SCM DTP-MR, MRC DTP, and iCASE Student Symposium 2025

Tuesday, 11th November
Clare College, University of Cambridge

UNIVERSITY OF CAMBRIDGE

Schedule

Time	Event
08.45 – 09:15	Registration
09:15 – 09:30	Welcome and Safety Briefing
09:30 – 10:00	**Keynote Speaker:** *Professor Julian Rayner*
10:00 – 10:30	**Student Speaker Session 1** *James Shonhard and Karolina Maria Kwiatkowska*
10:30 – 10:40	Poster Flash Talks
10:40 – 11:45	Poster Session 1 (Coffee Break)

Time	Event
11:45 – 12:30	**Student Speaker Session 2** *Jack Murzynowski, Paula-Peace James-Okoro and Ellie Fox*
12:30 – 13:00	**Flexible Funding Session** *Christian Neubacher*
13:00 – 14:00	Lunch
14:00 – 14:30	**Keynote Speaker:** *Professor Caroline Trotter*
14:30 – 15:30	**Student Speaker Session 3** *Kate Williamson, Benjamin Chidiac, Rofaida Desoki and Holly Monkhouse*
15:30 – 15:40	Poster Flash Talks
15:40 – 16:40	Poster Session 2 (Coffee Break)

Time	Event
16:40 – 17:10	**Student Speaker Session 4** *Sara Crooks and Jonny Else*
17:10 – 17:45	**Career Panel:** *Dr. Gabriel Funingana, Dr. Jonathan Benn, Professor Caroline Trotter, Professor Julian Rayner*
17:45 – 18:00	*Awards*
18:00 – 19:00	*Drinks Reception*
19:00 – 21:00	*Formal Dinner*

Keynote Speakers/ Career Panel

Professor Julian Rayner

After undergraduate education in New Zealand and a PhD at the MRC Laboratory of Molecular Biology in Cambridge, Julian began working on malaria as a post-doctoral fellow in 1998 at the Centers for Disease Control and Prevention in Atlanta. In 2002, he became an Assistant Professor at the University of Alabama at Birmingham, before returning to Cambridge in 2008 as a Group Leader in the Malaria Programme at the Wellcome Sanger Institute. While at Sanger, he worked closely with colleagues to adapt high-throughput tools to the study of Plasmodium parasites, co-leading the first ever genome-scale genetic screens in these organisms, using systematic screening to identify new vaccine targets, and understanding why some people are naturally more resistant to malaria. Strongly committed to training and engagement with research, from 2013-2024 Julian founded and led Wellcome Connecting Science, which delivers training, learning and engagement events to more than 10,000 scientists, healthcare professionals, students, teachers and members of the public every year. In 2019, Julian moved to the University of Cambridge, where he is Professor of Cell Biology and Director of the Cambridge Institute for Medical Research, an interdisciplinary institute with a focus on understanding the molecular mechanisms of rare and neglected diseases. His lab at CIMR uses molecular and cellular approaches to understand Plasmodium-erythrocyte interactions and to identify and prioritise drug and vaccine targets. Julian was elected a Fellow of the American Society for Tropical Medicine and Hygiene in 2021, a Member of the European Molecular Biology Organisation in 2022, and a Fellow of the UK Academy of Medical Sciences in 2023.

Professor Caroline Trotter

Professor of Global Health, Department of Veterinary Medicine, University of Cambridge

Caroline Trotter is Professor of Global Health at the University of Cambridge and Director of Cambridge-Africa, a University programme that supports African researchers and promotes equitable collaborations between Africa and Cambridge. Her research is focussed on the epidemiology and control of vaccine preventable diseases. She is a deputy chair of the UK Joint Committee on Vaccination & Immunisation and co-chair of the WHO Technical Taskforce for Defeating Meningitis by 2030.

Dr. Gabriel Funingana

Gabriel Funingana is a trained medical oncologist dedicated to understanding and improving biomarkers for precision cancer medicine. He is currently a Clinical Research Training Fellow and PhD student at the University of Cambridge and Cambridge University Hospitals NHS Foundation Trust. He has gained valuable experience through participation in first-in-human and first-in-class clinical trials, as well as in personalised medicine studies like the "Basket of baskets (BoB): A modular, open-label, phase II, multicenter study" aimed at matching therapies to a patient's unique tumour molecular characteristics. At present, he is leading the development of an umbrella trial that uses whole-genome sequencing (WGS)-based biomarkers specifically for ovarian cancer patients. His current research project focuses on personalising treatment for ovarian cancer patients. This project is a notable collaboration across various research groups at the CRUK Institute, CRUK Cancer Centre and Cambridge University Hospitals. It uniquely integrates AI-based decision-support tools into clinical pathways and champions the use of whole-genome sequencing to optimise patient-specific treatment plans.

Dr. Jonathan Benn

Exploratory Biologist at TRIMTECH Therapeutics

Jonathan (JoJo) started his MRC DTP PhD in 2019 at the Cambridge Dementia Research Institute in the lab of William McEwan. His PhD focused on developing genetically encoded constructs capable of selectively degrading the aggregated proteins believed to drive common neurodegenerative diseases. Following a brief post-doc in the McEwan lab he is now a scientist at TRIMTECH therapeutics, a new Biotech startup founded to identify small molecule compounds capable of selectively degrading pathogenic aggregated proteins.

Flexible Funding Information Session

Christian Neubacher

Christian Neubacher is a Policy Engagement Planning Coordinator at the Centre for Science and Policy (CsaP), University of Cambridge. He leads initiatives that strengthen connections between academia and public policy, helping researchers engage more effectively with policymakers. His work includes developing professional training for researchers, supporting large grant applications, and coordinating policy dialogues that bring together senior policymakers and Cambridge academics.

Student Talks (Session 1)

James Shonhard

DTP-MR, Clinical Neurosciences
James Shonhard, Dr. Daniel Rainbow, Dr. Joanne Jones

Title: Determining Best Practices for the Use of DESeq2 with NanoString NCounter Datasets for Progressive Supranuclear Palsy & Corticobasal Degeneration

Evaluating the application of DESeq2 and NACHO for the analysis of NanoString NCounter data, focussing on enhancing the transparency of the quality control (QC) and data processing when compared to NSolver, NanoString's own software. While NSolver is user friendly, it limits the analysis that can be conducted. In contrast to this, DESeq2 and NACHO offer detailed QC metrics and allow for finetuning of analysis. Normalisation methods were tested against NSolver to ensure that the data was processed similarly to NanoString's standards, and there were no issues with the normalisation in either NACHO or DESeq2. Genes expressed in fewer than half of a disease-region cohort were excluded, and the genes were thresholded to a set background. This helped to improve data quality by removing noise from the dataset. Genes were preliminarily identified as genes of interest from the differential expression plots produced. This analysis will support the ongoing analysis of NCounter and GeoMX datasets within the laboratory and further afield.

