Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional Genomics of SPHKAP Variants in Pancreatic β-Cells: Defining Causal Mechanisms Underlying Type 2 Diabetes

Lead Supervisor: Prof Alejandra Tomas

Lead Supervisor Email: a.tomas-catala@imperial.ac.uk

Department: Department of Metabolism, Digestion and Reproduction

Primary Institution: Imperial College London

Project details

Type 2 diabetes (T2D) affects >500 million people worldwide and is characterised by progressive pancreatic β-cell dysfunction and impaired insulin secretion. Although genome-wide association studies (GWAS) have identified hundreds of loci associated with T2D risk, the molecular mechanisms linking most genetic variants to disease remain poorly understood. A major challenge is translating genetic associations into mechanistic understanding. SPHKAP (Sphingosine Kinase Type 1 Interacting Protein) is an A-kinase anchoring protein (AKAP) that spatially organises cAMP-dependent protein kinase A (PKA) signalling by recruiting signalling enzymes into localised subcellular nanodomains, thereby controlling the specificity, magnitude and duration of cellular responses. Recent work from our laboratory identified SPHKAP as a key component of GLP-1 receptor (GLP-1R) signalling complexes in pancreatic β-cells, where it forms part of an endoplasmic reticulum-mitochondria contact site hub that regulates mitochondrial remodelling and β-cell function (Austin et al., Nat Commun 2025). Preliminary data from UK Biobank indicates that multiple independent genetic signals within SPHKAP are associated with T2D susceptibility, metabolic syndrome, obesity-related traits and glycaemic regulation. Rare variant analyses further implicate SPHKAP in glucose homeostasis. These findings suggest that SPHKAP may represent an important mechanistic link between human genetic variation and β-cell dysfunction.

The central question of this project is: How do diabetes-associated variants at the SPHKAP locus alter β-cell function and contribute to T2D risk?

To address this question, the student will combine human genetics, functional genomics, genome engineering and mechanistic cell biology. First, the student will integrate GWAS, fine mapping, eQTL and epigenomic datasets to identify causal variants and regulatory mechanisms at the SPHKAP locus. The student will learn how to prioritise variants using large-scale population and multiomic datasets and generate hypotheses regarding their biological function. Second, selected variants will be introduced into human stem cell-derived β-cell models using CRISPR-based genome engineering. These isogenic models will enable direct assessment of the effects of genetic variation in a disease-relevant context. Third, the student will investigate how SPHKAP variants influence β-cell signalling. Using advanced fluorescence microscopy, genetically encoded biosensors and quantitative proteomics, they will examine how SPHKAP genetic variation alters compartmentalised cAMP signalling, protein interaction networks and GLP-1R responses. Finally, single-cell transcriptomic and epigenomic approaches will be used to determine how altered signalling affects gene regulatory

networks and β-cell identity. Functional consequences will be assessed through measurements of insulin secretion, cellular stress and therapeutic responses to GLP-1R agonists.

The project is highly interdisciplinary and combines statistical genetics, functional genomics, genome editing, advanced imaging and diabetes research. The student will be supervised by Prof Alejandra Tomas, Imperial College London, an expert in β-cell signalling and mechanistic biology, and Prof Inga Prokopenko, University of Surrey, a leader in complex trait genetics and statistical genomics, with support from ECR co-supervisor Dr Affiong Oqua. The student will have access to world-class facilities, including high-performance computing, genomics and bioinformatics platforms, genome engineering capabilities, human stem cell-derived and primary β-cells, advanced light microscopy, single-cell sequencing and proteomics platforms. Expected outcomes include identification of causal variants at the SPHKAP locus, mechanistic understanding of how these influence GLP-1R and β-cell biology and new insights into the molecular pathways linking human genetic variation to diabetes susceptibility.

Relevant publications

1. Austin G, Oqua AI, El Eid L, Zhu M, Manchanda Y, Peres P, Coyle H, Poliakova Y, Balkhiyarova Z, Bouzakri K, Montoya A, Withers DJ, Solimena M, Jones B, Millership SJ, Bu… https://doi.org/10.1038/s41467-025-66115-x
2. El Eid L, Manchanda Y, Austin G, Deane-Alder K, Rujan R-M, Mariam Z, Oqua AI, Belousoff MJ, Bernardino de la Serna J, Sloop KW, Rutter GA, Montoya A, Withers DJ, Millers… https://doi.org/10.1126/sciadv.adw0899
3. Lagou V et al., Random glucose GWAS in 493,036 individuals provides insights into diabetes pathophysiology, complications, and treatment stratification. Nature Genetics… https://doi.org/10.1038/s41588-023-01462-3

Please direct project-specific enquiries to:

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Enhancer-promoter communication and the origins of drug-resistant epilepsy

Lead Supervisor: Srinjan Basu

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Department: Life Sciences

Primary Institution: Imperial College London

Project details

Background:

Neurodevelopmental disorders affect around 15% of children in Western countries, with most patients experiencing some form of altered brain development, cognitive and motor impairment and altered social milestones. Epilepsy is a key feature of many neurodevelopmental disorders, and a substantial proportion of patients do not respond to available drugs. A common thread running through many forms of epilepsy is an imbalance between excitatory neurons, which drive brain activity, and inhibitory neurons, which restrain it. This imbalance can be traced back to early brain development, when neural stem/progenitor cells (NSPCs) decide how many excitatory versus inhibitory neurons to produce. This decision is guided by environmental signals, transcription factors, and chromatin regulators — proteins that control how DNA is packaged and read. It is therefore no surprise that mutations in transcriptional regulators are strongly linked to treatment-resistant epilepsy, yet exactly how they influence NSPC decision-making is still poorly understood.

Key question and objectives:

This project focuses on MED13L, a subunit of the Mediator complex which is essential for global transcriptional regulation. Despite its ubiquitous expression, heterozygous variants in MED13L lead to a severe neurodevelopmental disorder, with clinical symptoms including developmental delay, hypotonia, dysmorphic facial features and epilepsy. Mediator is known to help organise the genome in 3D, bringing genes and their regulatory "enhancer" elements together, partly by forming small droplet-like structures inside the nucleus called condensates. How disease-causing mutations in MED13L disrupt this process — and how that disruption affects the balance of neuron types produced — is unknown.

The project has three connected objectives, asking how disease-associated MED13L mutations:

1. Dysregulate the differentiation of NSPCs into excitatory and inhibitory neurons.
2. Alter the 3D looping between enhancers and gene promoters.
3. Change the formation and behaviour of intra-nuclear condensates.

Interdisciplinary:

This project trains students across the breadth of modern functional genomics, bridging computational and bioinformatic approaches with experimental research in complex human disease models to elucidate the impact of genetic variation. Students will develop hands-on expertise in CRISPR and perturbation screening; disease modelling via stem-cell-derived NSPCs; 3D genomics and advanced imaging; single-cell approaches to resolve neuronal fate decisions; programming and data science; variant interpretation; and open, reproducible research practices.

Methodology:

The project combines CRISPR gene editing (to introduce disease-relevant MED13L mutations), live-cell super-resolution microscopy (to visualise nuclear condensates in real time), 3D genomics (to map enhancer-promoter interactions), and stem cell technology (to assess how molecular changes affect NSPC differentiation in a physiologically relevant model).

Expected outcomes:

This project will establish a direct link between MED13L disease mutations and functional consequences at three levels: nuclear condensate formation, 3D genome organisation, and NSPC fate decisions. Beyond MED13L, the pipelines developed will provide a reusable platform for studying other transcriptional regulators, as well as regulators of genome organisation, implicated in neurodevelopmental disorders. Looking ahead, we plan to automate this pipeline to support future use in clinical variant interpretation, helping stratify patients with neurodevelopmental disorders and treatment-resistant epilepsy based on the functional impact of their mutations.

Facilities & resources:

The student will access CRISPR and genomics platforms alongside state-of-the-art imaging infrastructure, including custom-built live-cell super-resolution microscopes in the Basu lab and light-sheet confocal microscopes in the institutional imaging facility.

Relevant publications

1. Expertise in Mediator variants: Reid, K. M. et al. MED27, SLC6A7, and MPPE1 Variants in a Complex Neurodevelopmental Disorder with Severe Dystonia. Mov Disord 37, 2139-2… https://doi.org/10.1002/mds.29147
2. Expertise in CRISPR, live-cell super-resolution imaging, chromatin regulators and enhancer-promoter looping: Basu S et al. (2023). Live-cell 3D single-molecule tracking… https://doi.org/10.1038/s41594-023-01095-4
3. Expertise in advanced stem cell models of NSPC differentiation: Kingston A et al (2026). Organoids reveal niche-specific mechanotransduction-guided human cortical patter… https://doi.org/10.64898/2026.07.15.736390

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Decoding Human Genetic Variation in Zinc Homeostasis Using Functional Genomics

Lead Supervisor: Michalis Barkoulas

Lead Supervisor Email: m.barkoulas@imperial.ac.uk

Department: Life Sciences

Primary Institution: Imperial College London

Project details

Context and background:

Zinc is essential for life: around one in ten human proteins requires zinc to function, yet excess zinc is toxic. Cells therefore maintain a finely balanced system of exporters (ZnTs), importers (ZIPs) and storage proteins that controls zinc concentration and localisation. Disruption can cause skin and gut disease, connective tissue disorders, immune deficiency and altered diabetes risk. Large-scale sequencing has now identified many naturally occurring variants in these genes, but most remain functionally uncharacterised. Computational predictors are valuable but imperfect because even variants predicted to be harmless can impair protein function experimentally. There is therefore a pressing need for systematic functional validation of variants in living organisms.

Key question and objectives:

Which human variants in the zinc-homeostasis machinery alter animal physiology, and through what mechanisms? Using the model nematode Caenorhabditis elegans, we will (1) prioritise human variants using population data, evolutionary conservation and protein structure; (2) recreate selected variants by CRISPR genome editing; (3) measure effects on zinc distribution, physiology and immunity; and (4) dissect the mechanisms underlying the most informative phenotypes. The project builds on our discovery that a subtle change in the worm orthologue of human ZIP7 activates an immune defence programme against oomycete pathogens, providing a sensitive in vivo readout of altered zinc homeostasis.

Interdisciplinary nature:

The project sits at the interface of functional genomics and metal biology, combining computational (human population genomic data analysis, protein-structure prediction) and experimental work (precision genome engineering, whole-animal genetics, quantitative fluorescence imaging, transcriptomics and synchrotron-based elemental mapping). This provides broad doctoral training while allowing the student to develop particular interests as the project progresses and potentially expand work to cell lines and zebrafish. Students from biology, biochemistry or bioinformatics backgrounds will be supported to acquire complementary skills, with full training provided in C. elegans genetics and the relevant experimental methods.

Methodology:

Variants will be mined from public resources and prioritised using conservation, predicted structural effects and existing functional evidence. Equivalent changes will be introduced into endogenous C. elegans genes using CRISPR, with humanised strains providing an alternative where conservation is insufficient. Phenotypes will be assessed using fluorescent immune reporters, physiological assays, chemical zinc probes and genetically encoded sensors that report zinc dynamics in living animals. Total and tissue-level metal content will be measured using ICP-MS and X-ray fluorescence imaging. Genetic analysis and transcriptomics will be used to investigate mechanisms. The staged design allows results from early experiments to determine which variants merit deeper investigation, keeping the project feasible within a PhD.

Expected outcomes:

The project will generate an experimentally validated catalogue of variant effects, converting uncertain human variants into functional knowledge. Comparing experimental results with computational predictions will also reveal where current variant-effect predictors succeed or fail. Negative as well as positive results will provide useful functional evidence. The student will gain a broad, highly transferable skill set spanning genomics, functional genetics, imaging, and data analysis.

Facilities and resources:

The project will be based in Imperial College London's Department of Life Sciences, with access to expertise and infrastructure for C. elegans genetics, genome editing and microscopy. Metal analysis will be carried out at the London Metallomics Facility (King's college) and through existing links to the Diamond Light Source.

Relevant publications

1. Cryptic genetic variation in a heat shock protein modifies the outcome of a mutation affecting epidermal stem cell development in C. elegans. Koneru SL, Hintze M, Katsan…
https://doi.org/10.1038/s41467-021-23567-1

2. Aryl hydrocarbon receptor utilises cellular zinc signals to maintain the gut epithelial barrier. Hu XL, Xiao W, Lei Y, Green A, Lee X, Maradana MR, Gao Y, Xie X, Wang R,…
https://doi.org/10.1038/s41467-023-41168-y

3. Dynamic control of Argonautes by a rapidly evolving immunological switch. Ewe CK, Teichman G, Weiss S, Knott MML, Anava S, Gingold H, Sarmiento MB, Troemel E, Rechavi O.…
https://doi.org/10.1016/j.cub.2025.05.039

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional genomics of organelle communication networks controlling human β-cell maturation

Lead Supervisor: Shamith Samarajiwa

Lead Supervisor Email: s.samarajiwa@imperial.ac.uk

Department: Department of Metabolism, Digestion and Reproduction

Primary Institution: Imperial College London

Project details

Our cells depend on highly organised communication networks between intracellular organelles. Many of these interactions occur at membrane contact sites, where organelles exchange signals, calcium and metabolites without fusing. In pancreatic β-cells, this communication must be precisely regulated to coordinate glucose sensing, energy production, calcium dynamics, lipid metabolism and insulin secretion. However, we do not know how these networks are genetically programmed as β-cells develop and which features distinguish mature from immature networks.

This question is important for both type 1 (T1D) and type 2 diabetes (T2D). Human pluripotent stem cells can now be differentiated into insulin-producing β-like cells with considerable potential for cell replacement in T1D, but incomplete functional maturation remains a major challenge, as these cells do not fully reproduce the sophisticated metabolic and signalling integration of primary β-cells. In T2D, progressive loss of β-cell function and resilience contributes to failure to maintain glucose homeostasis. Understanding how healthy β-cell architecture and organelle communication are established could reveal strategies to generate better replacement cells for T1D and identify mechanisms that maintain endogenous β-cell function in T2D.

We hypothesise that acquisition of mature β-cell identity requires coordinated remodelling of organelle communication networks, and that the genes controlling this process can be discovered through high-content functional genomics.

The student will first establish a quantitative atlas of organelle organisation during human stem cell differentiation into β-cells, initially focusing on communication between the endoplasmic reticulum (ER), mitochondria and peroxisomes. Genetically-encoded membrane contact site reporters and Cell Painting will generate multidimensional phenotypic profiles across developmental stages. These will be integrated with measurements of β-cell function, including glucose-stimulated insulin secretion, calcium signalling and mitochondrial metabolism. Mature human and mouse primary β-cells will provide a physiological benchmark for features associated with successful β-cell maturation.

CRISPR-based genetic perturbation combined with automated high-content microscopy will next identify genes whose manipulation shifts immature cells towards, or away from, the organelle architecture and interaction networks of mature β-cells. Quantitative image analysis will enable the identification of genetic regulators of organelle communication at different stages of β-cell

maturation. Transcriptomic and chromatin accessibility profiling will provide complementary information linking selected phenotypes to underlying gene regulatory programmes.

Selected candidate regulators will then undergo mechanistic validation using focused CRISPRi/CRISPRa perturbation, organelle contact site imaging and functional β-cell assays. Particular attention will be paid to ER-mitochondria and ER-peroxisome communication, while retaining scope for the student to pursue unexpected genes and pathways emerging from the screen.

The project is intrinsically interdisciplinary, integrating human stem cell and β-cell biology, functional genomics, genome engineering, high-content microscopy and computational phenotyping, drawing on complementary expertise across the Tomas and Child laboratories and the London Biofoundry. The student will receive training spanning experimental and computational biology, from designing reproducible functional genomic screens to mechanistic validation of individual hits.

The project will generate a functional genomic map linking gene perturbation to organelle architecture, β-cell maturation and function. By identifying causal regulators of β-cell maturation, it could uncover pathways for generating more mature and resilient replacement β-cells for T1D, while revealing fundamental mechanisms governing β-cell dysfunction in T2D.

Relevant publications

1. Austin et al., GLP-1R associates with VAPB and SPHKAP at ERMCSs to regulate β-cell mitochondrial remodelling and function. Nature Communications 2025 Dec 10;16(1):11010 https://doi.org/10.1038/s41467-025-66115-x

2. Buenaventura et al., A Targeted RNAi Screen Identifies Endocytic Trafficking Factors that Control GLP-1 Receptor Signaling in Pancreatic Beta Cells. Diabetes 2018 Mar;67… https://doi.org/10.2337/db17-0639

3. Das et al., CORe Designer: a CRISPR design tool for proteome engineering. bioRxiv 2026.06.12.731864; doi: https://doi.org/10.64898/2026.06.12.731864

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: The Hidden Landscape of Human Protein Variation

Lead Supervisor: Matthew Child

Lead Supervisor Email: m.child@imperial.ac.uk

Department: Life Sciences

Primary Institution: Imperial College London

Project details

Context/background:

Nucleotide allele frequencies reflect genetic diversity in humans and are widely used to assess disease associations and the functional consequences of variation. However, when nucleotide changes occur within protein-coding regions, selection ultimately acts on the encoded protein and the resulting change in amino acid sequence and function. Mutational tolerance is determined by the sequence-function relationship of an individual protein, including residue position within three-dimensional structure, the biochemical nature of a substitution, and involvement in ligand binding or protein-protein interactions. Variation within coding regions should therefore also be considered at the level of codons and amino acids. Surprisingly, population-level amino acid frequencies across the human proteome have not been determined.

This reflects an inherent challenge: amino acid frequencies cannot simply be reconstructed by combining nucleotide allele frequencies. Such an approach assumes that (1) other positions within a codon remain 'wild type', and that (2) variation at the three nucleotide positions is independent. Neither assumption is necessarily correct. Variation can occur at multiple positions within a codon, and these variants can co-vary. Amino acid frequencies therefore need to be determined directly from observed whole-codon sequences across human genomes.

Key question and objectives:

The central question is how population-level amino acid variation reflects the biochemical and functional constraints operating on human proteins. To address this, the project will determine codon and amino acid frequencies at every protein-coding position across a population-resolved human proteome.

The student will:

- Build the population-resolved codon/amino acid resource, establishing the pipeline and quantifying codon and amino acid frequencies across the human proteome.
- Determine what amino acid-level analysis reveals that nucleotide allele frequencies miss, including multi-nucleotide variation, codon covariation, synonymous versus nonsynonymous constraint, population-specific patterns and potential protein-level codon bias.

- Use the resource to investigate protein sequence-function relationships, asking how observed amino acid variability relates to biochemical conservation, protein structure, domains, ligand/interface residues, PTMs, essentiality and disease-associated variation. We will also test whether amino acid-level frequency filtering improves existing Exomiser-based diagnostic pipelines using 100,000 Genomes Project data.

- Evaluate how observed human variation relates to contemporary variant-effect predictions, including ProtVar, AlphaMissense/AlphaGenome and existing pathogenicity scores.

Methodology and interdisciplinarity:

The project will combine population genomics, bioinformatics and protein science. Genome-scale data from Genomics England will be analyzed to identify equivalent codon positions between individuals and quantify observed codon frequencies. These will be translated into residue-level amino acid frequencies and integrated with established protein annotation and variation resources.

Expected outcomes and resources:

The principal outcome will be the first population-resolved map of codon and amino acid frequencies across the human proteome, revealing the variation tolerated at each position in human proteins. By moving beyond nucleotide-level frequencies, this resource will enable genetic variation to be interpreted directly in the context of protein sequence, chemistry and function, providing an empirical framework to investigate mutational constraint, identify functionally important protein features, and improve interpretation of disease-associated variation. Data and analytical tools will be made widely available through resources including UniProt and ProtVar.

Relevant publications

1. Stephenson JD, Totoo P, Burke DF, Jänes J, Beltrao P, Martin MJ. ProtVar: mapping and contextualizing human missense variation. Nucleic Acids Research 52, W140–W147 (202…
https://doi.org/10.1093/nar/gkae413

2. Benns HJ, Storch M, Falco JA, et al., Child MA. CRISPR-based oligo recombineering prioritizes apicomplexan cysteines for drug discovery. Nature Microbiology 7, 1891–1905…
https://doi.org/10.1038/s41564-022-01249-y

3. 100,000 Genomes Project Pilot Investigators; Smedley D, Smith KR, Martin A, et al. 100,000 Genomes Pilot on Rare-Disease Diagnosis in Health Care – Preliminary Report. N…
https://doi.org/10.1056/NEJMoa2035790

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Understanding how genetic variation causes disease through cell-specific protein interactomes

Lead Supervisor: Alessia David

Lead Supervisor Email: alessia.david09@imperial.ac.uk

Department: Life Sciences

Primary Institution: Imperial College London

Project details

Background: Understanding how genetic variation contributes to human disease remains a major challenge in genetics and personalized medicine. Large-scale sequencing studies have identified millions of genetic variants in the human population, many of which remain difficult to interpret, particularly when their functional consequences are context dependent. This challenge is particularly relevant to conditions such as cancer and brain disorders, where genetic variation can affect complex molecular pathways and protein interaction networks.

Several computational approaches, such as AlphaMissense, EVE and CADD, have been developed to predict whether variants are damaging or benign. However, most of these algorithms study variants using the canonical (reference) protein sequence and only predict the effect at the level of the individual protein.

Alternative pre-mRNA splicing enables a single gene to generate multiple RNA transcripts and protein isoforms, with potentially distinct functions and 3D structure. The difference between a canonical protein and its alternative isoforms can range from a few amino acids to the loss or gain of an entire protein domain. These changes can lead to functional/structural changes that can be minor or profound. Importantly, the absence or modification of residues crucial for the interaction of a protein with other molecules can produce substantial changes, not just at protein level, but also at system level.

Alternative splicing is particularly important in the central nervous system (CNS) and plays a key role in neuron cell differentiation in pre- and post-natal life. Furthermore, changes in splicing have been associated with neurological and neurodevelopmental disorders. Our team have used long-read transcript sequencing to identify thousands of novel RNA isoforms in the human brain, several of which are predicted to encode novel and uncharacterized protein isoforms. These data provide a unique opportunity to investigate how brain-specific isoforms modulate protein interaction networks and influence the interpretation of genetic variation.

This project addresses the hypothesis that the analysis of these alternative protein isoforms can reveal previously unrecognised mechanisms by which genetic variation contributes to disease, with a particular focus on brain disorders, including neurodevelopmental and neurodegenerative conditions.

Objectives and Methodology:

1. Review and establish the limitations of current variant effect predictors for alternative isoforms.

2. Develop a novel framework to analyse how novel alternative protein isoforms identified in the human CNS can modulate the protein interactome.

3. Develop a novel computational pipeline to predict the impact of genetic variants on individual proteins and within a biological network.

4. Apply the novel pipeline to study genetic variants identified in unsolved brain disorder cases from the 100K Genomes Project and Genomic Medicine Service.

The project will leverage several data sources including whole genome sequencing, 3D structures, interaction and long-read transcriptomics. State of the art AI structure modelling algorithms, such as AlphaFold and Boltz, will be implemented for structural modelling of the novel protein isoforms and protein complexes, and for in-silico mutagenesis. The project will require working with "big" data and extensive coding in Python.

Expected outcomes: The results of this project will: i. Generate novel insights into protein diversity in the CNS; ii. Identify new mechanisms of disease and improve the prioritization and characterization of genetic variants; iii. Generate a novel computational pipeline that can be transferred and adapted to investigate other tissues and diseases.

Interdisciplinary: This project is highly interdisciplinary and brings together expertise in genetics, transcriptomics, proteomics, 3D protein structure data, computational prediction and interpretation of genetic variants.

Relevant publications

1. Missense3D-DB web catalogue: an atom-based analysis and repository of 4M human protein-coding genetic variants Hum Genet. 2021 May;140(5):805-812. doi: https://doi.org/10.1007/s00439-020-02246-z

2. An atlas of expressed transcripts in the prenatal and postnatal human cortex, BioRxiv May 26, 2024 https://doi.org/10.1101/2024.05.24.595768

3. Efficient reinterpretation of rare disease cases using Exomiser NPJ Genom Med. 2024 Dec 18;9(1):65. doi: https://doi.org/10.1038/s41525-024-00456-2

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Decoding the functional role of glaucoma risk genes using advanced bioengineered models

Lead Supervisor: Darryl Overby

Lead Supervisor Email: d.overby@imperial.ac.uk

Department: Bioengineering

Primary Institution: Imperial College London

Project details

Glaucoma is the leading cause of irreversible blindness, affecting 80 million people. Eye pressure is its main treatable risk factor, and risk rises steeply even within the normal range (e.g. 18 vs 14 mmHg). It is largely set by the cells lining Schlemm's canal (SC). Fluid leaves the eye by crossing this barrier through microscopic pores, which are fewer in glaucoma, obstructing drainage. Hundreds of genes are linked to eye pressure and glaucoma, but how these variants affect SC barrier function is largely unknown.

The Overby lab has developed advanced bioengineered models, including new approach methodologies (NAMs), that recreate for the first time in vitro the microenvironmental cues regulating SC barrier function: stretch, flow and substrate geometry. AI image analysis, developed by Dr Jacques Bertrand, yields quantitative readouts of pore formation and permeability; the student will apply and refine these tools. Professor Dan Stamer (Duke University, USA) provides 35 primary SC cell strains from donors with and without glaucoma, ten already genotyped for CAV1 variants.

The student will genotype all strains and relate risk variants to barrier readouts, focusing on GWAS genes mechanistically linked to SC barrier function:

- ARHGEF12 regulates junctional actomyosin in vascular endothelium and alters SC junctions when knocked down.
- TMCO1 regulates ER calcium homeostasis; our unpublished work shows ER calcium release is required for transcellular pore formation.
- CAV1 forms caveolae, which control NOS3-derived nitric oxide and are implicated in pore formation.
- KDR mediates VEGF signalling, which controls vascular permeability and, as we have shown, outflow facility.

Pathways will be probed pharmacologically, by inflammatory challenge and by siRNA knockdown, with key findings tested in perfused eyes ex vivo. The student will choose which genes to pursue as data emerge, and may link cellular phenotypes to clinical imaging, connecting gene function across cellular, tissue and clinical scales.

The team combines bioengineering (Overby, Imperial), glaucoma genetics and clinical ophthalmology (Khawaja, UCL Institute of Ophthalmology/Moorfields), endothelial barrier biology (Matter, UCL Institute of Ophthalmology) and AI image analysis (Bertrand, ECR mentor). Professor Khawaja's programme links genomic data to clinical records from UK Biobank and other cohorts, including Moorfields patients with different glaucoma types. Training spans academia, NHS and industry; data and code will be shared through the FGx Data Coordination Centre.

The project will deliver the first functional map linking glaucoma risk genes to drainage mechanisms, revealing new therapeutic targets.

Relevant publications

1. Overby DR et al., PNAS 2014;111:13876-81; Khawaja AP et al., Nat Genet 2018;50:778-82; Kelly RA et al. (incl. Overby DR, Stamer WD), J Clin Invest 2025;135:e183440.S2 up… https://doi.org/10.1172/JCI183440
2. Khawaja AP, Cooke Bailey JN, Wareham NJ, Scott RA, Simcoe M, Igo RP Jr, et al. Genome-wide analyses identify new loci associated with intraocular pressure. Nature Genetics. 2018. https://doi.org/10.1038/s41588-018-0126-8
3. Kelly RA, et al. J Clin Invest. 2025;135:e183440. https://doi.org/10.1172/JCI183440

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: From genetic risk to disease mechanism: functional genomics of steatotic (fatty) liver disease

Lead Supervisor: Inês Cebola

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Department: Metabolism, Digestion and Reproduction

Primary Institution: Imperial College London

Project details

Background

About a third of people worldwide have excess fat in their liver. In a substantial proportion this condition, metabolic dysfunction-associated steatotic liver disease (MASLD), progresses to scarring, liver failure or liver cancer, and associates strongly with diabetes and cardiovascular disease. Hundreds of genetic variants alter MASLD risk, most of which sit outside genes, in regulatory elements such as enhancers – switches that control when, where and how strongly genes are turned on. Enhancers often act on distant genes rather than their closest one. Thus, for most MASLD variants the gene affected is unknown, limiting our ability to turn genetic findings into therapeutic targets. This matters, as drug mechanisms with human genetic support are ~2.6 times more likely to succeed clinically (PMID 38632401). Our group has resolved individual loci, implicating CYP7A1 in MASLD using liver chromatin maps to prioritise a functional variant, then CRISPR-mediated activation to link its enhancer to the gene (PMID 40452229). Characterising one locus this way can take years. With hundreds unexplained, the field needs approaches that test many variants at once.

Key question and objectives

We hypothesise that mapping MASLD risk variants to the genes they act through will reveal the pathways driving disease. The project asks: which genes do these variants affect, and what do those genes do in the liver?

Aims:

1. Test hundreds of regulatory elements simultaneously and determine which genes each controls.

2. Characterise those candidate genes by high-content imaging of lipid storage, mitochondrial state and cellular stress.

3. Learn the rules by which genetic variation alters liver enhancer function.

Within these aims the student will set the priorities: which loci, which phenotypes, and the balance of laboratory and computational work.

Interdisciplinarity

The project spans genomics, molecular and cell biology and computational biology, and the student will work in all three: running screens, then analysing single-cell sequencing data and thousands of image-derived measurements per cell. It connects partners in engineering biology, a national industry-partnered screening facility, pharma, and academic labs in the UK, Spain and the USA. Students from biology, biochemistry, bioinformatics, computing, physics or engineering could all find a way in. The student will gain an unusual combination of skills: CRISPR screening, single-cell and image-based data analysis, and regulatory genomics, applied here to MASLD but portable to any disease area.

Methodology

CRISPR activation screening with a single-cell RNA-seq readout will link hundreds of candidate MASLD enhancers to the genes they control; the cell lines and an ~8,000-guide library are already established. Candidate genes will then be profiled by LipocyteProfiler, a microscopy assay measuring over 3,000 features per cell, fingerprinting each gene's function. Massively parallel reporter assays with saturation mutagenesis, and prime editing of the most informative variants, will define the sequence rules governing enhancer activity.

Expected outcomes

A map linking MASLD risk variants to their target genes and to the cellular processes those genes disturb, converting statistical associations into candidate drug targets, alongside general rules for what makes a liver enhancer active. The student should expect to lead a first-author research paper and a review.

Facilities and resources

Reagents and pipelines in place: CRISPR-activation liver cell lines, the guide library, and validated workflows for single-cell screens and imaging. The student will have access to Imperial's genomics, imaging and high-performance computing facilities, the London Biofoundry and, by application, the HFGI Functional Genomics Screening Laboratory. Placements are agreed at the Broad Institute, the Centre for Genomic Regulation (Barcelona) and Novo Nordisk Research Centre Oxford.

Relevant publications

1. Miguel-Escalada I*, Bonàs-Guarch S*, Cebola I*, et al. Human pancreatic islet three-dimensional chromatin architecture provides insights into the genetics of type 2 diab… https://doi.org/10.1038/s41588-019-0457-0

2. PMID: 40452229; PMCID: PMC12538139. /3. Benns HJ, Storch M, …, Child MA. CRISPR-based oligo recombineering prioritizes apicomplexan cysteines for drug discovery. Nat Mic… https://doi.org/10.1038/s41564-022-01249-y

3. Benns HJ, Storch M, et al. CRISPR-based oligo recombineering prioritizes apicomplexan cysteines for drug discovery. Nature Microbiology. 2022. https://doi.org/10.1038/s41564-022-01249-y

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Epigenomic profiling of peripheral and brain-resident immune cells in Alzheimer's disease: from gene regulation to disease risk

Lead Supervisor: Alexi Nott

Lead Supervisor Email: a.nott@imperial.ac.uk

Department: Brain Sciences

Primary Institution: Imperial College London

Project details

AD genetic risk is concentrated in non-coding regulatory regions active in myeloid cells, implicating microglial gene regulation as a core disease mechanism. The immune contribution to AD is not restricted to resident microglia. Age-related microglial turnover involves infiltration of peripheral-derived monocytes, some carrying CHIP somatic mutations linked to reduced dementia risk. Leukocyte infiltration also accompanies cerebral amyloid angiopathy (CAA) and other AD-associated vascular pathology. Whether disease-associated microglia, peripheral-derived brain-infiltrating cells and their circulating counterparts share or diverge in the regulatory elements through which genetic risk and protection act remains unresolved and is central to prioritising drug targets and the correct immune population.

This project builds on our existing epigenomic profiling of microglia in AD and across the human lifespan, and public peripheral immune datasets, to resolve brain-resident and peripheral regulatory landscapes directly.

Key question and objectives

Does the gene regulatory landscape of disease-associated and peripheral-derived immune cells in the AD brain differ from that of their circulating counterparts, and what does this reveal about mechanisms of genetic risk and protection?

1. Generate single-cell H3K27ac profiles, with matched gene expression, of brain myeloid cells from AD and control cortex.

2. Develop FANS protocols to enrich peripheral T and B cell populations from brain and matched blood for the same assays.

3. Apply long-read sequencing across both compartments to call somatic mutations, including CHIP variants, and DNA methylation.

4. Integrate brain and blood regulatory maps with AD and neurodegenerative risk loci to identify the cell states and elements underlying risk and protection.

Interdisciplinary nature

The project sits at the interface of immunology, neuropathology, functional genomics and statistical/computational genetics, combining cell-type enrichment and multi-omic profiling of archived human tissue with integration against GWAS data. It suits candidates from any of these backgrounds keen to work across wet-lab and computational approaches.

Methodology

Nuclei from post-mortem frontal cortex of AD cases and controls will be depleted of neurons, oligodendrocytes and astrocytes prior to single-cell H3K27ac profiling with matched transcriptomic data. In parallel, FANS protocols will be developed and optimised to isolate T and B cell populations from peripheral blood, extending established nuclei-sorting approaches to lymphoid markers. Long-read sequencing will be applied across both compartments to resolve somatic mutations, including CHIP variants, and DNA methylation at single-molecule resolution.

Resulting datasets will be integrated with existing microglial epigenomic profiles spanning AD and the lifespan and with public peripheral immune datasets. Fine-mapped AD/neurodegenerative risk loci will be integrated with our cell-type- and compartment-specific regulatory elements to prioritise causal mechanisms.

Expected outcomes

The project will deliver the first cell-type- and compartment-resolved comparison of brain-resident and peripheral-derived immune regulatory landscapes in AD, identifying which populations and regulatory elements carry disease risk versus protection, including CHIP-associated states. Outcomes include validated FANS protocols for peripheral lymphoid populations, integrated multi-omic reference maps spanning brain and blood, and mechanistic candidates for drug target and cell-population prioritisation.

Facilities and resources

The student will access existing epigenomic profiles of microglia across AD and the lifespan, archived brain tissue, and established histone profiling pipelines for cell-type-enriched populations in the host lab (Nott, Imperial), with joint supervision from Marzi (KCL, long-read sequencing) and Mill/Dempster (Exeter, DNA methylation analysis and FANS).

Relevant publications

1. Ziegler KC, Askarova A, et al., Nott A. (2025). The brain neurovascular epigenome and its association with dementia. Neuron. DOI: Mapped gene regulatory elements across… https://doi.org/10.1016/j.neuron.2025.10.001

2. Marzi SJ, Leung SK, Ribarska T, et al. (2018). A histone acetylome-wide association study of Alzheimer's disease identifies disease-associated H3K27ac differences in the… https://doi.org/10.1038/s41593-018-0253-7

3. Shireby G, Dempster EL, Policicchio S, et al., Mill J. (2022). DNA methylation signatures of Alzheimer's disease neuropathology in the cortex are primarily driven by var… https://doi.org/10.1038/s41467-022-33394-7

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Linking Alzheimer's Disease genetic loci to metabolic pathways through molecular epidemiology and functional genomics

Lead Supervisor: Abbas Deghgan

Lead Supervisor Email: a.dehghan@imperial.ac.uk

Department: SPH

Primary Institution: Imperial College London

Project details

Genome-wide association studies have identified a growing number of genetic loci associated with Alzheimer's disease (AD), yet the biological mechanisms linking most of these variants to disease remain poorly understood. Identifying the molecular consequences of AD-associated variation is essential for translating genetic discovery into mechanistic insight and therapeutic opportunities.

Our previous work demonstrated the potential of metabolomics for this purpose. We propose to systematically test AD-associated genetic variants against circulating metabolic features. Previously we identified a strong association between variants at ABCA7 and lactosylceramides, implicating altered sphingolipid metabolism as a potential pathway linking ABCA7 to AD. Subsequent analyses integrating cognition, AD risk and Mendelian randomisation provided additional evidence supporting the biological relevance of this pathway. This project will extend this approach systematically across AD susceptibility loci to identify the metabolic pathways through which genetic variation may influence AD risk. The project will leverage novel high-dimensional metabolomics data available through the REACT cohort in ~10K individuals.

Aim 1 — Discovery: Link AD GWAS loci to untargeted metabolomic data in the REACT and Airwave studies, and identify robust genetic variant–metabolite associations using a metabolome-wide association study (MWAS) design.

Aim 2 — Causal inference: Use molecular epidemiology approaches such as fine-mapping, colocalisation, Mendelian randomisation and cell type-resolved molecular QTL data to distinguish shared causal signals and test whether prioritised metabolites may mediate the effects of AD-associated genetic variation. We will triangulate these findings against cognition, fluid and imaging AD biomarkers, and brain imaging phenotypes to identify loci with convergent genetic, molecular and phenotypic evidence.

Aim 3 — Mechanistic follow-up: For the strongest and most biologically plausible locus–metabolite associations, we will investigate the brain cell types and regulatory mechanisms through which genetic variation may alter metabolic pathways and influence AD risk. In collaboration with Dr Alexi Nott's group, the project will integrate cell type-resolved genomic, transcriptomic and chromatin data with targeted experimental studies in relevant cellular models. The precise experimental strategy will be guided by findings from Aims 1–2 and developed jointly with the student and supervisory team,

potentially including cell type-specific chromatin profiling and functional perturbation of prioritised genes or regulatory elements.

Relevant publications

1. Dehghan A, Pinto RC, Karaman I, Huang J, Durainayagam BR, Ghanbari M, Nazeer A, Zhong Q, Liggi S, Whiley L, Mustafa R, Kivipelto M, Solomon A, Ngandu T, Kanekiyo T, Aika… https://doi.org/10.1073/pnas.2206083119

2. Garcia-Segura ME, Durainayagam BR, Liggi S, Graça G, Jimenez B, Dehghan A, et al. Multi-omics analysis reveals lipid alterations in Alzheimer's disease. Journal of Neurochemistry. 2023. https://doi.org/10.1111/jnc.15719

3. Nott A, Holtman IR, Coufal NG, Schlachetzki JCM, Yu M, Hu R, et al. Brain cell type-specific enhancer-promoter interactome maps and disease risk. Science. 2019. https://doi.org/10.1126/science.aay0793

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: From genes to brain networks: where do rare and common genetic risks for neurodevelopmental disorders converge?

Lead Supervisor: Konrad Wagstyl

Lead Supervisor Email: konrad.wagstyl@kcl.ac.uk

Department: Biomedical Computing

Primary Institution: King's College London

Project details

Neurodevelopmental conditions like autism, epilepsy, and schizophrenia are strongly influenced by genetic risk factors - reflecting both rare and common forms of genetic variation. Rare variants are carried by few people but have large effects - a single gene damaging mutation can explain much of a person's condition. Common variants are shared by many people. Each variant contributes a small amount to the risk but many together can contribute substantially. Both can influence the same genes, or apparently similar pathways through different genes - but are often studied separately, so their neurobiological overlaps remain unclear. Identifying points of convergence could help us to better understand biological mechanisms for disease, boost future discovery of risk genes, and design novel therapies.

