura Itzhaki (lsi10@cam.ac.uk)

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

Department / UPI: Pharmacology

Research area:

The major focus of my group's research is a class of proteins with very distinctive architecture, known as tandem-repeat proteins, that are frequently deregulated in human diseases and whose simple modular architecture makes them uniquely amenable to the dissection of their biophysical properties as well as their rational redesign. Our research is at the interface of biology and chemistry; we also collaborate with computational groups and synthetic chemistry groups in Cambridge, and therefore students will be able to learn a broad range of techniques and approaches, including molecular biology, protein engineering, recombinant protein expression

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and purification, biochemistry and biophysical analysis, single-molecule techniques, cell biology and medicinal chemistry.

Keywords: protein engineering, protein design, targeted protein degradation, cancer, biotherapeutics

Selected references:

1. Burbidge et al. (2021) Nanobodies restore stability to cancer-associated mutants of tumor suppressor protein p16INK4a. <https://doi.org/10.1101/2021.07.01.450670>
2. Diamante et al. (2021) Engineering mono- and multi-valent inhibitors on a modular scaffold. Chemical Science. 10.1039/d0sc03175e
3. Xu et al. (2017) Macrocyclized extended peptides: Inhibiting the substrate-recognition domain of tankyrase. JACS. 10.1021/jacs.6b10234
4. Synakewicz et al. (2022) Consensus tetratricopeptide repeat proteins are complex superhelical nanosprings. ACS Nano. <https://doi.org/10.1021/acsnano.1c09162>

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Janet Kumita (jrk38@cam.ac.uk)

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

Department / UPI: Pharmacology

Research area:

Linking protein self-assembly with biological function and disease:

We use a multidisciplinary approach, including biophysics, cell biology and protein engineering, to study the molecular processes underlying protein self-assembly. Amyloid fibril formation is associated with a wide range of human disorders including Alzheimer's and Parkinson's diseases and motor neurone disease. Due to the prevalence of these disorders, we are studying the structural attributes of species formed during amyloid formation in order to increase our understanding of the mechanisms by which disease-associated proteins behave aberrantly. This will enable us to find ways to inhibit or neutralise the formation of toxic species that lead to cellular dysfunction.

But protein self-association is not only linked with disease, in fact Nature has an incredibly clever way of rapidly assembling and dissipating biomolecules for cellular functions. It does this by forming membraneless droplets involved in cellular processes such as signalling, cellular stress and protein degradation. We are exploring the use of engineered biomolecular condensates to gain mechanistic insight into how Nature utilizes phase-separation to facilitate protein degradation via autophagy. We are using this information to create precision autophagy-targeting therapeutics to bind neurodegenerative disease-causing proteins and facilitate their degradation.

Interestingly, some biomolecular condensates exist in a fine balance of function versus pathology and are emerging as key targets in amyloid disease. Given that amyloid and biomolecular condensates are not mutually exclusive, we are also exploring how and why protein recruitment into biomolecular condensates leads to formation of mature amyloid fibrils in an effort to develop therapeutic interventions.

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Supervisor: Dr Catherine Lindon (acl34@cam.ac.uk)

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

Department / UPI: Pharmacology

Research area:

We study ubiquitin-mediated protein degradation, a process that is critical in many cellular pathways and therefore key to understanding the rules of life. Our research seeks to decipher pathways that regulate ubiquitination, and to exploit them for therapeutic purposes. We offer projects that explore the role of ubiquitination in regulating the cell cycle, focusing on the regulation and function of a ubiquitin ligase complex called the Anaphase-Promoting Complex (APC/C) and one of its targets, the cell cycle kinase Aurora A.

In recent years we have also started to develop tools that aim to harness ubiquitination pathways, via the new therapeutic modality of targeted protein degradation (TPD, exemplified by 'PROTAC' technology), and are keen to develop new projects that investigate the molecular mode of action of TPD tools.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Maria Marti Solano (mm2402@cam.ac.uk)

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

Department / UPI: Pharmacology

Research area:

G protein coupled receptors (GPCRs) are an extensive family of proteins found across human cells and tissues. Individual family members detect different signals reaching the cell membrane (such as light, taste, neurotransmitters or hormones) and convey their messages to signalling partners that activate a variety of physiological responses inside our cells.

Importantly, due to their capacity to regulate a wide variety of cell responses, GPCRs have become the most common drug target class. And still, some fundamental questions on GPCR function remain unresolved:

- How do different signals reaching the same receptor promote specific intracellular responses?
- Why does receptor activation by a particular signal or drug often produce contrasting responses when we compare different cells or tissues?
- How does our age, sex or genomic background determine the way we respond to GPCR-based therapies?

To address these questions, we apply a range of computational biology techniques to integrate structural, multi-omics, network biology, cell signalling, and pharmacogenomics data. We also collaborate extensively with molecular pharmacologists, biophysicists, computational chemists, and clinicians within the UK and abroad.