Karolina Maria Kwiatkowska

DTP-MR, Cambridge Institute for Medical Research
Karolina M. Kwiatkowska, Scott A. Chisholm, Ross F. Waller, Julian C. Rayner

Title: Leveraging spatial proteomics to identify novel *Plasmodium vivax* malaria blood-stage vaccine targets

Plasmodium vivax malaria remains a major global health challenge, and its unique biological features present significant challenges to control and elimination. P. vivax has been understudied, largely because this parasite cannot be continuously cultured in vitro, and there are significant gaps in our understanding of protein function. The adaptation of the closely related species, P. knowlesi, to culture in human erythrocytes has opened up new opportunities for systematic study, such as recently published large-scale transposon mutagenesis studies. Here, we have taken the first steps towards spatially characterising the proteomic landscape of P. knowlesi schizonts via hyperplexed localisation of organelle proteins by isotope tagging (hyperLOPIT), a technique that combines gradient fractionation and mass spectrometry to predict protein localisation on a systematic scale. The pilot results show clear clustering, revealing the intracellular location of thousands of proteins for the first time. We are now focusing on proteins of putative or unknown function that are predicted to localise in the plasma membrane, micronemes, or Sinton and Mulligan's Stipples (the P. knowlesi equivalent of Maurer's Clefts). Their predicted location is currently being validated by CRISPR/Cas9-mediated protein tagging and immunofluorescence. In the near future, we are planning to scale up the project using a larger culture volume and multiple biological replicates to increase the resolution and potentially extend the analysis to purified merozoites.

Student Talks (Session 2)

Jack Murzynowski

MRC DTP iCASE, MRC Epidemiology Unit
Jack R.A. Murzynowski, Yajie Zhao, John R.B. Perry

Large-scale exome sequencing studies in population biobanks have identified several genes harbouring rare, protein-coding variants, which confer substantial risk of obesity. Notably, sex-specific effects have recently been reported for four genes - DIDO1, PTPRG, SLC12A5, SLTM – in the UK Biobank study, however these results were not confirmed in independent studies. We sought to replicate these observations using newly generated whole genome sequence data in the 'All of Us' study. Sex-combined and sex-stratified rare variant burden analyses in these data confirmed that heterozygous loss of function variants in SLTM (2.87 kg/m2, P = 1.3x10-2, N carriers = 38, Pmeta = 4.8x10-14) and DIDO1 (7.22 kg/m2, P = 7.8x10-5, N = 12, Pmeta = 8.6x10-11) are robustly associated with body mass index. We extended these analyses to demonstrate that rare missense variants predicted deleterious by AlphaMissense exhibit partial loss of function effects on DIDO1 (0.33 kg/m2, P = 1.4x10-2). In contrast to the previous study, we found no evidence that any of these effects are differential between sexes. Furthermore, we found no evidence to support an association with PTPRG or SLC12A5. Our study demonstrates that loss of function variants in DIDO1 exhibit the largest effects on obesity risk for any gene observed to date and reinforce existing studies that suggest sex-specific effects on obesity are uncommon.

Paula-Peace James-Okoro

DTP-MR, Institute of Metabolic Science
Paula-Peace James-Okoro, Jo E. Lewis, Fiona M . Gribble, Frank Reimann

GIP and glucagon-like peptide-1 (GLP-1) regulate insulin secretion and appetite. Combinatorial obesity therapies targeting both the GIP and GLP-1 receptor demonstrate superior glycemia- and weight-lowering effects compared to GLP1R agonists alone. However, the role of GIP in appetite regulation and its mechanism of action remains unclear. This study aimed to identify the central areas through which GIP modulates food intake and further explore the physiological functions of endogenous GIP.

Using transgenic Gip-Cre x Rosa26-hMD3Dq mice (GipDq) to stimulate intestinal GIP-secretion, or intraperitoneal D-Ala2-GIP injection, we observed significant suppression of food intake and increased neuronal activity (via c-Fos staining) in the hypothalamus and brainstem—key feeding centers of the brain. Co-localization of c-Fos and GFP in mice labelling Gipr-expressing cells Cre-dependently (GipreGFP) showed stronger overlap in the brainstem than in the hypothalamus, suggesting brainstem GIPR neurons as primary targets. Intraduodenal glucose infusion increased c-Fos expression in hypothalamic and brainstem GipreGFP neurons by ~200% versus saline, indicating that GIPR neurons respond to peripheral food-related cues. Additionally, stimulating intestinal K cells in GipDq mice blocked peptide YY (PYY)-induced avoidance responses, suggesting that GIP's anti-emetic effects are mediated by endogenous mechanisms rather than purely pharmacological actions (n = 6–10/group, One-way ANOVA).

Our findings highlight that GIP's appetite-suppressing effects are mediated by central GIPR signalling, particularly in the brainstem. Understanding these mechanisms provides insights that may guide the development of improved incretin-based therapies for obesity and type 2 diabetes.

Student Talks (Session 2)

Ellie Fox

DTP-MR, CIMR, IMS, AstraZeneca
Eleanor Fox, Dr Morag Rose Hunter, Dr Daniel Fazakerley, and Dr David Gershlick

Post-prandial glucose disposal depends on insulin-stimulated glucose transport into muscle and adipose tissues via the glucose transporter GLUT4. When insulin is low, GLUT4 is retained intracellularly in specialised vesicles, GLUT4 storage vesicles (GSVs). Upon insulin signalling, GSVs are rapidly mobilised to the cell surface, delivering GLUT4 to the plasma membrane (PM). Insulin-stimulated GLUT4 translocation is a key determinant of insulin sensitivity and is impaired in insulin resistance, yet there are currently no therapies that target this pathway.

Using a novel assay under the Retention Using Selective Hooks (RUSH) system, GLUT4 is released from the endoplasmic reticulum (ER) in a synchronized manner, allowing isolated study of its anterograde trafficking pathway. Within the same cell line, we expressed a control protein that is delivered to the PM via the classical biosynthetic pathway, showing which interventions specifically target the insulin-responsive GLUT4 trafficking pathway, not membrane trafficking in general.

This assay was used to screen 4,336 compounds for an effect on plasma membrane appearance of GLUT4. We have identified >50 compounds that affected GLUT4 delivery to the PM and are currently testing these in an adipocyte model. These compounds and their targets may reveal new insight into pathways that control GLUT4 traffic and could be used in the future to target GLUT4 and improve insulin responses in insulin resistance.

Student Talks (Session 3)

Kate Williamson

MRC-DTP, MRC Toxicology
Kate Williamson, Simone Mozzachiodi, Kiran Patil

Bugs, Drugs & Resilience - the effect of ecological interactions on microbial resilience to repeated drug treatment.

We are also now aware that the interactions between microbes strongly influence community composition and its overall stability. Different studies reach differing conclusions on the predominance of cooperative versus competitive interactions in natural and artificial communities however both interaction types have been associated with resilience/stability. These interactions are inextricably linked with metabolic strategies where the consumption or production of environmental factors including resources, by-products or toxins ultimately drive the ecology of social interactions. These interactions are expected to modulate the community response, composition and function under stressful environments, such as exposure to pharmaceuticals and environmental contaminants. And while a growing body of research considers the effect of single chemical treatments at varying concentrations, the effect of repeat treatment remains understudied despite being closer to real world scenarios. Using synthetic communities comprised of yeast with lactic and acetic acid bacteria isolated from kefir grains we can begin to disentangle the effect of cooperative vs competitive interactions on the outcome of repeated chemical perturbations in a synthetic laboratory community.