Question:

How do common and rare genetic risk factors for neurodevelopmental illness intersect across spatial scales of the developing human brain?

Objectives:

Build Gene2Brain, an open database and tool for bringing together cellular, circuit-based and regional gene expression across human brain development with data from both postmortem and in vitro disease models. Users will be able to project any gene list into Gene2Brain - instantly localizing significant enrichments in space and time.

Apply Gene2Brain to identify the functional genomic enrichments for common and rare genetic risk factors for major neurodevelopmental conditions. Statistical null models will be developed to test whether these two forms of risk act on the neurobiological pathways.

The final objective will be shaped by the student's interests e.g. machine learning models to predict new risk genes, finding subgroups of genes within a disorder or analysing shared neurobiology between disorders.

Methodology

Data integration. Aggregating public and in-lab datasets to capture single-cell, tissue and organoid - derived healthy and disrupted brain gene expression into a searchable database.

Statistics framework. Standard enrichment tests might highlight all of neuron, neural progenitor, synapse and ion channel. The student will develop a framework for joint modelling, to identify features that best explain what a set of genes has in common.

Rare and common variant convergence. Rare variant gene lists (e.g. SFARI, ClinGen) and common variant signals from Genome-Wide Association Studies (GWAS) will be collected. The student will use their annotation framework to test their neurobiological convergence.

Student-led methods: May include deep learning (e.g. autoencoders), clustering techniques or cross-disorder comparisons.

Interdisciplinary

The PhD student who co-develops and leads this project will receive tailored training from a supervisory team with expertise across psychiatric genetics, functional genomics, neuroimaging, computational biology and machine learning. The project is fundamentally interdisciplinary and ideally suited for applicants with biological, quantitative or computational backgrounds who wish to cross scales of brain analysis and bridge between basic and clinical applications.

Expected outcomes

Gene2Brain - an open resource and software package for linking any input gene list to molecular, cellular, circuit, network and neuroimaging maps of the brain.

Points of convergence between risk genes implicated by common and rare variation for major neurodevelopmental disorders.

Depending on the student: new candidate risk genes, mechanisms within disorders, neurobiology shared across disorders.

Facilities and resources available

The student will have access to multi-scale functional genomic datasets and unique rare cohorts of paired genomic, imaging and clinical data. They will access high-performance computing and receive training in bioinformatics, statistics, advanced machine learning and neurogenomics. They will join the IMAGINE lab (Biomedical Computing, KCL), and the new Oxford-based evolution of US NIMH Section on Developmental Neurogenomics.

Relevant publications

1. Wagstyl, K., Adler, S., Seidlitz, J., Vandekar, S., Mallard, T. T., Dear, R., DeCasien, A. R., Satterthwaite, T. D., Liu, S., Vértes, P. E., Shinohara, R. T., Alexander-... https://doi.org/10.7554/eLife.86933

2. Seidlitz, J., Nadig, A., Liu, S., Bethlehem, R. A. I., Vértes, P. E., Morgan, S. E., Váša, F., Romero-Garcia, R., Lalonde, F. M., Clasen, L. S., Blumenthal, J. D., Paquo... https://doi.org/10.1038/s41467-020-17051-5
3. DeCasien, A. R., Auluck, P., Liu, S., Feng, N., Elkahloun, A. G., Xu, Q., Marenco, S., Cookson, M. R. & Raznahan, A. Sex effects on gene expression across the human cere... https://doi.org/10.1126/science.aea9063

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Cellular phenotypes of in vivo grafted human neurons with autism risk mutations

Lead Supervisor: Laura Andreae

Lead Supervisor Email: laura.andreae@kcl.ac.uk

Department: Centre for Developmental Neurobiology

Primary Institution: King's College London

Project details

Genetic studies have identified hundreds of genetic variants that confer risk of autism, but how these variants lead to behavioural consequences remains unknown. We will focus on the cell-type specific, cellular consequences of specific high confidence risk gene mutations. While some information is available from animal models, the ability to understand the cellular consequences of such variants on human neurons has been limited by highly unphysiological in vitro preparations which lack regional specificity as well as failing to mature sufficiently. However, it is clear that cellular phenotypes are highly dependent on cell types and brain regions.

We will use human inducible pluripotent stem cell derived neurons with autism risk gene mutations and ask whether there are convergent cellular phenotypic alterations when these neurons are grafted into key cortical brain regions in mice and allowed to both integrate into living circuits and mature over much longer timescales. A combination of electrophysiology, functional and structural imaging and connectivity mapping, with FACS, single nucleus/cell and spatial transcriptomics, will define core cell-type specific phenotypes, map local and any long-range circuit integration, identify brain regional differences (including to what extent human neurons adopt local identities) and search for convergent or divergent phenotypes. In the long run, understanding cellular mechanisms downstream of genetic mutation in human neurons will identify altered pathways, leading the way to improved therapeutic targeting. Expected outcomes: 1) increased understanding of identity of grafted human neurons in specific brain regions, 2) cellular phenotypes of human cortical neurons with autism risk mutations over long term developmental maturation, 3) Regional and cell-type specificity of these phenotypes, 4) Cross-institute and interdisciplinary training for student.

This project links King's (grafting of human neurons, synaptic and physiological characterization) and Exeter (transcriptomics, analytical pipelines) in an interdisciplinary project with excellent skills training in a variety of techniques, as well as extensive network building and broader opportunities for development at both locations. The student will be encouraged to attend workshops and courses on human neurodevelopment, transcriptomics and stem cell approaches, as well as taking advantage of local transferable skills training and outreach opportunities, such as participation in DevNeuro Academy. Grafting techniques are already successfully established ensuring feasibility, and all facilities and resources are available, including dedicated electrophysiology rigs, confocal and 2-photon imaging and transcriptomic facilities. Monthly online meetings with all supervisors will ensure good communication, with additional in-person meetings with individual supervisors.

Relevant publications

1. Ellingford RA, et al..., Basson MA, Andreae LC. Cell-type-specific synaptic imbalance and disrupted homeostatic plasticity in cortical circuits of ASD-associated Chd8 hapl... https://doi.org/10.1038/s41380-021-01070-9
2. Keuss M, Harley P, et al. Loss of TDP-43 induces synaptic dysfunction rescued by UNC13A cryptic exon correction. bioRxiv. 2024. https://doi.org/10.1101/2024.06.20.599684
3. Clifton NE, et al. Cortical transcriptome and synaptosome disruption in SETD1A loss-of-function. Human Molecular Genetics. 2022. https://doi.org/10.1093/hmg/ddac105

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: From variant to developmental phenotype: functional genomics and chromatin regulation in the human cortical environment

Lead Supervisor: Katie Long

Lead Supervisor Email: katie.long@kcl.ac.uk

Department: Centre for Developmental Neurobiology

Primary Institution: King's College London

Project details

Genetic studies have identified hundreds of genes and variants associated with neurodevelopmental disorders. However, establishing that a variant causes disease does not explain how disruption of that gene alters the trajectory of human brain development. A significant proportion of these genes are involved in chromatin regulation – encoding proteins associated with chromatin structure, histone modification and transcription. Understanding how individual variants of these chromatin regulators alter human brain development remains a major challenge.

Our overarching hypothesis is that disruption of chromatin regulation alters the trajectory of human cortical neurogenesis through both cell-autonomous and developmental-context-dependent mechanisms.

This raises an important functional-genomics question: which consequences of disease-associated genetic variation are cell-autonomous and reproducible across experimental systems, and which emerge only within the appropriate human developmental environment?

We will address this question using an established patient-derived iPSC model of chromatin-regulator haploinsufficiency and its CRISPR-corrected isogenic control. Preliminary studies have identified abnormalities of neurogenic timing and neuronal development in conventional human neural models. Both genotypes can be distinguished using constitutive fluorescent reporters, providing an opportunity for direct comparison of genetically distinct cells within the same experimental environment. The student will combine human neural differentiation and cortical organoid approaches with an emerging experimental system in which fluorescently labelled iPSC-derived neural progenitors are introduced into organotypic human fetal cortical slices in culture. This will allow the same genetic perturbation to be studied across increasingly complex human developmental environments to investigate how developmental context shapes the consequences of disease-associated disruption of chromatin regulation.

The project will address three linked questions:

(1) How can genetically defined human neural progenitors be reproducibly studied within the developing human cortical environment.

(2) How does chromatin regulator haploinsufficiency alter progenitor fate, proliferation, migration, morphology and integration, and which phenotypes depend upon developmental context.

(3) Which molecular pathways underlie these context-dependent phenotypes? High-content imaging and spatial analysis will be combined with functional genomic approaches selected according to the emerging results, potentially including spatial or single-cell transcriptomics and targeted genetic or pharmacological perturbation.

These objectives will provide new insight into how disruption of a disease-associated chromatin regulator alters human cortical development, and whether the resulting phenotypes are preserved across experimental systems or modified by the surrounding developmental environment. By comparing genetically defined neural cells across in vitro and ex vivo models, the work will help distinguish cell-intrinsic effects from those that emerge through interactions with the developing human tissue context.

In parallel, the project will establish an experimental and analytical framework for studying genetically perturbed human neural cells within developing cortical tissue. This approach could subsequently be extended to additional neurodevelopmental genes and disease models, providing a platform for comparative functional studies across genetically distinct conditions. We will utilise existing machine learning pipelines for image analysis (DeepCellMap), and encourage the student to participate in the development of these tools as their project progresses.

In the longer term, the system could also support more scalable perturbation approaches, including targeted or arrayed CRISPR-based studies, in collaboration with the wider Functional Genomics network and Screening Laboratoboratory.

Relevant publications

1. Long et al, 2018; Neuron (DOI: , Paun et al, 2023; Genes Dev (DOI: , Perochon et al, 2025; N Comms (DOI: , https://doi.org/10.1016/j.neuron.2018.07.013
2. Paun O, et al. Genes & Development. 2023. https://doi.org/10.1101/gad.350269.122
3. Perochon J, et al. Nature Communications. 2025. https://doi.org/10.1038/s41467-025-56560-z

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Wiring the human inhibitory neuron: how MEF2C mutations disrupt excitatory synapse formation onto parvalbumin interneurons

Lead Supervisor: Beatriz Rico

Lead Supervisor Email: beatriz.rico@kcl.ac.uk

Department: Developmental Neurobiology

Primary Institution: King's College London

Project details

Background. Parvalbumin (PV) interneurons set the timing of activity across the cerebral cortex, and their dysfunction is one of the most reproducible findings in intellectual disability, epilepsy, autism and schizophrenia. These cells are not born mature: in mice they acquire their properties only after excitatory synapses form onto them, and the activity those synapses carry drives the programme that completes maturation. In humans this unfolds over months rather than weeks. MEF2C sits at the centre of this logic. It is an activity-dependent transcription factor that controls synapse number, it acts upstream of PPARGC1A, which is required for PV maturation, and its loss severely disrupts PV interneuron development in mice. Heterozygous MEF2C mutations cause intellectual disability, epilepsy and autism and increase schizophrenia risk. Whether human PV interneurons depend on MEF2C to acquire their excitatory input is unknown.

Key question and objectives. Does MEF2C control the formation of excitatory synapses onto human PV interneurons, and is failure of that input what arrests their maturation? Three objectives: (1) define the transcriptional consequences of MEF2C haploinsufficiency across the human interneuron lineage; (2) determine in vivo whether mutant human PV interneurons fail to acquire excitatory input and fail to mature; and (3) test whether that failure is cell-autonomous.

Methodology. The student will use a MEF2C heterozygous loss-of-function iPSC line and its isogenic control, both KOLF2.1J, from the Wellcome Sanger Institute library. From these, they will generate subpallial organoids that produce cortical interneurons, and assembloids in which excitatory and inhibitory neurons develop together. Single-cell RNA sequencing will determine whether the mutation alters MGE-derived interneuron production and the trajectory specifying PV lineage. Precursors will then be transplanted into the neocortex of newborn immunodeficient mice, the only system in which human PV interneurons fully mature. At nine months, spatial transcriptomics will resolve the identity of the transplanted cells in situ, and confocal imaging of pre- and postsynaptic markers will measure the excitatory input they have received. Pairing the two readouts in the same tissue is the core of the design: it links what a cell has become to what it is connected to. Finally, mutant and control cells carrying distinct fluorophores will be co-transplanted into the same cortex, so the student can compare genotypes within one animal. This removes host-to-host variability and tests directly whether the phenotype is cell-autonomous.

Interdisciplinarity. The student will generate and analyse their own data, integrating single-cell and spatial datasets with the head of the CDN Bioinformatics Core and annotating human interneuron states against foetal and post-mortem references. The balance between bench and analysis can shift with the student's interests.

Expected outcomes. The project will give the first account of whether MEF2C is required for human PV interneurons to be wired and to mature, with matched transcriptional and synaptic measurements in the same cells in vivo. If the mouse mechanism is conserved, synaptic input is where this mutation acts in humans and the stage a therapeutic must reach. If it is not, that matters as much: it would show that human PV maturation is not a slower version of the mouse programme.

Facilities and resources. Work will be carried out at the Centre for Developmental Neurobiology, King's College London. The Neurodevelopment Cluster of the UK Human Functional Genomics Initiative provides standardised, staff-supported organoid production at scale. Single-cell and spatial genomics run through the Single Cell Omics Platform and the Spatial Biology Facility, xenotransplantation through the Biological Services Facility, and computing through King's e-Research and the CDN Bioinformatics Core.

Relevant publications

1. Bernard C, Exposito-Alonso D, et al. (2022). Cortical wiring by synapse type-specific control of local protein synthesis. Science 378:eabm7466 https://doi.org/10.1126/science.abm7466

2. Jezequel J, et al. (2025). Cadherins orchestrate specific patterns of perisomatic inhibition onto distinct pyramidal cell populations. Nature Communications, 16(1):4481 https://doi.org/10.1038/s41467-025-59635-z

3. Kroon T, et al. (2026, in press Nature Neuroscience). Activity-dependent expression of Fezf2 regulates inhibitory synapse formation in pyramidal cells https://doi.org/10.1101/2024.01.11.575171

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Decoding the nuclear role of Teneurin-3 in human neural development

Lead Supervisor: Robert Hindges

Lead Supervisor Email: robert.hindges@kcl.ac.uk

Department: Centre for Developmental Neurobiology

Primary Institution: King's College London

Project details

Context and background

The brain's complexity emerges from the precise wiring of neurons into functional circuits during development. Teneurin-3 (TENM3) is a conserved cell-surface protein, expressed prominently in cortex, hippocampus and retina, that guides the formation of specific neuronal connections. Genetic variants in TENM3 have been associated with autism spectrum disorder, intellectual disability, and visual system abnormalities.

TENM3 can be proteolytically cleaved to release its intracellular domain (ICD) for nuclear translocation to regulate transcription, with the exact signals for this event unknown. ICD-mediated transcription, therefore, represents a direct link between extracellular signals and lasting changes in gene expression during sensitive windows of brain development. Whether this process operates in human neurons, which genes it controls, and what functional consequences follow, is entirely unknown. Understanding this mechanism would reveal how TENM3 integrates cues at the cell surface with developmental decisions in the nucleus.

Key question and objectives

The central questions of this project are: how is the TENM3 ICD released in human neurons, what genetic programs does it control and how does it shape neural development?

We will pursue three objectives: (1) determine when and where TENM3 ICD cleavage and nuclear translocation occur during human neuron differentiation; (2) define the transcriptional program controlled by the ICD; and (3) link ICD-driven transcription to functional outcomes.

Interdisciplinary approach

This project integrates molecular and cellular neuroscience, stem cell biology, functional genomics, and computational biology.

Stem cell biology provides iPSC-derived cortical/retinal neurons and brain organoids that recapitulate human brain development. Molecular biology enables CRISPR-based genetic tools. Functional genomics delivers genome-wide readouts of ICD-driven transcriptional changes. Proximity labelling proteomics identifies the nuclear partners through which the ICD acts. Computational biology integrates these datasets and cross-references findings with human genetic studies of neurodevelopmental disorders.

The student will gain broad, cross-disciplinary training at the interface of basic cell biology and translational neuroscience.

Methodology

The project proceeds across four phases.

Phase 1: engineer isogenic iPSC lines (TENM3 tagging) and differentiation to cortical/retinal neurons and organoids.

Phase 2: Bulk (cells) and snRNA (organoids) -seq in both ICD GOF and LOF conditions to identify affected transcriptional output.

Phase 3: Map ICD signalling mechanism, TurboID proximity labelling to identify nuclear interactors.

Phase 4: MEA electrophysiology, synapse quantification, and organoid layer profiling in both LOF/GOF ICD conditions.

Expected outcomes

The project will establish whether the TENM3 ICD functions as a transcriptional regulator in human neurons and produce a genome-wide map of ICD-controlled genes— a foundational resource for the human neurodevelopmental field.

It will reveal the functional logic of ICD-driven transcription and provide better molecular explanations for TENM3-linked ASD and visual deficits and identify transcriptional targets for future therapeutic investigation.

Facilities and resources

The Centre for Developmental Neurobiology houses a state-of-the-art stem cell/organoid facility providing the core infrastructure for iPSC culture, CRISPR-Cas9 genome editing, and neuron and organoid differentiation and a dedicated bioinformatics core to support all computational analysis. Electrophysiology equipment (MEA) is housed within the organoid facility. Proximity labelling proteomics is covered through our proteomics facility.

The student will be embedded in the broader neuroscience and stem cell research community at the Centre, with access to regular journal clubs and seminar series.

Relevant publications

1. Cheung A., Schachermayer G., Biehler A., Wallis A., Missaire M. & Hindges R. (2022) Teneurin paralogues are able to localise synaptic sites driven by the intracellular d… https://doi.org/10.3389/fnins.2022.915149
2. Karow, M., Camp, J.G., Falk, S. et al. Direct pericyte-to-neuron reprogramming via unfolding of a neural stem cell-like program. Nat Neurosci 21, 932–940 (2018) https://doi.org/10.1038/s41593-018-0168-3

3. Ana Dorrego-RivasDarren J ByrneYunyi LiuMenghon CheahCeren ArslanMarcela LipovsekMarc C FordMatthew S Grubb (2025) Strikingly different neurotransmitter release strategi…
https://doi.org/10.7554/eLife.105271

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Rescue rules: predicting protective and gain-of-function variant combinations in human disease genes

Lead Supervisor: Xianghua Li

Lead Supervisor Email: xianghua.li@kcl.ac.uk

Department: Medical and Molecular Genetics, School of Basic and Medical Biosciences

Primary Institution: King's College London

Project details

Background: About 5,000 human protein-coding genes have Mendelian disease associations, and variants rarely occur in isolation. In tumours especially, pathogenic variants often co-occur with other changes in the same gene. This complicates variant effect prediction, as combinatorial effects are not always additive: a second change can destroy or rescue protein function. For instance, several naturally occurring TP53 variants have been identified that restore folding and DNA binding in inactive hotspot mutants. However, researchers almost always study variant effects in isolation. We lack a systematic way to find them, and major variant-effect predictors and the ACMG framework still score variants individually.

Key question: Can we predict protective and gain-of-function variant combinations from the biophysical properties of single variants alone? We hypothesise that mutational effects on protein folding (ΔΔG_fold) and binding (ΔΔG_bind) are approximately additive, and because stabilising changes often cost activity and vice versa, variants chosen in energy coordinates rather than sequence coordinates should combine to recover or enhance function.

Objectives:

1. Map combinatory mutations from the database (months 1–12). Across ~5,000 protein-coding genes with established Mendelian disease association (OMIM morbid genes, ClinGen-curated), catalogue coding variants that co-occur in cis—from somatic multi-hit data (COSMIC, AACR GENIE, TCGA) and phased germline data (gnomAD, UK Biobank). Establish where combinations are enriched or depleted relative to chance. Then intersect with genes for which single-variant folding and binding energies can be inferred from published deep mutational scanning (currently ~50 human domains), define the testable subset, and evaluate additivity for every combination within it. A direct, falsifiable test on real human genotypes, at genome scale.

2. Design and test combinatory variant effects (months 6–24). Meanwhile, the student will build a pooled library of roughly 3,000 predicted double and triple variants in the TP53 DNA-binding domain, with predicted rescues, predicted neutrals, and coupled positions expected to violate additivity as built-in negative controls. The student will measure function by deep mutational scanning on the supervisor's established experimental platform, which can evaluate variants' effects on protein abundance and DNA binding at King's College London.

3. Validation of the biophysical effects (months 18–30, Manchester). Take around 200 informative variants into high-throughput, microfluidics-based assays at the Manchester Institute of Biotechnology to determine absolute parameters for stability and DNA-binding.

4. Predict (months 20–42, CRUK Cambridge), train an interpretable model that maps single-variant biophysics to combinatorial outcomes, benchmark it against various AI models including EVE and protein language models, and apply it to patient cohorts to ask whether predicted-rescued genotypes behave differently.

Scope: While generating a list of ~5,000 falsifiable, disease-relevant candidates, the student will use TP53 mutants as the experimental choice, because its existing suppressor mutations provide a positive control set no other human gene offers.

Interdisciplinarity: Human statistics and functional genomics (KCL), protein biophysics and microfluidics (Manchester), machine learning (CRUK Cambridge). The student sits at the join, and the project only works because all three are present.

Outcomes: The first systematic catalogue of protective variant combinations in human disease genes; a combinatorial variant-effect dataset of around 10,000 measurements deposited in MaveDB.

Facilities: KCL and MIB both have large-scale robotic-facilitated experimental platforms, sequencing analysis pipelines, imaging facilities, and HPC. CRUK provides AI model supervision and infrastructure. All Objective 1 datasets are public and need no additional access approval.

Relevant publications

1. Li X#, Lehner B#. TF-MAPS: fast high-resolution functional and allosteric mapping of DNA-binding proteins.BioRxiv. (2025) Doi: In Press at Nature Structural and Molecula… https://doi.org/10.1101/2025.10.20.683418v1

2. Xie et al., Dominance vs epistasis: the biophysical origins and plasticity of genetic interactions within and between alleles. Nature Commun 14: 5551 (2023) https://doi.org/10.1038/s41467-023-41188-8

3. Markin CJ et al. Revealing enzyme functional architecture via high-throughput microfluidic enzyme kinetics. Science 373:eabf8761 (2021) https://doi.org/10.1126/science.abf8761

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Nuclear genetic control of tissue-specific mitochondrial function: from human large-scale genomics to focused single-cell CRISPR screens

Lead Supervisor: Alan Hodgkinson

Lead Supervisor Email: alan.hodgkinson@kcl.ac.uk

Department: Medical and Molecular Genetics

Primary Institution: King's College London

Project details

Background:

Mitochondria are involved in many fundamental cellular processes, from energy production to calcium signalling and cell death. They carry their own small genome (mtDNA), but its correct functioning depends on hundreds of nuclear-encoded genes involved in its expression, processing and translation. Mitochondrial dysfunction is observed is almost all common diseases, including type 2 diabetes, obesity and neurodegeneration, yet it is not clear whether it is a cause or a consequence of disease.

One reason for this is that the role of mitochondria in disease is often hidden: a genetic variant may affect disease risk through a nuclear gene that controls mitochondria, but if this route is not recognised, the right therapeutic target is hard to identify. This picture is further complicated because mitochondrial processes are highly tissue-specific. In primary mitochondrial diseases the causal mutation is present in every cell, yet the disease often only affects certain tissues. In this project we will address these two questions directly: which disease-associated genetic variants act through mitochondria, and how tissue-specific are their effects?

Key question:

Which inherited genetic variants influence common disease risk through their effects on mtDNA gene expression, and in which tissues and cell types do they act?

Objectives:

1. Generate new maps of the genetic variants that influence mtDNA activity (expression) in key metabolic tissues, including brain, liver, skeletal muscle and adipose tissue, and identify the nuclear genes responsible for each signal using causal genetic inference, before testing how consistent these effects are across cell types using single-cell data.

2. Integrate these maps with large genetic studies of other mitochondrial measures, focusing on mtDNA copy number and mitochondria-related metabolite abundance and protein expression, to build a consensus map of how genetics shapes mitochondrial function. Test this map against risk of common metabolic diseases, such as type 2 diabetes and obesity, to find where mitochondria form part of the causal biology and may be targets for treatment.

3. Test the top candidate genes experimentally using CRISPR screens, to confirm their effects on mtDNA activity, and characterise how the strongest candidates affect mitochondrial function and cellular metabolism.

Methodology:

The student will harmonise large gene expression datasets from key metabolic tissues and map nuclear genetic variants associated with mtDNA gene expression. Causal genetic methods, such as colocalisation and Mendelian randomisation, will link these signals to candidate nuclear genes, and single-cell datasets will be used to refine where they act. These results will be combined with other genetic measures of mitochondrial function and tested against metabolic and neurological diseases. The strongest candidates will then be taken into the laboratory. Using pooled CRISPR screens, the student will activate or inhibit candidate genes and loci associated with specific nuclear variants in many cells at once. Phenotypic read-out will be through single-cell sequencing of both mtDNA and the total transcriptome, to measure the effects on mtDNA (copy number and variation), as well as nuclear and mitochondrial gene expression and nuclear genome accessibility.

Expected outcomes:

New tissue-resolved maps with direct functional validation of how genetic variation shapes mitochondrial gene expression and activity, together with a comprehensive characterisation of disease-associated variants and genes shown to act through mitochondria.

Facilities and resources:

High-performance computing facilities are available at King's College London, with access to UK Biobank and large tissue transcriptome datasets. Single-cell CRISPR screening and mitochondrial biology facilities are available and well-established at the MRC Mitochondrial Biology Unit, University of Cambridge.

Relevant publications

1. Centanini E, Pain O, Chinnery PF, Hodgkinson A. Nuclear genetic modulation of tissue-specific mitochondrial RNA processing contributes to common disease risk. Nature Com… https://doi.org/10.1038/s41467-026-72649-5
2. Burr SP, …, Chinnery PF, van den Ameele J. MitoPerturb-Seq identifies gene-specific single-cell responses to mitochondrial DNA depletion and heteroplasmy. Nature Structu… https://doi.org/10.1038/s41594-026-01779-7
3. Ali AT, Boehme L, Carbajosa G, Seitan VC, Small KS, Hodgkinson A. Nuclear genetic regulation of the human mitochondrial transcriptome. eLife 8, e41927 (2019) https://doi.org/10.7554/eLife.41927

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: From deletion to brain: AI-guided functional genomics of 22q11.2 deletion syndrome

Lead Supervisor: Anthony Vernon

Lead Supervisor Email: anthony.vernon@kcl.ac.uk

Department: Basic and Clinical Neuroscience

Primary Institution: King's College London

Project details

From deletion to brain: AI-guided functional genomics of 22q11.2 deletion syndrome

22q11.2 deletion syndrome (22q11.2DS) is the strongest known genomic risk factors for schizophrenia, yet carriers of the same deletion show substantial variation in cellular, neurobiological and clinical phenotypes. This raises a fundamental question: how much of an individual's biological phenotype is captured by the direct consequences of the deletion, and what additional biology may modify its expression in the brain and behaviour? We hypothesise that 22q11.2DS produces a reproducible core cellular signature, while variation around this signature captures individual-specific biology associated with neuroimaging endophenotypes and psychiatric symptoms. We will test this by integrating isogenic and patient-derived cellular models with machine learning, neuroimaging, and clinical phenotyping.

Aim 1 will define the cellular signature attributable to the 22q11.2 deletion. We will use an isogenic human ESC line (H1) engineered with the A-D 22q11.2 deletion, as compared to unedited clonal lines on the same genetic background. Multiple independent clones of each genotype will be differentiated into forebrain and ventral midbrain organoids. Molecular and functional phenotypes will be characterised longitudinally using single cell RNA sequencing and microelectrode array (MEA) recordings. Transcriptomic data will be analysed at appropriate biological-replicate or pseudobulk levels to avoid cellular pseudoreplication. Pathway- and gene-module representations will reduce dimensionality while retaining biological interpretability. A regularised linear support-vector machine (SVM) will then be trained to distinguish deletion from isogenic-control states, with model selection and validation performed across independent clones/differentiations. The resulting decision function will provide a continuous 22q11.2 deletion score, while stable feature weights and pathway enrichment will identify the molecular programmes most consistently associated with the deletion.

Aim 2 will quantify the cellular signature in patient-derived cell lines from individuals with 22q11.2DS. The isogenic SVM will be frozen and applied without refitting to cellular data from approximately 5–6 22q11.2DS donors as compared to an equivalent number of neurotypical age and sex matched controls. This will quantify the extent to which each donor expresses the experimentally defined deletion phenotype. We will then characterise the residual cellular variation not captured by the canonical deletion signature, using pathway and network analyses to identify candidate modifying

or compensatory processes. Where electrophysiological data are available, we will test whether deletion scores and residual molecular programmes correspond to neuronal-network phenotypes.

Aim 3 will bridge cellular phenotypes to the living human brain and clinical expression. The same donors have matched neuroimaging and clinical/symptom assessments. Given the small but deeply phenotyped sample, analyses will focus on cross-scale correspondence rather than high-dimensional prediction. We will test whether deletion-associated and residual cellular scores relate to dopamine synthesis capacity, prespecified structural MRI measures and symptom dimensions. Representational-similarity analyses will assess whether individuals who are biologically similar at the cellular level are also similar in brain structure and clinical phenotype. Conversely, low-dimensional MRI representations will be examined for correspondence with independently derived cellular signatures, providing proof-of-concept evidence that non-invasive brain phenotypes may reflect cellular biology.

Finally, experimentally derived signatures will be tested in larger independent human transcriptomic or post-mortem schizophrenia datasets, asking whether molecular patterns learned from a controlled genomic perturbation generalise to human disease.

Relevant publications

1. Sichlinger L, Hausherr M, Guerrisi S, Dutan-Polit L, Chennell G, Nagy R, Matuleviciute R, Nasser F, Farkas S, Bamford RA, Leung SK, Duarte RRR, Powell TR, Mill J, Marcus… https://doi.org/10.1126/sciadv.aea0755
2. Reid MJ, Rogdaki M, Dutan L, Hanger B, Sabad K, Nagy R, et al. Dopamine-related alterations in neurons derived from 22q11.2 deletion carriers. Schizophrenia Research. 2024. https://doi.org/10.1016/j.schres.2022.05.010
3. 3. Popovic D, Weyer C, Dwyer DB, Griffiths SL, Lalousis PA, Barnes NM, et al. Multivariate brain-blood signatures in early-stage depression and psychosis. JAMA Psychiatry. 2026. https://doi.org/10.1001/jamapsychiatry.2025.3803

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Deciphering protein post-translational modifications in neurodevelopmental disease

Lead Supervisor: Joseph Bateman

Lead Supervisor Email: joseph_matthew.bateman@kcl.ac.uk

Department: Basic and Clinical Neuroscience

Primary Institution: King's College London

Project details

Background

mTORopathies are rare neurodevelopmental disorders associated with epilepsy, autism and cognitive impairment. Tuberous Sclerosis Complex (TSC) is the most common mTORopathy. Mutations in TSC1 or TSC2 cause hyperactivation of mechanistic target of rapamycin (mTOR), a kinase that regulates protein phosphorylation. How these molecular changes disrupt brain development and cause neurological symptoms remains poorly understood. The Bateman lab has identified altered candidate mTOR-regulated proteins and phosphosites in TSC patient brain tissue and mouse and human neuronal models. Many of these proteins have roles in neurodevelopment.

We hypothesise that altered mTOR signalling changes the phosphorylation and function of key proteins, contributing to neurodevelopmental abnormalities in TSC and other mTORopathies.

Key question and objectives

This project will investigate which changes in mTOR-dependent phosphorylation contribute to abnormal neurodevelopment, and how they arise. The student will:

o determine how disease-associated mutant or hyperactive mTOR alters engagement with substrates and regulatory proteins

o establish which candidate phosphosites, recognition determinants and variants have functional consequences

o test prioritised mechanisms in disease-relevant neuronal models.

Interdisciplinary approach and methodology

The project combines the Bateman lab's mTORopathy biology and disease-derived datasets with complementary structural proteomics and functional genomics at Imperial.

To understand how mutant or hyperactive mTOR alters engagement with substrates and regulatory proteins, we will apply a kinase-enrichment and on-bead cross-linking mass spectrometry (XL-MS) approach developed at Imperial. Kinobeads capture kinase-associated complexes, while XL-MS reports protein proximity and interaction regions. Comparisons of control and TSC2-deficient cells and selected disease-associated MTOR variants will identify candidate changes in these assemblies.

Crosslinked peptides, integration with existing and new phosphoproteomic datasets, and targeted biochemical validation will define relationships. Co-immunoprecipitation and kinase assays will test prioritised interactions and substrate relationships.

To determine which molecular changes affect protein function, candidate phosphosites, recognition determinants and relevant variants from the Bateman datasets and interaction studies will be interrogated using the Child lab's human CRISPR-based oligo recombineering platform (huCORe). Precision mutagenesis, sequencing-based screens and targeted signalling measurements in control and TSC2 knockout HAP1 cells will prioritise consequential changes for neuronal testing. Selected isogenic edits can return to the interaction workflow to test altered kinase recognition.

Finally, biological significance will be tested in patient-derived and engineered TSC iPSC-derived neuronal models at KCL. Phospho-specific antibodies or targeted MS will validate selected phosphorylation changes. CRISPR/Cas9 editing of prioritised phosphosites or recognition determinants will test effects on neuronal development, morphology and signalling. Rescue experiments will ask whether correcting these molecular changes improves disease-relevant cellular phenotypes.

Expected outcomes

The project will identify functionally important mTOR-regulated events and establish how selected changes in protein engagement and phosphorylation contribute to abnormal neurodevelopment. Connecting patient and disease-model observations to mechanism and function will prioritise causal mechanisms for future therapeutic investigation.

Facilities and resources

The project is founded on the Bateman lab's disease-derived phosphoproteomic datasets, iPSC-derived TSC models, neurodevelopmental expertise and imaging systems at KCL. These are complemented by Imperial's huCORe engineering and Kinobead/XL-MS expertise and the Molecular Sciences Research Hub Proteomics Facility.

Relevant publications

1. Girodengo et al., (2026), The phosphoproteomic landscape of the neurological manifestations in tuberous sclerosis complex. Acta Neuropathologica, 151(1):60 https://doi.org/10.1007/s00401-026-03022-5
2. Sichlinger L, et al. (2026). Schizophrenia risk gene ZNF804A controls ribosome localization and synaptogenesis in developing human neurons. Sci Adv. 12(21):eaea0755 https://doi.org/10.1126/sciadv.aea0755
3. Benns HJ, Storch M, Falco JA, et al., Child MA. (2022). CRISPR-based oligo recombineering prioritizes apicomplexan cysteines for drug discovery. Nature Microbiology 7, 1… https://doi.org/10.1038/s41564-022-01249-y

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: The role of ICOS and ICOSL in maintaining tertiary lymphoid aggregates in Discoid Lupus Erythematosus

Lead Supervisor: Deborah Cunninghame Graham

Lead Supervisor Email: deborah.cunninghame-graham@kcl.ac.uk

Department: Medical and Molecular Genetics, KCL

Primary Institution: King's College London

Project details

Background: Discoid lupus (DLE) is an autoimmune skin of unknown aetiology, characterised by persisting inflamed, debilitating skin lesions. These lesions contain clusters of T and B lymphocytes, which may assemble into tertiary lymphoid aggregates (TLA). The factors driving skin homing, residence and the maintenance of TLAs are largely unknown. Co-stimulatory molecules, such as ICOS and ICOSL, expressed on activated T and B cells or stromal cells respectively, mediate the immune response in systemic lupus. Given the overlap of DLE with systemic disease, we propose that these co-stimulatory signals mediate persistence of skin lesions.

Hypothesis: Discoid lesions are characterised by the accumulation of ICOS+T cells within lymphoid aggregates within the skin. Blockade of co-stimulatory signals, at the ICOS-ICOSL axis, may disrupt the interaction between ICOS-expressing T cells and ICOSL-expressing antigen presenting or stromal cells, thereby causing regression of TLAs within DLE lesions, providing a mechanism for reducing the DLE disease burden.

Aim 1: Characterise in-situ transcript profiles of skin-resident lymphocyte cell-types within DLE skin lesions expressing ICOS or ICOSL. Aim 2: Identify immune cell types within DLE lymphocyte aggregates using spatial proteomics. Aim 3: Establish whether T cell ICOS expression increases the percentage of interacting ICOSL+B cells and determine the transcriptional programmes of ICOS+ vs ICOS-T cells and ICOSL+T cells and ICOS+B cells

Interdisciplinary skills: The project includes both dry and wet lab experimentation. The student will develop skills in both mechanistic molecular immunology, and analysis of spatial transcriptomic and proteomic datasets, within a busy multi-disciplinary environment, collaborating with clinical academics statisticians/bioinformaticians and basic scientists.

Methodology: Analysis of spatial transcriptomic and proteomic datasets: The student will analyse a large Xenium spatial transcriptomic dataset with paired spatial proteomic data from 40 DLE patients with/without confirmed TLAs within inflammatory skin lesions. A state-of the-art paired analytic workflow will be adopted, comprising traditional and AI-driven tools, from initial QC/normalisation dimensionality reduction and cell-type deconvolution, through to the identification of spatially differentially regulated genes. Co-Culture experiments: To verify the spatial analyses, flow sorted CD4+T cells and B cells from the same 40 individuals will be co-cultured and evidence of immune co-stimulation at Day 0 and at Day 6 sought by flow-cytometry to ascertain T and B cell proliferation,

differentiation and antibody secretion by B cells using ELISA. Finally, to identify whether the ICOS-ICOSL signal is driving T-B cell interaction we will block ICOS-ICOSL interaction with anti-human ICOS Ab.

Expected outcomes: The project will discover whether immune cells expressing ICOS or ICOSL are enriched within TLAs in DLE lesions. The student will establish the existence of shared transcriptomic and proteomic signatures in ICOS- and ICOSL expressing cells with other co-stimulatory molecules, such as OX40 and OX40L. Finally, the project will determine the functional consequences of ICOS expression in T cells, using co-culture experiments.

Facilities and resources: The student will be based in the Department of Medical and Molecular Genetics and Dermatology at King's College, London. There is well-equipped laboratory space to support tissue culture, flow cytometry and molecular biology experiments and access to the high-performance CREATE cluster with CPU/GPU architecture and fast network interconnectivity and data storage facilities to support all the analyses required for this project. Implementation support is available from expert research software engineers within the e-Research facility and the King's Hub for Applied Bioinformatics.

Relevant publications

1. Stoker K, ... Tull TJ, Tsoka S and Karagiannis SN. Tumor-infiltrating B cells evolve towards interferon-rich trajectories aligned with immunotherapy in melanoma. J Exp... https://doi.org/10.1186/s13046-026-03797-1
2. ICOS a genetic risk factor for SLE
3. Cunninghame Graham DS, Wong AK, McHugh NJ, Whittaker JC, Vyse TJ. Evidence for unique association signals in SLE at the CD28-CTLA4-ICOS locus in a family-based study. Hu... https://doi.org/10.1093/hmg/ddl395

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: From RNA to synapses: uncovering how ZNF804A controls neuronal development

Lead Supervisor: Deepak Srivastava

Lead Supervisor Email: deepak.srivastava@kcl.ac.uk

Department: Basic and Clinical Neuroscience

Primary Institution: King's College London

Project details

Schizophrenia is a highly heritable and complex psychiatric condition, but how associated genetic variants alter the development and function of human brain cells remains poorly understood. One of the first genes linked to schizophrenia through large-scale genetic studies was ZNF804A. Although often described as a regulator of gene transcription, its precise function in human neurons is unclear.