By exploring receptor signalling from a systems pharmacology perspective, we not only intend to boost our understanding of receptor pathway physiology and its influence on cell function, but also to suggest new advanced models for the study of GPCRs in health and disease, guide the

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selection of pathway specific GPCR drugs with improved efficacy and safety profiles, and ensure that we use the therapeutics that are currently in the clinic in a more personalised manner.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Paul Miller (pm676@cam.ac.uk)

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

Department / UPI: Pharmacology

Research area:

My research is aimed at understanding and developing novel antibody modulators with unique pharmacological properties against important ion channel targets such as g-aminobutyric acid Type-A (GABAA) receptors, glycine receptors and sodium channels. Linked to this, we are also studying and engineering natural protein toxins into useful pharmacological tools. We use electrophysiological, biochemical, protein engineering and structural biology approaches for a holistic overview of modes of action. Whilst small molecules have proven invaluable as pharmacological tools in basic research, selectivity between ion channel subtypes is often limited which hinders our ability to understand subtype contributions to biological function.

Protein modulators offer improved specificity, and with it selectivity, and so the opportunity to answer new questions in biological research, both in terms of modulating function and also in terms of direct receptor tracking (e.g. through fluorescent labelling).

To expand this research we are also studying ways to traffic proteins from the bloodstream into the central nervous system to widen their utility as research tools to the study of whole animal behaviour models. Advances in this area have obvious translational implications for the development of novel biologic therapeutics, which could treat conditions such as anxiety, epilepsy and chronic pain.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Prof Ewan Smith (es336@cam.ac.uk)

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

Department / UPI: Pharmacology

Research area:

Our research focuses on two main areas:

- 1) Understanding how the sensory nervous functions with regard to nociception, i.e. which receptors and ion channel are expressed by different sensory neurone subsets and how is their function modulated by interaction with non-neuronal cells?
- 2) Understanding healthy ageing using the naked mole-rat, an organism that lives for 35+ years, but shows limited signs of ageing throughout life: what features of naked mole-rat neurobiology support a healthy ageing brain?

We use a variety of techniques, from electrophysiology through to histology, molecular biology and animal behaviour.

Research Areas within Understanding the Rules of Life / AY 2023 -2024

Supervisor: Dr Walid Khaled (wtk22@cam.ac.uk)

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

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

Research area:

Our research is driven by the fact that we still have little understanding of how hundreds of identified genetic aberrations impact tissue homeostasis leading to tumour development. While hugely significant, work to date on large-scale sequencing efforts and a handful of well-characterised mutations has barely scratched the surface and the early stages of precancer tumour development remains poorly understood. Yet, it has a huge potential to improve success rates of early detection, prevention and treatment of cancer.

Recent sequencing studies of normal tissue suggest that acquiring putative oncogenic drivers is not sufficient to initiate tumour development. This points towards elements, such as the cell of origin, differentiation state and the microenvironment, all playing a key role in mediating tumour initiation.

Our team works on defining the early cellular and molecular events that drive tumour initiation and development. In particular, we focus on how the cell of origin affects the differentiation trajectory of nascent tumour cells and dictates changes in the microenvironment thus enabling tumour growth and immune evasion.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Diana Fusco (df390@cam.ac.uk)

Website: <https://dianafusco.wixsite.com/fuscolab>

Department / UPI: Physics

Research area:

Our lab combines experiments and modelling to understand how interactions at the single-cell level translate into collective phenomena at the population scale and, reciprocally, how natural selection at the population scale constrains the evolution of these interactions. We predominantly focus on two model laboratory systems that enable tunable and reproducible experiments: bacteriophage-bacteria ecosystems and bacterial biofilms.

In the former, we aim to elucidate the evolutionary forces that shape virus-host interactions as a function of host environment, in particular in conditions where the bacterial host population is highly heterogeneous in space and time. Our goal is to better understand how the viral and bacterial population co-evolve in scenarios that are far from ideal and more representative of natural environments in the wild, including our body, so to provide rational guidelines to design targeted phage therapies.

In the latter, we are fascinated by the adaptability and robustness that biofilms display in highly unpredictable and harsh environment. Our goal is to understand how cell to cell phenotypic variability allows this population made of unicellular organisms to respond collectively to an environmental challenge and unveil how these coordination mechanisms have evolved.

Research Areas within Understanding the Rules of Life / AY 2023 -2024

To address these questions, we use an iterative approach that uses experiments to generate mechanistic hypotheses that are tested via modelling, and models to provide predictions that challenge our understanding and can be experimentally verified.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Riccardo Beltramo (ric.beltramo@gmail.com)

Website: <https://www.beltramolab.org/>

Department / UPI: Physiology, Development and Neuroscience

Research area:

Research area: Aversive information processing across the visual and navigational systems.

When confronted with potential dangers, animals display adaptive fear-induced reactions that promote survival. Some of these behaviours are innate, such as escaping upon detection of distant predators; others are learned, such as freezing in response to stimuli previously associated with aversive outcomes.

Environmental cues are often ambiguous and do not always univocally signal a clear danger. Therefore, correctly identifying and discriminating potentially hazardous stimuli is crucial for the survival of organisms. Our lab studies how aversive stimuli are perceived and processed across the visual and navigational systems to generate avoidance behaviours.