Benjamin Chidiac

DTP-MR, Psychiatry
Benjamin Chidiac, Sarah E. Morgan, Petra E. Vértes

My research uses multimodal MRI to examine the brain networks involved in psychosis. Recently, we have identified distinct case-control differences that suggest there are two unique structural and functional pathways underlying psychotic symptoms in schizophrenia and bipolar I disorder, and that the nature of these pathways also differ across diagnostic categories. This information can be used to separate patients into biologically-informative groups that extend beyond traditional diagnostic categories and may offer insight into novel etiological and treatment pathways.

Student Talks (Session 3)

Rofaida Desoki

MRC Epidemiology
Rofaida Desoki, Ken Ong, Nick Wareham

Glucose homeostasis is regulated by the coordinated actions of pancreatic glucagon and the gut-derived incretin hormones—glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). Pharmacological agonists of their receptors are now widely used to treat type 2 diabetes (T2D) and obesity. To uncover novel therapeutic targets, we performed the largest genome-wide association studies (GWAS) to date of fasting and 2-hour post–oral glucose challenge levels of glucagon, GIP, and GLP-1, measured by immunoassay, in up to 10,752 participants from the Fenland study. We analysed >14 million genetic variants with minor allele frequency ≥0.1%, identifying 18 independent genome-wide significant loci, 14 of which are novel. One locus (ABHD15) was shared by GLP-1 and glucagon, and another (SLC5A1) by all three hormones, yielding 15 unique association signals. For GIP, five loci were identified (implicating GIPR, ABO, SLC5A1, FUT3, and ANO1); for GLP-1, three loci (SLC5A1, ABHD15, ISLR2/ISLR); and for glucagon, ten loci (ABHD15, CBY1, PDE3B, SLC5A1, ZNF91, PCSK1, SLC38A4, BCL2, ADAMTS5, ACTR3B). Functional studies showed SLC38A4 is highly expressed in murine pancreatic α-cells, where amino acid substrates of SLC38A4 stimulate glucagon secretion. These findings reveal new genetic determinants of incretin and glucagon regulation, offering mechanistic insights and potential avenues for developing novel T2D and obesity treatments.

Holly Monkhouse

DTP-MR, CIMR
Holly Monkhouse, Janet E. Deane

Gangliosides are sialic acid-containing glycosphingolipids located within the outer leaflet of plasma membranes, particularly enriched in neuronal cells. In lysosomal storage disorders, gangliosides accumulate resulting in brain and cognitive dysfunction, including neurodegeneration. In the lysosomal storage disorders Tay-Sachs and Sandhoff diseases, the ganglioside GM2 accumulates due to mutations in the α or β subunits of the enzyme β-N-acetylhexosaminidase A (HexA), which removes the terminal N-acetyl-galactosamine residue from GM2. The lipid-binding protein GM2 activator protein (GM2ap) is required to present GM2 to HexA for cleavage. How HexA, GM2ap and the GM2 substrate come together to form a functional complex remains unclear, despite the availability of individual component structures. We have expressed and purified both HexA and GM2ap and determined a crystallographic structure of the HexA-GM2ap complex, formed in the presence of the GM2 lipid substrate. Our structure differs to previously proposed models of the complex. The complex structure demonstrates how GM2ap and HexA interact and may provide insight into how the GM2 substrate is presented to HexA. This will support determination of how clinically relevant missense mutations cause disease and identify variants that prevent an interaction between HexA and GM2ap.

Student Talks (Session 4)

Sara Crooks

DTP-MR, Clinical Neurosciences
Sara Crooks, Aaditya Prabhu, Lorna Jarvis, Zoya Georgieva, Daniel Rainbow, Annabel Curle, Chris Bagnall, Heather Hulme, Annelies Quaegebeur, Caroline Williams-Gray, Joanne Jones

Inflammation is increasingly recognised as a pivotal feature of Parkinson's disease (PD) pathophysiology. Current models suggest that α-synuclein aggregation drives neurodegeneration while concurrently triggering neuroinflammation, creating a self-perpetuating cycle of damage. T-regulatory cells (Tregs), which constitute 5–10% of CD4 T-cells, are critical for immune homeostasis. However, their role in PD remains unclear, with conflicting reports and limited studies in adequately powered cohorts.

Using high-parameter spectral flow cytometry, I comprehensively characterised Tregs in individuals with PD compared to age and sex-matched controls (n=29 vs 26). While no major differences were observed, mean fluorescence intensity of HELIOS (a transcription factor known to be important in Treg stability) was reduced in specific Treg subsets in PD. Function and Treg stability were further explored through in vitro suppression assays and FOXP3 methylation status.

To broaden my work beyond peripheral immunity, I have now initiated a spatial proteomics study in collaboration with AstraZeneca, to map the inflammatory landscape in post-mortem PD brain tissue. This will allow me to explore neuroinflammation in situ at single-cell resolution.

Together, my work contributes to understanding how immune dysregulation shapes PD progression and may inform future strategies to modulate inflammation for therapeutic benefit.

Jonny Else

DTP-MR, Clinical Neurosciences
Jonny Else, Benjamin M Jacobs, Keiran Raine, Mollie McKeon, Raghda Al-Najjar, Maria Ban, David Kavanagh, Stephen Sawcer

Role of Short Tandem Repeat Variation in Multiple Sclerosis
Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system with a substantial heritable component. Whilst genome-wide association studies (GWAS) have identified over 200 common single nucleotide variants (SNVs) associated with MS susceptibility, they have largely excluded short tandem repeats (STRs)—polymorphic DNA sequences consisting of 1–6 base pair motifs repeated in tandem. STRs comprise ~3% of the human genome and are increasingly recognised for their role in polygenic conditions.
To explore the contribution of STRs to MS, we analysed whole-genome sequencing data from 8,186 individuals with MS and 38,798 controls from the UK Biobank. We assessed 134,004 autosomal STR loci for association with disease risk. Our analysis identified 14 STRs significantly associated with MS susceptibility, with all but one mapping to previously known MS risk loci. Fine-mapping revealed that at 7 of these loci, an STR allele was included in the 95% credible set, suggesting that STRs may be causal variants underlying known GWAS signals.
These findings highlight the potential role of STRs in MS susceptibility and suggest that incorporating STRs into association studies may improve our understanding of the genetic basis of polygenic disorders.

Poster Presentations (Session 1)

1 Eleanor Williams

MRC DTP iCASE, Stem Cell Institute

Eleanor C. Williams, Lovisa Franzén, Martina Olsson Lindvall, Gregory Hamm, Steven Oag, Muntasir Mamun Majumder, James Denholm, Azam Hamidinekoo, Javier Escudero Morlanes, Marco Vicari, Joakim Lundeberg, Laura Setyo, Aleksandr Zakirov, Jorrit J. Hornberg, Marianna Stamou, Patrik L. Ståhl, Anna Ollerstam, Jennifer Tan, Irina Mohorianu

Recent developments in spatially resolved -omics have enabled studies linking gene expression and metabolite levels to tissue morphology, offering new insights into biological pathways. By capturing multiple modalities on matched tissue sections, one can better probe how different biological entities interact in a spatially coordinated manner. However, such cross-modality integration presents experimental and computational challenges.