Our recent work used genetically matched human induced pluripotent stem cells, differentiated into cortical glutamatergic neurons, to examine the effects of reduced ZNF804A. Mutant neurons formed more excitatory synapses, accumulated ribosomal and translation-associated proteins within neuronal processes, and showed increased local protein synthesis. Yet reduced ZNF804A produced only modest changes in overall gene expression. These findings suggest that ZNF804A may connect RNA regulation, local protein production and synapse development.

Preliminary analysis has revealed a further unexpected result. Reduced ZNF804A is predicted to cause widespread changes in RNA splicing. Splicing allows cells to assemble different sections of RNA into distinct molecular instructions from the same gene. These alternative RNA forms, or isoforms, can determine where a protein is produced, how it functions and which molecules it interacts with. The central question is therefore: does ZNF804A regulate neuronal development through RNA splicing, and can altered splicing explain the abnormal protein synthesis and synapse formation observed in mutant neurons?

The project will integrate computational biology, stem-cell neuroscience, transcriptomics, spatial molecular biology and functional genomics. First, the student will analyse existing bulk RNA-sequencing data to predict splicing changes and determine whether affected transcripts share sequence motifs or biological functions. This will identify candidate RNA-binding proteins that may mediate the effects of ZNF804A. The strongest candidates will be examined in control and ZNF804A-mutant neurons to determine whether their abundance or cellular localisation is altered.

Second, the student will generate RNA samples from different neuronal compartments, separating the nucleus and cell body from neurites forming axons and dendrites. At the University of Exeter, Oxford Nanopore long-read RNA sequencing will identify complete RNA isoforms and test predictions derived from short-read data. This will provide an atlas of how loss of ZNF804A changes the RNA molecules present in different neuronal compartments and their likely effects on protein function.

Finally, the student will investigate the spatial and functional consequences of the strongest altered-splicing candidates. BaseScope RNA imaging will visualise specific isoforms within individual neurons, while super-resolution microscopy will test whether altered RNAs or proteins are redistributed within synapses and neuronal processes. Targeted CRISPR-based genome editing will manipulate selected RNA-binding proteins or splice variants. The student will test whether these interventions reproduce or reverse changes in protein-synthesis machinery and synapse formation in ZNF804A-mutant neurons.

The project will establish how disruption of a schizophrenia-associated gene alters RNA processing and local protein production during human neuronal development, and test whether ZNF804A-driven splicing changes contribute to altered synapse formation.

The student will work in an interdisciplinary environment at King's College London and the University of Exeter. King's supervisors will provide expertise and resources in human stem-cell-derived neuronal models, genome editing, computational analysis, and high-content and super-resolution imaging. Exeter supervisors will provide long-read sequencing, bioinformatics expertise and associated resources.

Relevant publications

1. Sichlinger L, et al. Schizophrenia risk gene ZNF804A controls ribosome localization and synaptogenesis in developing human neurons. Science Advances. 2026. doi: https://doi.org/10.1126/sciadv.aea0755
2. Clifton NE, et al. Developmental disruption to the cortical transcriptome and synaptosome in a model of SETD1A loss-of-function. Human Molecular Genetics. 2022. doi: https://doi.org/10.1093/hmg/ddac105
3. Deans PJM, et al. Psychosis Risk Candidate ZNF804A Localizes to Synapses and Regulates Neurite Formation and Dendritic Spine Structure. Biological Psychiatry. 2017. doi: https://doi.org/10.1016/j.biopsych.2016.08.038

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Chromatin gating of human interneuron maturation: how SETD1A mutations disrupt the parvalbumin gene regulatory programme

Lead Supervisor: Oscar Marín

Lead Supervisor Email: oscar.marin@kcl.ac.uk

Department: Centre for Developmental Neurobiology, Institute of Psychiatry, Psychology & Neuroscience

Primary Institution: King's College London

Project details

Background. Parvalbumin (PV) interneurons synchronise activity across the cerebral cortex, and their dysfunction is among the most reproducible findings across intellectual disability, epilepsy, autism and schizophrenia. In humans, these cells mature over months to years, far more slowly than in mice, and this protracted programme is the window during which disease mutations are likely to act. Heterozygous loss-of-function mutations in SETD1A, which encodes a histone methyltransferase that deposits H3K4 methylation at active promoters, cause intellectual disability, autism and epilepsy and are associated with one of the largest known effect sizes for schizophrenia. We have found that removing Setd1a from interneuron progenitors in mice selectively delays PV interneuron maturation and reduces expression of Ppargc1a and Erbb4, two genes required for this process. This suggests that SETD1A acts as a chromatin gate that is set when PV interneurons become competent to mature. Whether it does so in human cells, and through which regulatory elements, is unknown.

Key questions. The student will ask three questions. Which regulatory elements are marked by SETD1A-mediated H3K4me3 in human interneurons? Does heterozygous loss of SETD1A delay or block the maturation of human PV interneurons? And can the resulting deficit be corrected by restoring the downstream programme?

Methodology. To answer these questions, the student will use a SETD1A heterozygous loss-of-function iPSC line and its isogenic control obtained from the Wellcome Sanger Institute. From these lines, the student will generate subpallial organoids that produce cortical interneurons and combine them with separately patterned pallial organoids to build cortical assembloids in which excitatory and inhibitory neurons develop together. Three approaches will be used. First, chromatin and transcriptional profiling: single-cell multiome (RNA plus ATAC) of sorted interneurons at two stages and CUT&RUN for H3K4me3 to map where the mark is lost in mutant cells. This will identify the regulatory elements that are bound by SETD1A and the genes whose induction fails. Second, the student will perform xenotransplantation of organoid-derived interneuron precursors into newborn immunodeficient mice, which is currently the only system allowing human PV interneurons to fully mature. After nine months, spatial transcriptomics will be used to determine whether the mutant program recovers over time, stalls, or fails entirely. Third, the student will carry out a rescue experiment by reintroducing the strongest downstream candidate via lentivirus to determine if the deficit can be reversed after bypassing competence. Throughout the project, the student will analyse

multiome and spatial data, annotate affected regulatory elements against human fetal and post-mortem references, and incorporate SETD1A-dependent genes into cell-type-specific regulatory networks of the cortex. The balance between bench and computational work can shift with the student's interests.

Expected outcomes. The project will create the first map of SETD1A-dependent regulatory elements in human cortical interneurons and assess how heterozygous loss affects their maturation. These results may have relevance to human disease because SETD1A haploinsufficiency is strongly linked with developmental delay, epilepsy and schizophrenia.

Facilities and resources. The work will be carried out at the Centre for Developmental Neurobiology, King's College London. The organoid platform of the Neurodevelopment Cluster of the UK Human Functional Genomics Initiative provides standardised, staff-supported organoid production at scale. Single-cell and spatial genomics will be conducted through the Single Cell Omics Platform and the Spatial Biology Facility, xenotransplantation through the Biological Services Facility, and computing through King's e-Research and the CDN Bioinformatics Core.

Relevant publications

1. Moissidis M, et al. (2025). A postnatal molecular switch drives activity-dependent maturation of parvalbumin interneurons. Cell 188:5555-5575 https://doi.org/10.1016/j.cell.2025.06.029
2. Shi Y, Wang M, Mi D, et al. (2021). Mouse and human share conserved transcriptional programs for interneuron development. Science 374:eabj6641 https://doi.org/10.1126/science.abj6641
3. Bernard C, Exposito-Alonso D, et al. (2022). Cortical wiring by synapse type-specific control of local protein synthesis. Science 378:eabm7466 https://doi.org/10.1126/science.abm7466

Please direct project-specific enquiries to:

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Decoding cell-type-specific splicing: linking protein–RNA binding maps to saturation mutagenesis

Lead Supervisor: Jernej Ule

Lead Supervisor Email: jernej.ule@kcl.ac.uk

Department: Department of Basic and Clinical Neuroscience & UK DRI Centre at King's

Primary Institution: King's College London

Project details

Background. Genetic variants that disrupt RNA splicing are a major cause of human disease, yet most remain uninterpretable. Outside the canonical splice sites, clinical guidelines treat computational predictions as supporting evidence only, so the majority of such variants are classified as being of uncertain significance. Splicing predictors have variable performance, and especially struggle to identify the impact on cell-type-specific regulation.

Two recent advances change what is now possible. First, saturation mutagenesis has made experimental splicing data abundant: the OpenSplice resource measured the effect of more than 590,000 variants on 608 human exons, finding that the regulatory landscape of each exon is strikingly individual, with variable importance of splicing silencers versus enhancers. Second, nucleotide-resolution maps of where RNA-binding proteins (RBPs) contact pre-mRNA, generated by CLIP methods, reveal the trans factors that could explain those landscapes. What is missing is the bridge between them: we know which positions matter, and we know which proteins bind where, but not which binding events cause which variant effects, or how this differs between cell types.

Key question. Can protein–RNA binding maps explain, and then predict, why a variant changes splicing in one cell type but not another?

Objectives. The overarching objective is to integrate protein-RNA binding with saturation mutagenesis, transcriptome and splicing measurements in three human cell lines: an epithelial line (MCF7), a widely used reference line (HEK293), and neuronal cells derived from iPSCs. Specifically, this will be done by: (1) Assembling and performing (where needed) comparative CLIP binding maps for a panel of splicing-regulatory RBPs, alongside 'global CLIP' that represents the combinatorial binding landscape of all RBPs in several cell types. (2) Integrating these maps with measured variant effects from saturation mutagenesis, testing whether positions that are mutationally sensitive coincide with binding by specific RBPs, and whether the enhancer/silencer architecture of an exon can be assigned to named proteins. (3) Testing causality for a prioritised set of exons by perturbing candidate RBPs and re-measuring splicing. Moreover, specific prioritise variants will be functionally investigated further through prime editing studies in human iPSC-derived neurons in collaboration with other members of Ule lab. (4) Using the resulting binding-informed features to improve prediction of cell-type-specific variant effects, benchmarking against current deep-learning models,

and evaluating whether binding maps from accessible cell lines can extend predictions to additional cell types and tissues that cannot be cultured.

Interdisciplinarity. The project sits between two complementary traditions: the Ule lab's experimental and computational work on protein–RNA interactions, and the Lehner lab's large-scale measurement of genotype-to-phenotype relationships. The student will work across molecular biology, genomics, statistics and machine learning, with access to both environments.

Methods. CLIP and related crosslinking approaches; iPSC-derived neuronal culture; RNA-seq and splicing quantification; targeted RBP depletion; reporter-based validation of selected variants; and computational integration using established open pipelines, motif analysis, and model benchmarking and retraining.

Expected outcomes. A comparative atlas of RBP binding across cell contexts, aligned to measured variant effects; a mechanistic account of which proteins shape the regulatory architecture of alternatively spliced exons; and improved, openly released models and feature sets for interpreting splicing variants in a cell-type-aware way — directly useful for clinical variant interpretation and for designing RNA-targeted therapies.

Relevant publications

1. Quarantani G, Clarke J, Thompson M, Sang F, Valcárcel J, Lehner B. OpenSplice: the impact of half a million mutations on the alternative splicing of 600 human exons. bio… https://doi.org/10.64898/2026.05.22.727141
2. Capitanchik C, Wilkins OG, Wagner N, Gagneur J, Ule J. From computational models of the splicing code to regulatory mechanisms and therapeutic implications. Nature Revie… https://doi.org/10.1038/s41576-024-00774-2
3. Hallegger M, Chakrabarti AM, Lee FCY, et al., Ule J. TDP-43 condensation properties specify its RNA-binding and regulatory repertoire. Cell 2021;184:4680–4696. — Demonst… https://doi.org/10.1016/j.cell.2021.07.018

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional genomics of immune-epithelial communication at the human brain barrier

Lead Supervisor: Joana F Neves

Lead Supervisor Email: joana.pereira_das_neves@kcl.ac.uk

Department: Centre for Host-Microbiome Interactions

Primary Institution: King's College London

Project details

The choroid plexus is a specialized epithelial tissue located within the brain ventricles that produces cerebrospinal fluid (CSF) and forms the blood-CSF barrier. Beyond its traditional role in fluid secretion, the choroid plexus is increasingly recognized as a critical neuroimmune interface that regulates brain development, tissue homeostasis and responses to injury. Although the choroid plexus contains diverse populations of immune cells, little is known about how these cells interact with the surrounding tissue, or which gene regulatory programs encode this communication.

Studies in mice identified group 2 innate lymphoid cells (ILC2) as important residents of the choroid plexus contributing to brain development, cognitive function, neurogenesis and recovery from neurological injury. At other brain barrier tissues (lung, intestine, skin), ILC2 integrate signals from epithelial, neuronal and immune cells to maintain tissue homeostasis through dynamic transcriptional states. However, whether equivalent regulatory networks exist at the human choroid plexus is completely unexplored.

This project hypothesizes that the human choroid plexus establishes a specialised neuroimmune niche that regulates ILC2 phenotype, function and epigenetic state, while ILC2-derived signals reciprocally influence choroid plexus development, barrier properties and cerebrospinal fluid composition.

To test this hypothesis, this project will combine human induced pluripotent stem cell-derived choroid plexus organoids with primary human ILC2 to create the first model of human choroid plexus-ILC2 interactions. Bringing together stem cell biology, neuroscience, immunology and functional genomics, the project will uncover fundamental mechanisms of cellular communication at the human brain barrier.

Aim 1: Establish a human choroid plexus-ILC2 neuroimmune model

Choroid plexus organoids and primary human ILC2 will be co-cultured to determine how these cell populations influence one another. Cell localisation, survival, activation, and secretory activity will be assessed using advanced imaging, flow cytometry, cytokine profiling, and analysis of CSF-like fluid produced by the organoids.

Aim 2: Map the gene regulatory networks underlying choroid plexus-ILC2 communication

Paired transcriptomic and epigenomic profiling (RNAseq,ATACseq) on both the immune and the choroid plexus compartment of the co-cultures, will identify signalling pathways, gene regulatory networks and chromatin changes induced by choroid plexus-ILC2 interactions. Integration with extensive single-cell datasets generated by the supervisory team will enable construction of the first functional genomic atlas of this previously uncharacterized human neuroimmune niche and a ranked set of candidate regulatory nodes

Aim 3: Determine how physiological and inflammatory signals reshape the neuroimmune niche

The co-culture system will be challenged with neuroactive molecules and inflammatory mediators to determine how environmental cues influence communication between the choroid plexus and ILC2. Prioritized candidate pathways from Aim 2 will then be tested directly using CRISPR for functional validation.

The project will reveal how immune and epithelial cells cooperate at the human brain's borders and identify regulatory pathways that control brain development, homeostasis and inflammation, with implications for ageing, neurodevelopmental disorders and neuroinflammatory disease.

The project offers interdisciplinary training in human stem cell and organoid culture, advanced immunology, flow cytometry, transcriptomics, epigenomics and bioinformatics. It is supported by world-leading expertise in choroid plexus organoid technology, human innate lymphoid cell biology and functional genomics, together with access to established organoid platforms, unique multi-omics datasets and state-of-the-art imaging and sequencing facilities, ensuring the feasibility.

Relevant publications

1. Jowett GM, Read E, Roberts LB, Coman D, Vilà González M, Zabinski T, Niazi U, Reis R, Trieu TJ, Danovi D, Gentleman E, Vallier L, Curtis MA, Lord GM, Neves JF. Organoids… https://doi.org/10.1016/j.celrep.2022.111281
2. Pellegrini L, Bonfio C, Chadwick J, Begum F, Skehel M, Lancaster MA. Human CNS barrier-forming organoids with cerebrospinal fluid production. Science. 2020 Jul 10;369(65… https://doi.org/10.1126/science.aaz5626
3. Tang SS, Apsley EJ, Pellegrini L. Functional Imaging Methods for Investigating 3D Choroid Plexus Organoids. Methods Mol Biol. 2025 Jan 17. doi: Epub ahead of print. PMID… https://doi.org/10.1007/7651_2024_601

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional Genomics of Alzheimer's Risk: From Epigenetic QTLs to Functional Validation

Lead Supervisor: Sarah Marzi

Lead Supervisor Email: sarah.marzi@kcl.ac.uk

Department: Basic and Clinical Neuroscience

Primary Institution: King's College London

Project details

Background

AD genetic risk is concentrated in non-coding regions of the genome active in microglia, pointing to disrupted gene regulation as a key disease mechanism. Yet we still lack a clear picture of which variants drive these effects, which genes they act on, and how this differs across brain cell types. This project builds on a unique resource: neurons, microglia, oligodendrocytes and an astrocyte-enriched population from the frontal cortex of over 150 donors from the Brains for Dementia Research (BDR) cohort, profiled for H3K27ac, chromatin accessibility (ATAC-seq) and DNA methylation, with matched genotype and metadata. Two ongoing studies will extend this resource: histone acetylation profiling across intermediate disease stages and resilient individuals, and in extreme old age , spanning the full trajectory of brain ageing and disease.

Key questions

Which genetic variants alter histone acetylation, and more broadly other layers of gene regulation, in a cell-type-specific manner in the ageing and AD brain, and what does this reveal about mechanisms of AD risk?

1. Map histone acetylation QTLs (haQTLs) in different cell type populations, extending to additional cohorts as data become available.

2. Apply multi-omics factor analysis to jointly model histone acetylation, chromatin accessibility and DNA methylation, building a fuller picture of gene regulation per cell type.

3. Overlap fine-mapped haQTLs, and more broadly other epigenetic QTLs, with AD genetic risk loci to prioritise causal variants, target genes and cell types.

4. Functionally test a shortlist of candidate genes using CRISPR activation/interference in human stem cell-derived microglia and neurons.

The project sits at the interface of statistical genetics, genomics, computational biology and molecular neuroscience, combining large-scale data analysis with hands-on cell biology. It suits candidates keen to work across both.

Methodology

The student will first map haQTLs, testing association between genotype and histone acetylation at nearby regulatory regions, separately in four cell type populations. Multi-omics factor analysis be used to integrate multi level epigenetic data, identifying axes of variation linked to genotype, disease status and metadata (sex, medication history). Fine-mapped haQTLs will be overlapped with published AD risk loci via colocalisation to prioritise candidate genes and cell types. As new intermediate-stage/resilient and ageing cohort data arrive, analyses will extend to how regulatory effects shift across disease progression and ageing. Finally, prioritised genes will be tested via CRISPR activation/interference in our in-house iPSC-derived microglia and neurons, assessing effects on gene expression and cellular phenotypes.

Expected outcomes

The student will produce the first cell-type-resolved map of histone acetylation QTLs in the ageing and AD brain, extended across the disease trajectory and into extreme ageing, integrated with other epigenetic layers for a more comprehensive view of gene regulation. This will yield experimentally validated candidate causal genes underlying AD risk, alongside a reusable multi-omics pipeline applicable to other diseases.

Resources

The student will access the large-scale multi-omic BDR dataset with matched genotype and metadata, plus incoming data from resilience and ageing cohorts. Joint supervision from Dr Sarah Marzi and Prof Jonathan Mill provides genomic analysis infrastructure, in-house iPSC-derived microglia/neuronal models, CRISPR platforms, and training via the wider UK FGI DLA programme.

Relevant publications

1. Marzi, S. J., Leung, S. K., Ribarska, T., Hannon, E., Smith, A. R., Pishva, E., ... & Mill, J. (2018). A histone acetylome-wide association study of Alzheimer's disease… https://doi.org/10.1038/s41593-018-0253-7
2. Abbasova L, Urbanaviciute P, Hu D, Ismail JN, Schilder BM, Nott A, et al. CUT&Tag recovers up to half of ENCODE ChIP-seq histone acetylation peaks. *Nature Communications.* 2025;16:2993. https://doi.org/10.1038/s41467-025-58137-2 Nature
3. Hannon E, Gorrie-Stone TJ, Smart MC, Burrage J, Hughes A, Bao Y, et al. DNA-methylation QTLs, gene expression and complex traits. *American Journal of Human Genetics.* 2018;103:654–665. https://doi.org/10.1016/j.ajhg.2018.09.007

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: SHISA6-mediated synaptic resilience in human neurons: From genetic risk to disease-related challenge

Lead Supervisor: Prof. Kei Cho

Lead Supervisor Email: kei.cho@kcl.ac.uk

Department: Basic and Clinical Neuroscience

Primary Institution: King's College London

Project details

A family-based genetic study linked an intronic SHISA6 variant to the age of onset for cognitive impairment. However, its causal status and functional consequences remain unknown. SHISA6 is a postsynaptic scaffolding and auxiliary protein that regulates the function and synaptic anchoring of glutamate AMPA receptors which mediate fast synaptic communication between neurons. Emerging evidence indicates that SHISA6 expression declines with natural aging in human post-mortem brain tissue and may be vital for maintaining the stability of synaptic connections, a process critical for memory preservation. Building on our preliminary rodent findings demonstrating that SHISA6 upregulation protects synaptic function during disease-related challenges, this project investigates whether SHISA6 can similarly safeguard human neuronal networks and whether human genetic risk variants modulate these resilience pathways. Utilising human induced pluripotent stem cell (iPSC)-derived excitatory neurons, this project will test whether SHISA6 dosage and specific intronic mutations stabilise synapses and networks exposed to amyloid-beta (Aβ) or pathological tau.

Objective 1 – Test SHISA6-dependent resilience in human neurons. The student will establish reproducible Aβ and tau challenge models, employing SHISA6 overexpression and gene knockdown to determine whether the protein is both necessary and sufficient for neuroprotection. Calcium imaging will measure spontaneous activity and network responses to single neuron stimulation. High-resolution imaging of AMPA receptors and PSD-95 will evaluate synapse structure, complemented by targeted electrophysiological validation to link network-level changes directly to underlying synaptic mechanisms. Findings will be rigorously replicated across independent preparations and at least two distinct iPSC genetic backgrounds.

Objective 2 – Investigate the human SHISA6 genetic signal. Although an intronic SHISA6 variant correlates with age at cognitive impairment, it remains unknown whether this locus directly alters SHISA6 expression or acts via alternative regulatory mechanisms. The student will integrate existing human genetic and brain expression quantitative trait locus datasets, followed by functional assays comparing the regulatory activity of alternative alleles in iPSC-derived neurons. This will establish whether the genetic association points toward a direct, SHISA6-mediated mechanism.

Objective 3 – Elucidate mechanisms of SHISA6-mediated synaptic protection. The student will test whether altered SHISA6 modifies AMPA receptor localisation or synapse retention and whether this preserves functional responses during pathological challenges. A focused comparison between wild-

type SHISA6 and a mutant construct lacking a key synaptic interaction domain will define the structural determinants required for protection, guiding downstream functional validation. The student will choose the most informative follow-up from these results.

Professor Kei Cho will lead the project within an established synapse research environment at King's College London. The laboratory will provide iPSC-derived neurons and access to advanced microscopy tools; the £5,000 annual wet-lab allowance will support the focused perturbation and validation experiments. The student will gain training in human neuronal models, genetics, quantitative imaging, coding, statistics and synaptic physiology. The first three months will be used to refine the hypothesis, select endpoints and agree a training plan. The student will present across FGx-DLA and explore a genomics or data-analysis placement.

Experiments will be randomised where practical, analysed blind and repeated across differentiations and cell lines. Predefined image and culture quality criteria, openly shared protocols and version-controlled analysis code will support reproducibility. Donor background and sex will be recorded; supervision will be individualised.

Relevant publications

1. doi.org/ doi: doi: https://doi.org/10.1016/j.crmeth.2026.101418
2. Cho supervisory team. Brain Communications. 2025. https://doi.org/10.1093/braincomms/fcaf234
3. Cho supervisory team. Acta Neuropathologica Communications. 2023. https://doi.org/10.1186/s40478-023-01703-w

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Integrating human genetics and TDP-43 functional genomics to prioritise therapeutic targets in ALS

Lead Supervisor: Ahmad Al Khleifat

Lead Supervisor Email: ahmad.al_khleifat@kcl.ac.uk

Department: Basic and Clinical Neuroscience

Primary Institution: King's College London

Project details

Context/background of the project

Motor neurone disease (MND) is a progressive neurodegenerative disease in which motor neurons lose function. In most cases, the RNA-binding protein TDP-43 becomes dysfunctional, causing widespread changes in gene expression and RNA processing, including abnormal splicing and cryptic RNA events. The challenge is to determine which of these thousands of molecular changes contribute to disease and which are secondary consequences. This project will combine experimentally defined TDP-43 changes with human genetics and disease datasets to identify the most relevant mechanisms and therapeutic targets.

Key question and objectives

The central question is: Which consequences of TDP-43 dysfunction are supported by human genetics and human disease data, and therefore represent the strongest therapeutic targets?

The student will identify TDP-43-regulated RNA-processing events that are reproduced in human MND, test their support using common and rare genetic variation and clinical phenotypes, and develop an interpretable computational framework to prioritise RNA events, genes and pathways for further investigation.

Interdisciplinary

The project combines human genetics, bioinformatics, statistical genomics, neuroscience, RNA biology and machine learning. The student will be primarily supervised by Dr Ahmad Al-Khleifat and embedded in his computational genetics group, with day-to-day support in genomic analysis, Project MinE, genotype–phenotype analysis and therapeutic target discovery. Dr Matthew White will co-supervise the TDP-43/RNA-biology components, providing expertise in RNA processing, splicing, nonsense-mediated decay and human neuronal models.

Methodology

The project will start from existing human iPSC-derived neuronal datasets in which TDP-43 function has been perturbed, including transcriptome-wide expression and splicing, cryptic and NMD-sensitive RNA events, direct TDP-43 binding by iCLIP and regulatory sequence features.

Candidate events will be tested in independent human MND datasets, including post-mortem tissue, patient-derived neurons and single-cell/single-nucleus data. Human genetic analyses will include GWAS, eQTL/sQTL integration, fine-mapping and colocalisation, targeted rare-variant analyses using Project MinE sequencing, and existing TWAS/PWAS evidence. High-priority candidates may also be assessed against age at onset, progression and survival. An interpretable computational or machine-learning framework will integrate these evidence layers and identify why individual candidates are prioritised.

Expected outcomes

The project will generate an integrated map of TDP-43-regulated RNA-processing abnormalities and identify events, genes and pathways supported by convergent experimental, human-disease and genetic evidence. It will also produce an interpretable framework for therapeutic target prioritisation. The strongest candidates may be taken forward for focused experimental validation and could inform future therapeutic development, biomarkers or patient stratification.

Facilities and resources available

The student will be primarily based in Dr Al-Khleifat's group at King's College London. Resources include Project MinE individual-level sequencing and clinical phenotypes, large post-mortem and patient-derived transcriptomic datasets, neuropathologically characterised TDP-43/FTLD-MND material, and established fine-mapping, TWAS and PWAS analyses. An approximately 9,000-sample EPIC DNA-methylation dataset with phenotype information is available for targeted follow-up. The White laboratory provides complementary TDP-43 perturbation, splicing, iCLIP and human neuronal-model resources for biological interpretation and focused experimental validation.

Relevant publications

1. White, M. A., Kim, E., Duffy, A., Adalbert, R., Phillips, B. U., Peters, O. M., Stephenson, J., Yang, S., Massenzio, F., Lin, Z., Andrews, S., Segonds-Pichon, A., Metter… https://doi.org/10.1038/s41593-018-0113-5
2. Hu, J., Pain, O., Al Khleifat, A., Shatunov, A., Andersen, P. M., Basak, N. A., Cooper-Knock, J., Corcia, P., Couratier, P., de Carvalho, M., Drory, V., Glass, J. D., Go… https://doi.org/10.1101/2025.04.12.25325716
3. Vallikivi, J., Maarten Kooyman, M., Consortium, P. M. ALS. S., Kirby, J., Nigel Leigh, P., Iacoangeli, A., Al-Chalabi, A., & Al Khleifat, A. (2026). CYP2D6 variants in a… https://doi.org/10.1093/brain/awag178

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: In vivo barcoding-enabled functional CRISPR screens to optimise CAR T cell therapy for cancer

Lead Supervisor: Rahul Roychoudhuri

Lead Supervisor Email: rr257@cam.ac.uk

Department: Department of Pathology

Primary Institution: University of Cambridge

Project details

Background

CAR T cell therapy has transformed treatment of certain blood cancers but most patients relapse, and efficacy against solid tumours remains limited, largely because T cells become dysfunctional within tumours. CRISPR knockout screens can identify gene deletions that improve T cell performance, but most are performed in culture, missing the complexity of the in vivo tumour microenvironment. In vivo screens are far more informative but technically difficult.

The Liston laboratory (Babraham Institute) has developed FlowCode, a fluorescent barcoding system that labels cells with unique combinations of fluorescent proteins before transfer into mice (Burton OT et al., Immunity 2024; 57: 1586-1602). After recovery, flow cytometry identifies each cell's barcode (and therefore its genetic perturbation) while simultaneously measuring phenotype. Together, our laboratories have generated proof-of-concept data showing that FlowCode-barcoded, CRISPR-perturbed CAR T cells can be resolved after tumour challenge, with individual perturbations identified across tumour and spleen.

Objectives

The project will systematically identify genetic perturbations that enhance CAR T cell function in vivo. The student will: (1) optimise the FlowCode-CRISPR platform, increasing barcode complexity and refining hit-calling analytics; (2) execute targeted CRISPR screens in CAR T cells using focused libraries in syngeneic tumour models with multi-tissue harvest; (3) validate and mechanistically characterise top hits.

Interdisciplinarity

The project spans cancer immunology, functional genomics, synthetic biology, high-dimensional cytometry, and computational biology. The supervisory team brings together T cell immunology and cell therapy engineering (Roychoudhuri) with functional genomic screening and FlowCode barcoding (Liston; Burton et al., Immunity 2024).

Methodology

CAR T cells transduced with a pooled CRISPR sgRNA library, each sgRNA coupled to a unique FlowCode barcode, will be transferred into tumour-bearing mice. Cells recovered from tumour,

spleen, lymph nodes, and blood will be analysed by flow cytometry to resolve barcode identity alongside phenotypic and functional markers. Computational analysis will identify perturbations enriched or depleted in defined states or compartments. Hits will be validated in single-gene experiments including rechallenge models.

Expected outcomes

(i) An optimised in vivo CRISPR screening platform for cell therapy products; (ii) a ranked catalogue of perturbations enhancing CAR T cell persistence, effector function, or tumour infiltration; (iii) mechanistic characterisation of top hits; (iv) candidate edits for next-generation CAR T products.

Facilities and resources

Roychoudhuri laboratory, Department of Pathology, Cambridge. Established expertise in CRISPR screening, CAR T engineering, and murine tumour models; FlowCode barcoding through collaboration with the Liston laboratory. Access to spectral flow cytometry, SPF animal facilities, and Cambridge Genomics Services.

Relevant publications

1. For a full list of publications, see roychoudhurilab.org https://roychoudhurilab.org/publications/
2. Conti AG*, Evans AC*, von Linde T*, Deguit CDT, Whiteside SK, Wesolowski AJ, Imianowski CJ, Yamashita-Kanemaru Y, Dahmani L, Chapman J, Pillay AM, Al-Deka A, Greaves R,... https://doi.org/10.1038/s41590-025-02389-z
3. Wesolowski AJ, Pillay AM, Vardaka P, Nasrallah R, Greaves R, Li H, Loffreda I, Jenkin C, James AM, Nubling A, Ward CJ, von Linde T, Conti AG, Tzeng SF, Dahmani L, Evans... https://doi.org/10.1126/science.adz8203

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: How Genetic Diseases of Lipid Metabolism Differently Impact Brain Cell Development and Function

Lead Supervisor: Janet Deane

Lead Supervisor Email: jed55@cam.ac.uk

Department: Cambridge Institute for Medical Research, Dept of Clinical Neuroscience

Primary Institution: University of Cambridge

Project details

Most research into early-onset neurodevelopmental and neurodegenerative diseases have, quite sensibly, focussed on neuron-based models of disease. However, it is becoming clear that additional brain cell types such as microglia and astrocytes play crucial, but poorly understood, roles in these diseases. Our lab studies paediatric brain diseases caused by disrupted lipid metabolism. We recently demonstrated that loss-of-function of ST3GAL5, which causes a fatal childhood epilepsy, abolished electrical activity in neurons [1]. We have preliminary data showing that the same genetic disruption also causes severe dysfunction in astrocytes, including disruption of both calcium and cytokine signalling. Interestingly, this is caused by different lipid compensation pathways due to the novel ways these cell types express and utilise glycosphingolipids.

Glycosphingolipid metabolism is almost entirely unexplored in astrocyte biology opening new avenues for understanding how rare genetic diseases impact brain cell functions beyond neuronal dysfunction. This project will exploit comparative lipidomics and proteomics in CRISPRi-based models of iPSC brain cells to map how the same genetic changes impact different cell types. In addition to astrocytes, we have iPSC microglial models where we expect that phagocytic and cytokine-mediated phenotypes will be affected by GSL disruptions. There are opportunities for the student to select alternative GSL-related neurodevelopmental diseases or neurodegenerative lysosomal storage disorders for phenotypic characterisation.

In addition to the wet-lab based work, this project will involve generating and analysing relatively large datasets and developing pipelines for comparative analyses between cell types and GSL diseases. Depending on the student's interests and the insights from these data, there will also be the opportunity to focus in on specific changes to explore more detailed molecular mechanisms.

The project will be based in the Cambridge Institute for Medical Research (CIMR) which is based on the Cambridge Biomedical Campus which includes the Addenbrooke's Hospital and major biotech including AstraZeneca. The CIMR houses outstanding facilities for techniques to be implemented in this project. Our proteomics facility houses a cutting-edge Orbitrap Astral mass spectrometer enabling exceptional coverage of whole cell and plasma membrane proteomes. Our microscopy facility includes multiple confocal instruments enabling super-resolution imaging. The structural biology facility supports both experimental and computational approaches as well as direct access to national facilities including Diamond Light Source. Our lab has extensive expertise in lipid and protein

biochemistry, genetic modification and differentiation of iPSC disease models, functional cell assays including electrophysiology and structural biology. Furthermore, CIMR is a highly collaborative and supportive research environment enabling expansion of collaborations and enhancement of technical expertise.

Relevant publications

1. [1] Sialylated Gangliosides are Required for Neuronal Function by Maintaining the Plasma Membrane Proteome (2026) Barrow, H.G., Han, Z.Z. et al. Deane, J.E. BioRχiv and... https://doi.org/10.64898/2026.03.18.712603
2. [2] Plasma membrane remodeling in GM2 gangliosidoses drives synaptic dysfunction (2025) Nicholson AS, et al. Deane JE. PLoS Biol. 23:e3003265 https://doi.org/10.1371/journal.pbio.3003265
3. [3] Conformational dynamics and membrane insertion mechanism of B4GALNT1 in ganglioside synthesis (2025) Welland JWJ, et al. Deane JE. Nat Commun. 16:5442 https://doi.org/10.1038/s41467-025-60593-9

Please direct project-specific enquiries to:
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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Gut instinct: investigating epigenetic regulation and dysregulation using epigenome editing in patient-derived organoids

Lead Supervisor: Professor Matthias Zilbauer

Lead Supervisor Email: mz304@medschl.cam.ac.uk

Department: Cambridge Stem Cell Institute (CSCI); Department of Paediatrics

Primary Institution: University of Cambridge

Project details

How does a cell remember its job, and what happens when it mis-remembers? The intestinal epithelium renews itself every few days, yet its cells reliably adopt and hold distinct identities and functions. Epigenetic marks, including DNA methylation (DNAm) and histone modifications, carry much of this information. When that control fails, cells can settle into abnormal states that persist. Patient-derived intestinal epithelial organoids (IEOs) retain the epigenetic memory of the biopsies they came from. Our lab uses IEOs to study epigenetic mechanisms in health and inflammatory bowel disease (IBD). IBD is a chronic inflammatory condition of the gut, in which localised inflammation repeatedly relapses and remits in the same location. This pattern suggests a stable underlying change, which may be epigenetically mediated. We identified specific DNAm changes in IEOs from patients with severe disease that underlie dysregulated major histocompatibility complex class I (MHC-I) antigen presentation (ref. 1). In collaboration with the Milner-MRC-AZ Functional Genomics Screening Laboratory (FGSL), we have since completed an arrayed CRISPR screen to identify regulators of MHC-I activation in IBD. Our results suggest that regulators of other epigenetic marks, such as histone modifications, may play a role in MHC-I activation in this context. Building on these findings, this PhD project asks how histone modifications and DNAm act together to regulate epithelial cell state, and how that control breaks down in IBD. The student will address three aims:

1. Epigenetic characterisation of DNAm-stratified organoids.

The student will combine arrayed screening data with existing IEO datasets, including DNAm array, RNA-seq, ATAC-seq and clinical data, to identify candidate loci dysregulated in IBD, generate testable hypotheses about the epigenetic mechanisms involved and identify DNAm-selected IEOs for follow-up analysis. To test the resulting hypotheses, a small number of IBD and control IEO lines will be profiled for specific histone mark(s) using CUT&Tag. IEO lines will be obtained through interaction with the MRC Hub for Human Disease Models led by Prof. Zilbauer.

2. Functional interrogation using modified CRISPR/Cas9.

Guided by the analyses from Aim 1, the student will use CRISPR-based epigenome editing (catalytically dead Cas9 fused to chromatin or DNAm effectors) in IEOs coupled with gene expression readouts, to dissect the mechanisms underlying epigenetic maintenance of disease-associated cell states. Small-molecule inhibitors will provide an independent means of perturbation.

3. Phenotyping using advanced imaging.

Finally, the student will extend these perturbation readouts beyond gene expression. In collaboration with FGSL, the student will use high-content imaging and develop bespoke analysis pipelines to investigate how altered epigenetic regulation affects cell fate determination, lineage composition and MHC-I expression at scale.

Training will span organoid biology, CRISPR and epigenetic editing, clinically linked omics bioinformatics and quantitative imaging, with wet and dry work integrated throughout. The Cambridge Stem Cell Institute (CSCI), Milner Therapeutics Institute, FGSL and MRC Hub are all housed in the Jeffrey Cheah Biomedical Centre, giving access to an extensive organoid biobank with linked molecular and clinical data, and to laboratory, imaging and computing infrastructure. The student will also have access to a PhD network and training opportunities through the wider CSCI.

Together, this project will identify the epigenetic mechanisms that establish and maintain disease-associated epithelial states in IBD, moving from correlative multiomic signatures in patient organoids to functional characterisation of the regulatory landscape of DNAm and MHC-I expression. These data will support the identification of novel therapeutic targets and may help explain inter-patient variability in disease severity and treatment response.

Relevant publications

1. Dennison TW, Edgar RD, Payne F, et al. Patient-derived organoid biobank identifies epigenetic dysregulation of intestinal epithelial MHC-I as a novel mechanism in severe… https://doi.org/10.1136/gutjnl-2024-332043
2. Bello E, Long K, Iwama S, Steer J, Cooper SE, Alasoo K, et al. Alzheimer's-associated PTK2B regulatory variant alters microglial function. iScience. 2026. https://doi.org/10.1016/j.isci.2026.115688
3. Matte JC, Bakker OB, Ohl MA, Cisternino F, Manrique-Rincón AJ, Husmann A, et al. High-content imaging of lymphocyte activation and dysfunction. bioRxiv. 2026. https://doi.org/10.64898/2026.02.10.704860

Please direct project-specific enquiries to:
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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional Genomics of safety of RNA therapeutics

Lead Supervisor: Ritwick Sawarkar

Lead Supervisor Email: rs2099@cam.ac.uk

Department: Departments of Biochemistry, Genetics and Pharmacology

Primary Institution: University of Cambridge

Project details

RNA-targeted Therapeutics such as Antisense Oligonucleotides (ASOs) and small interfering (si)RNA represent a transformative class of emerging drugs capable of treating previously undruggable genetic disorders. Despite their clinical success, sequence- and class-dependent liver and kidney toxicity remain a critical safety issue affecting a small proportion of patients. The molecular mechanisms driving sequence-independent cytotoxicity and why individual patient sensitivity varies are poorly understood. In collaboration with AstraZeneca and Functional Genomics Screening Lab at Cambridge, we carried out a genome-wide CRISPR knock-out screen in human cells to identify cellular modulators of ASO cytotoxicity. 18 out of top 50 hits in the screen belong to a single unexpected biological pathway. Investigating how genetic variation within this pathway influences population-wide toxicity to RNA therapeutics is critical for improving therapeutic index enabling personalized medicine.