Using the mouse visual and navigational systems as a model, we study how changes in the neural representations of dangerous and safe visual stimuli affect the animals' ability to discriminate them. Through chronic calcium imaging, large-scale electrophysiology, optogenetics and innovative behavioural tasks, we dissect the neural circuits that assign emotional value to sensory information, and the network that weights potential threats against previously learned associations.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Prof Albert Cardona (ac2040@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/users/dr-cardona>

Department / UPI: Physiology, Development and Neuroscience

Research area:

Whole-brain connectomics: mapping neural circuits at nanometre resolution with volume electron microscopy using machine learning, analyzing neural circuits with graph theoretic approaches, and probing neural circuit function with computational modeling. The species of choice include to date *Drosophila*, pygmy squids, *Tribolium* beetles, and small lizards.

BBSRC DTP secondary strategic theme: Understanding the rules of life

Research Areas within Understanding the Rules of Life / AY 2023 -2024

Supervisor: Prof William Colledge (whc23@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/bill-colledge>

Department / UPI: Physiology, Development and Neuroscience

Research area:

We are interested on the neuroendocrine regulation of the mammalian reproductive axis using transgenic mice as a model. In particular, we are studying the molecular and electrophysiological profiles of Kiss1 neurons in the hypothalamus which regulate the reproductive axis and how these change during puberty.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Elisa Galliano (eg542@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/elisa-galliano>

Department / UPI: Physiology, Development and Neuroscience

Research area:

Neuroscience

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Courtney Hanna (cwh36@cam.ac.uk)

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

Department / UPI: Physiology, Development and Neuroscience

Research area:

The placenta forms the maternal-foetal interface in pregnancy, controlling nutrient and waste exchange, hormone production and immunotolerance. Impaired placental function is linked to poor pregnancy outcomes. Yet, early regulators of placental development that lead to a functional placenta and healthy pregnancy are poorly understood.

After implantation, embryonic stem cells undergo a process of 'priming,' a necessary transition that allows these pluripotent cells to be receptive to signalling for differentiation into all of the cell types of the body. A hallmark of this priming event is the deposition of epigenetic marks throughout the genome. Failure to prime the embryonic genome results in developmental defects and embryonic lethality. The extent to which epigenetic programming in trophoblast stem cells is essential for subsequent placental development remains largely uncharacterised.

The aim of a PhD project in the Hanna lab would be to characterise and test the functional importance of epigenetic marks in placental cells, linking impaired priming to defects in placentation and consequences on foetal growth and development. This research project will train students in mouse genetics, embryology, histological analysis, multi-omics, and single-cell sequencing approaches.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Research Areas within Understanding the Rules of Life / AY 2023 -2024

Supervisor: Prof Allan Herbison (ae36@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/allan-herbison>

Department / UPI: Physiology, Development and Neuroscience

Research area:

Neural control of the central pattern generator driving fertility

The student will learn cutting-edge cellular and whole animal neuroscience approaches in genetic mouse models including GCaMP calcium imaging in vivo and in acute brain slices, chemogenetics, in vivo CRISPR-mediated gene knockdown and immunohistochemistry. These tools will be used to discover how brainstem serotonin neurons modulate the activity of the hypothalamic pulse generator that drives pulsatile reproductive hormone secretion.

The understanding of how the brain controls pulsatile hormone secretion is fundamental to unlocking treatments aimed at the beneficial regulation of fertility in the clinic.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Julija Krupic (jk727@cam.ac.uk)

Website: www.krupiclab.com

Department / UPI: Physiology, Development and Neuroscience

Research area:

Research Area: Neuroscience

Understanding the hippocampal cognitive map

Our research aims to understand how neuronal representations of the hippocampal cognitive map are formed and used for navigation and memory. The hippocampus plays a key role in spatial memory, learning and navigation and is one of the first areas affected by Alzheimer's disease.

We use state-of-the-art techniques such as in vivo two-photon imaging and neurophysiological recordings (e.g. Neuropixels) to record from and manipulate multiple neurons as an animal navigates in virtual and real enclosures.

We also use in vivo single-cell monosynaptic tracing techniques to probe the functional anatomy of hippocampal-entorhinal circuitries. The student will be able to join research projects asking how hippocampal neurons integrate multi-modal stimuli to form spatial representations; what is the relation between medial entorhinal and CA1-CA3 cognitive maps; the role of astrocytes in supporting place cell remapping; and how CA1 place cell activity may directly control an animal's environment in virtual reality.

BBSRC DTP secondary strategic theme: Transformative technologies

Research Areas within Understanding the Rules of Life / AY 2023 -2024

Supervisor: Prof Kathy Niakan (kkn21@cam.ac.uk)

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

Department / UPI: Physiology, Development and Neuroscience

Research area:

During preimplantation development human embryos are comprised of pluripotent embryonic cells, which eventually form the fetus, and extra-embryonic cells, which contribute to the placenta and yolk sac. The aim of research in our laboratory is to provide molecular insights into how early human development is controlled. The mechanisms that regulate early cell lineage decisions in human development remain poorly understood, despite their fundamental biological importance.