To align multimodal datasets into a shared coordinate system and facilitate enhanced integration and analysis, we propose MAGPIE (Multi-modal Alignment of Genes and Peaks for Integrated Exploration), a framework for co-registering spatially resolved transcriptomics, metabolomics, and tissue morphology from the same or consecutive sections.

We illustrate the generalisability and scalability of MAGPIE on spatial multi-omics data from multiple tissues, combining Visium with both MALDI and DESI mass spectrometry imaging. MAGPIE was also applied to newly generated multimodal datasets created using specialised experimental sampling strategy to characterise the metabolic and transcriptomic landscape in an in vivo model of drug-induced pulmonary fibrosis, to showcase the linking of small-molecule co-detection with endogenous responses in lung tissue.

MAGPIE highlights the refined resolution and increased interpretability of spatial multimodal analyses in studying tissue injury, particularly in pharmacological contexts, and offers a modular, accessible computational workflow for data integration.

2 Ella Lacey

DTP-MR. Clinical Neurosciences

Ella Lacey, Will McEwan

Alzheimer's disease (AD) is characterised by neurofibrillary tangles of hyperphosphorylated tau and amyloid-beta (Aβ) plaques, with inflammation identified as a pivotal driver of neurodegeneration. Antiviral type-I interferons (IFN-I) have emerged as key mediators of neuroinflammation in AD, with upregulation of IFN-I pathway components identified in post-mortem tissue and a variety of AD mouse models, even in the absence of infection. By promoting interferon-stimulated gene (ISG) expression through IFNAR-induced JAK/STAT signalling, IFN-I drive a phenotypic shift in microglial populations towards neurotoxic interferon-responsive microglia, and also drive neuronal tau aggregation. The molecular basis of the link between Aβ and tau pathology in AD remains unclear; given the observed role of IFN-I in potentiating tau pathology, and the ability of Aβ to drive an IFN-I response, the role of IFN-I linking the two pathologies will be investigated. By elucidating the relationship between Aβ, IFN-I signalling, and tau pathology, my work aims to advance understanding of inflammation-mediated protein aggregation and provide insights into the mechanisms driving the dual proteopathies in AD.

Poster Presentations (Session 1)

3 Emily Todd

MRC-Cognition and Brain Sciences Unit, Clinical Medicine
Emily G. Todd, Laura E. Hughes, Alexander G. Murley, Robert Durcan, Michelle Naessens, Rebecca Williams, Sean Tan & James B. Rowe

Prefrontal GABA deficits in progressive supranuclear palsy (PSP) and frontotemporal dementia (FTD) are associated with motor and cognitive impairment. Pharmacologically modifying GABA restores cortical neurophysiology and improves motor learning, in some patients short-term. Here we use the selective GABAa agonist Zolpidem (vs placebo) to examine neurophysiological changes in people with PSP and behavioural variant FTD.

A double blind-placebo controlled crossover design is underway, including 20 healthy controls, 25 people with bvFTD and 25 with PSP. Participants undertake two sessions of magnetoencephalography (MEG), two weeks apart: one 2h after oral 5mg Zolpidem, and one 2h after oral placebo. Each MEG session comprises three paradigms: resting-state, an auditory roving oddball paradigm, and a behavioural inhibition task. Separately, participants undergo MRI with MR-sLaser spectroscopy (7T or 3T), Positron Emission Tomography (PET) MR with [11C]UCB-J ((R)-1-((3-(methyl-11C)pyridin-4-yl)methyl)-4-(3,4,5-trifluorophenyl)pyr-rolidin-2-one) tracer and additional cognitive assessments.

We continue to recruit patients and have performed an interim partial unblinding. I will present some of the preliminary analyses from the current partial unblinded data to demonstrate the pipeline of methods, and show how I will link PET with MEG and behaviour to understand the impact of loss of GABA neurotransmission in FTLD.

4 Jana Sebestikova

MRC DTP, Cambridge Stem Cell Institute

Idiopathic Parkinson's Disease (iPD) is a relatively heterogenous age-related neurodegenerative disease with an unknown cause. One of the hallmarks of iPD is the progressive loss of functional nigral dopaminergic neurons, mitochondrial dysfunction, and the presence of aggregates of protein alpha-synuclein (a-syn) in post-mortem brain tissue. Other brain regions are affected too but tend to be impacted much later during the disease and it is unclear what are all the factors defining differential neuronal vulnerability. Growing evidence suggests that mitochondrial dysfunction is a key pathological driver of early-stage iPD. My project uses in vitro primary human neurons, a stem cell-derived model, and an a-syn aggregation model to study early changes in molecular pathways in the context of differential vulnerability and early mitochondrial dysfunction.

Poster Presentations (Session 1)

5   JiaYi (Jessy) Zhu

DTP-MR, CIMR

JiaYi Zhu, Giulia Emanuelli, Glenn R Masson, Vanesa Vinciauskaite, Henriette Willems, Andrew Lim, Christopher Alan Brown, David Winpenny, Murray Clarke, Rebecca Gilley, Fergus Preston, Jordan Wilson, Aldo Bader, Taufiq Rahman, Joseph E Chambers, John Skidmore, Nicholas W Morrell, Stefan J Marciniak

Rationale: The Integrated Stress Response (ISR) is a key component of the cellular protein quality control network, modulating protein synthesis in response to various stresses. GCN2, a serine/threonine kinase that phosphorylates eIF2α, is a master regulator of the ISR and is activated by ribosome stalling. Dysregulation of GCN2 has been implicated in a number of ageing-related pathologies, including pulmonary arterial hypertension (PAH), neurodegeneration, and cancer, where it plays complex roles in cell survival and immune modulation. In PAH, loss of GCN2 functions has been shown to lead to inherited forms of the disease and some mutant GCN2 are amenable to pharmacological activation. In light of its therapeutic potential and the value of novel tools to study these proteostatic disorders, we set out a chemical screen for GCN2 modulators.

Methodology: The activities of putative disease-associated GCN2 variants identified in a large cohort of PAH patients were characterised by a suite of computational and biochemical techniques. In parallel, we performed an in cellulo chemical screen for GCN2 modulators, screening over 130,000 small molecules to identify novel ISR activators. In vitro and cellular assays enabled target identification and functional characterisation.

Results: Our chemical screen identified three structurally distinct compounds with low micromolar stimulatory activities. Unlike previously described GCN2 activators, one of the molecules activates GCN2 independently of GCN1. Modelling supported by structure activity screens suggests it binds to the ATP-pocket of GCN2, but unlike existing ligands does not protrude inward into the allosteric pocket or outward into the solvent. Among the disease associated GCN2 variants, we identified hypomorphic variants that could be rescued by small molecule activators.

Conclusion: We have characterised disease associated variants of GCN2 and identified examples that can be activated pharmacologically. In addition, we report the discovery of a novel GCN1-independent small molecule activator of GCN2, expanding the pharmacological toolkit for probing ISR and proteostasis.

6   Jose Izcue Gana

MRC Epidemiology Unit, School of Clinical Medicine

Jose Izcue-Gana; Louise Foley

Kenya is undergoing a nutrition transition—a shift from traditional diets toward greater consumption of foods high in added sugars, unhealthy fats, and refined carbohydrates. This transition is accelerating due to urbanisation and globalised food systems. As a result, Kenya faces a triple burden of malnutrition: the coexistence of undernutrition, micronutrient deficiencies, and overnutrition-related chronic diseases such as obesity and type 2 diabetes.