This proposed studentship will address one core question: How do genetic variants within the identified pathway modulate RNA-therapeutic toxicity across diverse patient cohorts? The project will address this question in three independent objectives, leveraging different strengths of the UK human FGI network.

- Objective 1: Validate primary screen hits using a focused pooled secondary CRISPR knock-out and CRISPR interference (CRISPRi) screen across multiple human cell models (e.g., primary hepatocytes/iPSC-derived lines) using toxic ASO and siRNA.

- Objective 2: Interrogate human population databases (e.g., UK Biobank, gnomAD) to identify naturally occurring coding and regulatory variants within candidate pathway genes and then to link them with toxicity seen in clinical trials of ASO and siRNA.

- Objective 3: Mechanistically evaluate the effect of identified human variants on ASO uptake, protein binding, nucleolar stress, signaling and subcellular localization using cell line models.

This project operates at the intersection of functional genomics, chemical biology, pharmacogenomics, and computational biology. The student will combine high-throughput experimental genomics (screening, RNA-seq) with bioinformatic pipelines (GWAS integration, variant annotation) for holistic training across both wet- and dry-lab.

Methodology

- Secondary CRISPR Screening: Design a custom pooled gRNA library targeting candidate pathway genes and regulatory elements. Perform dose-response toxicity screens in cellular models (e.g. hepatocytes) to rank key mediators.

- Population Genetics & Bioinformatic Prioritization: Map common and rare SNP/indel variants in candidate genes using UK Biobank and gnomAD datasets. Prioritize functional variants based on predicted loss-of-function (LoF) or expression quantitative trait loci (eQTL) profiles.

- Functional Characterization: Engineer human variants into cell lines and measure phenotypes to diverse siRNA and ASOs (PS-gapmers, LNA modifications) using high-content imaging, transcriptomics, and assays for cellular stress response/ signaling.

Expected Outcomes

- Identification of essential genes and pathways governing ASO and siRNA toxicity.

- A catalogue of human genetic variants that confer altered susceptibility to ASO/ siRNA-induced cellular stress.

- Predictive rules for patient stratifications in clinical trials to minimize adverse drug reactions.

- Open-access functional genomics datasets benefiting the broader RNA therapeutics community and FGI network.

The PhD candidate will have access to state-of-the-art infrastructure, including Next-Generation Sequencing (Illumina NovaSeq/Oxford Nanopore), and high-content fluorescent microscopy platforms. Computing resources include access to high-performance computing (HPC) clusters pre-configured for population-scale genomics workflows. The host labs provide established cell culture pipelines, established ASO/ siRNA chemistry libraries, and know-how in secondary screens.

Relevant publications

1. Integrating transcriptomics and proteomics to assess antisense oligonucleotide safety and efficacy: a time-resolved approach. van Leeuwen D, et al. NAR Mol Med. 2026 Mar… https://doi.org/10.1093/narmme/ugag016
2. HSP70 binds to specific non-coding RNA and regulates human RNA polymerase III. Leone S, Srivastava A, Herrero-Ruiz A, Hummel B, Tittel L, Campalastri R, Aprile-Garcia F,… https://doi.org/10.1016/j.molcel.2024.01.001
3. N1-methylpseudouridylation of mRNA causes +1 ribosomal frameshifting. Mulroney TE, Pöyry T, Yam-Puc JC, Rust M, Harvey RF, Kalmar L, Horner E, Booth L, Ferreira AP, Ston… https://doi.org/10.1038/s41586-023-06800-3

Please direct project-specific enquiries to:

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Establishing an Arrayed Synthetic mRNA Functional Genomics Platform

Lead Supervisor: Catherine Wilson

Lead Supervisor Email: chw39@cam.ac.uk

Department: Department of Pharmacology/Gurdon Inst.

Primary Institution: University of Cambridge

Project details

Pooled CRISPR screens have transformed functional genomics, but they remain restricted to binary readouts and cannot capture complex morphological outcomes. Arrayed screens offer direct genotype-to-phenotype linkage and high-content imaging but current gain-of-function approaches, such as plasmid cDNA, lentiviral open reading frames (ORFs)eomes, or CRISPRa, suffer from bottlenecks such as toxicity, slow continuous expression, or epigenetic silencing.

This project will establish a fundamentally new capability for the UK functional genomics landscape: the first high-throughput, arrayed synthetic mRNA gain-of-function screening platform. By merging high-content imaging with an arrayed library of modified synthetic mRNAs, we aim to bypass the integration and delivery bottlenecks of traditional screens. The new platform will unlock the ability to systematically discover transcription factors (TFs) capable of rapidly forcing cell fate transitions. Initially, we will determine whether a transient TF pulse can route mesoderm into First vs. Second Heart Field (FHF vs. SHF) cardiac lineages. This PhD project integrates vector engineering, automated RNA synthesis, high-content imaging, and human iPSC differentiation.

Phase 1: Vector Engineering & Transfection Optimisation

The student will use a novel standardised plasmid backbone (generated within the Wilson lab) that allows easy entry of ORFs with negative selection. The plasmid contains cis regulatory regions within the 3'UTR that have been designed to maximise protein yield. A Poly(A) tract is incorporated into the plasmid to allow for efficient and high-yield in vitro translation (IVT). mRNA will be generated using modified nucleosides and enhanced Cap to maximise translation kinetics and limit activation of innate immunity pathways. The student will optimise efficient cloning (by either Golden Gate or HiFi assembly) and IVT reaction of multiple ORFs across multi well plates for arrayed high-throughput workflows.

Using reporter genes, the student will establish high-efficiency transfection in Day 2 hiPSC-derived mesoderm to achieve >80% delivery with <10% cytotoxicity. In parallel, immunofluorescent imaging will be performed to assess FHF and SHF markers (e.g. ISL1, MEF2C, TBX1, HCN4, TBX5, and NKX2-5) for downstream High-Content Imaging (HCI) assays.

Phase 2: Library Synthesis and Primary Arrayed Screen

A targeted library of ~200 developmental TFs will be cloned into the IVT backbone. Using liquid handling robotics at the FGSL, the student will establish an automated 384-well platform for plasmid

linearisation, IVT synthesis, DNase treatment, and RNA purification. Day 2 hiPSCs in 384-well plates will be mesoderm-induced, transfected with the synthetic mRNA library, and fixed/stained at Day 4 (48 hours post-transfection) for HCI evaluation.

Phase 3: Hit Validation and Mechanistic Profiling

The student will perform a hit confirmation screen of up to 30 genes with at least two independent replicates, each with at least two technical replicates per mRNA. The student will chart the biological landscape of the TFs to understand specific enrichment in developmental processes, signalling pathways, and lineage networks. The student will map the downstream epigenetic and transcriptomic consequences of the top 2-4 confirmed FHF and SHF drivers Using RNA-seq and ATAC-seq. Standardised protocols and raw multi-omics datasets will be formatted for open-access deposition into the UKHFGI data portal, with an aim to ultimately expand the mRNA platform and make it available for researchers with a wide variety of biological questions.

Relevant publications

1. https://doi.org/10.1101/2023.08.02.551469
2. , https://doi.org/10.1093/nar/gkaf496
3. https://doi.org/10.1101/2025.03.13.643129

Please direct project-specific enquiries to:

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Identifying Druggable Synthetic-Lethal Vulnerabilities in Primary Human VEXAS Blood Stem Cells

Lead Supervisor: Paul Lehner

Lead Supervisor Email: pjl30@cam.ac.uk

Department: Cambridge Institute for Therapeutic Immunology and Infectious Disease

Primary Institution: University of Cambridge

Project details

Background and proposed methodology:

VEXAS syndrome is a recently described severe adult-onset disease causing systemic inflammation, bone marrow failure and death. It is driven by the acquisition of a somatic mutation in UBA1, an X-linked gene encoding the main ubiquitin-activating enzyme, in haematopoietic stem cells (HSCs). The mutation impairs ubiquitylation, triggering proteostasis stress and innate immune activation. Current therapies predominantly suppress inflammation without eliminating the underlying mutant clone. There is therefore a compelling need to identify genotype-selective vulnerabilities that can be exploited to eliminate UBA1-mutant HSPCs while preserving normal haematopoiesis.

By combining a novel ex vivo HSC culture system developed by the Wilkinson lab with the VEXAS expertise developed in the Lehner Lab, the key aim of this project is to identify druggable genetic dependencies of VEXAS in primary human CD34+ HSCs. Using functional genomic CRISPR screen technologies we will identify a VEXAS HSC synthetic lethality, where losing a second gene is toxic to those cells carrying the VEXAS-specific mutation.

Using established protocols in the Lehner/Wilkinson labs, isogenic mutant and control human HSCs will be generated by base editing. Pooled lentiviral libraries targeting roughly ~5,000 genes (ubiquitin/proteostasis, stress response, inflammation, druggable genes) will be screened in ex vivo HSC expansion cultures. Guide depletion will be analysed with established frameworks (e.g. MAGeCK) to identify genes with differential dependency between mutant and control HSCs and top hits may be followed up with Perturb-seq. Putative hits will be prioritised based on novelty, tractability, and druggability, and validated using targeted CRISPR deletion and/or small-molecule inhibitors. Functional validation will be performed using in vitro and in vivo assays and followed up with mechanistic studies.

This interdisciplinary project spans functional genomics, stem cell biology, genome engineering, computational genomics and haematology/immunology. The student will work between and Prof Paul Lehner's lab (Cambridge Institute of Therapeutic Immunology and Infectious Disease) and Prof Adam Wilkinson's lab (Cambridge Stem Cell Institute). The student will gain skills in functional genomic screens, human HSC culture and gene editing, single-cell analysis, bioinformatics, colony forming unit assays, xenotransplantation assays.

Key question:

Can we identify genotype-selective, druggable vulnerabilities that can be exploited to eliminate UBA1-mutant HSCs while preserving normal haematopoiesis?

PhD project objectives:

1. Optimise CRISPR screens to identify genes selectively essential in VEXAS mutant HSCs
2. Validate and prioritise druggable targets for VEXAS syndrome
3. Investigate the mechanism of action for identified CRISPR hits

Expected outcomes:

1. A pipeline for functional genomic screens in mutant human HSCs
2. A map of selective genetic dependencies in VEXAS-mutant HSCs
3. A functionally and molecularly validated VEXAS-specific essential gene in VEXAS-mutant HSCs
4. Open datasets, protocols, and results in a peer-reviewed publication

Facilities and resources:

Based at the Jeffrey Cheah Biomedical Centre (JCBC), on the Addenbrookes Biomedical Campus, the student will have access to world class core facilities for flow cytometry and cell sorting, single-cell sequencing, histology, imaging, high-performance computing and bioinformatics, and animal facilities. The Milner Institute is also located in the JCBC and available to provide local support with CRISPR screening.

Relevant publications

1. Tchasovnikarova et al., Science 2015 https://doi.org/10.1126/science.aaa7227
2. Meaker et al., Blood 2025 https://www.sciencedirect.com/science/article/pii/S0006497125022360
3. Wilkinson et al., Nature 2019 https://www.nature.com/articles/s41586-019-1244-x

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Mapping genetic variation in disease through pooled imaging screen

Lead Supervisor: Prof Catherine Tralau-Stewart

Lead Supervisor Email: CJT92@cam.ac.uk

Department: Milner Therapeutics Institute, School of Biological Sciences, University of Cambridge

Primary Institution: University of Cambridge

Project details

Background

Approximately 90% of missense variants in ClinVar are variants of uncertain significance (VUS), a major bottleneck in clinical genomics that prolongs diagnosis. The burden falls most heavily on rare disease, where private variants lack the population frequency and segregation data that interpretation typically requires, and two thirds of patients remain undiagnosed following exome sequencing. Multiplexed assays of variant effect address this gap. Saturation genome editing installs variants at the endogenous locus and resolves their effects at nucleotide resolution. However, the readout is cell survival, informative only where the gene is required for proliferation in the assay line. This approach may miss variants in non-essential genes, those that impair function without compromising viability, and gain-of-function variants.

Rationale

Cellular organisation offers a broader readout, capturing effects that may not reach the threshold of cell death. Organelle and nuclear morphology, membrane trafficking and cytoskeletal architecture are tightly regulated, and their disruption is pathogenic. Protein mislocalisation patterns can distinguish missense variants in the same gene that cause distinct diseases (PMID:39353438). Morphological profiling has predicted variant pathogenicity with high accuracy (PMID:42127894). Using imaging to study cellular organisation offers omics-scale richness at a fraction of the cost of sequencing-based profiling, retaining throughput and high resolution at single-cell and subcellular levels.

Objectives

The project asks how genetic variation reshapes cellular organisation. The student will build a pooled, image-based variant phenotyping method, combining imaging readouts (e.g. multiplexed immunofluorescence, Cell Painting) with in situ sequencing (ISS) for variant identification. These generate a multidimensional spatial profile per variant, group variants by mechanism of disruption and severity, and establish their functional consequences.

Methodology

The project builds on a new collaboration between the FGx cluster at Imperial College London (variant engineering and characterisation at scale) and the MRC-AZ-UCam Joint Functional Genomics Screening Laboratory at the Milner Therapeutics Institute (target discovery in human cells). The

student will engineer a panel of prioritised VUS in human haploid cells using CRISPR/Cas9 and homology-directed repair pipelines established at Imperial. Pooling cells that harbour different variants makes the approach scalable, but is only feasible if genotype can be decoded from the same cells through ISS. Padlock probes designed against the VUS region are imaged over successive cycles, revealing each cell's genotype in place. The student will optimise this workflow for robustness and for compatibility with protein and marker staining.

Training

Training spans genome editing, spatial imaging, cell biology and computational analysis, and suits students from molecular biology, bioengineering, bioimaging, or computational biology backgrounds. The student will be encouraged to shape the project's direction according to their own interests, for example, incorporating machine vision approaches, integrating other omics, performing mechanistic studies on identified phenotypes, and designing microfluidic systems to scale ISS. The strongest candidate will be curious This project will suit a student who is enthusiastic about techniques and methodological innovation, and comfortable refining and iterating experiments until they are robust, and able to work across disciplines. The student will be embedded within the highly collaborative and supportive environment across the research labs, developing technical and transferable skills for careers in functional genomics.

Expected outcome

The project will extend systematic variant phenotyping to genes beyond binary viability, with cellular spatial organisation as a complementary, multidimensional readout.

Relevant publications

1. Benns HJ, Storch M, Falco JA, et al. CRISPR-based oligo recombineering prioritizes apicomplexan cysteines for drug discovery. Nat Microbiol. 2022;7:1891-905 https://doi.org/10.1038/s41564-022-01249-y
2. Das A, Grech J, Hung S, Wu J, Callafe C, Corrie A, Yeung K, Goodwin I, Yu D, Hassan S, Reid K, Storch M, Child M. CORe Designer: a CRISPR design tool for proteome engine… https://doi.org/10.64898/2026.06.12.731864
3. Wong CH, Wingett SW, Qian C, Hunter M, Taliaferro JM, Ross-Thriepland D, Bullock SL. Genome-scale requirements for dynein-based transport revealed by a high-content arra… https://doi.org/10.1083/jcb.202306048

Please direct project-specific enquiries to:

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Epigenetic regulation of transcript choice across brain ageing and neurodegeneration

Lead Supervisor: Mina Ryten

Lead Supervisor Email: mr2022@cam.ac.uk

Department: Clinical Neuroscience

Primary Institution: University of Cambridge

Project details

Background: Ageing is the major risk factor for neurodegenerative disease, but how age-related molecular changes alter gene function across brain cell types remains poorly understood. Two processes change markedly with age: the epigenome and RNA processing, which determines which full-length transcript isoforms a gene produces. Both are highly cell-type specific, yet it is unclear how epigenetic state relates to RNA processing across neurons, astrocytes and oligodendrocytes, or how these relationships change with age and disease.

A major obstacle is the difficulty of studying chronological ageing in experimentally tractable human brain cell types. This project will exploit a human cellular ageing resource generated by semi-direct reprogramming of fibroblasts from healthy donors aged 3 months to 92 years, including 20 lines. Unlike conventional iPSC reprogramming, this approach retains age-associated donor features and can generate cortical neurons, astrocytes and oligodendrocytes.

Key Questions & Objectives: The central question is whether age-associated epigenetic remodelling contributes to cell-type-specific changes in RNA processing and full-length transcript choice, and whether these relationships are altered in neurodegenerative disease.

The project will:

(1) identify age- and cell-type-associated relationships between epigenetic state and transcript usage;

(2) test whether these are reproduced in human brain ageing and neurodegenerative disease; and

(3) functionally test selected relationships in age-retaining cellular models.

Interdisciplinarity: The project integrates epigenomics, transcriptomics and experimental modelling, combining expertise in long-read DNA and epigenetic analysis (Mill, Exeter), human brain RNA processing and long-read transcriptomics (Ryten, Cambridge), and age-retaining neuronal and glial models with experimental phenotyping (Mortiboys, Sheffield).

Methodology: A central innovation will be to pair long-read DNA and RNA sequencing. Native long-read DNA sequencing can localise epigenetic modifications on individual DNA molecules and distinguish modification types. Preliminary data from the Mill group suggest striking cell-type differences, including substantially higher hydroxymethylation in sorted neurons than glial populations. Long-read RNA sequencing provides a complementary readout, resolving complete

transcript structures, including promoter choice, exon combinations and alternative transcript ends. Integrating these layers will move beyond broad associations between “methylation” and “expression” to test whether age- and cell-type-associated epigenetic states are coupled to RNA processing and full-length transcript choice. The strongest relationships will then be examined in human brain datasets spanning development, ageing and neurodegenerative disease, using published resources and in-house unpublished datasets from the Mill and Ryten laboratories, including cell-type-resolved epigenomic and transcriptomic datasets.

Expected Outcomes: The project will define age- and cell-type-associated epigenetic–transcript relationships and determine which are preserved, exaggerated, lost or redirected in neurodegenerative disease. A small number of high-confidence loci will then be prioritised for mechanistic testing in the age-retaining cellular models. Targeted perturbation of the relevant epigenetic or regulatory state will test whether altering that state changes transcript usage and downstream cellular phenotypes. The student will therefore move from association towards causal functional genomics.

Facilities & Resources: The project is supported by age-retaining cellular models, long-read sequencing and analytical infrastructure, human brain datasets and established computational pipelines across the three centres. The student will gain training in computational genomics, epigenomics, long-read DNA and RNA sequencing, human cellular models and targeted perturbation.

Relevant publications

1. García-Ruiz S, Gustavsson EK, Zhang D, et al., Ryten M. Splicing accuracy varies across human introns, tissues, age and disease. Nature Communications 16, 1068 (2025). D… https://doi.org/10.1038/s41467-024-55607-x
2. Franklin A, Davies JP, Clifton NE, et al., Mill J. Cell-type-specific DNA methylation dynamics in the prenatal and postnatal human cortex. Cell Genomics 5, 101010 (2025)… https://doi.org/10.1016/j.xgen.2025.101010
3. Gatto N, Dos Santos Souza C, Shaw AC, et al., Mortiboys H. Directly converted astrocytes retain the ageing features of the donor fibroblasts and elucidate the astrocytic… https://doi.org/10.1111/acel.13281

Please direct project-specific enquiries to:

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Why do immune killer cells fail in tumours?

Lead Supervisor: Anneliese Speak

Lead Supervisor Email: as3234@cam.ac.uk

Department: Medicine

Primary Institution: University of Cambridge

Project details

Context and background

Cytotoxic T cells (CTLs) and natural killer (NK) cells are immune cells that can kill cancer cells. Inside solid tumours they are often worn down by the hostile environment and become dysfunctional, or "exhausted". Drugs that release the brakes on T cells (checkpoint inhibitors) have transformed care for some patients, but many do not respond, side effects can be serious, and the reasons are unclear. NK cells can attack tumours that T cells miss, yet we know far less about how they become dysfunctional or how to modulate it.

Key question and objectives

Which genes drive killer cells into dysfunction, and can we switch them off to restore anti-tumour activity? The student will:

1. Nominate candidate genes by analysing public and in-house bulk and single cell RNA-seq data.

2. Run genome-wide CRISPR screens in primary human NK cells and/or CTLs under tumour-like stress.

3. Validate hits and uncover their mechanism, including in tumour co-culture models.

4. For the top candidates use single cell RNA sequencing combined with CRISPR perturbations (Perturb-seq) to see how each knockout reshapes a cell's gene-expression programme.

The balance between NK cells and CTLs will be shaped by the student's interests.

Interdisciplinarity

This project combines immunology, genome engineering and data science. The student will both generate and analyse data (statistics, single-cell and network analysis), with training provided in both experimental and computational skills.

Methodology

We have validated CRISPR-Cas9 editing, pooled screening and Perturb-seq workflows in primary human CD8 T and NK cells, so the student can move quickly to screening.

Year 1: learn primary cell culture and gene editing, analyse existing datasets, and test a few genes by flow cytometry (proliferation, surface markers, cytokines, killing).

Years 2-3: design and run screens, analyse them with established pipelines, and follow up hits with Perturb-seq and co-culture.

Years 3-4: mechanistic insights, data integration and thesis.

While some computational tools have been developed these are evolving rapidly with AI/ML approaches and it is expected the student will investigate relevant tools where appropriate. Data will be integrated with existing human genetic resources including those curated by Open Targets and via key collaborators and other sources including the 100,000 genomes project.

Expected outcomes

- A ranked list of new regulators of immune-cell dysfunction and a reusable open dataset.
- Validated candidates with mechanism, as potential targets for cell therapy or immunotherapy.
- First-author publications; open code and data following FAIR principles.
- Skills in functional genomics, primary cell engineering, computational analysis and communication, for careers in academia, industry or clinical research.

Facilities and resources

Hosted by the Speak group at the Cambridge Institute for Therapeutic Immunology and Infectious Disease (CITIID), University of Cambridge, with established screening and analysis pipelines and access to the facilities within the Jeffrey Cheah Biomedical Centre (JCBC), including the BRC flow phenotyping facility. The University of Cambridge hosts multiple high-performance computing clusters to facilitate the downstream analysis.

Career development and impact

Within CITIID there is a strong community of PhD and post-doctoral associates to provide a peer network and fortnightly seminar series. More broadly there is a busy calendar of events within the Biomedical campus including Cambridge AI club, Cambridge Immunology Network and Milner Seminar series.

Relevant publications

1. Publication supplied by supervisory team. https://pubmed.ncbi.nlm.nih.gov/40678524/
2. Publication supplied by supervisory team; accepted in Science Advances. 2026. https://www.biorxiv.org/content/10.64898/2026.03.19.709783v1

Please direct project-specific enquiries to:

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Prime editing screens in appetite-regulatory neurons

Lead Supervisor: Florian Merkle

Lead Supervisor Email: fm436@cam.ac.uk

Department: Pharmacology

Primary Institution: University of Cambridge

Project details

Background and rationale

Obesity has a strong genetic basis, and many obesity-associated genetic variants are enriched in appetite-regulatory neuron populations. While animal models have been instrumental in characterising these neurons, they differ substantially from human neurons in their functional responses, hampering clinical translation. We therefore developed robust methods to generate large numbers of human appetite-regulatory cell populations in culture from induced pluripotent stem cells (iPSCs). These human neurons resemble their counterparts in the brain in the genes they express and their functional responses to drugs like semaglutide (Ozempic/Wegovy). These cultures present a unique opportunity to test how human obesity-associated genetic variants lead to functional changes in variant-to-function (V2F) studies that could identify novel therapeutic targets for obesity.

Methodology

We have shown that gene knockout (KO) in iPSC-derived hypothalamic neurons is efficient (>80%), but most obesity-associated genetic variants are single nucleotide variants (SNVs) that do not knock out gene function. Historically, SNV editing has been relatively inefficient, but now a current PhD student in our group (jointly supervised by Prof. Michael Ward) has shown that prime editing can introduce SNVs in iPSCs at efficiencies of 50-90%.

Objectives

1) Validate prime editing efficiency of obesity-associated SNVs. We will first prioritise candidate obesity-associated SNVs based on their computationally predicted editing efficiency and likely effect on cellular (e.g. coding variants likely to affect protein structure). We will then use targeted sequencing to test the efficiency and zygosity of SNV introduction into iPSCs or iPSC-derived hypothalamic neurons.

2) High-throughput SNV screening with prime editing. Next, we will introduce mRNA encoding the prime editor and guide RNAs for ~200 candidate SNVs in arrayed format to facilitate both single-cell transcriptomics and image-based readouts to correlate genotype to phenotype.

3) Validate hits. For any SNVs that significantly alter cellular phenotypes, we will carry out deeper functional phenotyping such as calcium imaging and neuropeptide secretion to gain insight into mechanisms of action.

Contingencies: Since efficient gene KO is established in hypothalamic models, there are countless opportunities to carry out V2F studies using CRISPR KO should prime editing prove technically challenging, or if effect sizes are small.

Interdisciplinarity and training opportunities

This study provides a rich training environment for a PhD student, since it will expose them to state-of-the-art iPSC culture and CRISPR methods (Merkle & Ward), training in human genetics and computational biology (Barroso & Perry) and training in functional genomic study design and target prioritisation from our colleagues at FGSL and AstraZeneca to maximise the potential impact of the studentship.

Facilities and resources

Our group at the Department of Pharmacology at the University of Cambridge has the necessary cell cultures facilities, ethical approvals, and expertise to carry out the proposed project. Our proposal builds on strong and established relationships with FGSL and AstraZeneca at the Cambridge Biomedical Campus, with whom we are carrying out a CRISPR KO screen in the proposed iPSC-derived hypothalamic model system and who have access to liquid handling robotics and automated imaging required for the proposed V2F studies. We envision these studies will benefit from its intellectual and financial resources of a new national obesity research institute (UK-ORI) funded by the MRC and BHF.

Expected outcomes

Upon completing this project, the successful applicant will have gained experience in cutting-edge functional genomics approaches and model systems, trained in human genetics and screen design, and generated unique datasets with direct translational potential.

Relevant publications

1. Merkle F, et al. Neuron. https://www.cell.com/neuron/fulltext/S0896-6273(19)30640-3
2. Merkle F, et al. bioRxiv. 2024. https://www.biorxiv.org/content/10.1101/2024.04.02.587825v2
3. Merkle F, et al. Nature Genetics. 2024. https://www.nature.com/articles/s41588-024-01694-x

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Decoding immunogenetic risk in psychiatric disorders

Lead Supervisor: Mary-Ellen Lynall

Lead Supervisor Email: mel41@cam.ac.uk

Department: Department of Psychiatry

Primary Institution: University of Cambridge

Project details

Genome-wide association studies (GWAS) have transformed our ability to identify the genetic architecture of complex diseases, but to understand how disease arises, the next challenge is to connect genetic variation to gene, protein, and cellular function across contexts.

Many psychiatric disorders have genetic associations within the Major Histocompatibility Complex (MHC), a complex, gene-dense region containing genes with diverse functions, including key roles in immunity. Alongside epidemiological evidence linking some infections to subsequent risk of psychiatric disorders, these associations raise the possibility that immune processes, including antigen presentation, contribute to psychiatric disease. However, an association within the MHC does not imply an immune mechanism: psychiatric risk could act through classical immune pathways, non-immune functions of genes within the locus, or context-dependent functions shared across or unique to immune and brain cells. Distinguishing between these possibilities requires resolving the genes underlying psychiatric MHC associations and determining the cellular and molecular contexts in which they act.

Resolving these mechanisms has been challenging because of the complexity of the MHC. In schizophrenia, the strongest MHC association has been linked to complement component 4 (C4), however the contribution of additional MHC signals remains unresolved. MHC associations in other psychiatric disorders, including bipolar disorder, are comparatively under-explored and are distinct from the MHC associations for schizophrenia. Further, little is also known about how psychiatric MHC associations interact with other structurally complex immunological loci (KIR genes,T cell receptor and immunoglobulin loci).

The effects of genes within these loci may also depend strongly on cellular context and state. Immune-gene regulation can change substantially following stimulation, while genes classically associated with immunity can also function outside immune cells (e.g., classical MHC genes PMID: 42304380).

Newly available whole-genome sequencing (WGS), stimulated-cell molecular datasets, allele based MHC-QTL and gene-perturbation screens now provide an unprecedented opportunity to apply complementary approaches to resolve genetic signals in the MHC and investigate their downstream consequences. These approaches can be applied in parallel to psychiatric and autoimmune disorders, where MHC-mediated mechanisms are better understood. By analysing and integrating these emerging WGS and functional genomic data, this project will determine how MHC-associated risk

acts across genes, cell types and cellular states, and which mechanisms are shared or distinct across psychiatric and autoimmune disease.

This project builds on our unpublished findings demonstrating that (1) epigenomically active regulatory elements shared between the brain and immune system are particularly enriched for SNP-based heritability of psychiatric conditions and show unique phenotypic associations, and (2) genetic associations at genes outside the MHC colocalise with expression in both brain and lymphoid cells.

Data sources will include GWAS summary statistics, WGS, genetic regulation of gene and protein expression summary statistics, and MHC-focused and genome-wide CRISPR screens (e.g. All of Us, UK Biobank, EBI eQTL & Perturbation Catalogues, PMIDs: 34031600,42664972,35113687,30449619, MHC pQTL data: medRxiv 2026.09.08.26362390). The student will have the opportunity to undertake wet-lab validation of their findings if desired.

The project will prioritise disease-associated genes and alleles within genetically complex immune loci, identify the tissues, cell types and molecular contexts in which their effects may act; determine which mechanisms are shared across psychiatric and autoimmune conditions; and generate testable hypotheses linking genetic variation to cellular function and disease risk.

Relevant publications

1. McGrath, I. M., & Lynall, M. E. (2026). Immune dysfunction in psychiatric disorders: emerging genomic insights. Curr Opin Genet Dev, 98, 102467. doi: Lynall, M. E., Sosk… https://doi.org/10.1016/j.gde.2026.102467

2. Lynall ME, Soskic B, Hayhurst J, Schwartzentruber J, Levey DF, Pathak GA, et al. Psychiatric disorder variants are enriched at active sites in lymphoid cells. Nature Communications. 2022. https://doi.org/10.1038/s41467-022-33885-7

3. Erady C, Bethlehem R, Bullmore E, Lynall ME. Peripheral blood transcriptome in depression. Biological Psychiatry. 2025. https://doi.org/10.1016/j.biopsych.2025.09.008

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Multiplexed assays of variant effect for sex hormone receptors in hormone-dependent cancer and rare disease

Lead Supervisor: Robert Semple

Lead Supervisor Email: rsemple@ed.ac.uk

Department: Institute of Neuroscience and Cardiovascular Research

Primary Institution: University of Edinburgh

Project details

Context

The androgen (AR) and oestrogen receptors (ESR1) are drivers and drug targets in prostate and breast cancer, are mutated in Mendelian hormone resistance syndromes, and harbour genetic variants influencing general population hormone-dependent traits. Sequencing of tumours and germline genomes has amassed large numbers of variants of unknown significance (VUS) in these genes: The ClinVar dtabase holds 207 AR VUS (194 germline) plus c.150 somatic AR missense mutations in The Cancer Genome Atlas. ESR1 has 35 curated VUS and 115 unclassified somatic missense variants. Recurrent ligand-binding-domain (LBD) mutations in both receptors act as 'agonist switches' that defeat specific drugs – e.g. AR T878A and L702H are activated by abiraterone “therapy”, F877L converts enzalutamide into an agonist, and ESR1 Y537S/D538G drive oestrogen-independent growth resistant to aromatase inhibitors; a licensed drug is already restricted to ESR1-mutated disease by tumour DNA genotyping, with AR likely to follow. Yet almost all functional evidence covers a handful of LBD hotspots: the N-terminal AF1 region, the hinge and the C-terminal F domain are essentially uninterrogated, and no systematic variant-effect map exists for either receptor.

Key question

What does every possible missense variant in AR and ESR1 do - across all domains and in clinically-relevant ligand and cellular contexts?

Objectives

(1) build a standardised cell model with null background suitable for interrogating function of both receptors

(2) generate full-coding saturation variant-effect maps in response to selected endogenous ligands and clinically-used drugs, comparing FACS/reporter assays and scRNAseq readouts

(3) analyse effects domain by domain, including the disordered AF1 region

(4) validate representative variants in disease-relevant cancer cell lines and benchmark computational predictors.

Methodology

We will use U2OS osteosarcoma cells, which lack endogenous AR and ER yet are robustly validated for interogating physiologically faithful AR/ESR1 function. The student will build U2OS reporter lines with a single-copy genomic landing pad +/- fluorescent reporter. Pooled codon-mutagenesis libraries will be generated covering the full coding sequences of AR and ESR1. Pooled cells will be treated with increasing doses of androgens or oestrogens and a selection of clinically-relevant drugs; deep sequencing of reporter and landing-pad cassettes will yield a ligand-resolved effect score for every variant, with comparison of scRNAseq and reporter-based readouts. Endogenous target-gene induction will be measured for selected variants, and the highest-priority variants will be studied in breast and prostate cancer cell lines for validation.

Interdisciplinarity

The project weaves together mammalian cell engineering, pooled functional-genomic screening, next-generation sequencing informatics, machine-learning variant-effect prediction, and endocrine cancer pharmacology, supervised across cell biology, computational genomics and molecular endocrine oncology.

Expected outcomes and translation

The first empirical, ligand-resolved variant-effect maps for AR and ESR1, covering all protein domains; direct identification of agonist-switch and drug-resistance behaviour for every LBD variant; functional classification of germline VUS relevant to androgen insensitivity and of the uncurated somatic reservoir; a benchmark resource for variant-effect predictors. All maps will be deposited in MaveDB, with protocols on protocols.io and analysis code on GitHub, so diagnostic laboratories and ClinVar curation panels can use them immediately.

Facilities and resources

Cell engineering, imaging and sequencing cores at the MRC Human Genetics Unit and INCR (Edinburgh); breast cancer and genome-engineering laboratories at the Hammersmith campus (Imperial). The project can be delivered within FGx-DLA funding plus supervisor grant support for sequencing costs

Relevant publications

1. Aslanzadeh V…Kudla G, Semple RK (2025) Deep mutational scanning of the human insulin receptor ectodomain to inform precision therapy for insulin resistance. Nature Comms… https://doi.org/10.1038/s41467-025-64178-4
2. Harrod A….Ali S (2022) Genome engineering for estrogen receptor mutations reveals differential responses to anti-estrogens and new prognostic gene signatures for breast… https://doi.org/10.1038/s41388-022-02483-8
3. Xu J, Aslanzadeh V, Kudla G, Semple RK (2026) Massively parallel functional genomic assays in endocrinology: from promise to delivery J Mol Endocrinol 2026 5;76(4): e250… https://doi.org/10.1530/JME-25-0134

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Understanding the molecular pathogenesis of psychiatric illness by combining functional genomics and artificial intelligence.

Lead Supervisor: Andrew Bretherick

Lead Supervisor Email: a.bretherick@ed.ac.uk

Department: Centre for Clinical Brain Sciences, School of Neurological and Cardiovascular Sciences, College of Medicine and Veterinary Medicine, University of Edinburgh

Primary Institution: University of Edinburgh

Project details

Aim

To identify tissue and cell-type specific molecular changes that confer genetic risk of schizophrenia and/or major depressive disorder.

Background

Psychiatric illness has a clear global impact. Depressive Disorder (depression) affects around 322 million people in the world, and schizophrenia around 27 million [1,2]. Both conditions carry a significant mortality and morbidity burden. The most recent genome-wide association (GWA) study meta-analysis of Major Depressive Disorder (MDD) identified 635 illness-associated genetic loci [3] and that of schizophrenia, 287 loci [4]. However, these and previous studies, have resulted in limited advancement of our understanding of the molecular pathogenesis of these complex conditions.

Deep-learning approaches are emerging as an effective way to predict RNA expression, and other molecular changes, secondary to DNA sequence variation. The predictive accuracy of such methods derives from 'learning' the regulatory syntax of DNA directly: how the letters of DNA are put together to make the words and sentences that are the language of the cell itself. AlphaGenome provides the current state-of-the-art in this arena [5] and will be used and built upon here to identify gene transcripts and other molecular changes that affect schizophrenia and depression risk.

AlphaGenome can assay large regions of DNA sequence in one go and simultaneously predict thousands of genome tracks (e.g. tissue-specific RNA expression) in humans, at base-pair resolution [5]. Such models are not constrained to naturally occurring genetic variation and handle local genetic epistasis explicitly. Revealing the molecular consequences of illness-linked genetic variants will help us understand what causes illness and find better treatments.

Method

At each of the genetic loci associated with major depressive disorder and/or schizophrenia we will predict the molecular changes that affect the risk of developing these illnesses using DNA sequence-to-function deep-learning models and genome sequence data. We will compare the predicted molecular outcomes (e.g., RNA expression) across tissues and cell-types between cases and controls.

The results generated will be compared and contrasted with the results from more traditional techniques used to annotate GWA signals, for example Mendelian Randomisation; noting, however, that the new approach proposed has a number of key advantages over previous methods. For example, analysis can be performed for tissues and genomic regions without any known expression quantitative trait loci.

Contingency Planning

AlphaGenome has been selected for the analyses described here due to the comprehensive nature of the genome tracks it predicts and its state-of-art-performance linking genetic variation to genes. However, if any issue arises with its use, another DNA sequence-to-function model will be used as an alternative. This will allow the project to proceed, as planned, with minor changes only.

Research Environment

The student will be based within the Centre for Clinical Brain Sciences, an interdisciplinary research centre at the University of Edinburgh that is part of Edinburgh Neuroscience – one of the largest neuroscience groupings in Europe – and is hosted within the Institute for Neuroscience and Cardiovascular Research. The student will have access to high-performance compute with state-of-the-art GPU capabilities.

Long Term Vision

The long-promised potential of GWA studies to allow unbiased exploration of disease pathogenesis is, as yet, undelivered. The proposed integration of genomics and deep-learning is powerful and novel and likely to play a major part in the field in the future.