Our laboratory seeks to develop and utilise genetic perturbation, advanced imaging and single-cell multi-omics methods to dissect the function of genes during human embryogenesis. We are especially interested to determine the evolutionarily conserved and divergent mechanisms that regulate lineage specification across mammalian species. These methods will enable us to uncover the mechanisms that regulate the first and second lineage specification events in human embryos.

The knowledge gained from these studies will provide fundamental insights into human biology and facilitate the development of conditions for the further refinement of implantation models and the establishment of novel human stem cells and integrated stem cell-based models of human development. Altogether, we seek to make significant advances in our understanding of the molecular programs that shape early human embryogenesis. The methods we develop will also be applicable to other challenging to study primary human cellular contexts or in species that are historically challenging to study to understand evolutionarily conserved and divergent mechanisms.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Prof Ole Paulsen (op210@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/ole-paulsen>

Department / UPI: Physiology, Development and Neuroscience

Research area:

My research group is interested in the relations between network oscillations and synaptic plasticity in the context of hippocampus-dependent memory. We have primarily been focusing on reward-based spatial memory in the mouse. Using a combination of whole-cell recording, multi electrode recording, calcium imaging and optogenetics, both in vitro and in vivo, we aim to understand the rules that govern memory formation, consolidation and retrieval. We are also interested in the translational potential of our basic insights, and for this we use human stem cell-derived brain organoids from patients with neurodevelopmental and neurodegenerative disorders.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Research Areas within Understanding the Rules of Life / AY 2023 -2024

Supervisor: Dr Jasper Poort (jp816@cam.ac.uk)

Website: www.pdn.cam.ac.uk/svl

Department / UPI: Physiology, Development and Neuroscience

Research area:

We investigate how our brain is able to selectively process the most relevant sensory information for decision-making. This capacity is crucial given the constant overload of sensory information and the limited capacity of the brain and the need to make rapid decisions. Altered selection of information is associated with cognitive deficits observed in neurodevelopmental disorders such as schizophrenia and autism. We focus on the following topics:

- 1) The effects of learning on neural activity in early visual areas (specialized in representing detailed feature information) and high-level visual cortical areas (closely linked to decision-making). What are the long-term neuronal response changes when we learn what sensory features are relevant, and how do they improve decision-making?
- 2) The effects of attentional selection on neural activity. What are the neuronal changes in early and high-level visual areas that enable fast and flexible task-dependent selection of information?

We study these questions in mice performing visually-guided decisions, taking advantage of similarities between the rodent and primate visual systems, and unique genetic research methods available in mice to dissect neuronal circuits.

Two-photon imaging in identified cell-types combined with optogenetic cell-type specific targeting allows us to measure and manipulate specific circuit components to establish their contribution to behaviour. We study circuits in healthy mice and genetic and pharmacological mouse models of schizophrenia to understand both successful and unsuccessful sensory selection.

To generalize our results in controlled visual conditions, we also develop tools to measure behaviour and neural activity in mice freely behaving in complex and natural environments.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Prof Bénédicte Sanson (bs251@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/benedicte-sanson>

Department / UPI: Physiology, Development and Neuroscience

Research area:

Mechanisms of developmental morphogenesis in vivo

Understanding how a 3D tissue is built from the genetic blueprint is a key frontier in biology. In addition to genetic programs, physical forces play a major role in shaping tissues (morphogenesis). As geneticists and developmental cell biologists interested in morphogenesis, we aim to understand how the genetic inputs integrate with the mechanical properties of the cells and tissues to produce form.

We focus our research on specific morphogenetic processes, including axis extension at gastrulation and compartmental boundary formation. We study cell behaviours such as cell sorting, polarised cell intercalation and cell division, in the context of developmental morphogenesis in vivo. We investigate the integration between gene function and the action of

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mechanical forces in the developing tissues. Our research uses a model organism, the *Drosophila* embryo, because this is one of the simplest (and cheapest) multicellular models that are genetically tractable. In addition, this embryo is accessible to in vivo imaging, develops fast and is increasingly exploited as a paradigm for the mathematic modelling of morphogenesis. Our research is interdisciplinary, combining cell biology, genetics, quantitative and in silico approaches to find novel and universal morphogenetic rules.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Milka Sarris (ms543@cam.ac.uk)

Website: <https://www.pdn.cam.ac.uk/directory/milka-sarris>

Department / UPI: Physiology, Development and Neuroscience

Research area:

Inflammation is our body's primary response to injury, ensuring tissue defence from invading microbes. Furthermore, dysfunctional inflammation is implicated in many diseases, from autoimmunity to cancer. It is critical therefore to fully understand the migratory response of leukocytes, which is at the heart of inflammation. The first cells to infiltrate damaged tissues are neutrophils and macrophages (collectively referred to here as 'myeloid cells'), which eliminate microbes and promote repair. The function of these cells is often assumed to end at inflammatory lesions. However, recent evidence challenges this view and indicates that myeloid cells can also disseminate from these sites (i.e. spread to other tissues in the body). Such emigration could potentially influence secondary inflammation elsewhere as myeloid cell function can be conditioned by prior microbial experience.