Yet, prevailing descriptions of this transition in low- and middle-income countries overemphasise epidemiological and demographic shifts, overlooking important drivers such as household-level food procurement strategies, transformations in local food environments, the expansion of ultra-processed food corporations, amongst others.

This work draws on Kenya Demographic and Health Survey data collected in 2014 and 2022. Using a repeat cross-sectional design, it examines whether changes in household food procurement strategies are associated with changes in food security, dietary patterns, body mass index (BMI), and the prevalence of non-communicable diseases. Preliminary findings from multivariate logistic regression indicate that, compared to households that rely exclusively on purchased food, those that also produce some of their own food—after adjusting for wealth, residence type, gender and education of household head, and household size—are significantly less likely to report food insecurity.

Poster Presentations (Session 1)

7   Marguerite Colin

MRC Unit, MRC Toxicology Unit
Marguerite Colin, Peter Oliver, Andrew Hall, Anne E. Willis

Antisense oligonucleotides (ASOs) are nucleic acid-based therapeutics that can modulate gene expression but face translational challenges due to safety, efficacy, and delivery limitations. Cross-species differences limit rodent model utility, necessitating advanced human-relevant systems to assess ASO toxicity and therapeutic potential, especially in complex cardiac diseases like hypertrophic cardiomyopathy (HCM).

This study examines ASO-induced toxicity and distribution in healthy and diseased human cardiac models, including hiPSC-derived cardiomyocytes (hiPSC-CMs) and cardiac spheroids (CMTs) composed of endothelial cells, fibroblasts, and cardiomyocytes. Endothelin-1 stimulation in CMTs induced hypertrophy, shown by increased spheroid size, upregulation of hypertrophic markers (NPPB, COL1A1), activated signalling (p-ERK1/2, OMA1), and reduced basal mitochondrial respiration typical of HCM.

Tool ASOs were screened for cytotoxicity in 2D and 3D models. Toxic ASO LNA43 induced dose-dependent ATP depletion and caspase 3/7 activation, validating its use as a positive control. Hypertrophic spheroids showed increased sensitivity to both toxic and non-toxic ASOs. Disease-specific sensitisation may relate to increased mitochondrial dysfunction, central to hypertrophy, and replicated in vitro. Both toxic and non-toxic ASOs impaired mitochondrial respiration in healthy hiPSC-CMs, suggesting mitochondrial involvement in ASO toxicity.

These results highlight the importance of disease-relevant human in vitro models for mechanistic toxicity screening of therapeutic ASOs.

8   Maroš Rovný

MRC Unit, MRC Cognition and Brain Sciences Unit
Maroš Rovný, Danyal Akarca, Jascha Achterberg, Iva Ilioska, John Duncan, Duncan Astle

Recent advancements in computational neuroscience have focused on bridging the gap between artificial neural networks and biological neural systems. Our work contributes to these efforts by introducing a novel method for modelling regional and whole-brain function based on the underlying structure.

Building upon the framework of spatially embedded recurrent neural networks (Achterberg & Akarca et al., 2023) we implement a flexible regularisation method for constraining the weights within artificial neural networks based on target topology. This allows for the replication of brain-like structural connectivity at varying levels of granularity: global measures, distribution comparisons, and matrix distances.

Results demonstrate structural and functional divergence depending on target topology. Fully trained networks are capable not only of performing tasks, their weight matrices show clear differences in trajectories and endpoints across targets. Importantly, the differences can be observed not only in the structural properties of the networks but also in their functional organisation, with networks achieving equivalent accuracy yet differing in localisation of task processing on functional readouts.

Our approach opens new avenues for investigating how select aspects of (brain) topology impact computational efficiency, potentially offering insights into the organisational principles underlying both artificial and biological neural systems.

Poster Presentations (Session 1)

9   Teresa von Linde
MRC DTP iCASE, Pathology
Teresa von Linde, Rahul Roychoudhuri

In solid tumours, chronic antigen stimulation and a highly immunosuppressive microenvironment drive CAR-T cells toward terminal exhaustion, resulting in loss of effector function and persistence. As multiple inhibitory mechanisms converge on shared signalling pathways, targeting these nodes may confer broad resistance to suppression.

We developed a syngeneic mouse model of hepatocellular carcinoma in which anti-GPC3 CAR-T cells induce partial but incomplete tumour regression, providing a platform to test genetic strategies for enhancing CAR-T cell efficacy.

To enable high-dimensional, single-cell characterisation of pooled CRISPR-Cas9 screens in tumour-infiltrating CAR-T cells, we employed FlowCode, a newly developed protein-epitope barcoding system. This technology uses unique triplet combinations of protein tags fused to a carrier protein, which can be decoded by antibody panels, allowing simultaneous sgRNA identification and multiparametric phenotyping. We barcoded a CRISPR retroviral library targeting 56 transcription factors and assessed tumour-infiltrating CAR-T cells for functional and phenotypic markers. This approach enabled the integrated analysis of genetic perturbations with single-cell resolution, overcoming the limitations of transcript-only readouts in conventional single-cell RNA-sequencing screens.

We identified transcriptional regulators whose modulation may improve CAR-T cell function in solid tumours and demonstrates the potential of FlowCode-enabled pooled screening to accelerate the discovery of novel strategies to overcome CAR-T cell exhaustion and immunosuppression in the solid tumour setting.

10   Thomas Eve
DTP-MR, CClinical Neurosciences
Thomas Eve, Stefano Pluchino, Alexandra Nicaise

Multiple sclerosis (MS) is a debilitating neurodegenerative disease characterised by autoimmune attacks on myelin in the relapsing-remitting phase, and by axonal loss in the progressive phase (PMS). Although therapies are effective for relapsing-remitting MS, options remain inadequate for PMS, suggesting new pathological mechanisms may advance our understanding and treatment of the disease. Research has recently unveiled the role of dysfunctional neural stem cells (NSCs) in PMS. In vitro models and post-mortem spatial transcriptomics demonstrate that a subset of proliferative glia, termed disease-associated radial glia-like cells (DARGs), are senescent and pro-inflammatory, impacting surrounding cells. These effects are likely mediated, in part, by paracrine factors, but the exact mechanisms are unknown. Therefore, we are aiming to elucidate DARG intercellular interactions by performing RABIDseq, a technique in which a barcoded rabies virus is utilised to trace interactions of a specific target population through single-cell RNA sequencing. This will be combined with spatial transcriptomics and proteomics in a hybrid organoid model containing healthy CNS cells and transplanted patient-derived NSCs. Through identifying paracrine and ligand-receptor interactions underlying the spread of pathology, we can discover potential new therapies for PMS.

Poster Presentations (Session 1)

11 Nick Hirschmuller

MRC DTP iCASE, Public Health and Primary Care
Nick Hirschmüller, Dirk S. Paul, Adam S. Butterworth

Cardiovascular disease (CVD) remains the leading cause of death worldwide, primarily driven by established risk factors such as high blood pressure and elevated lipid levels. Increasing evidence suggests that inflammation also contributes to CVD development. In this study, we used genetic, transcriptomic, and proteomic data from large cohorts, including the UK Biobank and INTERVAL, and apply Mendelian Randomization (MR) to evaluate whether NLRP3 inflammasome activity has a causal influence on CVD outcomes. Although we found strong evidence indicating that genetic variants regulate inflammasome activity, MR analyses provided no support for a causal link between reduced NLRP3 inflammasome activity and the risk of stroke, coronary artery disease, or myocardial infarction. These results suggest that targeting the inflammasome alone may not be sufficient to effectively prevent CVD.