References

[1] https://www.who.int/news-room/fact-sheets/detail/depression

[2] https://www.who.int/news-room/fact-sheets/detail/schizophrenia

[3] https://doi.org/10.1016/j.cell.2024.12.002

[4] https://doi.org/10.1038/s41586-022-04434-5

[5] https://doi.org/10.1038/s41586-025-10014-0

Relevant publications

1. Adams, Streit, Meng, Awasthi … McIntosh (2025) Trans-ancestry genome-wide study of depression identifies 697 associations implicating cell types and pharmacotherapies. C… https://doi.org/10.1016/j.cell.2024.12.002
2. Trubetskoy, Pardiñas, Qi, Panagiotaropoulou, … Adams … McIntosh … O'Donovan. (2022) Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature.… https://doi.org/10.1038/s41586-022-04434-5
3. Pairo-Castineira, Clohisey, Klaric, Bretherick, Rawlik … Baillie (2021) Genetic mechanisms of critical illness in COVID-19. Nature https://doi.org/10.1038/s41586-020-03065-y

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: A dual-MAVE framework for the interpretation of natural and synthetic transcription factor variants

Lead Supervisor: Grzegorz Kudla

Lead Supervisor Email: grzegorz.kudla@ed.ac.uk

Department: Institute of Genetics and Cancer

Primary Institution: University of Edinburgh

Project details

Context. Multiplexed assays of variant effect (MAVEs) bridge the gap between discovery and interpretation of genetic variants by measuring variant effects at scale. However, many achieve high throughput at the expense of biological detail, using simplified readouts. We recently performed MAVEs of several human transcription factors in bacteria and yeast, identifying mutations that affect sequence-specific DNA binding and protein stability (McDonnell 2024, Li 2025). Single-cell RNA sequencing gives detailed functional readouts in human cells, but has only been applied to few variants. This project combines the speed of mechanism-centred MAVEs in bacteria with the breadth of transcriptome-wide measurement in human cells: pools of variants are functionally enriched in the bacterial system, then the same physical constructs are characterised in depth in the human model.

We will apply this to interpret variants of HNF1A, the commonest cause of maturity-onset diabetes of the young, where a correct diagnosis changes treatment. A previous study identified gain-of-function HNF1A variants that protect from diabetes but raise hepatic lipoprotein secretion (DeForest et al., 2023), whereas our bacterial MAVE separated ~1,600 HNF1A variants into loss of abundance, loss of DNA binding, and altered activity (Li 2025). Building on these results, we will investigate the consequences of single amino-acid changes, the role of epistatic interactions, and the feasibility of designing synthetic variants that retain wild-type HNF1A function in human hepatocytes.

Key question. Do transcription factor variant effects measured in bacteria predict how the same variants reshape transcription in human cells?

Objectives.

1. Design and validate a Bxb1 landing-pad system for single-copy integration of variants into human hepatocyte-derived cells (using existing HEK293 or MEF cells as a fallback).

2. Perform a scRNA-seq MAVE on ~1,600 single-amino-acid HNF1A variants already scored in bacteria, so that every cell reports both the variant it carries and its transcriptional outcome.

3. Compare these phenotypes with bacterial functional scores and with patient outcomes, building a model that translates molecular mechanism into cellular and clinical consequence, then examine where the model fails.

4. Apply the strategy to libraries of bacterially evolved and designed variants, including multi-mutation libraries that expose epistasis, testing whether variants optimised for stability and DNA binding recapitulate the wild-type transcriptional response.

Methodology. The student will be based in the Kudla lab in Edinburgh, experienced in multimodal MAVEs in yeast and human cells; bacterial work will be done with co-supervisor Dr Li at King's College London, with the Semple (Edinburgh) and Patel (Exeter) groups advising on cellular models and clinical interpretation. Single-copy integration will use a Bxb1 landing-pad strategy we applied previously in HEK293, HeLa and MEF cells and will adapt here to hepatocytes. scRNA-seq will use the PARSE platform, with a barcoding strategy and AI-based interpretation established in the lab; variants enriched in the bacterial assay will be transferred into the human expression system by PCR, Gateway cloning and a barcoding toolkit held in the lab.

Interdisciplinarity. The work spans molecular, cell and computational biology. Students from any of these backgrounds are welcome and will be trained in the lab.

Expected outcomes. A mechanism-annotated map of HNF1A variants for diagnostic laboratories; a test of whether inexpensive assays can substitute for expensive ones; and a framework for designing transcription factors with chosen properties.

Facilities. Human MAVE capability including scRNA-seq and high-performance computing in Edinburgh; bacterial MAVEs at KCL; clinical sequencing of HNF1A variants through the Functional Genomics network, which adds screening infrastructure and clinical genetics expertise in monogenic diabet

Relevant publications

1. Li X#, Lehner B#. BioRxiv. (2025) Doi: In Press at Nature Structural and Molecular Biology. Aslanzadeh V, Brierley GV, Kumar R, Çubuk H, Vigouroux C, Matreyek KA, Kudla… https://doi.org/10.1101/2025.10.20.683418v1

2. Aslanzadeh V, Brierley GV, Kumar R, Çubuk H, Vigouroux C, Matreyek KA, et al. Deep mutational scanning of the human insulin receptor ectodomain. Nature Communications. 2025.

3. McDonnell AF, Plech M, Livesey BJ, Gerasimavicius L, Owen LJ, Hall HN, et al. Deep mutational scanning of PAX6 variants. Molecular Systems Biology. 2024. https://doi.org/10.1038/s44320-024-00043-8

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Which Isoforms Matter? Using AI and Human Genetic Variation to Decode Splicing in Disease

Lead Supervisor: Joseph Marsh

Lead Supervisor Email: joseph.marsh@ed.ac.uk

Department: Institute of Genetics and Cancer

Primary Institution: University of Edinburgh

Project details

Context and background

Genome sequencing is now routine in rare disease diagnosis, yet many patients remain undiagnosed because the significance of their variants is uncertain. Splicing is especially hard to interpret. Long-read sequencing reveals enormous transcript diversity, and even when we can predict that a variant alters splicing, we rarely know its functional consequences: the resulting protein change may be harmless, may abolish function, or may alter activity in subtler ways, and distinguishing these outcomes remains extremely difficult.

We hypothesise that functionally important alternative exons carry a clear signature of human population constraint, which protein structure and language models can expose even where conservation and standard constraint metrics fail.

Key question and objectives

Which alternative exons encode protein sequence that matters for health and disease? The student will:

1) develop a measure of protein-level constraint for individual alternative exons, using protein structure and language models to predict variant effects and detect selection;

2) apply it to long-read human brain transcriptomes, where alternative splicing is unusually extensive, to identify cell-type- and disease-specific isoforms likely to matter;

3) extend it to splice-altering variants, asking whether the exons they remove or introduce show evidence of protein-level constraint.

Interdisciplinary

The project combines computational structural biology and variant interpretation (Marsh, Edinburgh), long-read transcriptomics and neurogenetics (Ryten, Cambridge) and functional genomics (Biddie, Edinburgh). The student will work across human genetics, RNA biology, protein biophysics and AI; applicants from biology, computer science, physics or medicine are all well placed.

-Methodology

Alternative exons that encode important protein sequence should show depletion of damaging variation in humans. However, many are evolutionarily recent, making cross-species conservation a poor guide to their importance, while their enrichment in substitution-tolerant intrinsically disordered regions can obscure conventional constraint measures.

To address this, the student will develop a per-exon measure of protein-level constraint, combining human population variation with variant effects predicted by protein language models and by structural models of stability and interactions. In effect, the models predict which variants should be missing if an exon matters, and population data show whether they are.

The framework will then be applied to long-read human brain transcriptomes to identify alternative exons and isoforms showing evidence of protein-level importance, and to ask how these vary between cell types and disease states.

Finally, AlphaGenome and emerging genomic language models will predict variant-induced splicing changes and project them onto full-length transcripts. The resulting constraint scores will help distinguish splice changes affecting important protein sequence from those more likely to be inconsequential.

Expected outcomes

A new measure of protein-level constraint for alternative exons, a map of prioritised brain isoforms, and a route from splice-altering variants to their likely consequences. These could improve rare disease variant prioritisation and reveal isoform switches with therapeutic potential. The student will gain machine learning, genomics, structural biology and software skills, and learn to use and test AI models responsibly and critically.

Facilities and resources

Based primarily at the Institute of Genetics and Cancer in Edinburgh, the student will have access to computational infrastructure and expertise in functional genomics, structural and variant analysis, and the Ryten lab's long-read RNA expertise. The project will use public long-read resources, including the population-scale Isopedia catalogue, unpublished Ryten lab data and emerging single-nucleus long-read RNA-seq datasets from brain.

Relevant publications

1. Weykopf G, Badonyi M, Friman ET, Nguyen JMH, Ioannou A, Livesey BJ, Coutts A, Hird EF, Wham M, Stanton CM, Vitart V, Su J, Murphy L, Baillie JK, Gorrell MD, Marsh JA, Bi… https://doi.org/10.1038/s41467-026-74280-w
2. Gustavsson EK, Sethi S, Gao Y, et al., Ryten M. The annotation of GBA1 has been concealed by its protein-coding pseudogene GBAP1. Science Advances 10, eadk1296 (2024) https://doi.org/10.1126/sciadv.adk1296

3. Badonyi M, Marsh JA. Prevalence of loss-of-function, gain-of-function and dominant-negative mechanisms across genetic disease phenotypes. Nature Communications 16, 8392… https://doi.org/10.1038/s41467-025-63234-3

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Defining Causal Genetic Drivers of Fibroinflammation in Human Chronic Liver Disease via Single-cell eQTL Analysis

Lead Supervisor: Prakash Ramachandran

Lead Supervisor Email: Prakash.Ramachandran@ed.ac.uk

Department: Centre for Inflammation Research, Institute for Regeneration and Repair

Primary Institution: University of Edinburgh

Project details

Background

Chronic liver disease (CLD) causes 2 million deaths annually worldwide. Regardless of aetiology, chronic liver injury leads to inflammation and fibrosis, key drivers of disease progression and adverse outcomes. Recent advances in single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics (ST) have transformed understanding of the cellular and molecular mechanisms underlying liver fibroinflammation. However, no approved therapies specifically target this process. Although human omics studies have identified many potential targets, determining which are causally linked to disease progression remains a major challenge. Integrating genomic data with scRNA-seq and ST can address this gap by identifying expression quantitative trait loci (eQTLs), where genetic variants alter gene expression in specific fibroinflammatory cell populations and contribute directly to disease pathogenesis.

Research Question

Can single-cell eQTL analysis identify causal genetic drivers of fibroinflammation in CLD, link them to disease progression, and prioritise therapeutic targets?

Objectives

- Conduct single-cell eQTL analysis of multimodal omics datasets from CLD patients to identify candidate causal drivers of liver inflammation and fibrosis.
- Assess associations between candidate eQTLs and liver disease outcomes in external cohorts.
- Evaluate the functional effects of targeting prioritised disease drivers using human in vitro CLD models.

Methodology

Single-cell eQTL analysis will be performed using a multimodal dataset available within the supervisory team, including liver scRNA-seq, spatial transcriptomics (10X Genomics Xenium), serum proteomics (Olink), and whole-genome sequencing from patients across multiple CLD aetiologies and disease stages. Analytical workflows and statistical models will be developed and benchmarked. Candidate variants predicted to regulate pathogenic gene programmes within fibroinflammatory

niches will be tested for associations with adverse liver outcomes in UK Biobank and Our Future Health. Machine-learning approaches will be used to prioritise causal drivers supported across datasets and modalities. Lead candidates will undergo functional validation using CRISPR-Cas9, RNA silencing and in vitro transcription approaches in patient-derived cells and advanced multilineage CLD spheroid models developed through the MIMIC consortium (MRC Human In vitro Models of Complex Disease; University of Nottingham). These studies will assess effects on inflammatory and fibrogenic pathways and generate mechanistic insights into disease progression.

Team

The project combines expertise in liver disease biology, transcriptomics and perturbation screens (Ramachandran), computational genomics and therapeutic target identification (Baillie), statistical modelling, machine learning and causal inference (Khamseh), and advanced human in vitro CLD models (Ghaemmaghami). The student will work within a highly interdisciplinary environment involving clinicians, scientists and technical specialists.

Expected Outcomes

- Identification of causal genetic drivers of fibroinflammation in CLD.
- Functional validation of disease mechanisms and therapeutic targets in human CLD models.
- Training in computational genomics, single-cell analysis, artificial intelligence, large-scale health data and genome editing.
- Opportunities to build national and international collaborations and develop skills in scientific communication, dissemination and public engagement.

Resources

The student will have access to world-leading facilities at the Institute for Regeneration and Repair (IRR) and Institute for Genetics and Cancer (IGC), University of Edinburgh. Relevant omics datasets, computational infrastructure and access to external cohorts are already in place. Advanced CLD cellular models will be provided through the MRC-funded MIMIC project led by the University of Nottingham, creating an exceptional environment for training and discovery.

Relevant publications

1. Papachristoforou, E., Kong, K., Colella, F. et al. A human single-cell atlas identifies OLR1+scar-associated macrophages as a potential therapeutic target for chronic li… https://doi.org/10.1038/s41588-026-02774-w
2. Pairo-Castineira, E., Rawlik, K., Bretherick, A.D. et al. GWAS and meta-analysis identifies 49 genetic variants underlying critical COVID-19. Nature 617, 764–768 (2023) https://doi.org/10.1038/s41586-023-06034-3
3. Olivier Labayle, Breeshey Roskams-Hieter, Joshua Slaughter, Kelsey Tetley-Campbell, Mark J van der Laan, Chris P Ponting, Sjoerd V Beentjes, Ava Khamseh, Semiparametric… https://doi.org/10.1093/biostatistics/kxaf030

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Beyond Genes: AI models for isoform-resolved single-cell biology

Lead Supervisor: Konrad Rawlik

Lead Supervisor Email: konrad.rawlik@ed.ac.uk

Department: Baillie Gifford Pandemic Science Hub, Center for Inflammation Research, Institute for Regeneration and Repair

Primary Institution: University of Edinburgh

Project details

Background:

Machine Learning methods for single-cell transcriptomes are transforming how we represent cell state. Almost all of these, including the new "foundation" models, operate at the level of genes, ignoring isoform information, that is which exons and junctions build each transcript of a gene. Isoforms diversity carries much of protein function variation and is heavily implicated in disease. Effectively, gene-level models look at the transcriptome at too coarse summary level. Modelling isoforms natively is a clear open opportunity, and it aligns with the cluster's ambition to extract more knowledge from every cell.

A key challenge for working at the level of isoforms, in particular at a single cell level, is that standard assays to not contain the necessary information to infer which isoforms are expressed. The Molecular Mechanisms Cluster (MMC) is generating single-nucleus RNA-seq data in three human tissues across various perturbations, using a modified paired-end layout that greatly improves splice-junction coverage over standard assays, plus pilot Nanopore long reads that define full-length isoforms at lower throughput. This data provides a unique substrate for isoform-focused methods.

Objectives:

The project builds a connected pipeline from measurement to prediction:

1. Measure better. Develop AI to infer isoform-level expression from short reads, sharing statistical strength across cells, donors and perturbations, anchored on the paired long-read subset as ground truth, and explicitly modelling the nuclear intron retention that single-nucleus data expose. Work

2. Represent better. Use the resulting isoform-resolved data to extend current cell embedding and cell state models to isoform-aware representations. This ranges from variational auto encoder to foundation-style models whose vocabulary is transcripts and junctions rather than genes. Then benchmark where isoform-level information provides a view which diverges from the gene-level, a benchmark the field currently lacks.

3. Predict response. Apply these representations to map and predict isoform-level responses to perturbation, linking specific splicing and isoform changes to cell state and, where possible, to disease-associated genetic variation.

The student will actively drive a collaboration between FarmGTEx and MMC which provides genuinely complementary breadth and depth. Aims 1 and 2 greatly benefit from greater transcriptomic variation to enhance generalisation. FarmGTEx, which will provide raw single cell RNAseq data and well-powered splicing and expression maps across dozens of tissues and many species, provides that scale. This will serve as a cross-species pretraining backbone and sequence-to-splicing prior that transfers broadly conserved rules of RNA processing into the human single-cell setting, with evolution acting as a self-supervision signal. The human data provides what FarmGTEx cannot: single-cell resolution, matched perturbations and disease relevance.

Impact and outputs:

The project delivers openly released tools the community lacks, better isoform quantification, the first isoform-aware single-cell representations, and an isoform-level benchmark. These are delivered alongside biological insight into how isoform usage varies across cell states and responds to disease relevant perturbations. It positions the student at the leading edge of AI-for-genomics.

Facilities:

The project has access the computational resources of the MMC, including dedicated high performance compute through the Outbreak Data Analysis Platform, as well as the GPU cluster of the Generative AI Lab at the University of Edinburgh. It has also access to the data generated by the MMC as well as data accessible through the FarmGTEx consortium.

Relevant publications

1. GWAS and meta-analysis identifies 49 genetic variants underlying critical COVID-19 (https://doi.org/10.1038/s41586-023-06034-3
2. The Farm Animal Genotype–Tissue Expression (FarmGTEx) Project (https://doi.org/10.1038/s41588-025-02121-5
3. Same model, better performance: the impact of shuffling on DNA Language Models benchmarking (https://doi.org/10.48550/arXiv.2510.12617

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Data-driven development of in vitro models of immature human lung cell types

Lead Supervisor: Sara Clohisey Hendry

Lead Supervisor Email: sara.clohisey@roslin.ed.ac.uk

Department: The Roslin Institute & The Pandemic Science Hub.

Primary Institution: University of Edinburgh

Project details

Background: The molecular mechanisms driving human lung development during the final trimester of pregnancy remain poorly understood. This is a critical knowledge gap because this developmental window is also when bronchopulmonary dysplasia (BPD), a major chronic lung disease of prematurity, originates. Current BPD treatments are largely supportive and inconsistent in their effectiveness, highlighting the need to understand the developmental processes disrupted in affected infants.

Primary human foetal lung tissue is scarce and available only in limited quantities, making systematic perturbation experiments challenging. This project will address this bottleneck by combining cross-species functional genomics with established organoid models to recreate key stages of foetal lung development in a tractable experimental system. These models could ultimately enable genetic and drug screens at scale, allowing causal investigation of BPD-associated mechanisms and prioritisation of therapeutic targets.

Project Overview: The project will use cross-species comparisons to identify key transcriptional regulators of distal lung development at stages that are difficult or impossible to study directly in humans. The student will develop skills in organoid culture, scRNA-seq, trajectory inference and gene regulatory network analysis, drawing on complementary expertise across the University of Edinburgh (UofE) and Gurdon Institute (GI).

Based primarily at the UofE, the student will have access to the Genomics Platform and large-animal facilities at the Roslin Institute. They will also undertake hands-on training at GI in organoid culture techniques, benefiting from complementary expertise and opportunities for collaboration across both institutes.

Phase 1: Define the transcriptional trajectory of distal lung progenitor maturation

Trajectory inference and gene regulatory network approaches will be used reconstruct transcriptional programmes underlying progenitor maturation and identify candidate transcription factors. The student will use publicly available human and mouse scRNA-seq datasets integrated with new datasets from pig and sheep lungs at appropriate developmental stages. Candidate genes will be prioritised to generate a focused set for experimental validation.

Phase 2: Functionally validate candidate transcription factors

A focused expression screen will test whether prioritised transcription factors. Effects on cell identity, differentiation and developmental state will be assessed and integrated with the transcriptional and regulatory networks generated in Phase 1 to identify factors producing reproducible phenotypes.

Phase 3: Model neonatal lung disease in vitro

The final phase will test whether validated developmental regulators can model disease-relevant perturbations in lung organoids. Perturbations will be student-led and informed by findings from the preceding phases. CRISPR-based approaches will perturb prioritised transcription factors alongside candidate BPD-associated genes identified through GenOMICC and recent publications.

Resulting phenotypes will be characterised and compared with relevant in vivo and in vitro datasets to determine whether perturbation produces cellular states resembling neonatal lung disease.

Expected Impact: The project will establish a tractable framework for studying late foetal lung development and provide a sustainable platform for future CRISPR-based genetic and therapeutic screens. Each phase will deliver meaningful outputs while providing opportunities to build networks, exchange expertise and develop collaborations across both institutes.

Relevant publications

1. Happs, C., Khanna, P., Scoynes, C. et al. Systems-level insights into bronchopulmonary dysplasia from meta-analysis of genome-scale studies. Respir Res (2026) https://doi.org/10.1186/s12931-026-03787-z
2. // He P., Lim K. Sun D., Pett J.P. , Jeng Q., Polanski K., Dong Z., Bolt L., Richardson L., Mamanova L., Dabrowska M., Wilbrey-Clark A., Madissoon E., Tuong Z.K., Dann E... https://doi.org/10.1016/j.cell.2022.11.005
3. Lim K., Donovan A.P.A., Tang W., Sun D., He P., Teichmann S.A., Marioni J.C., Meyer K.B., Brand A.H., and Rawlins E.L. (2023). Organoid modeling of human fetal lung alve... https://doi.org/10.1016/j.stem.2022.11.013

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Bridging genomics and disease biology in Alzheimer's disease and glioblastoma using living human brain tissue

Lead Supervisor: Claire Durrant

Lead Supervisor Email: claire.durrant@ed.ac.uk

Department: CDBS, INCR

Primary Institution: University of Edinburgh

Project details

Background: Genetic studies have identified thousands of variants implicated in disease susceptibility and risk, including Alzheimer's disease (AD) and glioblastoma (GBM). Yet a critical "missing link" remains: we rarely know the biological mechanisms linking these variants with downstream disease processes. This is critical to risk stratification, therapy development, and could provide novel insights into the diseases themselves. Our team has pioneered the use of living human brain tissue (ethically sourced from neurosurgical waste tissue) as a translational tool to answer such questions, which is not possible in post-mortem brain or animal models.

Key question: "can our living-tissue models that faithfully reproduce brain diseases, including AD and GBM, be utilised to investigate how genetic risk drives disease?"

Objectives:

1. Apply perturbations to living human brain tissue to create disease-relevant states, and investigate the impact of genetic variants on these responses.

2. Test whether these perturbations reproduce disease-relevant phenotypes such as synapse loss and inflammation, and compare these to "real-disease" clinical and post-mortem datasets.

3. Integrate these observations with established and new single-nuclei datasets to determine which cell types and states are affected, and how human genetic variability shapes these responses.

4. Manipulate key molecular pathways identified by single-nuclei data in the slice models to test their role in disease and potential as a therapeutic strategy.

Interdisciplinarity: This project connects two internationally leading Edinburgh teams: the Molecular Mechanisms Cluster (MMC), part of the Human Functional Genomics Initiative, and the Edinburgh Living Human Brain Cluster, part of the UKRI novel human in vitro models of complex disease initiative. It forms a unique bridge between high-level genomics data, clinical data, and mechanistic wet-lab investigation. This is reflected in the supervisory team, uniting complementary expertise: neurodegeneration and living-tissue modelling (Dr Durrant), brain cancer, clinical insight and surgical neuro-oncology (Prof Brennan), and single-cell genomics and data science (Prof Baillie). The student will move between the laboratory bench and large molecular datasets, integrating experimental and computational approaches throughout.

Methodology: The student will perturb living human brain slices to model disease states and profile the resulting phenotypes. For GBM, this includes introducing glioma stem cells to model tumour behaviour in a realistic human brain environment. For AD, this includes applying amyloid-beta and tau to trigger changes such as synapse loss and inflammation. These readouts will be integrated with the single-nuclei transcriptomic data already shared between MMC and the Edinburgh Living Human Brain Cluster. By cross-comparing tissue responses against these reference datasets, and existing clinically relevant datasets for genuine disease cases, the student will identify which perturbations best capture true disease biology. The most robustly reproduced pathways will then be directly manipulated in living human tissue for mechanistic validation. The student will help shape the direction of the project as it evolves.

Expected outcomes: The project will run alongside the wider goals of both MMC and the Edinburgh Living Human Brain Cluster to deliver validated living human brain tissue models, and assess whether pathways identified in single-nuclei screens show real-world disease relevance. This will provide crucial understanding of how genetic risk translates into molecular and cellular change, and identify candidate pathways to guide future drug discovery.

Facilities and resources: The student will join a vibrant, collaborative environment with access to ethically sourced living human brain tissue, state-of-the-art laboratories, high-throughput single-cell platforms, and computational infrastructure and expertise.

Relevant publications

1. McGeachan, R.I., Meftah, S., Taylor, L.W. et al. Divergent actions of physiological and pathological amyloid-β on synapses in live human brain slice cultures. Nat Commun… https://doi.org/10.1038/s41467-025-58879-z
2. McGeachan, R.I., Keavey, L., Simzer, E.M. et al. Evidence for trans-synaptic propagation of oligomeric tau in human progressive supranuclear palsy. Nat Neurosci 28, 1622… https://doi.org/10.1038/s41593-025-01992-5
3. Pairo-Castineira, E., Clohisey, S., Klaric, L. et al. Genetic mechanisms of critical illness in COVID-19. Nature 591, 92–98 (2021) https://doi.org/10.1038/s41586-020-03065-y

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional Stratification of Gene(s) Variants linked to Neurodegenerative disorders

Lead Supervisor: Professor Miratul Muqit FRSE, FMedSci

Lead Supervisor Email: mmuqit@ed.ac.uk

Department: Centre for Clinical Brain Sciences

Primary Institution: University of Edinburgh

Project details

Context

Neurodegenerative disorders (NDs) such as Parkinson's, Alzheimer's and ALS affect millions worldwide, yet there are no effective disease-modifying treatments. Genetics has transformed diagnosis in the clinic as well as inform on targets and pathways for drug development. However, for most genetic variants found, we cannot say whether they cause disease or are harmless. These "variants of uncertain significance" (VUS) leave families without a clear diagnosis and hinder selection of patients for gene-targeted treatments. High-throughput Multiplexed Assays of Variant Effect (MAVEs) can now generate all possible variants of a gene and test them in a single experiment. Our team recently mapped almost every possible variant in Parkin, a Parkinson's disease gene, resolving many VUS and revealing key functional residues, paving the way for personalised medicine and drug development.

Key Question and Objectives

How do variants in NDs genes alter protein function; and how can this improve diagnosis and treatment? The student selects the gene(s) linked to NDs with supervisors, guided by clinical need, a robust cellular assay, and open biological questions.

Objectives: (1) build a functional map of variants in the chosen gene(s); (2) classify VUS; (3) relate variants to clinical features such as age at onset; (4) identify variants whose function may be restored by treatment, guide drug development, and advance structure–function understanding; (5) validate variants functionally in fly models and human brain.

Interdisciplinary Approach

The project combines neuroscience, clinical genetics, cell biology, synthetic biology, data science, fly models and human pathology with training in both laboratory and computational research. Supervision brings together a world leading clinician-scientist, and experts in large-scale functional genomics, MAVE, fly genetics and human neuropathology.

Methodology

The core of the project is an established MAVE pipeline, from variant library generation to functional assays, already applied to many genes in the Centre with optimised protocols, ensuring fast and accurate delivery. Variant libraries will be expressed in human cells and tested by disease-relevant

readouts, such as protein abundance, activity or localisation, with variant effects quantified by sequencing. Depending on the chosen gene, the student may extend this with complementary approaches, such as CRISPR base- or prime-editing screens of the endogenous gene, or single-cell readouts of variant effects on gene expression. Key variants will be validated in iPSC-derived neurons, fly models, and human brain. Computational work includes sequencing analysis, statistics, and comparison with AI variant effect predictors and patient genetic data.

Expected Outcomes

- Variant-effect maps for one or more neurodegeneration genes, shared openly (e.g., MaveDB) to support genetic diagnosis.
- Reclassification of uncertain variants.
- New insight into how the selected protein(s) fail in disease.
- New fly models of NDs.
- Identification of patients most likely to benefit from targeted therapies.
- Publications and transferable wet-lab and computational skills.

Facilities and Resources

The student will be based in the new UK DRI Centre for Parkinson's Research in Edinburgh, benefiting from networking and career development across Edinburgh as well as Cambridge and the other five UK DRI universities through regular meetings, as well as access to UK DRI research platforms. Prof Muqit is a member of the EMBO Young Investigator network and will support the student to attend the EMBO PhD course in Year 3 or 4 (nearly all his recent PhD students have attended). Through the team's patient engagement work with charities including Parkinson's UK, the student will meet patients at UK DRI lab Open Days, receive training in lay writing, and present to public audiences. The student will also have access to sequencing services and high-performance computing.

Relevant publications

1. Aslanzadeh V, Glendinning S, Sari Y, et al. A Functional Genetic Atlas of Parkin Resolves Variants of Uncertain Significance and Predicts Parkinson's Disease Age at Onse… https://doi.org/10.64898/2026.02.09.704817
2. Singh et al. (2025). Kinome screening identifies EIF2AK1/HRI as a negative regulator of PINK1 mitophagy signaling. Science Advances. https://doi.org/10.1126/sciadv.adn2528
3. Sanchez-Martinez, Martinez & Whitworth (2024). Analysis of Mitophagy Reporters in Drosophila. Methods in Molecular Biology. https://doi.org/10.1007/978-1-0716-4067-8_7

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Developing a variant effect predictor for multiple missense variants in the same protein molecule to aid clinical interpretation

Lead Supervisor: Caroline Wright

Lead Supervisor Email: caroline.wright@exeter.ac.uk

Department: Clinical and Biomedical Sciences

Primary Institution: University of Exeter

Project details

Context: Genome sequencing is becoming increasingly widespread in both research and diagnostics, and over a million people have already had their genomes sequenced. However, interpreting the effect of genetic variants is challenging and frequently delays diagnosis in patients with rare genetic diseases. The number of variants of uncertain significance (VUS) in clinical databases is growing exponentially, and >70% of them are missense variants, i.e. where one amino acid in a protein sequence is replaced with another. Numerous computational variant effect predictors (VEPs) have been developed to predict the effect of missense variants and are increasingly being used in genome sequencing analysis and diagnostic interpretation. However, despite every human having ~10,000 missense variants in their genome, and ~1000 genes on average with more than one missense, genetic variant interpretation still largely considers these variants individually. Although some computational models can predict the effects of multiple amino acid changes, these have mainly been developed for protein-engineering purposes.

Key question: The aim of this PhD project is to develop and validate a new VEP designed to predict the effect of multiple amino acid changes in the same protein to aid clinical interpretation.

Interdisciplinarity: This is a highly interdisciplinary project that involves in silico 3D protein structure modelling and machine learning methods, working with genetic (e.g. clinical, population), biochemical (e.g. AlphaFold) and functional (e.g. MAVEs) datasets. We have therefore assembled a team of supervisors with experience in genetics, bioinformatics and protein structure, who provide complementary expertise:

- Exeter (Wright, Leslie): applying and assessing VEPs for clinical diagnosis and gene-disease discovery in rare disease

- Edinburgh (Marsh): comparing and validating VEPs against different datasets

- Imperial (David): designing and developing VEPs using 3D protein structure

Methodology:

1. Review and benchmark existing approaches for predicting multiple missense variants, including evolutionary, protein language and 3D structure-based models

2. Develop existing methodology to predict the effect of one missense variant in the presence of another:

a. Within the same structured protein domain;

b. Within the same protein but in different domains;

c. Within the same protein but including unstructured/interdomain regions;

d. In different proteins within the same complex.

Predictions will use information about 3D proximity, interactions between the amino acids, substrate binding, post-translational modifications, contribution to domain stability, and standard metrics of conservation, constraint, etc.

3. Test whether predictions capture interactions beyond the individual variant effects using existing data, e.g. MAVEs with double mutants, known examples of pathogenic alleles in cis, genome sequencing data in population cohorts (with statistical or read-based haplotyping), etc.

4. Possible extension: further development of the VEP to include prediction of three or more missense variants in the same molecule.

Expected outcomes: The main outcome will be a new "multiVEP" for multiple missense variants in the same molecule that is validated against experimental and clinical data and available for use by the community.

Facilities and resources: This is a data project that will also use existing datasets for validation. The student will have access to large genetic databases (e.g. UK Biobank, All of Us, Our Future Health, Genomics England) as well as HPCs and cloud-based computing options supported by pre-existing funding. Further to this, co-supervisor Marsh is part of the Atlas of Variant Effect Alliance with responsibility for VEP comparisons (https://www.varianteffect.org/veps/); co-supervisor David is responsible for Missense3d (https://missense3d.bc.ic.ac.uk/) and is part of the PPTM Functional Genomics Cluster.

Relevant publications

1. Wright supervisory team publication. Journal of Medical Genetics. https://doi.org/10.1136/jmedgenet-2020-107003
2. Wright supervisory team publication. Genome Biology. 2025. https://doi.org/10.1186/s13059-025-03575-w
3. Wright supervisory team publication. Human Genetics. https://doi.org/10.1007/s00439-020-02246-z

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional genomic approaches to convergent mechanisms in chromatinopathies

Lead Supervisor: M. Albert Basson

Lead Supervisor Email: m.a.basson@exeter.ac.uk

Department: Clinical and Biomedical Sciences

Primary Institution: University of Exeter

Project details

Background

Chromatinopathies is a group of more than 180 rare genetic disorders caused by variants in genes encoding chromatin remodelling factors . Collectively, these disorders are amongst the most prevalent genetic conditions and are often characterised by neurodevelopmental features including developmental delay, intellectual disability and autism. Currently, no treatments exist for most chromatinopathies. Developing a personalised, targeted treatment for each of chromatinopathy represents a major, if not an impossible task. We hypothesised that the mechanisms of some chromatinopathies converge on overlapping pathways raising the possibility that the same drugs could potentially treat several chromatinopathies. Indeed, our initial studies have shown that the same class of drugs can rescue neurodevelopmental phenotypes in relevant mouse models. This opens an exciting opportunity to use functional genomics to investigate the fundamental biology of this important group of disorders and fulfil a major unmet medical need by discovering new treatments.

Key question and objectives

We have prioritised three related chromatinopathies to study in this project. The key question of this project is “What are the transcriptomic and epigenomic changes in the brain that characterise these chromatinopathies and how do they respond to treatment?”

Specific objectives are:

1. To identify the cell types, genes and chromatin changes that characterise each of these chromatinopathies and identify convergent pathways in relevant mouse models.

2. To test how treatment modifies the transcriptomic and epigenomic landscape in the brains of these mouse models.

3. To test is the treatment can rescue behavioural phenotypes in the mouse models.

Methodology

The student will work closely with an expert post-doctoral scientist in the lab and will use a range of next generation sequencing based approaches to investigate the effects of these treatments on the

epigenome and transcriptome and mouse behavioural assessments. The sequencing data for some of these experiments have already been collected and can be analysed straight away.

Parse snRNAseq will be used to compare gene expression differences in cell types of the mouse frontal cortex in mice, bulk RNA-seq to detect global transcriptional changes and CUT&Tag-seq to compare effects on the hypothesised convergent chromatin alterations.

Mouse behavioural tests will be employed to determine if key neurodevelopmental phenotypes in defined mouse models can be rescued by drug treatment. Tests for anxiety, activity, repetitive behaviours, social behaviours, motor function and learning and cognitive tests to assess learning and memory will be used.

Equivalent samples from mouse frontal cortex treated with drug will be analysed in parallel to identify the convergent molecular targets of drug treatment. Data from human neurons, from patient-derived and control induced pluripotent stem cells (hiPSCs) treated with the same drug is also available and can be compared directly with the data from the mouse models.

Expected outcomes

We expect to show that a single drug can rescue behavioural phenotypes in mouse models of several chromatinopathies and identify convergent epigenetic mechanisms that respond to the same drug to normalise aberrant gene expression in the frontal cortex.

Facilities and resources

Genetically modified mouse lines have been imported and developed by the Basson and Banka groups. Human iPSC lines modelling these disorders have been produced by the Banka group and RNA-seq and CUT&Tag-seq data generated after treatment with the same drug. State-of-the-art mouse and behavioural facilities are available at the University of Exeter. Access to high-performance computing for bioinformatic analyses are available and both institutions. The pharmaceutical company will provide sufficient clinical grade drug for our studies.

Relevant publications

1. Perez-Sisques et al. (2026) Autism-like phenotypes and increased NMDAR2D expression in mice with KDM5B histone lysine demethylase deficiency. Sci Adv 12. DOI: https://doi.org/10.1126/sciadv.adq6577
2. Cuvertino et al. (2025) Epigenome and transcriptome changes in KMT2D-related Kabuki syndrome Type 1 iPSCs, neuronal progenitors and cortical neurons. PLOS Genet https://doi.org/10.1371/journal.pgen.1011608
3. Bhatt et al. (2026) Inhibition of histone lysine demethylase restores learning and memory in aged mice. bioRxiv https://doi.org/10.64898/2025.12.22.695858

Please direct project-specific enquiries to:

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Dissecting Metabolic Heterogeneity in Severe Mental Illness Through Genetic Clustering and Single-Cell Functional Genomics

Lead Supervisor: Jess Tyrrell

Lead Supervisor Email: j.tyrrell@exeter.ac.uk

Department: Clinical and Biomedical Sciences

Primary Institution: University of Exeter

Project details

This PhD aims to understand why genetic liability to severe mental illness (SMI), particularly schizophrenia and bipolar disorder, is associated with different patterns of adiposity and metabolic health. Although obesity and type 2 diabetes (T2D) are more common in people with SMI, substantial heterogeneity exists, with many individuals remaining metabolically healthy despite a high burden of SMI risk. We hypothesise distinct components of psychiatric genetic liability influence metabolic health through different biological pathways, with some increasing susceptibility to obesity and T2D while others have little metabolic consequence.

The PhD builds on recent work led by supervisor Tyrrell demonstrating that genetic liability to major depressive disorder comprises biologically distinct clusters of variants with contrasting effects on T2D. Building on this, the student will apply genetic clustering approaches to SMI traits to identify biologically distinct components of psychiatric risk that differentially influence obesity and T2D. By integrating statistical genetics, causal inference approaches and functional genomics, the PhD will move beyond psychiatric diagnoses as single entities to identify the biological mechanisms underlying metabolic heterogeneity.

First, the PhD will identify genetically distinct clusters of psychiatric risk variants using large-scale genome-wide association study data and characterise their associations with obesity and T2D. The biological and clinical consequences of these clusters will be explored across population biobanks.

The PhD will then investigate the cellular mechanisms underlying these genetic pathways using unique single-cell multiomic datasets generated in Exeter. By integrating genetic association data with cell-type-specific gene expression and chromatin accessibility data, the student will determine whether metabolically distinct psychiatric risk pathways act through different neuronal and glial cell populations and identify the genes and regulatory networks involved.

Selected regulatory elements and candidate genes emerging from these analyses will be prioritised for functional investigation using experimental approaches (e.g. CRISPR-based perturbation, neuronal cell models). This will provide mechanistic insight into how distinct components of SMI genetic liability influence both brain function and metabolic health.

The PhD will provide multidisciplinary training in statistical genetics, genetic epidemiology, bioinformatics, single-cell genomics and functional genomics. The student will gain experience in

large-scale genomic datasets, causal inference and clustering methods, integrating transcriptomic data, and undertaking lab-based functional studies. Training in R, Python and high-performance computing will be complemented by experimental skills in molecular and cellular biology.

While the PhD has clearly defined objectives, there will be considerable scope for the student to shape the direction of the PhD according to their interests and emerging findings. Opportunities may include focusing on a specific SMI, ancestry-specific mechanisms, method development, particular neuronal cell populations, or in-depth functional characterisation of candidate genes. This flexibility will support the development of an independent research profile.

This PhD will address a key question in psychiatric and metabolic disease biology: why do some individuals with a high SMI genetic liability develop obesity and metabolic complications whilst others remain metabolically healthy? By identifying biologically distinct components of SMI risk and characterising the molecular mechanisms, the PhD has the potential to reveal new pathways linking brain function and metabolic regulation, improve understanding of disease heterogeneity, and identify novel targets. It will equip the student with a broad, highly transferable skills relevant to careers in academia, biotechnology and precision medicine.

Relevant publications

1. Babtie et al., A single-nuclei multiomics resource across four brain regions prioritises human neural cell types influencing brain-related traits; Handley et al., Cluste…
https://doi.org/10.64898/2026.09.24.754059v1

2. Handley et al. Genetic clustering of major depressive disorder identifies opposing effects on cardiometabolic risk. medRxiv. 2026.
https://www.medrxiv.org/content/10.64898/2026.03.16.26347391v1

3. Bretherick AD, et al. Molecular-QTL co-association predicts novel disease-associated genetic loci using a graph convolutional neural network. PLOS ONE.