Given these findings, it is important to discover what happens to myeloid cells post-infection: what journeys they take and what influence they have on inflammation resolution and on subsequent immune challenges. Answering these questions requires functional tracing of single cells in the entire animal. As this is challenging in large organisms, we propose to exploit disease models in zebrafish, coupled to state-of-the-art microscopy. Our general objective is to map the unexplored journeys of myeloid cells after microbial encounter and determine how they shape subsequent inflammatory responses.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Fengzhu Xiong (fx220@cam.ac.uk)

Website: <https://www.gurdon.cam.ac.uk/people/fengzhu-xiong/>

Department / UPI: Physiology, Development and Neuroscience / Gurdon Institute

Research area:

Tissue morphogenesis by mechanics and cell dynamics: What forces drive tissue morphogenesis? Embryos are made of soft materials consisting of cells with limited mechanical capacities, yet they develop in a robust and coordinated manner and produce large-scale deformations (morphogenesis). We are interested in the ways in which developing tissues produce and respond to mechanical forces in order to achieve the correct shape and pattern. We offer projects that aim at identifying the mechanisms of developmental morphogenesis on molecular, cellular, tissue and

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systematic level. We take an interdisciplinary approach combining biochemistry, genetics, embryology, imaging, modeling, physics and engineering.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Jake Harris (cjh92@cam.ac.uk)

Website: <https://www.plantsci.cam.ac.uk/research/groups/chromatin-and-memory>

Department / UPI: Plant Sciences

Research area:

The areas that we work on include epigenome engineering (molecular cloning, generating transgenic lines, qPCR validation), genomics (transcriptome, CHIP-seq, methylome, ATAC-seq - can offer both wet lab and computational projects) and priming plants for enhanced resistance to stress.

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

Supervisor: Prof Ian Henderson (irh25@cam.ac.uk)

Website: <https://www.plantsci.cam.ac.uk/research/groups/genetic-and-epigenetic-inheritance-plants>

Department / UPI: Plant Sciences

Research area:

Research in the Henderson investigates genetic and epigenetic inheritance in plants. We study the model plant *Arabidopsis thaliana*, as well as important crop species. We focus on how recombination creates genetic diversity during meiosis, and how this intersects with epigenetic mechanisms, including DNA and histone methylation. Most recently, we have been using long-read DNA sequencing to assemble highly repetitive parts of plant genomes, for example the centromeres, and to study how they function during cell division. Our work has fundamental significance for eukaryotic genomes, in addition to applied significance in crop improvement and breeding, especially in the face of challenges caused by climate change.

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

Supervisor: Dr Tristan Bekinschtein (tb419@cam.ac.uk)

Website: <https://www.psychol.cam.ac.uk/people/tristan-bekinschtein>

Department / UPI: Psychology

Research area:

Computational neuroscience, comparative functional physiology with the lab's database of direct cortical recordings in Rats, cats, monkeys and humans.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

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Supervisor: Prof Jeff Dalley (jwd20@cam.ac.uk)

Website: <https://www.psychol.cam.ac.uk/staff/professor-jeff-dalley>

Department / UPI: Psychology

Research area:

The Dalley group seeks to understand the principles that govern the functional organisation of inhibitory neural networks in the cerebral cortex. Although it is widely accepted that the inhibitory neurotransmitter, gamma-amino-butyric acid (GABA) mediates local and long-range inhibitory processes, the role of GABA in different forms of learning dependent on the cerebral cortex remains remarkably poorly understood.

Our lab adopts a translational approach to elucidate conserved neurobiological mechanisms that contribute to cerebral cortical function, specifically to reveal how the brain acquires, maps, and accumulates sensory information to mediate adaptive learning and purposeful behavioural output. The Dalley lab uses a range of convergent experimental approaches to address this objective, including high-field magnetic resonance imaging, intra-cerebral pharmacology, genetically engineered disruption of neural circuits, and in-vivo neurochemical monitoring with biosensors and other transformative technologies.

A related objective of our work is to understand how early life stress affects the neurodevelopmental trajectory of cortical brain networks, ultimately to determine the extent and persistence of longer-term neurobehavioural and cognitive outcomes.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Gregory Davis (gjd1000@cam.ac.uk)

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

Department / UPI: Psychology

Research area:

Visual Attention and Awareness, Eye-gaze detection and processing, Rapid processing of Naturalistic Stimuli, Zebra Stripes

Supervisor: Prof Amy Milton (alm46@cam.ac.uk)

Website: <https://www.psychol.cam.ac.uk/people/alm46%40cam.ac.uk>

Department / UPI: Psychology

Research area:

Our lab is interested in the transition between adaptive and maladaptive behaviour, with a particular focus on individual variation within the population and how reactivity to environmental cues interacts with the risk of developing compulsive behaviours. We use highly translational behavioural tasks in both rodents and humans to investigate the psychological and neurobiological rules driving behaviour.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Research Areas within Understanding the Rules of Life / AY 2023 -2024

Supervisor: Dr Sebastian Schornack (sebastian.schornack@slcu.cam.ac.uk)

Website: <https://www.slcu.cam.ac.uk/research/schornack-group>

Department / UPI: Sainsbury Laboratory

Research area:

Intracellular plant-microbe interactions.