12 Mohith M. Varma

PhD in Medical Science, MRC Cognition and Brain Sciences Unit
Mohith M. Varma & Michael C. Anderson

Cardiac activity during suppression of emotional memories:

The foray into the psychophysiology of emotional memory suppression is a new research direction within the field. This shift represents more than just an expansion of our methodological toolkit—it reflects a growing appreciation for how psychological processes manifest across the brain and the body simultaneously. By incorporating physiological measurements into line of research, the goal is to capture a more complete picture of how a complex psychological process such as exerting inhibitory control on unwanted emotional memories unfolds across different biological signals (e.g. neural, cardiac, electrodermal) and interact, providing insights that would remain hidden when examining any single type of signal in isolation. The current project employs such an integrative analytical approach to address a specific research question within the field of memory control: How does suppressing unwanted emotional memories affect cardiac activity? The goal of this project is to enhance our understanding of the intricate brain-heart interactions that support the regulation of emotional memories, potentially revealing cardiac biomarkers that distinguish successful memory control from conditions marked by difficulty in controlling intrusive memories.

Poster Presentations (Session 1)

13 Jade Scardham
MRC DTP iCASE, Physiology, Development & Neuroscience

Obesity is a major health issue in both humans and dogs, driven by complex genetic and environmental factors. Dogs offer a powerful comparative model due to their shared environment with humans and unique population structure. This project leverages a Wisdom Panel dataset, comprising over 700,000 genotyped companion dogs with veterinary-recorded body condition scores (BCS), to identify genetic variants associated with obesity-related traits.

A full-cohort GWAS using linear mixed models is being used to identify loci associated with BCS. Top loci will undergo fine mapping, functional annotation, and cross-species mapping to assess translational relevance in human obesity cohorts.

This project aims to uncover biologically meaningful obesity-associated variants in dogs, prioritise candidates such as GPR75, and ultimately support discovery of novel regulatory mechanisms contributing to energy homeostasis across species.

14 Connor Fitchett
MRC BSU
Connor Fitchett, David Robertson, Sofia Villar, Ayon Mukherjee

Adaptive clinical trials are a way to combine the statistical rigour of clinical trials with modern methodological advancements that benefit patients. Response adaptive randomisation (RAR) is such a method: modifying the typical 50/50 randomisation to a system that learns from the data already collected to try and make sure the patients currently in the trial receive the best treatment possible. Alongside RAR, I'll also be discussing the benefits a well timed interim analysis can have on a clinical trial. These will be presented in the context of BOP2, a Bayesian clinical trial design that has been used in over 50 clinical trials at MD Anderson.

Poster Presentations (Session 1)

15 Titus Mashilo

MRC Mitochondrial Biology Unit
Titus L. Mashilo. Martin S. King. Edmund Kunji

Carnitine-acylcarnitine translocase (CAC) deficiency is a rare autosomal recessive metabolic disorder caused by mutations in the SLC25A20 gene. SLC25A20 encodes CAC, a mitochondrial transporter essential for importing acyl-carnitines into mitochondria for fatty acid oxidation. Mutations in SLC25A20 disrupt this transport process, leading to impaired energy production, hypoglycaemia, cardiomyopathy, and potential neurological symptoms. Understanding the molecular impact of specific SLC25A20 mutations helps clarify disease mechanisms and could inform future therapeutic approaches. Although fourteen pathogenic mutations have been reported in the literature, only one has been functionally characterised to date. This study aims to characterise all fourteen known pathogenic CAC mutations to better understand their molecular and functional consequences.

Poster Presentations (Session 2)

16 Elizabeth McCall

MRC Unit, Epidemiology
E. McCall

Ultra processed foods and the NOVA classification system.

17 Ella Bishop

DTP-MR, CIMR
Ella Bishop, Dr Alex Nicholson, Dr Shannon McKie, Dr David Priestman, Prof. Julian Rayner, Prof. Janet Deane

Tryptophan Rich Antigens (TRAgs) are proteins of a multi-gene family unique to Plasmodium. They share a conserved tryptophan and threonine-rich domain with an extended, curved, three-helical bundle structure, referred to as the TRAg domain. In species of the Plasmodium subgenus, which includes four of the five species able to infect humans, TRAgs are significantly expanded in number.

There is currently no consensus on the function of TRAgs, but several strands of the existing literature implicate the family in red blood cell binding/invasion. New data suggest that TRAgs may have a lipid binding function, highlighting their structural similarity to BAR domains.

I have applied bioinformatic/structural prediction approaches to explore the TRAg family, revealing that despite their highly conserved core fold, they are complex and diverse. I have cloned, expressed and purified a subset that represent this diversity and analysed their oligomeric state – revealing that one exists as a concentration-dependent homodimer, consistent with the behaviour of BAR domains. I have also generated data which reveal the lipid profile of red blood cell plasma membranes. This will inform future work assessing TRAg-lipid binding specificity. Altogether these data provide important insights into the TRAg family and a foundation for further characterisation of TRAg biochemistry.

Poster Presentations (Session 2)

18

Jacob I. Browne
MRC DTP iCASE, Pharmacology
Jacob I. Browne., Vasiliki. Mavridou., Graham. Ladds., Edward. Stevens., Paul S. Miller.

Nav1.9 has been identified as a key target in inflammatory and chronic pain, conditions which lack effective treatments suitable for long-term use. Despite having low sequence homology to other Nav subtypes, there is currently no selective inhibitor for Nav1.9, preventing its full validation as a drug target. The lack of a selective inhibitor arises from a combination of unstable DNA, difficulty in generating stable cell lines, and low surface expression. Nav1.9 generates a low, persistent current at resting potential, making it unsuitable for traditional dye-based HTS campaigns. To overcome these challenges, we aim to design a bioluminescent resonance energy transfer (BRET) assay for Nav1.9.

A series of BRET donors consisting of nLuc-Navα or nLuc-Navβ constructs were designed and created, also including a variety of tags to measure surface vs total expression. We also produced a series of VSD-binding toxin-based BRET acceptors, which will be used to compete with potential binders.

These constructs will be used to run and optimize BRET assays, which in the future will be used for library screening for selective Nav1.9 inhibitors.

19

Jianhui Li
MRC Unit, MRC Mitochondrial Biology Unit
Jianhui Li, Denis A. Lacabanne, Martin S. King, and Edmund R.S. Kunji

The mitochondrial citrate carrier (CIC) is a member of the solute carrier family 25 (SLC25), responsible for transporting citrate, malate and phosphoenolpyruvate across the inner membrane of mitochondria, coupled to proton translocation. However, no structural information for this carrier exists, meaning that the molecular mechanism of substrate recognition and proton coupling is unresolved. In this study, human CIC (hCIC) was purified and its molecular properties were assessed by using a range of biochemical and biophysical techniques. For structural studies, Pro-macrobodies, which are modified nanobodies, were used to increase the size and stability and to lock the carrier into specific states. The purification protocol was improved to obtain pure and homogeneous samples suitable for cryo-electron microscopy (cryo-EM). Ultimately, three maps of hCIC in different states were obtained after data collection, laying the groundwork for further structural studies of hCIC to elucidate the structural determinants of substrate specificity and proton coupling.