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Uncovering the mechanism of minor spliceosome autoimmune diabetes

Lead Supervisor: Matthew Johnson

Lead Supervisor Email: m.johnson@exeter.ac.uk

Department: Clinical and Biomedical Science

Primary Institution: University of Exeter

Project details

Context/background

Before the instructions in a gene can be used, non-coding parts called introns must be cut out in a process called splicing. Most introns are spliced out by the major spliceosome. However, around 700 human genes contain a rare type of intron (U12 introns) that can only be removed by a separate minor spliceosome.

We recently discovered that inherited changes in two core minor spliceosome components, RNU4ATAC and RNU6ATAC, cause a single-gene (monogenic) form of autoimmune diabetes. In this condition, the immune system destroys the insulin-producing beta cells of the pancreas. This is a puzzle, as the minor splicing machinery is used by every cell in the body, yet when it goes wrong it results in a highly specific immune attack on the pancreatic beta cells. We do not yet know which of the 700 affected genes drive disease, or in which cells, though preliminary data suggests a major role for T cells, B cells and beta cells. Answering this could reveal new biology relevant to type 1 diabetes and to autoimmunity more broadly, uncovering new drug targets for autoimmune diseases.

Key question

Which incorrectly spliced U12-intron genes drive the immune system to attack beta cells and how?

Objectives

- Develop a computational framework to rank U12-intron genes by how likely they are to cause disease. This will combine single-cell gene expression atlases, genetic studies of type 1 diabetes and autoimmunity, and annotation to predict how sensitive each intron is to minor spliceosome failure
- Confirm that the top-ranked genes are misspliced in patient cells
- Switch off a small shortlist of genes in B cell, T cell and/or beta cell models. Test the effect on key processes such as immune activation, tolerance, antigen presentation, cell stress and survival.

Methodology

- Year 1 - prioritise candidate genes by analysis of publicly available data including single-cell RNA sequencing data from immune and pancreas cells, alongside existing patient RNAseq and immune data

- Year 2 - measure intron retention of key genes in patient-derived cells using our established droplet digital PCR assay and establish the cell models
- Years 2–3 - knockdown/knockout (e.g. CRISPR or siRNA) of 3–5 highest priority genes. Readouts will include flow cytometry, cytokine measurement and RNA sequencing
- Final year - integrate findings, publish data, write and submit thesis

Interdisciplinary aspects of the project

The project spans data science, human genetics, immunology and cell biology. The student will be trained in computational analysis (R/Python, single-cell and public genomic data) and in laboratory methods (cell culture, CRISPR gene editing, digital PCR, flow cytometry).

We welcome applicants from biological, biomedical, computational, mathematical or data science backgrounds. Full training will be provided in unfamiliar areas.

Expected outcomes

- An empirically defined set of U12-intron genes implicated in autoimmune diabetes
- New understanding of how U12-intron containing genes shape immune and beta cell behaviour
- New biomarkers and/or drug targets for type 1 diabetes and other common autoimmune conditions
- Publications, conference presentations and a versatile skill set spanning dry (computational) and wet laboratory research

Facilities and resources

The student will join Exeter's internationally recognised diabetes research team in the department of Clinical and Biomedical Sciences. They will have access to:

- The world's largest unique cohorts of people with early-onset and monogenic diabetes
- Access to a fully equipped molecular biology laboratory and established minor spliceosome assays
- High-performance computing and genomics facilities
- Flow cytometry, cell culture and gene-editing facilities
- Close links to NHS clinical and diagnostic genetics services and international collaborators
- Access to formal training opportunities, including from Exeter's Coding for Reproducible Research initiative

Relevant publications

1. Johnson MB, Russ-Silsby J, Blair PA, Govier M, Bonfield G, Domingo-Vila C, EXE-T1D consortium, ATAC clinical consortium, Wakeling MN, Oram RA, Flanagan SE, Tree TIM, Pat… https://doi.org/10.1016/j.ajhg.2026.02.017
2. Russ-Silsby J, Lee Y, Rajesh V, Amoli M, Mirhosseini NA, Godbole T, Johnson MB, Ibarra DE, Sun H, Krentz NAJ, Wakeling MN, Flanagan SE, Hattersley AT, Gloyn AL, De Franc… https://doi.org/10.1016/j.molmet.2025.102201
3. Johnson, M.B., Ogishi, M., Domingo-Vila, C., De Franco, E., Wakeling, M.N., Imane, Z., Resnick, B., et al. (2024) Human inherited PD-L1 deficiency is clinically and immu… https://doi.org/10.1084/jem.20231704

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: From variants to placental function: using cell-free DNA to dissect the functional genomics of adverse pregnancy outcomes

Lead Supervisor: Kiki Edith Cano-Gamez

Lead Supervisor Email: k.e.cano-gamez@exeter.ac.uk

Department: Clinical and Biomedical Sciences

Primary Institution: University of Exeter

Project details

Background: Adverse pregnancy outcomes (APOs) like preeclampsia, foetal growth restriction, and pre-term delivery affect up to 30% of pregnancies, significantly impacting quality of life. These complications are difficult to detect before the appearance of clinical symptoms, and their biology is poorly understood. Genome-wide association studies (GWAS) have identified dozens of genetic loci associated with these conditions, as well as with perinatal traits like placental weight and birthweight. However, the functional consequences of these variants are not currently understood.

Previous research suggests that placental development plays a key role in perinatal health, and that genetic variants associated with APOs may disrupt placental function. However, accessing placental tissue is impractical due to the associated risk of miscarriage, which limits placental monitoring. This severely hinders our ability to functionally interpret APO-associated variants.

During pregnancy a large proportion of circulating cell-free DNA (cfDNA) in the parental bloodstream comes from the placenta. This makes cfDNA a unique, minimally invasive biomarker which could be used to monitor placental health. Thus, we propose a project that leverages cfDNA sequencing to track gene activity in the placenta throughout pregnancy. We aim to use these observations to dissect the role of genetic variants associated with perinatal traits and APOs.

Research questions:

1) Can cfDNA information be used to estimate gene activity in the placenta in real time?

2) Do genetic variants associated with APOs modulate gene activity in the placenta?

3) Can cfDNA be used as a minimally invasive biomarker of APOs?

Project design: With guidance from their supervisors, the student will leverage single-cell RNA-sequencing (scRNA-seq) data to identify cell type-specific markers of key placental cell types, which they will use to interpret publicly available cfDNA sequencing data from healthy pregnancies and APO cases. They will do this by mapping nucleosomal footprints from cfDNA, which they will integrate with single-cell markers to infer placental gene activity. The student will lead on the design and development of computational tools to predict gene activity from nucleosomal footprints, extending previous work published by KECG. The student will next integrate cfDNA-derived gene activity metrics with GWAS associations for perinatal traits and APOs using statistical genetics

approaches like heritability partitioning and SNP enrichment. Where appropriate, the student may supplement these analyses with new data generation from plasma samples from pregnancies available via the Genetic Beta Cell Research Bank (GBCRB).

A key strength of our research environment is that, through their supervisory team, the student will have access to key data sets uniquely suited to answering these research questions. These include: 1) a collection of publicly available sequencing data sets of cfDNA from pregnancy cohorts, currently being curated by KECG and comprising both APOs and healthy pregnancies; 2) GWAS summary statistics for perinatal traits generated by RF, including associations with placental weight and birthweight; 3) a longitudinal data set of gene expression across pregnancy generated by ED within the Pregnancy Outcome Prediction Study 2 (POPS2); and 4) a scRNA-seq atlas of the placenta generated by the Vento-Tormo group at the Wellcome Sanger Institute. ED's close links with this group will enable the student to access key knowledge and expertise, fostering collaborations and enhancing the value of this project.

Expected outcomes: This project will address gaps in our understanding of APO associated variants and limitations in placental monitoring by delivering novel, cutting-edge computational methods to make the most of the molecular information contain in cfDNA. Moreover, this project will provide functional context to disease-associated genetic variation.

Relevant publications

1. Cano-Gamez K, Maclean P, Inoue M, et al. (2025). The circulating cell-free DNA landscape in sepsis is dominated by impaired liver clearance. Cell Genomics. 5, 10 https://doi.org/10.1016/j.xgen.2025.100971
2. Beaumont RN, Flatley C, Vaudel M, et al. (2023). Genome-wide association study of placental weight identifies distinct and shared genetic influences between placental an... https://doi.org/10.1038/s41588-023-01520-w
3. Hoffman S, Burnham KL, Cook E, et al. (2026). Maternal immune gene expression trajectories and dynamic genetic regulation throughout pregnancy. medRxiv https://doi.org/10.64898/2026.09.22.26363644v1

Please direct project-specific enquiries to:

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Rare variant functional genomics for better understanding, prevention and treatment of musculoskeletal disorders

Lead Supervisor: Harry Green

Lead Supervisor Email: H.D.Green@exeter.ac.uk

Department: Clinical and Biomedical Sciences

Primary Institution: University of Exeter

Project details

Background: Musculoskeletal disorders such as osteoarthritis and Dupuytren's contracture are severely disabling disorders that affect millions of people in the UK. Genome-wide association studies have identified hundreds of common genetic variants that increase risk of musculoskeletal disorders. Translating these associations into biological insight has, however, been limited because identifying the causal variants is very challenging. Rare variant associations are much simpler to interpret because they have large effect sizes and limited correlation with other genetic variants. In this studentship, the student will analyse millions of individuals across diverse ancestries with whole genome sequencing and medical record data to identify rare genetic variants causing musculoskeletal conditions. They will functionally characterise these variants in relevant tissues to gain mechanistic insights crucial for developing novel, targeted treatments for these disabling disorders.

Key questions and objectives: What are the biological mechanisms that drive the development of musculoskeletal disorders? We will:

1. Identify causal rare genetic variants associated with musculoskeletal disorders using whole genome sequencing from millions of individuals from UK Biobank, All of Us and Our Future Health biobanks

2. Establish the functional consequences of these prioritised variants in disease-relevant, primary human cell and tissue models.

3. Determine the molecular pathways connecting genotype to disease, identifying potential therapeutic targets.

Interdisciplinarity: The student will bridge two leading research environments: health data science and statistical genomics at the University of Exeter, and molecular genetics and cellular modelling at the University of Oxford. This cross-disciplinary approach ensures the student develops a highly sought-after, dual skill set in both computational analysis and experimental validation.

Methodology: The PhD will be divided into two integrated phases.

Phase 1 (Exeter - computational): The student will use large-scale genomic datasets to conduct cutting-edge WGS association testing. Firstly, the student will synthesise information from complex sources, including medical records and assessment data, to define MSK disease phenotypes in UK

Biobank, Our Future Health, and All of Us. This will facilitate analysing associated rare variants, structural variants, and integrating multi-omic data (e.g., eQTLs, pQTLs) using advanced bioinformatic pipelines and statistical modelling to prioritise candidate genes and regulatory regions.

Phase 2 (Oxford - laboratory): The student will then functionally validate the top-prioritised candidates. Developed as part of the UKRI HFGI MSK Cluster, the student will interrogate human tissue models of increasing complexity: primary human cells, ex-vivo tissue and humanoid robotic bioreactors. They will employ cutting-edge functional genomics tools - including CRISPR-Cas9 gene editing, transcriptomics, and cellular phenotyping - to define how these variants alter cellular function and cause disease.

Expected outcomes: The project will deliver novel insights into the genetic architecture and molecular drivers of musculoskeletal conditions. Outputs will include the identification of validated causal genes, a deeper understanding of disease pathways, and the potential discovery of new targets for drug repurposing.

Facilities and resources: At Exeter, the student will have access to resources such as UK Biobank, All of Us and Our Future Health as well as high-performance computing infrastructure, and the extensive data science expertise of the supervisors who lead the MSc Health Data Science at Exeter. At Oxford, the student will leverage state-of-the-art molecular biology laboratories, established disease model pipelines, and direct access to well-phenotyped patient tissue biobanks within the Musculoskeletal Cluster.

Relevant publications

1. Hawkes et al., Whole-genome sequencing analysis of anthropometric traits in 672,976 individuals reveals convergence between rare and common genetic associations. Nat Com… https://doi.org/10.1038/s41467-026-69208-3
2. Green et al., A genome-wide association study identifies 5 loci associated with frozen shoulder and implicates diabetes as a causal risk factor, PLoS Genetics, 2021: https://doi.org/10.1371/journal.pgen.1009577
3. Riesmeijier et al., A genome-wide association meta-analysis implicates Hedgehog and Notch signaling in Dupuytren's disease. Nat Comm. 2024 https://doi.org/10.1038/s41467-023-44451-0

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Decoding the rules of human gene interaction networks using combinatorial functional genomics

Lead Supervisor: Benjamin Housden

Lead Supervisor Email: b.housden@exeter.ac.uk

Department: Clinical and Biomedical Sciences

Primary Institution: University of Exeter

Project details

Large-scale sequencing initiatives have identified thousands of genetic variants associated with human traits and disease. However, understanding how these variants influence biology remains a major challenge because genes do not act independently but within interconnected networks. Existing approaches, including CRISPR screens, have transformed gene discovery but remain poorly suited to measuring dose-dependent and higher-order genetic interactions. This limits our ability to understand how gene networks generate cellular phenotypes and how genetic variation contributes to disease.

This project addresses a fundamental question in functional genomics: how do combinations of genes interact to determine cell behaviour? The student will develop and apply innovative technologies to map genetic interactions in human cells, generating new insights into how gene networks influence health and disease.

The project builds on our recently developed multiplexed Variable Dose Analysis (mVDA) technology, supported by preliminary data demonstrating robust detection of genetic interactions and integration with single-cell sequencing in Drosophila cells. mVDA enables simultaneous perturbation of multiple genes across a range of knockdown efficiencies, providing greater sensitivity and higher throughput than conventional screening approaches. Adapting mVDA for human cells represents a significant technical advance with the potential to transform genetic interaction mapping.

The project has three objectives. First, the student will adapt and optimise mVDA in human cells, using established control interactions. Second, they will integrate this approach with either live-cell microscopy or single-cell sequencing, depending on interest. Live imaging provides sensitive phenotypic measurements, while single-cell sequencing offers scalability for large screens. Third, the student will apply the platform as a proof-of-concept to investigate genetic interactions involving the tumour suppressor NF1. As NF1-associated tumours have proven difficult to treat with single agents, they provide an ideal test case for a screening platform designed to identify interacting genes and potential combination therapies.

The project is highly interdisciplinary, integrating functional genomics, molecular genetics, imaging, bioinformatics, statistics and data science. Training will include genetic perturbation technologies, advanced microscopy, single-cell genomics, computational analysis, statistical modelling and reproducible research practices. The project is intentionally flexible, allowing the student to shape its

direction as their interests and expertise develop. For example, there are opportunities to focus on technology development, computational methods, network analysis or biological applications depending on their interests and expertise.

The student will join a collaborative research environment with access to state-of-the-art facilities for high-throughput screening, live-cell imaging, single-cell sequencing and computational methods. The project will be supported by expertise within the Functional Genomics Screening Laboratory and the Exeter Living Systems Institute, providing opportunities to work across disciplines and engage with national functional genomics networks.

Expected outcomes include validation of mVDA for genetic interaction mapping in human cells, development of analytical approaches for interpreting combinatorial perturbation data, and new understanding of NF1-associated gene networks. The project will help overcome a major barrier in functional genomics by enabling systematic exploration of how gene interactions generate cellular phenotypes. The student will develop a unique combination of experimental, computational and transferable skills highly relevant to careers in academia and industry. Responsible research practices, including reproducibility, FAIR data stewardship and research integrity will underpin all aspects of the project.

Relevant publications

1. Stevens M, Wang Y, Bouley SJ, Mandigo TR, Sharma A, Sengupta S, Housden A, Perrimon N, Walker JA, Housden BE. Inhibition of autophagy as a novel treatment for neurofibro… https://doi.org/10.1002/1878-0261.13704
2. Sengupta S & Housden BE. Multidimensional variable dose analysis (mVDA) is a novel method for high-throughput mapping of genetic interactions. bioRxiv 2024.12.01.626212;… https://doi.org/10.1101/2024.12.01.626212
3. Mohanan S, Horsell D, Watters T, Ghasemi M, Henderson L, Müllenbroich C, Bub G, Burton F, Smith G, Corbett AD. Automated measurement of cardiomyocyte monolayer contracti… https://doi.org/10.1364/BOE.578208

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Next-generation machine learning for genetic interaction prediction with lab-in-the-loop validation in pancreatic cancer

Lead Supervisor: Dr Magdalena Strauss

Lead Supervisor Email: m.strauss@exeter.ac.uk

Department: Mathematics and Statistics

Primary Institution: University of Exeter

Project details

Background

Cancer cells often depend on specific genes to survive, making those genes attractive drug targets. CRISPR screens knock out genes to measure their importance for cancer cell survival, and large efforts such as DepMap and Project Score have mapped individual single-gene dependencies across many cancer models. However, single-gene studies miss vulnerabilities that only appear when two genes are disrupted together. These genetic interactions (GIs), including synthetic lethality, are a rich but under-explored source of oncology targets.

As testing ~400 million gene pairs is infeasible, computational prediction is essential. Current GI prediction methods combine limited pairwise screens with larger single-gene screens but rely on low-dimensional readouts and generalise poorly across disease contexts(1).

By contrast, a proof-of-concept study showed that perturb-seq, which couples CRISPR editing with single-cell transcriptomics, can support GI prediction using recommender-system approaches(2). Near genome-wide perturb-seq datasets are now available(3, 4), providing transcriptome-wide readouts that could enable scalable, accurate prediction models.

Objectives

1. Build next-generation GI prediction models using large-scale perturb-seq data.

Initial model development will use publicly available perturb-seq datasets, including large-scale data from a leukaemia cell line and induced pluripotent stem cells(3, 4). You will evaluate graph neural networks, autoencoders, and other architectures capable of learning joint gene embeddings from perturb-seq profiles. You will assess scalability to genome-wide prediction, handling of sparsity and batch effects, and generalisation across cancer types.

2. Insights into genetic interaction in pancreatic cancer.

Pancreatic cancer is one of the deadliest cancers, with average survival at diagnosis under six months. The AstraZeneca and Cancer Research Horizons Functional Genomics Centre (FGC) will generate perturb-seq data and GI screens in pancreatic cancer models. These experiments will support a "lab-in-the-loop" cycle, where new measurements fine-tune the computational model in the pancreatic

cancer context. Note that researchers at the FGC will contribute the experimental data and "wet-lab" work, while the student project is purely computational.

Expected outcomes

• A validated computational framework for GI prediction, released as open source software.

• Experimentally validated high confidence genetic interactions in a pancreatic cancer cell line.

• Insight into how GI predictions transfer across biological contexts.

• A reproducible and rigorous workflow integrating computation and experiment in a "lab-in-the-loop" cycle, while controlling bias and false discovery rates.

You will gain

• Expertise with modern machine learning methods applied to genomics.

• Expertise in single cell and CRISPR genomics.

• High performance computing skills.

• Industry aligned experience through FGC involvement, including exposure to data quality standards, model evaluation, and target prioritisation.

An interdisciplinary project

The main supervisor is an expert in statistical and machine-learning methods for genome editing; the co-supervisor specialises in statistics, reproducible coding and model evaluation. FGC supervisors (Dr Kalinka, Dr Ross-Thriepland, Dr Walter) will provide additional expertise in genome editing, genomics, cancer biology and bioinformatics.

Facilities and Resources

The University of Exeter will provide high performance computing for model development and training. The FGC will provide world-leading CRISPR and single cell screening facilities and technical expertise.

References

1. Y. Feng et al., Nat. Commun. 15, 9058 (2024).

2. T. M. Norman et al., Science 365, 786–793 (2019).

3. J. M. Replogle et al., Cell 185, 2559–2575.e28 (2022).

4. C. Feng et al., Cell Genomics 6 (2025).

Relevant publications

1. Gupta, N, Sayer, A, ..., Trehan, A, ..., Strauss, ME, Ross-Thriepland, D, Walter,D and Kalinka, A. Comparative Single-Cell Profiling of CRISPR Knockout and Interference… https://doi.org/10.64898/2026.08.26.747303
2. Cooper, SE*, Coelho, MA*, Strauss, ME* et al. scSNV-seq: high-throughput phenotyping of single nucleotide variants by coupled single-cell genotyping and transcriptomics…. https://doi.org/10.1186/s13059-024-03169-y
3. M. A. Coelho, M. E. Strauss et al. Base editing screens define the genetic landscape of cancer drug resistance mechanisms. Nat. Genet. 56, 2479–2492 (2024) https://doi.org/10.1038/s41588-024-01948-8

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional genomic characterisation of genetic risk for diabetic neuropathy using human stem cell models

Lead Supervisor: Akshay Bhinge

Lead Supervisor Email: a.bhinge@exeter.ac.uk

Department: Living Systems Institute, Clinical and Biomedical Science

Primary Institution: University of Exeter

Project details

Around half of all people with diabetes develop peripheral neuropathy, its commonest complication worldwide. It begins with the loss of the smallest sensory nerve fibres, causing pain, numbness and, in severe cases, ulceration and amputation. No treatment halts or reverses it. Yet severity varies widely between people with similar glucose control, pointing to inherited differences in how nerves withstand metabolic stress.

Genetic studies nominate risk genes but cannot say where they act. The pain sensory system is a two-cell partnership: the sensory neuron, and the Schwann cell that ensheathes and metabolically supports it. Which partner carries the risk determines what a treatment must target.

This project focuses on apolipoprotein E (APOE). Best known for Alzheimer's risk, APOE is also made by the non-myelinating Schwann cells supporting the small pain-sensing fibres lost earliest in diabetic neuropathy (10.1006/exnr.1998.6872). Clinical studies have repeatedly, but inconsistently, linked the APOE e4 variant to neuropathy severity (10.5114/aoms.2012.30279), a discrepancy cohort studies cannot resolve, because they cannot separate effects within the nerve from effects on whole-body metabolism.

Key question: does APOE genotype determine how human sensory neurons and Schwann cells withstand high glucose, and does it act through the neuron, the glial cell, or their partnership?

Objective 1. Establish a sensory neuron and Schwann cell co-culture from stem cells carrying APOE e2/e2, e3/e3 or e4/e4 on one genetic background. Both cell types carry the same genotype, as they do in a person. The student will determine how genotype affects cell survival, nerve fibre integrity, glial ensheathment and network activity under high glucose or cytokine challenge. Comparing all three variants will reveal whether risk changes stepwise with genotype; a strong test of causality. Because the disease involves network degeneration and abnormal excitability, nerve function will be measured by microelectrode arrays (MEAs) across networks and patch clamp electrophysiology in single neurons. Potential cell death will be measured using apoptosis assays.

Objective 2. Determine which cell carries the risk, by assembling mixed co-cultures in which only the neurons, or only the Schwann cells, carry e4, the partner carrying e3 (the “healthy” allele). Phenotypes will be assessed as above.

Objective 3. Identify the pathways responsible using long-read RNA sequencing, which resolves full-length transcripts, revealing not only which genes change but how they are spliced, including isoform switching. Neurons and Schwann cells will also be profiled in monoculture, giving reference profiles against which co-culture changes can be assigned to a cellular source. The project will then functionally test candidate genes, asking whether perturbing each rescues the phenotype with the student leading selection and our industrial partner advising on druggability.

Training is interdisciplinary throughout, spanning stem cell biology, genome editing, electrophysiology, transcriptomics and statistical modelling across three institutions and industry. Isogenic APOE lines come through an established collaboration, and we have a working protocol for generating sensory neurons, with a manuscript in preparation. Facilities include high-content imaging, super-resolution microscopy to resolve ensheathment of individual fibres, and Oxford Nanopore sequencing at Exeter. Experiments are tiered, so cheaper assays across all three genotypes focus the costlier sequencing.

Expected outcomes: a human isogenic model of the neuron-glia unit that degenerates in diabetic neuropathy, an answer to which cell type APOE acts in, and prioritised targets for protecting nerve cells.

Relevant publications

1. Leung, S.K., Bamford, R.A., Jeffries, A.R., Castanho, I., Chioza, B., Flaxman, C.S., Moore, K., Dempster, E.L., Harvey, J., Brown, J.T., Ahmed, Z., O'Neill, P., Richards… https://doi.org/10.1038/s41467-024-50486-8
2. Belal, M., Mucha, M., Monteil, A., Winyard, P.G., Pawlak, R., Walker, J.J., Tabak, J. & Belle, M.D.C. (2025). The background sodium leak channel NALCN is a major control… https://doi.org/10.1113/JP284036
3. Saghafi, T., Rumbell, T., Gurev, V., Kozloski, J., Tamagnini, F., Wedgwood, K.C.A. & Diekman, C.O. (2024). Inferring parameters of pyramidal neuron excitability in mouse… https://doi.org/10.1007/s11538-024-01273-5

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional interpretation of human NF1 genetic variation using precision genome editing and in vivo phenotyping

Lead Supervisor: Yosuke Ono

Lead Supervisor Email: Y.Ono@exeter.ac.uk

Department: Living Systems Institute

Primary Institution: University of Exeter

Project details

Neurofibromatosis type 1 (NF1) is a genetic disorder that causes a range of symptoms and affects approximately 1 in 3,000 people. These include abnormalities in skin pigmentation, problems with the heart and circulatory system, and nerve tumours that cause chronic pain and movement problems. This multisystem genetic disorder is caused by mutations in the NF1 gene, which encodes the neurofibromin protein. Neurofibromin contains seven functional domains and each domain interacts with different signalling pathways. Although mutations throughout the entire NF1 gene can cause disease, it remains unclear how genetic variants in different domains are associated with distinct clinical phenotypes. This PhD project addresses the gap between genetic variants in humans, molecular functions, and organismal phenotypes in NF1.

The project will be delivered by combining data science and in vitro and in vivo analyses to address three objectives; 1) Identification and prioritisation of human NF1 variants, 2) Assessment of their effects on NF1-dependent signalling, and 3) Validation of the genetic variants in zebrafish model. The student will screen and prioritise NF1 pathogenic variants using population data focusing on genotype–phenotype association. In addition, AI-based approaches such as biological foundation models will be used to predict their functional effects and select variants representing different NF1 domains. Next, effects of selected variants on the signalling pathways downstream of neurofibromin will be investigated using human cell culture systems. The student will quantitatively measure cellular phenotypes and investigate the rescue by drug treatment with the existing chemical compounds such as MEK inhibitors targeting the oncogenic Ras pathway regulated by neurofibromin.

To connect molecular function to organismal phenotype, the student will establish a novel humanised zebrafish platform during the project. Zebrafish possess two paralogs of the human NF1 gene, referred to as nf1a and nf1b, both of which show comparable levels of conservation across DNA sequences and protein domain structures. Interestingly, nf1a/b mutant zebrafish reproduce many of the common NF1 phenotypes, such as the loss of pigmentation and abnormal patterning of the central nervous system. To generate a precise disease model, the protein-coding sequence of the zebrafish nf1 is excised and replaced with the human NF1 sequence using CRISPR/Cas9-based genome editing technologies. By using the humanised zebrafish, the student will create a multidimensional functional map of NF1 which links the genetic variants, signalling activities, and organismal phenotypes. The selected variants will be introduced into the replaced human NF1 gene using precise genome editing technologies such as prime editing and donor DNA-based knock-in.

Functional effects of the variants on tissue patterning and pharmacological responses will be assessed by imaging transgenic reporter zebrafish lines that label oligodendrocytes, Schwann cells, or endothelial cells in blood vessels.

This integrated functional genomics project which combines data science and cell and developmental biology will lead to a deeper mechanistic understanding of neurofibromin function and the contributions of individual genetic variants to organismal phenotypes relevant to symptoms observed in NF1 patients. By connecting individual variants to quantitative in vivo phenotypes and signalling outputs, this platform will provide a scalable strategy for variant interpretation, understanding of disease mechanisms, and improved therapies.

The PhD project will be primarily conducted at the Living Systems Institute and Medical School at the University of Exeter, with technical support from its core facilities including the Aquatic Resource Centre (ARC), which provides the facilities for generating and maintaining genetically modified zebrafish, and Bio-imaging centre.

Relevant publications

1. Cheng J, Taylor KR, Nicolaisen L, Pan J, Bycroft C, Perino M, Ward T, Hawkes G, Covill LE, Weilert M, Thomas RW, Latysheva N (2026). AlphaGenome Atlas: in silico mutagen… https://doi.org/10.64898/2026.09.16.26363192
2. Stevens M, Wang Y, Bouley SJ, Mandigo TR, Sharma A, Sengupta S, Housden A, Perrimon N, Walker JA & Housden BE (2025). Inhibition of autophagy as a novel treatment for ne… https://doi.org/10.1002/1878-0261.13704
3. Ono Y, Peterka M, Love M, Khan A, Bowers F, Bhandari A, Gordon E, Ball JS, Hammond C, Tyler CR, Rees S, Bohlooly-Y M, Maresca M & Scholpp S (2026). Optimised genome edit… https://doi.org/10.7554/eLife.107475.3

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional genomics of health and unhealthy fat distribution

Lead Supervisor: Michael Weedon

Lead Supervisor Email: M.N.Weedon@exeter.ac.uk

Department: Clinical and Biomedical Sciences

Primary Institution: University of Exeter

Project details

Where fat is stored in our bodies is a major determinant of health. Storing fat safely under the skin (subcutaneous fat) protects against metabolic disease like heart failure and type 2 diabetes, while storing fat centrally around the organs (visceral fat or "lipodystrophy") drastically increases disease risk. Although human genetics has identified some protein-coding genes that substantially affect fat distribution, the vast majority of disease-associated variation is hidden in non-coding regulatory regions that have been difficult to access and interpret at scale. Now, with increasing availability of whole-genome sequencing from millions of individuals; fat-specific genetic regulatory maps; AI variant interpretation tools, and advances in functional models of fat cells, we are in prime position to effectively interrogate these regions. This will allow us to determine which variants and genes affect fat distribution.

Key Question and Objectives: Which genetic regulatory switches and genes drive human visceral versus subcutaneous adipocyte identity, and what are the biological mechanisms?

The student will:

1) Identify coding and non-coding variants associated with fat distribution using whole genome-sequencing data across massive multi-ancestry cohorts.

2) Integrate genetic signals with multi-omic epigenetic maps, including AlphaGenome AI predictions, to prioritise and interrogate causal regulatory elements.

3) Establish human iPSC-derived adipocyte models patterned toward visceral and subcutaneous adipocytes.

4) Quantify the functional impact of prioritized genes and regulatory variants on adipocyte phenotypes using CRISPR-based perturbations.

Interdisciplinarity: This project is interdisciplinary, bridging data science with experimental biology. The studentship will comprise world-leading computational genomics and population genetics at the University of Exeter, alongside cutting-edge stem-cell biology and CRISPR-Cas9 genome editing at the University of Cambridge. The supervisors also include leading senior clinical academics with expertise in lipodystrophy providing important clinical insight for the student.

Methodology:

1) At Exeter, you will harness established population-genetic association pipelines to analyse WGS and fat measurements from highly diverse cohorts. You will integrate these genetic signals with adipose-specific regulatory information (including gene expression, chromatin accessibility, enhancer-gene relationships) and AI-based tools such as AlphaGenome to prioritise and test a set of candidate variants, regulatory elements and target genes.

2) At Cambridge, you will develop iPSCs patterned towards visceral and subcutaneous adipocyte identity, guided by developmental cues. A stable Cas9-expressing iPSC line will establish a reproducible perturbation pipeline, benchmarked using established adiposity genes like ALK7/ACVR1C and PLIN1. You will use high-content imaging and biochemical assays will quantify adipogenesis, lipid storage, and lipolysis. Your validated functional framework will then run a primary CRISPR knockout screen of genetically prioritised candidates.

Expected Outcomes: The studentship will deliver a validated platform of human iPSC-adipocytes and uncover the biological mechanisms behind non-coding variants controlling human fat distribution. This will identify new therapeutic drug targets for cardiometabolic disease that focus on safe fat storage rather than just overall weight loss.

Facilities and Resources: At Exeter, you will use large-scale computational platforms and Cloud Trusted Research Environments (DNANexus) to analyse over 1 million genomes. At Cambridge, you will be embedded in world-leading metabolic science facilities with comprehensive access to advanced iPSC infrastructure, high-content imaging, and flow cytometry.

Relevant publications

1. Hawkes G, et al., Whole-genome sequencing analysis of anthropometric traits in 672,976 individuals reveals convergence between rare and common genetic associations. Natu… https://doi.org/10.1038/s41467-026-69208-3
2. Patel et al., PLIN1 Haploinsufficiency Causes a Favorable Metabolic Profile, JCEM, 2022: https://doi.org/10.1210/clinem/dgac104
3. Saeed S*, Siegert A*, Tung YCL* et al., Biallelic variants in SREK1 downregulating SNORD115 and SNORD116 cause a Prader-Willi-like syndrome. J Clin Invest. 2025: https://doi.org/10.1172/JCI191008

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: One read, one cell: Decoding cell identity with long-read sequencing

Lead Supervisor: Eilis Hannon

Lead Supervisor Email: e.j.hannon@exeter.ac.uk

Department: Clinical and Biomedical Sciences

Primary Institution: University of Exeter

Project details

Background

What if we could resolve the epigenome of individual cell types from complex human tissues without ever having to physically separate the cells?

The majority of disease-associated genetic variants exert their effects by modulating gene expression, driving considerable interest in profiling epigenomic variation at scale. Epigenomic patterns, chemical modifications to DNA and chromatin that controls which genes are active, are highly cell-type specific. When studying epigenetics, the tissue choice strongly influences the findings. A critical limitation of existing studies is that bulk tissues (such as whole blood) comprise a mixture of cell types, potentially masking true biological signals.

Historically, resolving this has required the physical isolation of individual cell populations, costly, low-throughput and impractical for population-level studies. Long-read sequencing changes this paradigm by detecting epigenetic modifications alongside genetic sequencing, and by capturing continuous stretches of a single DNA molecule so that each read provides a snapshot of its cell type of origin. We have developed a framework that classifies cell type for individual reads by comparing methylation patterns to reference profiles for different cell types. This enables the generation of cell-type-specific epigenetic profiles directly from long-read sequencing data, bypassing the need for experimental cell separation. The project will exploit ~50,000 Oxford Nanopore long-read genomes available in UK Biobank, providing a unique opportunity to resolve cell-type-specific epigenetic variation at population scale.

Objectives

1. Evaluate the predictive accuracy and optimal conditions for computational cell-type-of-origin prediction from long-read sequencing data.

2. Curate a comprehensive atlas of reference cell-type methylomes to generalise the approach across multiple tissues.

3. Apply the framework to large population biobank datasets to generate cellular composition estimates and cell-type-specific epigenetic profiles at scale.

4. Leverage these cell-type-resolved profiles to conduct epigenome-wide association studies in large cohorts, identifying epigenetic effects linked to disease in specific cell types.

Methodology

The student will apply our suite of computational tools to blood-based long-read sequencing datasets, benchmarking cell-type-of-origin predictions against reference purified datasets to determine optimal conditions for the approach. This phase will include systematic fine-tuning of the prediction framework. The validated tools will then be applied to large biobank cohorts to generate cell composition predictions and cell-type-specific epigenetic profiles at population scale. Finally, these profiles will be used to perform a cell-type-specific epigenome-wide association study, identifying methylation changes associated with phenotypes of health and disease such as smoking and age, that are resolved to individual cell types.

Interdisciplinarity, Facilities and Resources

The supervisory team work at the intersection of functional genomics, mathematics and computer science, with expertise in large complex genomic datasets, method development, and advanced data science and AI methodologies. The student will work across two world-leading research groups, the Complex Disease Epigenetics Group at Exeter and the Birney Group at EBI. They will need strong mathematical and programming skills, a genuine interest in cutting-edge biotechnologies such as long-read sequencing, and willingness to engage with cell biology to interpret their findings. While predominantly a data-science project, long-read sequencing facilities are available to generate reference datasets where appropriate, and computational work will be supported by local (ISCA) and regional (ISAMBARD 3) HPC clusters. The student will benefit from training through Exeter's Coding for Reproducible Research programme and EBI's suite of resources.

Relevant publications

1. Walker EM, Dempster EL, Franklin A, et al. Guidance for the design and analysis of cell-type-specific DNA methylation epidemiology studies. Brief Bioinform. 2025;26(4):b... https://doi.org/10.1093/bib/bbaf427

2. Hannon E, Dempster EL, Davies JP, et al. Quantifying cell types in the human cortex using DNA methylation profiles. BMC Biology. 2024. https://doi.org/10.1186/s12915-024-01827-y

3. Hannon E, Mill J. Epigenetic signatures identify cell type of origin from long-read sequencing. bioRxiv. 2024. https://doi.org/10.1101/2024.06.03.597114

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Allele-resolved genetics and epigenetics in type 2 diabetes

Lead Supervisor: Nick Owens

Lead Supervisor Email: n.d.l.owens@exeter.ac.uk

Department: Department of Clinical and Biomedical Sciences

Primary Institution: University of Exeter

Project details

Type 2 diabetes (T2D) affects over 800 million people worldwide. It is a complex disorder and an individual's genetics influences disease risk. Understanding how DNA differences drive this risk can enable disease prediction and personalised approaches to diagnosis and treatment, addressing the shortfall between genetic discovery and patient benefit.

Large scale genetic studies have identified hundreds of DNA regions linked to increased T2D risk. Most lie in regulatory regions, areas of DNA outside the genes that control when and where a gene is turned on. Changes here impact how islets – clusters of pancreatic cells that produce hormones including insulin – regulate blood glucose. Interpreting these DNA changes is complicated because we inherit two parental copies of our genome, and the disease-causing changes generally reside on only one. Standard technologies merge data from both copies, making it challenging to resolve which DNA changes contribute to disease.

This project will use chromatin stencilling (known as Fiber-seq), a cutting-edge technology, to address this problem. This long-read sequencing technology simultaneously measures regulatory activity, epigenetic state, and genotype and allows us to distinguish the two parental copies of the genome.

Key question

How do genetic variants associated with T2D alter regulatory activity on each inherited copy of our genome in pancreatic islets? This will be achieved by:

1. Generating unprecedented chromatin stencilling maps of DNA regulatory activity from healthy pancreatic islet donors.

2. Targeting specific disease loci in islets from genetically selected type 2 diabetes donors to pinpoint failing regulation.

3. Decoding how genetic changes affect DNA regulation, enabling the interpretation of diabetes-associated genetics in large studies like the UK Biobank.

Interdisciplinary Approach

This project brings together laboratory genetics, epigenetics, long-read sequencing and extensive data science. The student will join the Gene Regulatory Defects in Disease Group at the University of Exeter, an interdisciplinary team of laboratory and computer scientists. The project will allow the

student to shape the research direction, and they will receive expert supervision, training, and collaboration with international leaders. The student will develop translatable skills in experimental design, DNA sequencing, bioinformatics and interpreting complex biological data.

Methodology

Healthy and T2D islets will be selected using genetic, clinical, and existing molecular data. The islets will undergo our chromatin stencilling protocol, and the DNA will be sequenced using Oxford Nanopore. These long reads allow us to map activity to each inherited DNA copy and assess copy-specific regulation. Targeted sequencing will also provide deep coverage at selected disease regions. Computational analyses will then identify differences in DNA accessibility and methylation, resolving cell-type specific regulation and annotating regulatory protein binding sites. This will be combined with large-scale genetic (e.g. UK Biobank) to improve interpretation of variants in T2D.