We use molecular biology, genetics, cell biology, biochemistry, evolutionary approaches and bioinformatics to study the plant and microbial mechanisms which underpin plant engagement rules with symbiotic and pathogenic microbes.

Our expertise extends from arbuscular mycorrhiza fungi to the oomycete pathogen *Phytophthora palmivora*. Both microbes can engage with a wide range of plants to form a symbiosis, called Mycorrhiza, or to cause diseases.

This provides us with the opportunity to explore microbial colonisation across divergent land plant lineages including *Marchantia* liverworts, legumes, *Nicotiana benthamiana*, and barley. Studying a range of distantly related plants uncovers fundamental mechanisms of quantitative disease resistance and symbiosis support.

Through researching structures and functions of microbial effector proteins and their plant cellular target processes we explore options for reprogramming of plant growth and development.

Outcomes of our research may enable translational approaches in biotechnology and sustainable agriculture. We strive to ensure an inclusive and supportive research environment at the Sainsbury Laboratory.

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

Supervisor: Dr Carl Anderson (carl.anderson.1980@sanger.ac.uk)

Website: <https://www.sanger.ac.uk/person/anderson-carl/>

Department / UPI: Sanger Institute

Research area:

Our lab uses high-throughput genetic and genomic screens to aid understanding of the cellular and molecular regulation of intestinal homeostasis. We apply large-scale genome sequencing, single-cell sequencing and CRISPR screens to gain causal insights into the genes that regulate intestinal homeostasis. We undertake both computation and wet lab research, and PhD projects can be offered across this broad remit to suit the needs of the student and their project.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Research Areas within Understanding the Rules of Life / AY 2023 -2024

Supervisor: Prof Mark Blaxter (mb35@sanger.ac.uk)

Website: <https://www.sanger.ac.uk/person/blaxter-mark/>

Department / UPI: Sanger Institute

Research area:

The Tree of Life programme is generating very high quality genome sequences from across eukaryotic diversity. My laboratory explores pattern and process in genome evolution using laboratory and bioinformatic approaches, especially in the areas of karyotype evolution in animals, the genomics of neglected taxa, the effects of symbiosis on genomic change, and the evolution of parasitism. Current projects include

* the evolution of chromosome structure in Nematoda and Hexapoda. Animal chromosomes often show long range patterns in the distribution of genes, repeats and other elements. How do these patterns arise, and how are they affected by, or how do they drive, dynamic genome rearrangement?

* inferring the genomic content and structure of ancestral taxa across Metazoa. We use chromosomally-complete genomes of extant species to infer the genome structures of ancestors. Can we robustly infer the structure and content of the last common ancestor of major clades (Ecdysozoa, Spiralia) or kingdoms?

* the evolution of genomic architecture in species with holocentric chromosomes. Most species have centromeres but many species (over 15% of all animals, for example) have holocentric chromosomes. How does holocentrism impact chromosome and genome evolution? Do the genomes of all holocentric groups evolve in the same way?

* the evolutionary origins and mechanisms of programmed DNA elimination. The germline in (most) animals is set aside from the soma during development. In some species the differentiation between soma and germline includes the programmed elimination of specific portions of the genome from somatic cells. How and why do species do this?

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

Supervisor: Dr Victoria Carr (vc11@sanger.ac.uk)

Website: <https://www.sanger.ac.uk/person/carr-victoria/>

Department / UPI: Sanger Institute

Research area:

The student's research would be in respiratory pathogens, microbiome and antimicrobial resistance using metagenomic approaches.

The respiratory system (lungs, nasal cavity, oral cavity and their connections) is an important site of microbial communities. In a significant proportion of healthy adults and children, the microbial communities carries clinically important opportunistic pathogens, (such as *Streptococcus pneumoniae* and *Staphylococcus aureus*) which have potential to gain a foothold to cause disease when conditions allow it (co-infection, antibiotic resistance, immunocompromised, mechanical ventilation etc.). However, it is still unclear how the microbial community influences the prevalence and invasiveness of respiratory pathogens.

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The goal is to better understand the composition and genetic elements of respiratory microbial communities. This will enable a better prediction of pathogen invasiveness, clinical outcome, and provide personalised treatment alternatives and healthcare interventions.

Supervisor: Dr Leopold Parts (lp2@sanger.ac.uk)

Website: <https://www.sanger.ac.uk/person/parts-leopold/>

Department / UPI: Sanger Institute

Research area:

The high level goal of research in our lab is to predict and control phenotypes of human cells with a given genome. To achieve this, we use existing and generate novel large-scale datasets to map the genetic causes of reproducible cellular traits, develop models for prediction, and test these by engineering new genomes.

We usually offer a range of project options on loss- and gain-of-function mutation effect measurement in different genetic backgrounds, as well as data analysis and modeling. However, we also welcome (and encourage) other ideas that fit under this mold, or our other research themes of using large-scale screens to understand variation in gene function between genetic backgrounds, and perturbation effects on single cell gene expression phenotypes.