Poster Presentations (Session 2)

20

Nora Haanaes
MRC DTP iCASE, Pharmacology
Nora Haanaes, Julia Maristany, Tin Long Chris Ng, Will Arter, Rosanna Collepardo, Laura S. Itzhaki and Janet R. Kumita.

The essential role of biomolecular condensates in organising cellular biochemistry is becoming increasingly clear. Being membraneless and entropy-driven through phase separation, biomolecular condensates can facilitate processes transiently and without requiring energy-expenditure from the cell. Our group is leveraging the unique chemistry of biomolecular condensates and their natural role in autophagic degradation for therapeutic purposes. We have established synthetic consensus tetratricopeptide repeat protein (CTPR) condensates that enable the grafting of short linear motifs (SLiMs) to facilitate specific binding to target and autophagy-related proteins. We are developing an iterative pipeline of in silico, in vitro and in cellulo experiments to guide the further design of CTPR condensates. Using molecular dynamics simulations and emerging AI tools, we are evolving the CTPR condensate sequences, and measuring how rational changes impact condensate properties. Importantly, we are building complexity into our in silico and in vitro experiments to better translate our structure-function relationships to the cellular environment. By directly targeting the autophagy pathway, we hope to use the CTPR-condensates for proximity-induced degradation of disease-related proteins.

21

Ying Xu
MRC Epidemiology Unit
Ying Xu, Fumiaki Imamura, Nita G Forouhi

Diet and multimorbidity: a systematic review and meta-analysis.

The crucial role of diet and nutrition is recognised in the aetiology of many individual non-communicable diseases, but its contribution to the co-occurrence of these conditions, commonly referred to as multimorbidity, remains unclear. Evidence linking diet to multimorbidity, incluging dietary patterns, food groups or nutrients, is limited and heterogeneous, with inconsistent findings across studies. The aims of this systematic review and meta-analysis are to characterise the definitions and measurement approaches of multimorbidity in published epidemiological studies on the diet-multimorbidity association and synthesise evidence on the association between dietary exposures and incident multimorbidity. In this systematic review and meta-analysis, we searched five electronic databses for prospective studies in any settings, published until 6 June 2025. All types of dietary exposures or interventions are considered. The primary outcome of this review is the incidence of multimorbidity and the secondary outcome is the disease burden of multimorbidity. The full-text review process is ongoing so far. This systematic review will contribute to address the methodological gaps in the measurement of multimorbidity, evaluate the consistency and quality of diet-multimorbidity findings, and inform future research and policy directions.

Poster Presentations (Session 2)

22 Yiran Li

MRC Biostatistics Unit
Yiran Li, John Whittaker, Sylvia Richardson, Hélène Ruffieux

Motivation:
Biobanks with unprecedented sample sizes and rich phenotypic diversity have become essential for genomic studies, enabling analyses across traits and populations. To harness this complexity, Bayesian hierarchical models provide a principled way to jointly model multiple units—such as traits, cells, or experimental conditions—by sharing information to improve statistical power. Yet their adoption at biobank scale remains limited, largely due to the computational challenges of posterior inference in high-dimensional spaces. While variational inference offers a scalable alternative to Markov Chain Monte Carlo, existing approaches often fail to exploit the structure of genome-wide, multi-unit modeling, where relevant biological effects are typically concentrated in a subset of units.

Results:
We introduce an adaptive focus (AF) strategy within a block coordinate ascent variational inference (CAVI) framework. AF selectively updates subsets of parameters at each iteration, focusing on units deemed relevant from current estimates. We illustrate the method in protein quantitative trait locus (pQTL) mapping using hierarchically linked regressions with shared parameters across traits. In simulations and in UK Biobank proteomic data, AF-CAVI reduces runtime by up to 50% while maintaining accuracy. We further provide a genome-wide pipeline for multi-trait pQTL mapping, demonstrating AF-CAVI as an efficient solution for large-scale Bayesian analysis in biobank studies.

23 Yunyue Wang

MRC toxicology
Yunyue Wang, Lajos Kalmar, Roberto Campalastri, Andres Herrero, Anwit Pandit, Ritwick Sawarkar

Antisense oligonucleotides (ASOs) are chemically modified polynucleotides that modulate gene expression by targeting RNA transcripts for degradation or splicing modulation. Gapmers, a subclass of ASOs, contain a central DNA region flanked by modified ribonucleotides and recruit RNase H to catalyze RNA cleavage within RNA–DNA hybrids. While designed for high specificity, gapmers can induce hybridization-dependent off-target effects by binding partially complementary RNAs, resulting in unintended protein depletion and increased toxicity. To improve ASO design and mitigate such risks, we developed Cleave-Seq, a high-throughput, unbiased approach that accurately maps RNA cleavage sites and identifies sequence preferences of RNase H. Using this platform, we demonstrate that human RNase H preferentially cleaves after the 7th nucleotide from the 5′ RNA/3′ ASO interface (equivalent to the 4th nucleotide in the DNA gap of a 3-8-3 gapmer), with symmetrical cleavage flanking this site. Notably, a guanine at the -2 position relative to the cleavage site was consistently enriched across diverse sequence contexts. Standardization of Cleave-Seq, in combination with complementary assays including Bind-Seq, CLIP, and RNA-Seq, will enable comprehensive mapping of RNase H binding and cleavage specificity both in vitro and in cellulo. Ultimately, these insights lay the foundation for predictive algorithms that guide ASO design by minimizing off-target activity and enhancing therapeutic precision.

Poster Presentations (Session 2)

24   Eva Pennink

DTP-MR, Cambridge Institute for Medical Research (CIMR)
Eva Pennink, Jake Oscherwitz, Aditi Kulkarni, Andras Lakatos and Folma Buss

Astrocytes are glial cells that reside in the central nervous system and form extensive interactions with the neuronal circuitry. In Amylotrophic Lateral Sclerosis (ALS), familial or sporadic mutations cause an accumulation of pathological protein inclusions. In response, astrocytes proliferate and act to promote neuron survival but in the later stages of disease can accelerate their death, causing a loss of muscle function. Interestingly, mice that lack MYO6 mimic some of the key pathological hallmarks of neurodegeneration. They exhibit reduced synaptic numbers, impaired neuroactivity and wide-spread astrogliosis. These in vivo phenotypes support the hypothesis that MYO6 expression, its interactome and functions are remodelled during ALS pathogenesis.

To mimic ALS and model the healthy brain, I generate 3D cortical brain organoids (CBOs) from iPSCs harbouring mutations in the C9orf72 gene and an isogenic control line, respectively. Through long read RNA-seq and via PCR I identify alternative mRNA splicing events that occur during CBO development, giving rise to novel MYO6 isoforms. Using immunofluorescence microscopy on 2D dissociated CBO cultures I localise MYO6 to the actin cytoskeleton, endocytic compartments and autophagic machinery where many of its key binding partners reside. These results indicate that MYO6 isoform expression is altered during brain development and may have downstream effects on its directed functions in astrocytes via isoform-specific protein-protein interactions.