Outcomes

This project will generate the most detailed maps to date of gene regulation in healthy and T2D pancreatic islets, improving our understanding of the genetic basis for T2D. The resulting openly shared annotations and datasets will be a resource for the community. Student training will also be a significant output, they will gain cross-discipline expertise in long-read sequencing, epigenetics, computational biology, and statistical genetics.

Facilities & Resources

The group has established chromatin stencilling protocols, our own Oxford Nanopore sequencing platforms and high-performance computing infrastructure. Human islets will be provided by the Alberta IsletCore, with matched genotype, RNA-seq, proteomic, and single-cell transcriptomic data available through through collaboration with Professor Gloyn.

Relevant publications

1. MacCalman A, De Franco E, Franklin A, Flaxman CS, Richardson SJ, Murrall K, Burrage J, Barts Pancreas Tissue Bank (BPTB), Walker EM, Morgan NG, Hattersley AT, Dempster E… https://doi.org/10.1186/s12864-024-10450-8
2. Stankovic S*, Shekari S*, Huang QQ*, Gardner EJ*, *Ivarsdottir EV, Owens ND*, Mavaddat N, Azad A, Hawkes G, Kentistou KA, Beaumont RN, Day FR, Zhao YN, …. Genetic links… https://doi.org/10.1038/s41586-024-07931-x
3. Wakeling MN*, Owens NDL*, Hopkinson JR, Johnson MB, Houghton JAL, Dastamani A, et al. A novel disease mechanism leading to the expression of a disallowed gene in the pan… https://doi.org/10.1038/s41588-022-01204-x

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Mapping and functional interrogation of mitochondrial DNA modifications in Parkinson's disease

Lead Supervisor: Professor Katie Lunnon

Lead Supervisor Email: k.lunnon@exeter.ac.uk

Department: Department of Clinical & Biomedical Sciences

Primary Institution: University of Exeter

Project details

There is increasing evidence that the mitochondrial genome may be regulated by DNA modifications, but their extent, identity and functional importance remain unclear. This uncertainty partly reflects technical limitations, as conventional approaches for measuring DNA methylation can generate artefacts when applied to mtDNA. Long-read sequencing technologies now provide an opportunity to directly investigate multiple DNA modifications in native mtDNA. This is particularly relevant to Parkinson's disease (PD), where mitochondrial dysfunction is strongly implicated in disease pathogenesis. We hypothesise that mtDNA contains reproducible patterns of DNA modification that influence mitochondrial genome regulation and are altered in PD. We will address this through 3 objectives.

(1) To develop and validate Oxford Nanopore Technologies (ONT) approaches to accurately characterise mtDNA modifications. ONT sequencing will be performed on native enriched mtDNA, enabling genetic variation and DNA modifications to be measured on individual molecules. We will generate artificial mtDNA molecules containing known levels of specific modifications and use these to establish the sensitivity, specificity and reproducibility of current modification-calling approaches. This will allow us to look at a range of DNA modifications (e.g. 5mC, 5hmC, 6mA).

(2) To define the landscape of mtDNA modifications in PD brain. We will apply the validated approach to an existing, well-characterised PD case-control cohort to determine the distribution and abundance of modifications across the mitochondrial genome and identify differences associated with disease. The single-molecule nature of ONT sequencing will also enable DNA modifications to be considered alongside mtDNA sequence variation and heteroplasmy, providing an integrated view of mitochondrial genetic and epigenetic variation. Analyses will encompass the entire mitochondrial genome while specifically testing the hypothesis that modification of regulatory regions, including the D-loop, is important in PD.

(3) To determine the functional relevance of mtDNA modifications by integrating them with molecular phenotypes in the same brains. We will initially test whether variation in mtDNA modifications, particularly within regulatory regions, is associated with mitochondrial transcription and mtDNA abundance. We will then integrate modification profiles with existing bulk and snRNA-seq, small RNA-seq, nuclear DNA methylation and genetic data to determine how mtDNA modification states relate to cellular pathways and PD-associated molecular changes. This will

prioritise candidate regulatory modifications for future causal investigation using emerging mitochondrial epigenome-editing approaches. The project will establish a validated experimental and computational framework for studying mtDNA modifications, and determine their relationship with mitochondrial genome activity and wider cellular phenotypes in PD brain. It is highly interdisciplinary, combining long-read sequencing, mitochondrial genetics, epigenetics, bioinformatics and multiomic data integration. The project will exploit existing PD brain samples and extensive matched genomic and transcriptomic datasets, substantially reducing the requirement for costly new data generation. The supervisory team brings complementary skills that directly reflects the project: Prof Lunnon has extensive expertise in neurodegenerative disease epigenetics and has led research investigating the mitochondrial epigenome in human brain; Prof Chinnery is an international leader in mitochondrial genetics, including the application of long-read and multiomic technologies; Dr Kouhsar brings expertise in bioinformatics, long-read sequencing analysis and multiomic data integration, whilst Dr Smith has experience in developing novel ONT approaches. Together, these existing samples, datasets, expertise and sequencing and computational infrastructure provide a strong PhD environment.

Relevant publications

1. Devall M, Soanes DM, Smith AR, Dempster EL, Smith RG, Burrage J, Iatrou A, Hannon E, Troakes C, Moore K, O'Neill P, Al-Sarraj S, Schalkwyk L, Mill J, Weedon M, Lunnon K.... https://doi.org/10.3389/fendo.2022.1059120

2. Bicci I, Calabrese C, Golder ZJ, Gomez-Duran A, Chinnery PF. Single-molecule mitochondrial DNA sequencing and CpG methylation. Nucleic Acids Research. 2021. https://doi.org/10.1093/nar/gkab1179

3. Stoccoro A, Smith AR, Baldacci F, Del Gamba C, Lo Gerfo A, Ceravolo R, et al. Mitochondrial D-loop methylation and copy number in Parkinson's disease. Genes. 2021. https://doi.org/10.3390/genes12050720

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Decoding cellular diversity in the brain: functional annotation of neuronal subtypes across development and disease

Lead Supervisor: Jonathan Mill

Lead Supervisor Email: j.mill@exeter.ac.uk

Department: Clinical and Biomedical Sciences

Primary Institution: University of Exeter

Project details

The human brain contains an extraordinary diversity of cell types, each with distinct functions, molecular programmes and roles in disease. Even within neurons, numerous excitatory and inhibitory subtypes differ across brain regions and change across development and ageing. Understanding this diversity is essential for determining how the brain functions and why particular neuronal populations are selectively vulnerable in different brain diseases.

Single-cell RNA sequencing has transformed our understanding of neuronal transcriptional diversity, but the regulatory mechanisms that establish and maintain these identities remain much less well characterised, particularly for rarer neuronal populations. We have developed methods for isolating defined cell populations from human post-mortem brain and generated multi-omic regulatory maps of major cell classes. This PhD will extend these approaches to resolve the functional genomics of specific neuronal subtypes.

The central objective is to isolate distinct neuronal populations, including excitatory and inhibitory subtypes and regionally specialised populations such as motor neurons, and determine how their regulatory landscapes vary across brain regions, development and ageing. The student will use existing single-cell and multiomic datasets to identify nuclear markers that distinguish neuronal populations, then develop fluorescence-activated nuclei sorting strategies to isolate them from human brain tissue. Samples will span cortex, hippocampus, amygdala, hypothalamus and other disease-relevant regions, with opportunities to examine development and ageing.

The project will use functional genomic technologies to characterise gene regulation within these populations. Approaches will include Oxford Nanopore long-read sequencing to map DNA modifications, ATAC-seq to identify accessible regulatory elements, and CUT&Tag profiling of H3K27ac to identify active enhancers and promoters. A particular focus will be direct measurement of DNA hydroxymethylation, an abundant neuronal DNA modification likely to have important regulatory functions. Long-read RNA sequencing will define full-length transcripts and cell-specific isoform usage, with opportunities to explore direct RNA sequencing and the neuronal epitranscriptome.

Together these datasets will provide a functional annotation of neuronal diversity, identifying regulatory elements, transcripts and epigenetic features that distinguish populations across regions and stages of life. They will also be used to interpret human genetic studies of neurological and

psychiatric disease, including whole-genome sequencing and association datasets from large national cohorts.

A further objective will be to use these high-resolution reference maps to develop computational methods for estimating the proportions and molecular states of specific neuronal populations in bulk brain datasets. These deconvolution approaches can then be applied to extensive in-house DNA methylation datasets from disorders such as Alzheimer's disease, enabling disease-associated molecular changes to be assigned to specific neuronal populations.

This is a highly interdisciplinary project spanning epigenomics, genomics, molecular biology, neuroscience and computational biology. The student will be based in Exeter (Mill, Dempster, Bamford) with collaborators at Imperial (Nott), KCL (Marzi), Cambridge (Ryten) and EBI-EMBL (Birney).

The project is supported by exceptional resources, including existing multiomic human brain datasets, post-mortem tissue (multiple brain regions and developmental stages), cell-sorting platforms, state-of-the-art sequencing facilities, and extensive high-performance computing. The resulting datasets and computational tools will provide a framework for understanding neuronal function and identifying the cell populations and regulatory mechanisms through which genetic and epigenetic variation contributes to brain disease.

Relevant publications

1. Chioza B et al. Optimised fluorescence-activated nuclei sorting for epigenomic analysis of cortical cell types. bioRxiv. 2026 https://doi.org/10.64898/2025.12.22.695789v1
2. Franklin et al. Cell-type-specific DNA methylation dynamics in the prenatal and postnatal human cortex. Cell Genomics. 2025 https://doi.org/10.1016/j.xgen.2025.101010
3. Leung et al. Long-read transcript sequencing identifies differential isoform expression in the entorhinal cortex in a transgenic model of tau pathology. Nature Communica… https://doi.org/10.1038/s41467-024-50486-8

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Editing the Alzheimer's Epigenome: From Human Brain Variation to Functional Mechanisms

Lead Supervisor: Emma Dempster

Lead Supervisor Email: e.l.dempster@exeter.ac.uk

Department: Clinical and Biomedical Sciences

Primary Institution: University of Exeter

Project details

Alzheimer's disease (AD) is characterised by distinctive molecular changes across multiple cell types in the human brain. Epigenome-wide association studies (EWAS) have identified widespread alterations in epigenetic modifications associated with AD pathology, but a major challenge remains: which of these changes have functional consequences for gene regulation and disease biology. This question is particularly important in the brain, where different cell types have highly distinct regulatory landscapes. Using fluorescence-activated nuclei sorting (FANS), we have generated cell-type-specific epigenomic datasets from human post-mortem brain, including DNA methylation, chromatin accessibility (ATAC-seq) and H3K27 acetylation (H3K27ac), a marker of active regulatory elements (Ref. 1). These unique datasets provide an opportunity to move beyond association and identify disease-associated epigenetic changes occurring within functional regulatory elements in specific brain cell types.

The central question of this PhD is to identify AD-associated regions with regulatory potential, and to functionally characterise how they influence gene regulation and cellular phenotype.

The project will address this through three complementary objectives.

First, the student will integrate cell-type-specific DNA methylation, ATAC-seq and H3K27ac data to identify and prioritise candidate regulatory loci from our AD EWAS (Exeter). These data will be combined with available gene expression, genetic association, and regulatory annotations to identify disease-associated epigenetic changes occurring within active promoters and enhancers and establish their likely target genes. This multi-omic approach will move beyond conventional annotation of EWAS signals based simply on proximity to the nearest gene and instead prioritise loci with strong evidence for a functional regulatory role.

Second, selected regulatory loci will be functionally interrogated using targeted CRISPR epigenome editing. Catalytically inactive Cas9 (dCas9) fused to DNA methylation, demethylation, or chromatin remodelling enzymes will be used to induce or reverse disease-associated epigenetic states in relevant cell lines and human induced pluripotent stem cell (hiPSC)-derived neural cells (cortical neurons/microglia). These novel methods are currently being optimised by the supervisory team funded by an FGx innovation and collaboration fund award (PI Bello, Milner Institute).

Initial studies will focus on microglia, where we have identified prominent AD-associated DNA methylation differences and the possess relevant expertise (Washer), but still allowing the student to investigate neuronal or other glial mechanisms emerging from the computational analyses.

Third, the student will determine the molecular and cellular consequences of these perturbations. Targeted assays will confirm epigenetic editing (e.g. bisulfite pyrosequencing), followed by analysis of gene expression and relevant cellular phenotypes. For the strongest candidates, transcriptomic, methylomic and/or chromatin-accessibility profiling will establish how perturbation alters regulatory networks and cellular states.

This interdisciplinary project combines human disease epigenomics, computational biology, stem-cell models and CRISPR-based functional genomics. The student will develop expertise spanning multi-omic data integration, reproducible bioinformatics, experimental epigenomics, cell culture, epigenome editing and functional assays. Importantly, the initial analyses will allow the student to shape which loci, cell types and biological pathways are pursued experimentally.

The project is supported by extensive existing cell-type-specific datasets, established FANS and epigenomic pipelines (Dempster & Mill, Exeter), access to hiPSC-derived models of neurodegeneration (Washer (Oxford) & Bello (Cambridge)), omics (Dempster & Mill, Exeter), and expertise in targeted DNA methylation editing (Exeter, Oxford and Cambridge)

Relevant publications

1. Chioza B, Policicchio S, Burrage J, Blake GET, Bamford RA, Franklin A, Soanes D, Wells PM, Babtie A, Flores Payan M, Davies JP, Klokkaris A, Walker EM, Ismail JN, Urba… https://doi.org/10.1371/journal.pone.0359643
2. Perez-Alcantara et al. (2026). Integrated QTL mapping and CRISPR screening in pooled iPSC-derived microglia reveals genetic drivers of neurodegenerative risk. https://doi.org/10.1101/2025.08.18.670767
3. Bello et al. (2026). An Alzheimer's disease-associated common regulatory variant in a PTK2B intron alters microglial function. iScience. https://doi.org/10.1016/j.isci.2026.115688

Please direct project-specific enquiries to:

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: A Splice of Life: From Novel Brain mRNA Isoforms to Functional Proteins

Lead Supervisor: Rosemary Bamford

Lead Supervisor Email: r.bamford@exeter.ac.uk

Department: Medical School, Clinical and Biomedical Sciences

Primary Institution: University of Exeter

Project details

Alternative splicing enables a single gene to produce multiple mRNA isoforms, and potentially proteins with distinct functions. It is especially important in the brain, where transcript diversity supports development and ageing. Studies have implicated disrupted RNA splicing in neurodevelopmental, neuropsychiatric and neurodegenerative disorders. Yet detecting a novel mRNA isoform does not prove that it is translated into a stable, functional protein. Establishing which transcripts reach the proteome is a major challenge in functional genomics.

Long-read sequencing allows complete RNA molecules to be characterised, and studies have uncovered extensive unannotated transcript diversity in the human brain. If transcripts are predicted to have coding potential, then these novel transcripts contain uncharacterised coding sequences (CDS). Our research has identified over 20,000 novel transcripts in the brain with CDS. These are a result of alternative splicing events such as exon skipping, alternative transcriptional start/end sites and fusion transcripts. Preliminary analyses suggest that genetic variation affecting these sequences is associated with neurodevelopmental and neuropsychiatric conditions.

The key question is 'which novel brain mRNA isoforms are translated into proteins, and what are their functional and disease-relevant consequences?'

Objective 1 is to identify and prioritise novel CDS predicted to generate new protein isoforms, alter known proteins, or change the balance between functionally distinct isoforms. The initial focus will be on genes involved in brain development, ageing and disorders. Objective 2 is to determine whether prioritised transcripts are translated. The student will integrate transcriptomic and proteomic data and validate selected candidates using mass spectrometry and Quantum-Si single-molecule protein sequencing. These approaches will also investigate protein isoforms and post-translational modifications. Objective 3 is to establish how selected isoforms affect protein expression, localisation, interactions, and function using cell models.

This interdisciplinary project combines bioinformatics, transcriptomics, proteomics and molecular biology. It is a combined bioinformatics and wet laboratory project. The focus will be on brain and blood, not any neuropsychiatric disease or disorder – this is open for the student to take a lead on genes of interest (candidate genes are available).

This project can be steered towards where the student's talent meets interest. The project involves bioinformatic analysis - prioritising the best targets to take forward for proteomics and then

functional validation. The student will analyse long-read datasets and can incorporate single-nucleus, spatial transcriptomic and public data to select candidates for experimental validation. Full computational and laboratory training will be provided, with opportunities to work with international collaborators developing methods for long-read transcriptome–proteome analysis and integration. The student will prepare proteomics samples from postmortem human brain for mass spectrometry and Quantum-si single protein molecule sequencing. Key splicing events will be investigated in cell models using protein extraction, co-immunoprecipitation and Western blotting to determine whether the resulting proteins have distinct biological effects.

The expected outcome will be a comprehensive analysis and validation of predicted novel CDS in the brain, with a better understanding of the functional consequences of these downstream and their involvement in neuropsychiatric disease and disorder.

The student will join an internationally recognised environment in brain genomics, long-read sequencing and functional genomics, with extensive datasets, advanced bioinformatics and high-performance computing. The student will have access to all necessary laboratory facilities and equipment to support the project.

Relevant publications

1. Bamford et al. (2024). An atlas of expressed transcripts in the prenatal and postnatal human cortex. bioRxiv. https://doi.org/10.1101/2024.05.24.595768
2. Leung et al. (2021). Full-length transcript sequencing of human and mouse cerebral cortex identifies widespread isoform diversity and alternative splicing. Cell Reports. https://doi.org/10.1016/j.celrep.2021.110022
3. Baran et al. (2026). Spatial Mapping of Genetic Liability to Psychiatric Disorders in the Adult Human Hippocampus. Biological Psychiatry Global Open Science. https://doi.org/10.1016/j.bpsgos.2026.100719

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Genome to Drug: Autonomous Functional Genomics for Personalised Cancer Vaccines

Lead Supervisor: Lennard lee

Lead Supervisor Email: lennard.lee@immonc.ox.ac.uk

Department: Nuffield Department of Medicine, University of Oxford

Primary Institution: University of Oxford

Project details

Cancer genomics has generated extraordinary quantities of data. The challenge is increasingly what we do with it: how do we identify which genomic changes matter, experimentally determine their functional consequences, and translate those discoveries into new drugs?

This DPhil builds on a major UK experiment in a new approach to scientific discovery. In 2025, the Advanced Research + Invention Agency (ARIA) launched its AI Scientist programme, seeking systems capable of moving beyond conventional AI prediction towards generating hypotheses, designing and executing experiments, interpreting results and iteratively learning from them. The programme attracted 245 proposals internationally. Twelve teams were initially selected to develop competing approaches. Following this programme, only the Oxford cancer vaccine AI Scientist programme has progressed to four-year funding to develop an integrated AI Scientist, autonomous laboratory and cancer vaccine discovery platform.

Cancer vaccines provide a powerful model for testing this concept because there is a direct potential path from genome to drug. Sequencing a patient's cancer can reveal thousands of genomic alterations. Functional genomics is required to determine which alterations are biologically meaningful, expressed, presented to the immune system and capable of generating an anti-cancer immune response. The challenge is therefore no longer simply to sequence cancer, but to learn how to interpret its genome sufficiently well to design a medicine.

Our proof-of-principle is CancerVaccineGPT, an AI model developed specifically for cancer vaccine target prediction. We assembled large-scale cancer genomic and immunological datasets, comprising more than one billion training parameters/data relationships, to train models to predict which tumour-derived peptides are most likely to represent useful vaccine targets. Like the first generations of large language models, these models demonstrate that biological information can be learnt at scale, while also revealing a fundamental limitation: prediction alone is insufficient. Models need experimental feedback to determine when they are right, learn from their errors and improve.

The central question of this DPhil is therefore: can an AI Scientist learn functional genomics by connecting genomic prediction directly to experimental biology, and use this knowledge to accelerate the journey from genome to drug?

The student will combine cancer genomics, transcriptomics, immunology, AI and experimental functional genomics. Candidate genomic alterations will be identified and prioritised computationally,

then experimentally tested using cellular and immune assays. Results will be returned to the AI Scientist, allowing hypotheses and models to be refined through repeated predict → test → learn cycles. The strongest functionally validated targets will progress into mRNA vaccine design and experimental manufacture, creating an end-to-end genome → function → drug pathway.

A distinctive feature will be integration with autonomous laboratories. Hamilton automated liquid handling and UFACTORY robotics will enable reproducible, scalable experimentation, while Unchained Labs technology will support translation of validated targets into mRNA/LNP vaccine formulations. The student will therefore work across functional genomics, cancer immunology, AI, robotics and therapeutic development.

The expected outcome is both biological and methodological: improved understanding of which genomic alterations generate functional anti-cancer immune targets, alongside a new model of scientific discovery in which human scientists, AI Scientists and autonomous laboratories work together. Ultimately, the project asks whether the enormous genomic datasets accumulated over recent decades can be transformed from maps of disease into a practical engine for discovering new medicines.

Relevant publications

1. Sovereign AI supercomputers: a global landscape review of unprecedented biomedical research infrastructure". L Wang, M Bryan, E Viega... LYW Lee. Frontiers in Artificial I... https://doi.org/10.3389/frai.2026.1796682
2. M. Bryan, J Conway, G Bloomfield... LYW Lee. What if Every Patient's Immune System Could be Guided by the World's Most Powerful Computers to Fight Cancer? The UK Cancer Va...
3. Storey B, Bryan M, Shellard J, D'Costa J, Kim I, Aggarwal D, et al. UK Cancer Vaccine AI Scientist and Supercomputing Consortium. Lancet Oncology. 2026.

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Tissue-specific selection of mosaic mutations in development and disease

Lead Supervisor: Anne Goriely

Lead Supervisor Email: anne.goriely@imm.ox.ac.uk

Department: Radcliffe Department of Medicine

Primary Institution: University of Oxford

Project details

Postzygotic somatic mosaicism (PZM) is an important and under-recognised cause of rare developmental disorders. Diagnosis is challenging because pathogenic variants may be present in only a subset of cells and may be absent or detected at very low levels in blood, despite being enriched in clinically affected tissues. Consequently, patients with mosaic disease may receive delayed, incomplete or incorrect molecular diagnoses, limiting accurate prognosis, genetic counselling and access to appropriate clinical management.

The clinical impact of mosaicism depends not only on the pathogenic variant itself, but also on its distribution across tissues and cell types. During development, mutant and wildtype cells may differ in their survival or proliferative capacity, resulting in tissue-specific enrichment or depletion of pathogenic cells. However, these processes of developmental selection have not been systematically quantified across tissues and cell types. Understanding them is therefore essential for interpreting mosaic variants and determining which tissues are most informative for genetic testing.

This project will determine how developmental selection shapes the tissue distribution of pathogenic mutations. We will exploit complementary mouse models of genetic mosaicism and high-throughput single-cell transcriptomics to quantify mutant cell representation across tissues at single-cell resolution. We will focus on Cornelia de Lange syndrome (CdLS) and ATR-X syndrome, rare multisystem developmental disorders for which our team has established relevant mouse models and expertise.

The project has three objectives:

Objective 1: Quantify tissue-specific selection in postzygotic mosaicism. We have developed an inducible mouse model of mosaic CdLS in which Nipbl is deleted in a subset of cells during early embryogenesis. Neonatal mice will undergo whole-animal dissociation, and multiplexed single-cell RNA sequencing will quantify mutant cell representation across major tissues and cell types, identifying populations that selectively enrich or deplete pathogenic cells.

Objective 2: Identify shared principles of selection across different forms of genetic mosaicism. Female carriers of X-linked pathogenic variants are functional mosaics because of X chromosome inactivation (XCI). We will perform equivalent single-cell analyses in female mice carrying pathogenic Hdac8 or Atrx variants. Integrating these datasets with the PZM model will test whether common tissue- and cell-type-specific selective pressures operate across genetically distinct developmental disorders.

Objective 3: Establish an experimental system for mechanistic studies of developmental selection. Wildtype and mutant mouse embryonic stem cells will be combined and differentiated into selected lineages. Additional lineages will be prioritised from the in vivo single-cell results.

The project will generate a quantitative atlas of developmental selection across tissues and forms of genetic mosaicism, together with openly available single-cell datasets and analytical approaches.

This interdisciplinary project will provide the student with unique training opportunities in state-of-the-art technologies spanning rare disease biology, genetics, single-cell genomics, Next-Generation sequencing, genetic counselling, ethics and quantitative data analysis. A central training objective will be to develop the ability to integrate experimental and computational approaches to address clinically relevant questions in human genetics.

The student will gain practical experience in genetically engineered mouse models, experimental analysis of developmental mosaicism, tissue dissociation, flow cytometry and cell isolation. They will develop expertise in the design and application of multiplexed single-cell RNA sequencing experiments, including experimental design, quality control and interpretation of complex cellular datasets.

Relevant publications

1. Personalized recurrence risk assessment following the birth of a child with a pathogenic de novo mutation. Nat Commun 14(1):853 [PMC9932158]; Dynamics of the 4D genome d... https://doi.org/10.1093/hmg/ddad075

2. Dynamics of the 4D genome during in vivo lineage specification and differentiation. Nature Communications. 2020. https://pubmed.ncbi.nlm.nih.gov/32483172/

3. A new mouse model of ATR-X syndrome carrying a common patient mutation. Human Molecular Genetics. 2023. https://doi.org/10.1093/hmg/ddad075

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Finding the machinery that builds TREM2: a genome-wide CRISPR screen for the biogenesis of an Alzheimer's risk receptor

Lead Supervisor: Haoxi Wu

Lead Supervisor Email: haoxi.wu@bioch.ox.ac.uk

Department: Biochemistry

Primary Institution: University of Oxford

Project details

Key question. How is the TREM2-DAP12 complex assembled and delivered to the cell surface?

Background. TREM2 is a surface receptor on microglia and other macrophages. Microglia use it to detect damaged and dying cells or tissues, especially during neurodegeneration. Rare TREM2 variants are among the strongest genetic risk factors known for Alzheimer's disease, and several reduce how much receptor reaches the surface during biogenesis. TREM2 cannot signal alone and must first pair with a signalling partner, DAP12, in the endoplasmic reticulum, through charged residues within their membrane-spanning segments. Homozygous loss of either gene causes an early-onset dementia. These charges are buried in the productive complex yet exposed during biogenesis. Exposed charges are recognised for degradation, by an unknown mechanism. Making a working receptor means escaping the degradative fate, completing assembly and routing the complex toward the cell surface, by machinery not yet identified.

Objectives. (1) Identify the genes that raise or lower surface TREM2, using genome-wide CRISPR knockout screens. (2) Establish what the strongest candidates do, separating those acting during assembly from those acting in export, quality control or internalisation. (3) Determine whether disease-associated mutations in TREM2 affect biogenesis, and test whether the factors identified can be manipulated to restore wild-type behaviour.

Methodology. Screens use Cas9-expressing THP-1 monocytes, which differentiate into macrophages on induction. Because TREM2 is expressed only after differentiation, every perturbation is established in cells that have never made the protein, and potential compensatory effects are minimised. Surface TREM2 is quantified by flow cytometry with two orthogonal reagents, a commercial antibody and a designed protein binder, alongside a second macrophage marker to exclude effects on differentiation or surface delivery broadly. Two guide RNA libraries will be used: a focused membrane proteome library the student designs from the host laboratory's annotation of the human membrane proteome (Wu and Hegde, J Cell Biol 2026), then a genome-wide macrophage-optimised library available through collaborators. Transduction, differentiation, staining and sorting are in Oxford; DNA extraction, sequencing and analysis follow in Cambridge, in a collaborating laboratory the student visits. Hits are validated in stem-cell-derived macrophages and microglia, and in primary murine bone-marrow-derived macrophages.

Mechanism is dissected in Oxford. Assembly of TREM2 with DAP12 is reconstituted in a cell-free system containing ER membranes, with and without each candidate, and photo-reactive amino acids

on the charged surfaces capture what contacts the receptor at each step. These factors, along with mutations in binding interfaces, are tested in macrophages by knockout, pulse-chase labelling and surface measurement.

Interdisciplinarity. The project spans functional genomics, immune cell biology, biochemistry and computational analysis. The screening strategy is developed together with Dr Roni Levin-Konigsberg at the MRC Laboratory of Molecular Biology, Cambridge, who provides the macrophage library and guides the screen design and analysis.

Expected outcomes. A first map of TREM2 biogenesis, with factors assigned to steps, and an explanation of why particular disease variants fail and whether they can be corrected. Since both raising and lowering surface TREM2 are pursued therapeutically, these factors are of translational interest.

Facilities. The Wu group in the Department of Biochemistry at Oxford runs the cell culture, transduction, cell-free reconstitution and photocrosslinking platforms required, and Oxford provides cell sorting and imaging facilities. Cloning, sequencing and computational capacity are in Cambridge.

Relevant publications

1. Wu & Hegde (2023). Mechanism of signal-anchor triage during early steps of membrane protein insertion. Molecular Cell. https://doi.org/10.1016/j.molcel.2023.01.018
2. Wu, Smalinskaitė & Hegde (2024). EMC rectifies the topology of multipass membrane proteins. Nature Structural & Molecular Biology. https://doi.org/10.1038/s41594-023-01120-6
3. Smalinskaitė, Wu & Hegde (2026). Pairwise transmembrane domain insertion during multipass protein biogenesis. Molecular Cell. https://doi.org/10.1016/j.molcel.2026.06.006

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional genomics of IGF-1 signalling at the sensory neuron-connective tissue interface in carpal tunnel syndrome

Lead Supervisor: Akira Wiberg

Lead Supervisor Email: akira.wiberg@ndorms.ox.ac.uk

Department: Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS)

Primary Institution: University of Oxford

Project details

Carpal tunnel syndrome (CTS), caused by compression of the median nerve at the wrist, is the commonest compression neuropathy, and its surgery the commonest hand operation globally. Surgery is the most effective treatment, yet up to 25% do not improve or have recurrent symptoms. There is yet no disease-modifying drug treatment, despite CTS being unusually tractable to genetic investigation.

Multiple lines of evidence implicate increased IGF-1 signalling in CTS: a genome-wide significant hit at DIRC3/IGFBP5, higher circulating IGF-1 in patients than controls, and Mendelian randomisation supporting causality. DIRC3/IGFBP5 is one of 50 CTS risk loci identified to date, a set whose signal is strongly enriched for extracellular matrix genes. This is a drug repurposing opportunity: teprotumumab, a licensed anti-IGF1R antibody, or similar agents, could in principle treat CTS. But IGF-1 is also a potent neurotrophic factor supporting nerve growth and regeneration, so blocking it to treat the tissue could cost the nerve. However, functional studies to date, including our transcriptomic atlas of the subsynovial connective tissue (SSCT), a gliding layer whose fibrosis is central to CTS pathogenesis, have studied the tissue in isolation from the nerve itself.

This project brings these two compartments together for the first time, combining patient-derived SSCT fibroblasts with a validated iPSC-derived sensory neuron platform to build a genetically informed model of the nerve-connective tissue interface.

Our central, testable hypothesis: dysregulated IGF-1 signalling, acting via the DIRC3/IGFBP5 locus, has discordant effects at this interface, potentially promoting nerve regeneration while driving the SSCT's fibrotic response. Clinical precedent exists: teprotumumab relieves fibrotic orbital tissue in thyroid eye disease but causes sensorineural hearing loss. This could identify biological determinants of nerve recovery after decompression surgery, potentially helping to explain why sensory recovery varies between patients. Should this locus prove intractable, the pipeline can interrogate alternative fine-mapped CTS loci from our data, letting the student shape the genetic focus.

The functional genomics strategy has three stages. First, statistical fine-mapping of the causal variant(s) with eQTL, chromatin accessibility and single-nucleus RNA-seq data, to nominate the effector gene and cell type. Second, targeted Capture-C in patient-derived SSCT fibroblasts and iPSC-derived sensory neurons to confirm tissue-specific chromatin interactions. Third, functional

perturbation (CRISPR editing or CRISPRa/i) of the prioritised gene in parallel fibroblast and sensory-neuron systems, reading out fibrotic markers in SSCT and neurite outgrowth in neurons.

Guided by these results, the model will progress toward an interface co-culture, beginning with SSCT fibroblasts co-cultured directly with sensory-neuron outgrowth before extending, if feasible, to a whole-tissue SSCT explant wrapped around the neurons - a "median nerve in a dish".

The project is strongly interdisciplinary, spanning statistical and functional genomics, chromatin biology, human tissue and iPSC-neuron biology, and translational pharmacology. The student will help decide how far and how fast the model progresses towards a full interface system.

Expected outcomes: a fine-mapped CTS locus with functional evidence identifying its effector gene and tissue of action; a scalable nerve-connective tissue interaction model; and evidence for or against the IGF-1 discordance hypothesis, informing whether anti-IGF1R strategies help or harm nerve recovery.

The research infrastructure includes the Oxford UKRI MSK Functional Genomics cluster's CTS SSCT multi-omic data (including long-read RNA-sequencing), our SSCT transcriptomic atlas, an SSCT collection pipeline, a validated iPSC sensory neuron platform, and, via a secondment to Manchester, established Capture-C and CRISPRa/i pipelines.

Relevant publications

1. Patel B, Kleeman S, Neavin D, Powell J, Baskozos G, Ng M, Ahmed W, Bennett D, Schmid A, Furniss D, Wiberg A. Shared genetic susceptibility between trigger finger and car... https://doi.org/10.1016/S2665-9913(22)00180-1
2. Clark AJ, Kaller MS, Galino J, Willison HJ, Rinaldi S, Bennett DL. Co-cultures with stem cell-derived human sensory neurons reveal regulators of peripheral myelination.... https://doi.org/10.1093/brain/awx012
3. Primary osteoarthritis chondrocyte map of chromatin conformation reveals novel candidate effector genes. Bittner N, Shi C, Zhao D, Ding J, Southam L, Swift D, Kreitmaier... https://doi.org/10.1136/ard-2023-224945

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Decoding psychiatric risk: linking 3D genome regulation to calcium signalling in human brain cells

Lead Supervisor: Jeremy Hall

Lead Supervisor Email: jeremy.hall@psych.ox.ac.uk

Department: Department of Psychiatry

Primary Institution: University of Oxford

Project details

Schizophrenia and bipolar disorder are highly heritable, but translating genetic discoveries into biological mechanisms remains a major challenge. Genome-wide association studies (GWAS) have identified hundreds of associated loci, yet most risk variants lie outside protein-coding regions. Consequently, we often do not know which genes these variants regulate, in which brain cell types they act, or which cellular pathways they ultimately perturb. Several lines of evidence suggest calcium signalling may be disrupted in neurons in people with schizophrenia and bipolar disorder.

This project asks a central question:

How do non-coding psychiatric risk variants alter cell-type-specific gene regulation, and do these mechanisms converge on calcium signalling?

Answering this requires moving beyond the common assumption that a non-coding variant regulates its nearest gene. Regulatory DNA can act across considerable genomic distances through three-dimensional (3D) chromatin interactions, and these relationships differ between cell types. The project will exploit high-resolution Micro-C maps from adult human brain neurons, oligodendrocytes and microglia to identify the genes physically connected to psychiatric risk-associated regulatory regions.

Calcium signalling provides a strong biological hypothesis through which to investigate convergence. Psychiatric genetics has implicated multiple components of calcium biology, while calcium regulates neuronal excitability, synaptic function and activity-dependent transcription as well as important functions in oligodendrocytes and microglia. The project will test this systematically and compare calcium pathways with other regulatory networks emerging from the data.

This project will address three linked objectives:

Objective 1 – From psychiatric risk variant to target gene.

Fine-mapped schizophrenia and bipolar disorder GWAS variants will be integrated with adult human brain Micro-C data generated by one of the Co-supervisors1 to identify regulatory regions and promoters that physically interact in neurons, oligodendrocytes and microglia. This will generate cell-type-specific maps linking non-coding psychiatric risk to candidate target genes and determine whether the same locus has different regulatory consequences across brain cell types.

Objective 2 – From target genes to biological pathways.

Candidate target genes will be integrated with ATAC-seq 2and complementary gene-expression datasets3 to test whether genetically implicated regulatory mechanisms are supported transcriptionally. Pathway and network analyses will then ask whether independently associated psychiatric loci converge on calcium channels, intracellular calcium stores, calcium-dependent signalling and calcium-responsive transcription—or identify alternative pathways of convergence. Comparisons across neurons, oligodendrocytes and microglia will reveal shared and cell-type-specific mechanisms.

Objective 3 – From human brain regulatory mechanisms to experimentally testable models.

Prioritised genes and pathways will be compared with expression data from iPSCs and iPSC-derived neurons (e.g. https://www.hipsci.org/#/). This will determine which regulatory mechanisms identified in adult human brain are represented in experimentally tractable human cellular models. Where appropriate, CRISPR experiments will exploit expertise and infrastructure available through the UK Human Functional Genomics Initiative Functional Genomics Screening Laboratory in Cambridge.

The project integrates psychiatric genetics, 3D genomics, transcriptomics, bioinformatics and human cellular neuroscience. Existing GWAS, Micro-C, ATAC-seq and iPSC datasets provide an immediately accessible starting point, while the discoveries made during the project will determine which loci and mechanisms progress to experimental investigation. This gives the student substantial ownership of the direction of the PhD.

Refs

1. PMID:36991220.
2. PMID:37824643.
3. PMID:42778698.

Relevant publications

1. Mapping chromatin structure at base-pair resolution unveils a unified model of cis-regulatory element interactions. Li H, ...Davies JOJ. Cell. 2025 Dec 11;188(25):7175… https://doi.org/10.1016/j.cell.2025.10.013
2. The psychiatric risk gene CACNA1C encodes distinct full-length isoforms in human brain, heart and aorta. Hall NA..... Tunbridge EM. Mol Psychiatry. 2026 Sep 11. doi:… https://doi.org/10.1038/s41380-026-03890-z
3. CACNA1C Genetic Variants Differentially Affect Neuronal Networks Through Divergent Pathways. Wilkinson G, ... Hall J, Harwood AJ. Biol Psychiatry Glob Open Sci. 2026 Ju… https://doi.org/10.1016/j.bpsgos.2026.100792

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Multi-ancestry GWAS of drug-safety phenotypes across global biobanks

Lead Supervisor: Dr Junqing Xie

Lead Supervisor Email: junqing.xie@ndorms.ox.ac.uk

Department: Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), Botnar Research Centre, University of Oxford

Primary Institution: University of Oxford

Project details

Background.

Around one in six hospital admissions in the UK involves an adverse drug reaction (Osanlou 2022), and safety problems stop roughly a quarter of drug-development programmes (Ferolito 2026). Genetics ought to help as variants affecting drug response typically carry large effects (Maranville 2016), and a recent European trial showed a twelve-gene test cut clinically important adverse reactions by 30% (Swen 2023). Yet almost every genetic discovery here describes the same narrow kind of reaction: rare, immune-driven, caused by one powerful variant, usually in the HLA region. The far larger burden of dose-related organ injury remains unexplained.

The largest study of aspirin-induced stomach ulceration analysed 247 patients and found one gene (Bourgeois 2021). Understanding of statin muscle injury still rests on 85 cases published in 2008 (SEARCH 2008; Carr 2019). For kidney injury caused by anti-inflammatory painkillers, no genetic study of any kind has been published. When the same organ damage is studied as an ordinary disease, without regard to which medicine the patient was taking, genetic studies routinely include more than 50,000 cases (He 2023; Siew 2024). Drug-safety genetics therefore works with a hundred to a thousand times fewer cases, not because the biology is harder, but because nobody has assembled enough treated patients into one analysis, or agreed how to define the outcome.