If you have an interest in these topics, I'm happy to chat to explore possible projects that link to work in our lab.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Dr Sarah Teichmann (st9@sanger.ac.uk)

Website: www.teichlab.org

Department / UPI: Sanger Institute

Research area:

In my lab we study human cell and tissue identity using cell atlas technologies, with innovative wet- and drylab components. A major focus of the group is the development, maturation and response of T lymphocytes as well as other immune cells, and an understanding of our distributed immune system across the lifespan.

We seek to answer questions such as when, how and where do immune cells develop? How do they contribute to sculpting and maintaining tissues? Many of the individual projects in the group contribute to assembling the Human Cell Atlas (www.humancellatlas.org), an international project aiming to map the cells of the human body using single cell and spatial genomics technologies.

BBSRC DTP secondary strategic theme: Transformative technologies

Research Areas within Understanding the Rules of Life / AY 2023 -2024

Supervisor: Dr Roser Vento-Tormo (rv4@sanger.ac.uk)

Website: <https://ventolab.org/>

Department / UPI: Sanger Institute

Research area:

Genomes are organised into gene circuits that control cell fate decisions and how cells organise themselves in tissues. We want to figure out how these circuits are wired and how the cellular microenvironment influences them during human development and regeneration. To understand how the tissue microenvironment influences cell fate choices, we take a quantitative genomics approach. We profile multiple layers of regulation within individual cells using single-cell multiomics tools, and study their intercellular connections using spatial transcriptomics tools. We build reference tissue atlases that allow us to understand perturbations during disease and bioengineer cells and tissues in a dish.

Essential to navigate these atlases is the development of computational and statistical tools. Our team has developed CellPhoneDB, which allows us to uncover the cell-cell communication processes driving differentiation using single-cell genomics approaches. Recent updates of this tool include the incorporation of (i) spatial data, to consider proximity between interacting partners, and (ii) multiomics data, to connect external and internal cellular circuits. We are interesting in continuing to develop advanced computational and machine learning tools to make accurate predictions from our datasets.

Finally, we use and develop robust, scalable in vitro cultures combining organoids and other supporting cells, such as fibroblasts or immune cells. These allow us to perturb gene circuits using gene editing tools or synthetic drugs. Combining all these tools we can mechanistically dissect biological processes and generate models for personalised medicine. We are interested in using high- throughput gene editing assays in complex in vitro models to reconstruct major gene regulatory networks involved in cell fate decisions as well as to identify how the microenvironment modulates them.

Major publications from our team: Garcia-Alonso L et al., Nature 2022 & Garcia-Alonso L et al., Nat Gen 2021. Complete list of publications: <https://pubmed.ncbi.nlm.nih.gov/?term=vento-tormo+r&sort=date>

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Andrew Grant (ajg60@cam.ac.uk)

Website: <https://www.vet.cam.ac.uk/directory/ajg60%40cam.ac.uk>

Department / UPI: Veterinary Medicine

Research area:

We use genomic and functional genomic approaches, combined with advanced molecular, proteomic and microscopy techniques, to determine the basis by which bacterial pathogens survive in different environments colonise their hosts and cause disease. We work on a number of different pathogens of clinical significance for humans and other animals, particular interests include foodborne zoonoses. Through this research we aim to translate our findings into novel

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intervention strategies, including small-molecule therapeutics and immunotherapies including vaccination.

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

Supervisor: Prof Julian Parkhill (jp369@cam.ac.uk)

Website: <https://www.vet.cam.ac.uk/staff/professor-julian-parkhill-frs-fmedsci>

Department / UPI: Veterinary Medicine

Research area:

My group works on the evolution of bacterial pathogens. We use genomics and phylogenetics to understand the emergence of novel lineages, adaption to the host, transmission amongst and between humans and animals, and the development of resistance to antibiotics. Work in the group ranges from experimental studies of host-pathogen interactions using mutagenesis and 'omics tools to development of new analytical approaches for genomics and phylogenetic data, and includes the application of phylogenetics to study transmission and evolution in a number of human and animal pathogens.

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

Supervisor: Dr Maria P. Alcolea (mpa28@cam.ac.uk)

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

Department / UPI: Wellcome - MRC Cambridge Stem Cell Institute

Research area:

The ability of epithelial cells to rewire their programme of cell fate in response to tissue perturbations has emerged as a new paradigm in stem cell biology. This plasticity improves the efficiency of tissue repair by enabling differentiated/lineage committed cells to reacquire stem cell-like behaviour in response to damage. However, despite obvious implications for regenerative medicine, we still know virtually nothing as to how epithelial plasticity contributes to tissue repair and how this process is affected by ageing.

In my laboratory we investigate cell fate plasticity in response to epithelial regeneration by making use of a novel in vivo model that enables tracing the fate of squamous epithelial cells from the earliest stages of commitment towards differentiation. This tool offers a unique opportunity to identify the mechanisms dictating epithelial cell fate plasticity, in particular de-differentiation, and determine whether aged-associated changes in this process hold the key to understand why the regenerative capacity of epithelial tissues declines over time.