Key question and objectives.

Can the world's largest genomic cohorts be pooled, under one reproducible definition of a drug-safety outcome, to reveal the biology of common adverse drug reactions, and can those signals be traced to mechanism?

Four objectives follow. First, build an openly shared library of drug-safety phenotypes in the OMOP common data model, specifying exposure, time at risk and objectively graded outcomes, using large language models to extract adverse-event evidence from clinical text and benchmarking this against coded definitions. Second, run discovery genome-wide analyses in Our Future Health, testing gene-by-drug interaction rather than disease association alone. Third, replicate in UK Biobank, FinnGen and All of Us and meta-analyse within and across ancestries. Fourth, prioritise signals by fine-mapping, colocalisation and machine-learning prediction of regulatory effect, then test the strongest candidates experimentally.

Three domains of drug safety outcome will be prioritised: gastrointestinal bleeding and acute kidney injury with anti-inflammatory painkillers, muscle injury with statins, and harms from prescribed opioids. Each is common, serious, genetically unexplained, and measurable against objective criteria rather than self-report.

Interdisciplinarity.

The project spans statistical genetics, pharmacoepidemiology, health informatics, machine learning and functional genomics, with regulatory science through the MHRA and international collaboration with the FinnGen and All of Us.

Methodology.

Exposure-anchored designs restricted to treated individuals and respecting time at risk; genome-wide testing with explicit drug-by-genotype interaction terms; cross-biobank meta-analysis; fine-mapping and colocalisation against expression; and an experimental package testing prioritised regulatory variants through an HFGI screening facility.

Expected outcomes.

The first genetic map of several common adverse drug reactions; a reusable, openly published phenotype library and analysis specification any biobank can run; and mechanistic evidence for a small number of prioritised variants, positioned to inform prescribing and regulatory guidance.

Facilities.

The student will work with Our Future Health, UK Biobank, FinnGen and All of Us; Oxford's Botnar Research Centre and Biomedical Research Computing; the team's established OMOP infrastructure; and HFGI training, data coordination and screening facilities.

Relevant publications

1. Xie J, Mothe B, Alcalde Herraiz M, Li C, Xu Y, Jödicke AM, Gao Y, Wang Y, Feng S, Wei J, Chen Z, Hong S, Wu Y, Su B, Zheng X, Cohet C, Ali R, Wareham N, Prieto-Alhambra… https://doi.org/10.1038/s41467-024-48339-5
2. Papez V, Moinat M, Voss EA, Bazakou S, Van Winzum A, Peviani A, Payralbe S, Kallfelz M, Asselbergs FW, Prieto-Alhambra D, Dobson RJB, Denaxas S. Transforming and evaluat… https://doi.org/10.1093/jamia/ocac203
3. Riesmeijer SA, Kamali Z, Ng M, Drichel D, Piersma B, Becker K, Layton TB, Nanchahal J, Nothnagel M, Vaez A, Hennies HC, Werker PMN, Furniss D, Nolte IM. A genome-wide as… https://doi.org/10.1038/s41467-023-44451-0

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional Genomics of Microglial-Neuronal Lipid Crosstalk in Parkinson's Disease Target Discovery

Lead Supervisor: Elena Navarro-Guerrero

Lead Supervisor Email: elena.navarroguerrero@ndm.ox.ac.uk

Department: Nuffield Department of Medicine

Primary Institution: University of Oxford

Project details

Background. Parkinson's disease (PD) represents the fastest-growing neurological disorder globally, yet existing clinical treatments remain strictly symptomatic. Historical drug discovery efforts in PD have suffered from high attrition rates, driven primarily by an over-reliance on animal models that fail to capture human immunological complexity and an exclusive focus on neuronal protein aggregation, specifically alpha-synuclein. Emerging genomic, clinical, and histological evidence indicates that systemic and cellular lipid metabolic dysregulation plays a causative role in PD pathogenesis. Post-mortem tissue profiling of the human PD substantia nigra demonstrates prominent intracellular lipid droplet (LD) accumulation within midbrain microglia and dopaminergic neurons. Microglia, the resident innate immune cells of the brain, experience chronic inflammatory activation when loaded with intracellular lipid storage, which severely compromises their homeostatic clearing capacities and induces non-cell-autonomous neurotoxicity that accelerates neuronal death. Unravelling the genetic mechanisms governing microglial and neuronal lipid immunometabolism thus offers an unprecedented frontier for discovering disease-modifying therapeutic targets.

Objectives. This project aims to target genetic regulators of microglial lipid accumulation to restore immune homeostasis and protect dopaminergic neurons across three core objectives:

1. Computational multi-omic triage & target prioritisation. Integrate functional genomics screen data (from neurons and microglia) with human PD proteomics and metabolomics pathways to filter genes and evaluate translational druggability using the Open Targets platform to isolate a shortlisted portfolio of high-confidence genetic targets.

2. Human patient-derived cell modelling. Leveraging neurons and microglia that we have previously shown to have robust and relevant phenotypes to evaluate target-driven phenotypic rescue.

3. Evaluate neuroprotective rescue to validate small-molecule repurposing leads by using: automated high-content imaging of multiple readouts relevant for PD at the cellular level and lipidomics & transcriptomics.

Interdisciplinary. Delivering this workflow requires an integrated, cross-disciplinary consortium spanning stem cell engineering, computational genomics and neurophysiology. The supervisory team (Early Career Researchers) will provide expertise in iPSCs-myeloid and neuron CRISPR platforms, high-content phenotypic screening, industrial target discovery, and novel neuronal models of disease

to identify and modify the early mechanisms of cellular dysregulation. Importantly, Assoc Prof Winchester provides expertise in applying large-scale multi-omics and integrative and machine learning methodologies to develop new biomarkers and understand disease mechanisms. Our supervisory structure demonstrates complementary strengths that will enable the student to deliver the required methodology.

Expected outcomes: The project will yield a preclinically validated target portfolio, establish human-relevant drug repurposing candidates, generate multi-omic functional datasets (microglial and neuronal), and provide a standardised 2D neuro-glial phenotypic screening pipeline.

Resources available: Hosted at the University of Oxford across three departments (Nuffield Department of Medicine, Department of Physiology, Anatomy and Genetics, and Psychiatry), the student will (1) access high-content confocal imaging, automated high-throughput screening robotics, lipidomics platform, and iPSC facilities; (2) benefit from established computational expertise and analytical pipelines, alongside access to Departmental (Psychiatry) and University computing infrastructure, including secure, GPU-enabled resources for machine learning and large-scale genomic and multi-omic data analysis and integration.

Relevant publications

1. Ali, M., Erabadda, B., Chen, (...), Laura Winchester & Carlos Cruchaga. Shared and disease-specific pathways in frontotemporal dementia and Alzheimer's and Parkinson's d... https://doi.org/10.1038/s41591-025-03833-1
2. Hugo J.R. Fernandes, Nikolaos Patikas, Stefanie Foskolou, Sarah F. Field, Jong-Eun Park, Meg L. Byrne, Andrew R. Bassett, Emmanouil Metzakopian, Single-Cell Transcriptom... https://www.sciencedirect.com/science/article/pii/S2211124720312523?via%3Dihub
3. Elena Navarro-Guerrero, Chwen Tay, Justin P. Whalley, Sally A. Cowley, Ben Davies, Julian C. Knight, Daniel Ebner. Genome-wide CRISPR/Cas9-knockout in human induced Plur... https://www.nature.com/articles/s41598-021-82137-z

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: The immune repertoire as a window on the life course

Lead Supervisor: Alex Clarke

Lead Supervisor Email: alexander.clarke@kennedy.ox.ac.uk

Department: Kennedy Institute of Rheumatology

Primary Institution: University of Oxford

Project details

The immune system profoundly changes with aging, contributing to the dramatic increase in serious infection and mortality seen in later life. Age-associated immune dysfunction also impedes normal tissue repair, homeostasis, and limits the response to cancer.

Yet not everyone ages equally, and some individuals maintain strong immune health whilst others do not. Why this should be so, and to what extent genetics and environment contribute remains to be understood.

The adaptive immune system, which includes T and B lymphocytes, allows immune memory to develop and is pivotal to protection from recurrent infection and for effective vaccination. Over a lifetime, exposure to immune challenge leads to the formation of a distinctive immune repertoire formed of lymphocytes with specific receptor sequences which can be captured transcriptionally. The immune repertoire is known to change and skew with age, but the genetic and environmental drivers of this have not been fully elucidated, and it is to be explored how the immune repertoire predicts healthy aging (Cipriano et al., Nat. Med, 2026).

In this project, you will work with the TwinsUK resource to answer these questions. TwinsUK is the largest longitudinal twin study in the UK, and its scale and depth of phenotyping provides an unprecedented opportunity to address your research question.

You will work as part of an interdisciplinary team of immunologists and geneticists based at Oxford and King's College London (KCL), to leverage existing data from the resource (Moustafa et al., Science, 2026), and develop multimodal models of immune repertoire dynamics. In this phase of the project, you will examine how genetic and environmental effects interact to shape the immune repertoire, using inferential statistics and machine learning. You will then move on to the functional component of the PhD, mechanistically testing in the lab how responses to important pathogens such as influenza are controlled by phenotype-associated factors such as metabolites or gene variants. This will be done by recall-by-genotype of twins, and CRISPR editing of lymphocytes to generate prioritised genetic variants.

Methodology

This project will provide training and experience across domains of computational biology, analysing transcriptional, epigenetic, metabolomic, and genetic datasets, and combining them with clinical metadata and environmental questionnaires. You will gain expertise in sample handling, sequencing,

and library preparation. Functional work will include single cell RNA sequencing and its analysis, flow cytometry, cell culture, and multiplex immune assays.

Expected outcomes

You will develop a multimodal model of immune repertoire dynamics across a large longitudinal cohort of twins, uncovering how combining it with genetics, gene expression, and epigenetic factors can predict clinically relevant outcomes. You will mechanistically test in the laboratory how the factors you discover influence immune signalling in response to antigens.

Facilities and resources

The TwinsUK resource based at KCL has deeply-phenotyped datasets available from the start of the project. Biobanked samples are also available for additional analysis. KCL has world-class genomics facilities and computational biology expertise. Functional work will be performed at the Kennedy Institute of Rheumatology, University of Oxford, a world-leading translational research centre with full resourced and state of the art facilities.

Relevant publications

1. El-Sayed Moustafa JS, Ramisch A, Raza YN, Leday GGR, Jiao Y, Wang D, et al. Longitudinal dynamics of gene expression and metabolomics in an aging population cohort. *Science*. 2026;393:eaed6452.
https://doi.org/10.1126/science.aed6452 PubMed

2. Yazicioglu YF, Marin E, Andrew HF, Bentkowska K, Johnstone JC, Mitchell R, et al. Asparagine availability controls germinal center B cell homeostasis. *Science Immunology*. 2024;9(102):eadl4613.
https://doi.org/10.1126/sciimmunol.adl4613 PubMed

3. Roberts AL, Morea A, Amar A, Zito A, El-Sayed Moustafa JS, Tomlinson M, et al. Age acquired skewed X chromosome inactivation is associated with adverse health outcomes in humans. *eLife*. 2022;11:e78263.
https://doi.org/10.7554/eLife.78263

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: How does human genetic variation shape transposable element silencing?

Lead Supervisor: Rebecca Berrens

Lead Supervisor Email: rebecca.berrens@bioch.ox.ac.uk

Department: Biochemistry

Primary Institution: University of Oxford

Project details

Almost half of the human genome originates from transposable elements (TEs). Most are now inactive, but individual TE copies can still produce transcripts and influence gene regulation. Cells therefore use specialised mechanisms to keep many TEs silent. One important pathway involves KRAB zinc-finger proteins (KZFPs), which recognise specific DNA sequences and recruit TRIM28 to establish epigenetic repression.

Despite this, closely related TE copies can behave very differently. Their sequences also vary between people, raising an important question: can natural human genetic variation determine whether an individual TE remains silenced or becomes regulatory or transcriptionally active? This DPhil will investigate how sequence variation at individual human TE loci influences their susceptibility to epigenetic silencing.

The project will first establish how individual TE loci respond when KZFP–TRIM28-mediated repression is disrupted. We will combine complementary long-read technologies: CELLO-seq, a single-cell approach that resolves full-length transcripts from individual TE copies, and allele-resolved Fiber-seq, which measures chromatin accessibility and DNA methylation at base-pair resolution. Using human embryonic stem cells in which TRIM28 can be rapidly depleted, we will determine which TEs lose repression, how their chromatin state changes and which subsequently become transcribed. Importantly, loss of repression may not always lead to immediate transcription: some elements may instead become accessible or transcriptionally competent, with activation dependent on cellular context. Single-cell measurements will reveal whether escape from silencing occurs uniformly or only in a subset of cells.

We will then connect these functional differences to natural human genetic diversity. Long-read and haplotype-resolved human genome resources will reveal how responsive TE loci vary across human genomes. Rather than considering isolated SNPs alone, we will examine naturally occurring TE alleles and ask whether sequence differences predict susceptibility to silencing. Existing KZFP–TE binding information and computational modelling will help identify candidate sequence features underlying different regulatory behaviours.

The project will then move from prediction to mechanism. The student will select informative natural human TE alleles for causal testing. Alternative alleles can be reconstructed in an established genomic landing-pad system to test whether their sequences confer different susceptibility to TRIM28-

dependent repression. Candidate regulatory sequences can then be modified and, where a specific KZFP is implicated, its recognition site disrupted or restored to test the mechanism directly.

The project combines human genetics, machine learning, single-cell and long-read genomics, epigenetics, stem-cell biology and genome engineering. The supervisory team provides complementary expertise in locus-specific TE transcription and computational modelling, KZFP/TRIM28 biology and human stem-cell perturbation, and long-read chromatin and DNA-methylation profiling. Established TRIM28 perturbation and landing-pad systems, CELLO-seq, Fiber-seq, genome-engineering approaches and computational infrastructure are available across the collaborating laboratories.

The project will reveal why individual TE copies differ in their susceptibility to silencing and whether natural variation between human genomes contributes to these differences. More broadly, it will connect human genetic variation to chromatin state and locus-specific transcription in a substantial but poorly understood part of the genome. The specific loci, variants and mechanisms pursued will emerge from the initial data, giving the student substantial scope to shape the direction of the DPhil.

Relevant publications

1. De Franco E, Owens NDL, Montaser H, Wakeling MN, Saarimäki-Vire J, Triantou A, Ibrahim H, Balboa D, Caswell RC, Jennings RE, Kvist JA, Johnson MB, Muralidharan S, Ellard… https://doi.org/10.1038/s41588-023-01565-x
2. Berrens, R.V., Yang, A., Laumer, C.E. et al. Locus-specific expression of transposable elements in single cells with CELLO-seq. Nat Biotechnol 40, 546–554 (2022) https://doi.org/10.1038/s41587-021-01093-1
3. Russ-Silsby J, Colclough K, Johnson M et al. Loss of function variants in the primate-specific gene ZNF808 cause neonatal, transient and adult-onset diabetes eBioMedicin… https://doi.org/10.1016/j.ebiom.2025.106113

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Molecular Characterisation of Early-Onset and Late-Onset Parkinson's Disease Using Multi-Omics

Lead Supervisor: Laura Winchester

Lead Supervisor Email: laura.winchester@psych.ox.ac.uk

Department: Psychiatry

Primary Institution: University of Oxford

Project details

Background: Early Onset Parkinson's Disease (EOPD) commonly occurs in patients younger than 50 years of age. It is detected in 5-10% of Parkinson's disease (PD) cases. The early onset of the disease is said to reflect a distinct clinical and biochemical profile compared to Late Onset Parkinson's Disease (LOPD) whereby patients have slower symptom progression but increased motor symptoms (rigidity and bradykinesia). Additionally, there is evidence of differences in biochemistry and fluid biomarkers profiles between EOPD and LOPD.

Key Question: How do genetic variants in early-onset and late-onset Parkinson's disease change the proteins, metabolites and lipids in blood, and which of these changes lie on the path to disease?

Objectives:

1. Link PD gene variants to blood proteins, metabolites and lipids.

2. Compare EOPD and LOPD at the molecular level to understand common and unique mechanisms.

3. Identify which molecules are likely causal, using Mendelian randomisation.

4. Validate the top candidates by mass spectrometry in patient samples.

The project is inherently interdisciplinary, integrating laboratory and computational approaches across genomic, proteomic and metabolomic data. It will combine complementary experimental and analytical methodologies and bring together expertise across two institutes, providing broad training in both wet-lab and data-driven research.

Analysis Method: The student will analyse genetic data to identify rare variants in individuals with EOPD within the Genomics England resource. Detailed variant analysis will then be implemented in the Tracking PD and OPDC cohorts to understand associations between variants and multi-omics measures and differences in LOPD.

Additionally, unsupervised machine-learning approaches will be applied to proteomic and metabolomic data to identify molecular signatures, disease axes and potential Parkinson's disease subgroups. Protein and metabolite quantitative trait locus (pQTL and mQTL) analyses will identify genetic determinants of prioritised molecular features. Integration with Parkinson's disease GWAS

using colocalisation and Mendelian randomisation will help prioritise proteins, metabolites and pathways with potential causal relevance to disease.

Bench methods: At King's, the student will validate prioritised molecules by targeted mass spectrometry in Tracking Parkinson's plasma. The focus is on lipids controlled by Parkinson's genes: glucosylceramides (GBA1), BMP (LRRK2) and sphingomyelins (SMPD1). Variant carriers will be compared with non-carriers, and early-onset with late-onset patients.

Outcomes: A map linking Parkinson's genes to blood molecules; molecular signatures that separate early-onset from late-onset disease; a short list of causal candidates validated in patient samples; and open code and data for the FGx community.

Resources: The student will be hosted at two institutes giving them access to a broad range of expertise, cohorts, data resources and equipment. In Oxford, the student will benefit from established computational expertise and analytical pipelines, alongside access to Departmental (Psychiatry) and University computing infrastructure, including secure, GPU-enabled resources for machine learning and large-scale genomic and multi-omic data analysis. Tracking Parkinson's cohort is hosted by the Oxford Brain Bank providing biosample access for validation studies. Multi-omic data has been generated for this cohort (proteomic, metabolite and genetic). This novel longitudinal cohort contains extensive clinical and biosample data for over 2500 participants followed up for ten years.

At King's, the student will join Dr Legido-Quigley's Systems Medicine Lab at the Institute of Pharmaceutical Science. The lab runs UPLC-Q-TOF lipidomics and metabolomics, and the student will be trained in sample preparation, targeted mass spectrometry and lipid data analysis, with day-to-day support from Dr Asger Wretlind.

Relevant publications

1. Winchester L, Lawton M, Barber I, et al. Identification of a novel proteomic Biomarker in Parkinson's Disease: Discovery and Replication in Blood, brain and CSF. Publish... https://doi.org/10.1101/2021.12.26.21268282
2. Ali M, Erabadda B, Chen, et al., Winchester L, Cruchaga C. Shared and disease-specific pathways in frontotemporal dementia, Alzheimer's and Parkinson's disease. Nature Medicine. 2025. https://doi.org/10.1038/s41591-025-03833-1
3. Wretlind A, Xu J, Chen W, Velayudhan L, Ashton NJ, Zetterberg H, et al. Lipid profiling in women with Alzheimer's disease. Alzheimer's & Dementia. 2025. https://doi.org/10.1002/alz.70512

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: From variant to function: defining how inherited STING1 variation controls persistent viral infection

Lead Supervisor: Alexander Mentzer

Lead Supervisor Email: alexander.mentzer@ndm.ox.ac.uk

Department: Centre for Human Genetics

Primary Institution: University of Oxford

Project details

Why do individuals exposed to the same virus experience profoundly different outcomes? Human genetic studies can identify variants associated with infection and disease, but translating these associations into biological mechanisms remains a major challenge. This project will address that challenge using an intriguing genetic association involving STING1, a central regulator of innate antiviral immunity, and Merkel cell polyomavirus (MCPyV), a common human virus capable of establishing persistent infection.

Our population-scale studies identified a strong association between inherited variation at STING1 and antibody responses to MCPyV. The same genetic region is associated with several cancers, while functional genomic analyses suggest a potential mechanism: the associated haplotype alters STING1 RNA splicing, increasing an alternative isoform predicted to inhibit antiviral signalling. This provides an unusual opportunity to follow a human genetic observation from population discovery through causal variant identification to experimental mechanism.

The central question is: how does naturally occurring STING1 variation alter human antiviral immunity and control of persistent viral infection?

The student will initially pursue three linked objectives. First, they will use genotype-stratified human cells and long-read genomic and transcriptomic approaches to define how the naturally occurring STING1 haplotype alters transcription, splicing and protein function. Second, candidate causal variants will be prioritised using statistical and functional genomic evidence and tested using CRISPR-based genome editing, providing direct tests of causality in isogenic cellular models. Third, the student will determine whether genetically altered STING signalling changes cellular control of MCPyV infection, with the opportunity to extend key findings into human skin organoids capable of supporting persistent infection.

The project is deliberately interdisciplinary, spanning human genetics, functional genomics, molecular immunology, virology and human disease modelling. Depending on the student's interests, there will be opportunities to develop computational analysis of genomic and transcriptomic data alongside experimental skills including cell culture, CRISPR perturbation, quantitative antiviral signalling assays, long-read sequencing and advanced cellular imaging. Single-cell or spatial approaches can be introduced where they provide the most informative route to resolving genotype-dependent effects within complex tissue models.

Expected outcomes include identification of the functional consequences of the STING1 risk haplotype, prioritisation and experimental testing of causal variant(s), and mechanistic understanding of how inherited variation alters antiviral immunity and viral persistence. More broadly, the project will establish a transferable framework for moving from population genetic association to experimentally validated mechanism.

The student will work within a highly collaborative environment at Oxford's Centre for Human Genetics, with access to the Multi-omics Technology Platform, Pluripotent Stem Cell Facility and advanced cellular imaging expertise. The project additionally draws on established collaborations in STING biology and MCPyV infection, including access to specialist expertise in long-term MCPyV skin-organoid models. Together with the wider FGx network, this provides an environment in which the student can develop genuinely cross-disciplinary functional-genomics expertise.

Relevant publications

1. Mentzer AJ et al. Identification of host–pathogen–disease relationships using a scalable multiplex serology platform in UK Biobank. Nature Communications (2022). Establi… https://doi.org/10.1038/s41467-022-29307-3
2. Chong AY et al. A common NFKB1 variant detected through antibody analysis in UK Biobank predicts risk of infection and allergy. American Journal of Human Genetics (2024)… https://doi.org/10.1016/j.ajhg.2023.12.013
3. Bridgeman A et al. Viruses transfer the antiviral second messenger cGAMP between cells. Science (2015). This demonstrated that virus particles can transfer cGAMP between… https://doi.org/10.1126/science.aab3632

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: From GWAS to mechanism to treatment repurposing: defining and testing NGF-signalling in human frozen shoulder

Lead Supervisor: Dominic Furniss

Lead Supervisor Email: dominic.furniss@ndorms.ox.ac.uk

Department: NDORMS

Primary Institution: University of Oxford

Project details

Frozen shoulder (FS) is a common and painful condition where the shoulder capsule becomes inflamed, fibrotic, contracted, painful and stiff. Symptoms persist for 1–3 years, and current treatments (physio, steroid injection, hydrodilatation, surgery) do not treat the underlying biology. A genome-wide association study identified five associated loci. One signal, lead variant rs5777216, lies within a regulatory neighbourhood containing TSPAN2 and NGF. NGF is of special interest because it regulates pain and neural signalling, and studies of frozen-shoulder tissue have reported increased NGF/NGF-receptor expression, increased nerve fibres and increased vascularity. Anti-NGF antibodies have provided analgesia in osteoarthritis, but their development was limited by rare induction of rapidly progressive osteoarthritis (RPOA). FS offers the potential for repurposing, as the disease has a finite clinical course, creating the possibility of a time-limited intervention. Also, the recent LEVI-04 trial, which targets the pathway through a p75NTR fusion protein, reported improved pain and function without an increased incidence of serious adverse events or joint pathology.

The central question is whether the rs5777216 locus alters regulation of NGF, TSPAN2 or another nearby gene, and whether this points to a therapeutically tractable NGF-dependent mechanism in FS. The project will: (1) fine-map the locus using cross-ancestry genetic data and functional annotation to define a 99% credible set of candidate variants; (2) map regulatory elements and chromatin contacts in human FS derived fibroblasts using ATAC-seq, Hi-C and Capture-C, focusing on interactions with denNGFR/p75NTR and other pathway components in control and FS tissue, and in existing FS snRNA-seq data; (4) use spatial transcriptomics to identify the disease-relevant cellular compartments; and (5) where feasible, perturb NGF/neurotrophin signalling in fresh human capsular tissue using exogenous NGF, anti-NGF antibodies and LEVI-04, measuring transcriptional, inflammatory, neurogenic, fibroblast and extracellular-matrix responses.

The project is strongly interdisciplinary, combining human statistical genetics, computational genomics, epigenomics, chromatin biology, single-cell and spatial transcriptomics, human tissue biology and translational pharmacology. The student will develop skills in GWAS fine-mapping, Bayesian credible sets, linkage disequilibrium and colocalisation, ATAC-seq and chromatin-interaction analysis, single-cell and spatial data analysis, primary human tissue experiments, molecular perturbation and experimental-medicine design. There will be potential to shape the later stages of the project around the strongest causal gene or cell state, and possibly collaborate with industrial partners.

The primary research environment will be Oxford, within the Furniss / Wiberg and Dakin groups and the UKRI Human Functional Genomics Initiative Musculoskeletal Cluster, with access to established surgical, human tissue and functional genomics infrastructure. The Orozco (Manchester) group will provide complementary computational and wet lab chromatin-genomics expertise. The project will also draw on an existing FS snRNA-seq atlas, a repository of human FS tissue, spatial transcriptomics capability, and the wider HFGI network and infrastructure.

Expected outcomes are a fine-mapped and functionally annotated FS locus; a disease-tissue regulatory and spatial map; identification of the cells and molecular pathways through which the locus acts; experimental evidence for or against a functional role for NGF signalling; and, if supported, preclinical target validation to inform a future biomarker-defined experimental medicine study. If NGF is not the causal mechanism, the same functional genomics pipeline will identify and prioritise the most plausible alternative gene or regulatory mechanism at the locus.

Relevant publications

1. Ng MTH, Borst R, Gacaferi H, Davidson S, Ackerman JE, Johnson PA, Machado CC, Reekie I, Attar M, Windell D, Kurowska-Stolarska M, MacDonald L, Alivernini S, Garvilles M,... https://doi.org/10.1038/s41467-024-45341-9
2. Zhu L, Kamalathevan P, Koneva LA, Zarebska JM, Chanalaris A, Ismail H, Wiberg A, Ng M, Muhammad H, Walsby-Tickle J, McCullagh JSO, Watt FE; Oxford Hand Surgical Team, Sa... https://doi.org/10.1126/scitranslmed.abm4054
3. Shi C, Zhao D, Butler J, Frantzeskos A, Rossi S, Ding J, Ferrazzano C, Wynn C, Hum RM, Richards E, Gupta M, Patel K, Yap CF, Plant D, Grencis R, Martin P, Adamson A, Eyr... https://doi.org/10.1186/s13059-025-03492-y.PMID:

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How to Apply

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: One gene, many transcripts; decoding RNA dysfunction in Parkinson's disease using single-cell 'omics, CRISPR, and stem cell models.

Lead Supervisor: Sophie L. Farrow

Lead Supervisor Email: sophie.farrow@dpag.ox.ac.uk

Department: Department of Physiology, Anatomy & Genetics

Primary Institution: University of Oxford

Project details

Parkinson's disease (PD) is a progressive neurodegenerative disorder, and currently the fastest growing neurological condition worldwide. Although the cause(s) of sporadic PD remain incompletely understood, genome-wide association studies have identified >150 genetic variants associated with disease risk. However, the majority lie in non-coding regions of the genome, hence complicating functional interpretation. Efforts to understand these variants have largely focused on their effects on overall gene expression, but genetic variation can also influence how RNA transcripts are generated and processed. Emerging evidence suggests that these mechanisms may be important in PD; at the SNCA locus, for example, genetic variation has been associated with differential transcript expression (10.1101/2025.03.13.25323837). The contribution of genetic variation to RNA processing in PD nevertheless remains largely unexplored, particularly at cell-type resolution.

The key research question is: how does genetic variation shape RNA regulation in disease-relevant cell-types, and can these molecular effects help explain genetic risk for Parkinson's disease?

The project will address this through three complementary objectives, moving from computational discovery to experimental validation.

Aim 1: Identify genetic variants influence splicing in human iPSC derived microglia

The student will explore microglial specific splicing QTLs (sQTLs) using our unique cell village resource (Washer), comprising 247 healthy iPSC-derived microglial lines, with matched whole genome sequencing, single-cell RNAseq, and phenotypic readouts. This dataset has previously been utilised to identify novel eQTLs associated with Alzheimer's disease (10.1101/2025.08.18.670767). They will generate an established list sQTLs in microglia, which can then be combined with in-house and publicly available gene expression and GWAS data sets to establish colocalization scores and prioritise disease-relevant mechanisms. These hits would further feed directly into Aim 2 and Aim 3.

Aim 2: Define the impact of genetic variation on RNA processing in human PD brain

The student will then determine whether sQTLs identified in Aim 1 are reproduced in disease-relevant human brain cell-types, using recently generated post-mortem datasets combining genomic, single-nucleus transcriptomic and epigenomic profiling of the substantia nigra and anterior cingulate cortex (10.64898/2026.03.15.711881; 10.64898/2026.03.20.713192). Next, long-read whole genome sequencing will enable to the student to investigate how structural variants influence gene

expression and splicing events. Integration with available matched chromatin accessibility and DNA methylation will provide additional insight into the regulatory mechanisms linked genetic variation to RNA processing. Emerging population-scale datasets, such as UK Biobank long-read sequencing, will provide additional opportunities to further validation as they become available.

Aim 3: Establish causal links between genetic variation, RNA processing and cellular function

Finally, the student will experimentally investigate the functional impact of two prioritised genetic mechanisms: a SNP associated with altered splicing (sQTL), and a structural variant. Using isogenic iPSC- models and genome engineering, variants will be introduced or corrected to test their predicted effects on RNA processing (10.1016/j.isci.2026.116143; 10.1093/nar/gkaf809). Targeted long-read RNA sequencing will resolve transcript-level consequences, while cellular assays will establish whether these molecular changes contribute to disease-relevant phenotypes and whether their correction can rescue cellular dysfunction.

The project integrates human genetics, single-cell genomics and stem cell biology, supported by extensive PD expertise, iPSC resources and experimental infrastructure within the Oxford Parkinson's Disease Centre, alongside computational expertise from Roche.

Relevant publications

1. DOI: (accepted at Nature Genetics) "Integrated QTL mapping and CRISPR screening in pooled iPSC-derived microglia reveals genetic drivers of neurodegenerative risk" Perez… https://doi.org/10.1101/2025.08.18.670767v1.full
2. DOI: "Dissecting genotype-specific effects of disease-associated genetic variants" Farrow et al. This study establishes an experimental framework for dissecting the func… https://doi.org/10.1016/j.isci.2026.116143
3. DOI: "Establishing gene regulatory networks from Parkinson's disease risk loci" Farrow et al. This study used a computational approach to integrate publicly available ge… https://doi.org/10.1093/brain/awac022

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Mapping Pathological Isoform Switching in Parkinson's Disease for Precision RNA Therapeutics

Lead Supervisor: Laura Parkkinen

Lead Supervisor Email: laura.parkkinen@ndcn.ox.ac.uk

Department: Nuffield Department of Clinical Neurosciences, University of Oxford

Primary Institution: University of Oxford

Project details

Context and Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder with no effective disease-modifying therapies. Antisense oligonucleotides (ASOs) enable precise modulation of RNA and have shown promise in other neurodegenerative diseases. However, developing effective ASOs for PD requires understanding the molecular changes driving pathology.

Most PD transcriptomic studies focus on overall gene expression, overlooking alternative splicing, whereby one gene generates multiple isoforms with distinct or opposing functions. Emerging evidence suggests that PD-associated genes show altered isoform usage, with potentially protective isoforms reduced and pathogenic isoforms increased. Whole-gene suppression could therefore inadvertently eliminate beneficial isoforms.

A critical unmet need is to determine where, in which cells, and under what molecular conditions pathological isoform switching occurs in the Parkinson's brain. Spatially resolving these changes could reveal disease mechanisms obscured by gene-level analyses and identify precise therapeutic targets.

Key Question and Objectives

How do pathological isoform switches arise within the spatial and cellular architecture of the Parkinson's brain, and which represents potential therapeutic targets?

The project has three objectives:

1. Map pathological isoform switching: Generate a high-resolution spatial map across vulnerable and resilient brain regions, identifying disease-associated splicing events within specific cells and tissue environments.

2. Identify molecular and spatial drivers: Apply spatial statistics, machine-learning and causal-inference to investigate how cellular neighbourhoods, cell–cell interactions and local molecular environments relate to pathological RNA processing.

3. Prioritise therapeutic targets: Integrate spatial and computational evidence to prioritise disease-relevant splicing events and design precision splice-switching ASOs targeting pathological isoforms while preserving beneficial gene functions.

Interdisciplinary Nature

This project integrates computational biology, spatial omics, artificial intelligence and clinical neuropathology. The student will combine molecular data from human brain tissue with isoform analysis, spatial modelling, machine learning and causal inference. Linking human disease biology with computational target discovery and therapeutic design will provide interdisciplinary training across molecular neuroscience and data science.

Methodology

10x Genomics Atara and Akoya PhenoCycler will enable spatial analysis of RNA transcripts, proteins, cell identities and cellular neighbourhoods across vulnerable and resilient regions. Multimodal spatial datasets will be integrated using spatial statistics and causal-modelling approaches, including Multiscale Geographically Weighted Structural Equation Modelling (MGW-SEM).

Expected Outcomes

The project will generate a spatially resolved atlas of alternative splicing and isoform usage in PD, revealing how disease-associated changes vary across cells and brain regions. Integration of spatial transcriptomic and proteomic data will identify candidate mechanisms associated with selective neuronal vulnerability and prioritise therapeutically tractable splicing events.

A key translational outcome will be a prioritised set of splice-switching ASO candidates designed to redirect pathological RNA processing towards beneficial isoforms, providing a foundation for experimental validation and preclinical development.

Facilities and Resources

The student will be embedded within the Translational Neuropathology Group and Oxford Brain Bank, Nuffield Department of Clinical Neurosciences, with advanced sequencing, spatial-omics and computational infrastructure. The supervisory team and wider UK Dementia Research Institute network will provide training and collaboration across neuropathology, spatial biology, computational modelling and therapeutic development.

Relevant publications

1. Volpato, V., et al. A deep cellular atlas of the human ventral substantia nigra in Parkinson's identifies a genetic and molecular overlap with insulin resistance. Nature… https://doi.org/10.1101/2025.05.28.25328401
2. Nassiri, I., Gilchrist, J., Tong, O., et al. Genetic determinants of monocyte splicing are enriched for disease susceptibility loci. Nature Communications 16, 8616 (2025) https://doi.org/10.1038/s41467-025-63624-7
3. Nassiri, I., Kwok, A.J., Bhandari, A., et al. Demultiplexing of single-cell RNA-sequencing data using interindividual variation in gene expression. Bioinformatics Advanc… https://doi.org/10.1093/bioadv/vbae085

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Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: From Genetic Risk to Cellular Dysfunction: Decoding Lysosomal Pathways in Dementia

Lead Supervisor: Brent Ryan

Lead Supervisor Email: brent.ryan@dpag.ox.ac.uk

Department: DPAG

Primary Institution: University of Oxford

Project details

Predicting who will develop dementia, and finding ways to prevent or slow this progression, are major unmet needs for people with Parkinson's. This project investigates cellular transport and recycling systems that may link Parkinson's dementia with Alzheimer's disease. We will ask whether Parkinson's-associated genes produce shared patterns of dysfunction, whether comparable changes occur in Alzheimer's patient-derived neurons, and whether genetic risk in these pathways relates to dementia.

You will combine CRISPRi/a, which turns gene activity down or up, with LysoPAINT. Lysosomes break down unwanted cellular material. LysoPAINT measures their acidity, protein breakdown and cellular recycling to create a functional "fingerprint".

Aim 1: Adapt and benchmark assays in neurons. You will begin with small-scale experiments in established cell lines, where the assays already work, using compounds followed by around 20 guide RNAs targeting genes with clear effects on lysosomes, autophagy (recycling cellular components) or endocytosis (bringing material into cells), alongside controls. You will generate reference fingerprints, assess reproducibility and help select readouts, shaping which biological processes are captured. You will then adapt and optimise the workflow in human stem-cell-derived cortical neurons generated using the NGN2 method, a scalable model for screening.

Aim 2: Map genetic effects and investigate mechanisms. Using an established CRISPRi/a library provided in-kind by our Parkinson's UK-funded project, you will screen Parkinson's-associated genes in cortical neurons. Computational analysis will identify genes producing similar fingerprints. You will select priority findings for validation using independent guide RNAs and complementary biochemical or cellular assays, distinguishing specific recycling defects from general changes in cell health.

Aim 3: Explore relevance to dementia. A planned placement of up to six months with Dr Natalie Connor-Robson at the UK Dementia Research Institute at Cardiff will provide training in lysosomal and endosomal biology and Alzheimer's disease. You will generate cortical neurons from existing Alzheimer's donor stem-cell lines with contrasting genetic risk in these pathways and compare their fingerprints with those from the CRISPR screen to investigate shared mechanisms. Using existing Parkinson's genetic and clinical datasets, you will then test whether risk scores combining genetic variation within these gene groups are associated with cognitive decline or dementia.

Training and resources. The project integrates neuroscience, cell biology, population genetics, imaging and computation. In the Ryan Group at Oxford's Kavli Institute for Nanoscience Discovery, you will access stem-cell and neuronal culture facilities, automated microscopy, screening equipment and analysis pipelines. Dr Sophie Farrow in Oxford will support population genetics and computational training. Dr Natalie Connor-Robson at the UK Dementia Research Institute at Cardiff will provide complementary training in lysosomal and endosomal biology, Alzheimer's disease and patient-derived neuronal models. Existing assays and the contributed library provide a foundation for neuronal adaptation and discovery.

Training will be tailored to your experience, with experimental scale and independence growing alongside your skills. We welcome applicants from biological, physical and computational disciplines, valuing potential over specialist experience. You will shape readouts, analyses and follow-up questions while developing skills in reproducible research, collaboration and communication.

Expected outcomes are a benchmarked neuronal LysoPAINT workflow, a reusable map linking genes to cellular recycling, and validated gene groups to investigate shared mechanisms across Parkinson's, Parkinson's dementia and Alzheimer's disease.

Relevant publications

1. CRISPRi: a way to integrate iPSC-derived neuronal models. Franks SNJ, Heon-Roberts R, Ryan BJ. Biochem Soc Trans. 2024 Apr 24;52(2):539-551. doi: https://doi.org/10.1042/BST20230190
2. Mitochondrial dysfunction and mitophagy defects in LRRK2-R1441C Parkinson's disease models. Williamson MG..... Connor-Robson N, Ryan BJ and Wade-Martins R. Hum Mol Genet... https://doi.org/10.1093/hmg/ddad102
3. Cell type-specific functions of Alzheimer's disease endocytic risk genes. Maninger JK, et al., Connor-Robson N. Philosophical Transactions of the Royal Society B. 2024. https://doi.org/10.1098/rstb.2022.0378

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