To address this aim, we make use of an interdisciplinary approach combining our expertise in in vivo quantitative lineage tracing, single-cell RNA sequencing approaches, mathematical network analysis and a novel 3D organ culture system that recapitulates squamous tissue regeneration ex vivo. Importantly, work in this area will provide a benchmark to identify potential targets to improve regeneration and partially reduce/reverse the unwanted effects of ageing.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Research Areas within Understanding the Rules of Life / AY 2023 -2024

Supervisor: Dr Brian Hendrich (bdh24@cam.ac.uk)

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

Department / UPI: Wellcome - MRC Cambridge Stem Cell Institute

Research area:

Investigate the function of chromatin remodellers in enhancer resetting during signal response in pluripotent cells. Assess how mutations in different remodeller proteins impacts enhancer resetting to help dissect the molecular mechanisms of signal response.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Prof Simon Mendez-Ferrer (sm2116@cam.ac.uk)

Website: <https://www.stemcells.cam.ac.uk/people/pi/mendez-ferrer>

Department / UPI: Wellcome - MRC Cambridge Stem Cell Institute

Research area:

Regulation of haematopoietic stem cell niches

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Mekayla Storer (ms2786@cam.ac.uk)

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

Department / UPI: Wellcome - MRC Cambridge Stem Cell Institute

Research area:

Using the mouse digit tip as a model system, my lab offers projects aimed at understanding the cellular decisions and pathways that define mammalian regeneration. In doing so, we aim to learn how to modulate these processes, with the ultimate goal of improving regenerative outcomes in human patients.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health

Supervisor: Dr Richard Tyser (rt593@cam.ac.uk)

Website: <https://www.stemcells.cam.ac.uk/people/pi/dr-richard-tyser>

Department / UPI: Wellcome - MRC Cambridge Stem Cell Institute

Research area:

Investigating the relationship between form and function during early mammalian heart development.

Research Areas within Understanding the Rules of Life / AY 2023 -2024

Supervisor: Dr Srinjan Basu (sb451@cam.ac.uk)

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

Department / UPI: Wellcome - MRC Cambridge Stem Cell Institute / Physiology, Development and Neuroscience

Research area:

Mammalian embryo development: towards a single-molecule perspective.

In the early mammalian embryo, pluripotent cells emerge and then differentiate via multipotent progenitors to lineage-restricted cell types. Despite years of investigation, a lack of appropriate technology have hindered progress on revealing the molecular mechanisms that govern this process. To address this, our lab develops single-cell next-gen sequencing (e.g. single-cell Hi-C) and single-molecule localisation microscopy approaches that provide insight into the dynamics of molecules that influence cell fate choice in the early mammalian embryo. We are currently establishing ways to image at the single-molecule level how ligands move through tissue, the chromatin binding kinetics of transcription factors, enhancer-promoter dynamics and transcriptional bursting kinetics. Because the chemical and mechanical signals that influence these molecular dynamics are not accurately reconstructed in vitro, we are also establishing imaging and machine learning image analysis tools to monitor these molecular dynamics in vivo and within organoid model systems (e.g. gastruloids and early brain organoids). Using these approaches, we are beginning to reveal how embryos develop at an unprecedented nanoscale level. Our findings impact the field of regenerative medicine, uncovering general molecular mechanisms governing multipotency and cell fate choice within the early embryo. Because many of the molecules we study are commonly mutated or mis-regulated in developmental disorders such as epilepsy and paediatric cancers, our approaches also provide insight into disease progression.

BBSRC DTP secondary strategic theme: Transformative technologies

Supervisor: Prof Matthias Landgraf (ml10006@cam.ac.uk)

Website: <https://www.zoo.cam.ac.uk/research/cell-and-developmental-biology/neural-network-development>

Department / UPI: Zoology

Research area:

Critical periods of nervous system development

As brains develop, the transition from development to function remains enigmatic. An essential requirement for this transition is to arrive at a physiologically appropriate, stable and sustainable activity 'set-point', to which homeostatic systems calibrate.

We are studying these fascinating transitional developmental windows, also called 'critical periods'. How and when are 'set-points' established? Does this occur at single cell or network level? We are interested in understanding how biological systems deal with unpredictable biophysical/environmental parameters (e.g. temperature) or with variability inherent in biological systems, while maintaining robust output, as required for behaviour and to avoid seizures.

These processes are fundamental to nervous development and highly conserved. To study underlying mechanisms, we work with the exceptionally experimentally tractable *Drosophila*

Research Areas within Understanding the Rules of Life / AY 2023 -2024

model system. We use state-of-the-art genetics to manipulate single cells with precision, and super-resolution (expansion and STED) microscopy to visualise changes in connections between nerve cells. Electrophysiology reveals changes in excitable properties and cell-cell communication, while behavioural analysis gives a systems-level readout. RNA Seq and mapping epigenetic modifications identifies the underlying molecular mechanisms.

Already we discovered that homeostatic set-points - all important for network stability - are specified during a defined 'critical period'. Changes made then are lasting; in humans thought to cause many neuro-developmental conditions, including epilepsy. We identified metabolic signals (reactive oxygen species) as instructing cells how to adjust, suggesting metabolic activity the basic information currency. We are now studying mechanisms by which transient developmental experiences cause lasting changes in gene expression and cell specification.

BBSRC DTP secondary strategic theme: Biosciences for an integrated understanding of health