25   Jia Yi Lee

MRC Epidemiology Unit
Jia Yi Lee, Nazmul Sarwar, Fumiaki Imamura, Nita G. Forouhi

Diet plays an important role in the development of type 2 diabetes (T2D), and research has shown that certain dietary patterns can help reduce the risk. However, people from different ethnic backgrounds may have varying risks of T2D, and it is unclear whether the benefits of healthy diets differ across ethnic groups. To address this, we conducted a systematic review and meta-analysis of studies that investigated common dietary patterns. We searched several major research databases and included prospective studies that followed adults over time, assessing how closely they followed these dietary patterns and whether they developed T2D. In total, 46 publications covering 43 cohort studies were included, with 180 ethnic-specific results for six healthy dietary patterns. Overall, individuals who more closely followed these diets had a 17–21% lower risk of developing T2D compared to those with the lowest adherence. We found no clear differences in the potential protective effects of these diets across European, Asian, African, and Hispanic ethnic groups. This suggests that adopting healthy dietary patterns can lower the risk of T2D across diverse populations, highlighting the broad public health relevance of promoting these eating habits.

Poster Presentations (Session 2)

26 Boris Iliev Vasilev

MRC Biostatistics Unit
Boris Iliev Vasilev, Elena Vigorito, John Whittaker

Causal gene regulatory relationships can be inferred from two complementary sources: natural genetic variation and experimental perturbation. Expression quantitative trait loci (eQTLs) leverage inherited genetic variants as natural "perturbations" of gene expression, ensuring causality and capturing regulatory effects in primary tissues. However, their small effect sizes and the multiple testing burden limit power. In contrast, pooled CRISPR screening with single-cell RNA-seq readouts such as Perturb-seq enables targeted, high-powered perturbations in controlled cell line settings, producing strong causal signals but at the cost of reduced physiological relevance. This work explores how these approaches align by systematically comparing perturbation-induced transcriptional changes from Perturb-seq with cis- and trans-eQTL effects. Differential expression analysis was applied to Perturb-seq data to obtain robust effect size estimates, which were then integrated with eQTL summary statistics through hierarchical Bayesian models assessing co-occurrence and directional concordance. To further evaluate model relevance, chromatin accessibility profiles and heritability enrichment analysis were used to benchmark cell line data against primary cell types. Together, these establish a framework for validating whether pooled CRISPR screens can faithfully reconstruct causal gene regulatory networks, using eQTLs as a natural reference. This integrative approach has the potential to unify experimental and population-based evidence for gene regulation.

27 Anna Ceesay

MRC Mitochondrial Biology Unit
Anna Ceesay, Denis Lacabanne, Edmund Kunji

The mitochondrial ATP-Mg/Pi carrier (APC), a member of the SLC25 family, transports adenine nucleotides and phosphate across the inner mitochondrial membrane to regulate the matrix nucleotide pool in response to cellular energy demands. APC comprises three key domains: an N-terminal regulatory domain with calcium-binding ability, an amphipathic α-helix, and a C-terminal carrier domain. A proposed "locking pin" mechanism suggests that the amphipathic helix inhibits transport by occupying the carrier in calcium-depleted conditions, while in calcium-bound conditions, it binds to the regulatory domain to allow transport. However, structural evidence has been lacking. To investigate this, the structure of wild-type human APC in calcium-free conditions was determined using cryo-EM, aided by pro-macrobodies to increase particle size. The structure revealed the amphipathic α-helix inserted into the carrier domain, supporting its inhibitory role. To study the molecular determinants of helix release from the regulatory domain, a quadruple mutant predicted to disrupt helix-domain interactions was engineered. Thermostability assays showed this mutant was more rigid than calcium-free wild-type and single/double mutants, consistent with helix binding to the carrier site. Structural analysis confirmed a conformation indistinguishable from the calcium-free wild type. These findings provide the first structural validation of the locking pin mechanism, revealing calcium-dependent APC regulation.

Poster Presentations (Session 2)

28   Annalise Whines

MRC DTP, MRC Cognition and Brain Sciences Unit
Annalise Whines, Sara Z. Mehrhof and Camilla L. Nord

Low mood and anhedonia often emerge during the perimenstrual phase, when estradiol levels are low or falling. In contrast, the periovulatory phase, characterised by peak estradiol, is generally associated with fewer mood disturbances. While these hormone-related mood shifts are well documented, the neurocognitive mechanisms underlying them remain unclear. One hypothesis is that hormone fluctuations affect mesolimbic dopamine functioning and thus motivational decision-making.

To investigate this, 90 participants (preliminary analysis, target: 243) completed an effort-based decision-making task during both the periovulatory and perimenstrual phases. On each trial, they decided whether to exert physical effort (sustained mouse clicks) to earn rewards (points). We used linear mixed-effects models to analyse three computational free parameters: effort sensitivity, reward sensitivity, and acceptance bias – the likelihood of accepting an effortful challenge for a reward.

For acceptance bias, including menstrual cycle phase significantly improved model fit ($\chi^2(1) = 7.92$, $p = .005$). Acceptance bias was also lower during the perimenstrual phase ($B = -0.56$, $p = .005$), suggesting reduced motivation to engage in effortful behaviour. These findings suggest that hormonal shifts may influence motivational decision-making, offering a possible mechanism for increased vulnerability to mood symptoms during the perimenstrual stage.

29   Tom Wight

Medical sciences , MRC Mitochondrial Biology Unit
Thomas H. Wight, Federica De Lazzari, Alexander J. Whitworth

Mitochondria play vital roles in cellular metabolism, reactive oxygen species production and cell death pathways. Many of these functions are regulated by the versatile second messenger, calcium, relying on a tightly regulated balance of calcium homeostasis. This is achieved by strict control of calcium transfer from the ER at mitochondria-ER contact sites, entry through MCU and efflux through NCLX. Dysregulation of calcium, and particularly at the mitochondrial level, has been hailed as a hallmark of neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. My project explores the effects of modulating mitochondrial calcium handling machinery in two different Drosophila neurodegenerative disease models and the mechanisms responsible for organismal benefit in vivo. We have found that Pink1 and Aβ42 Drosophila mutants accumulate Ref(2)p, suggesting an autophagic blockage, and that loss of MCU or partial loss of ITPR (Drosophila homolog of IP3R), rescue this phenotype, implicating mitochondria-ER calcium signalling in the pathogenesis of PD. These data point to a potential mechanism for the phenotypic rescue observed in the Pink1 mutants when combined with loss of MCU and ITPR, however more exploration is required. Future plans for this project to investigate how mitochondrial calcium effects autophagy and mitophagy, with a focus on the Parkin substrate, Cisd, will be discussed.

Poster Presentations (Session 2)

30 Bethan Hawkins

DTP-MR, Clinical Biochemistry

Bethan L. Hawkins, Felix R. Day, Jack R.A. Murzynowski, Ken K. Ong, Daniel J. Fazakerley, John R.B. Perry

In insulin resistance, a state where target tissues become less responsive to insulin, a higher-than-normal level of insulin is required to maintain glucose homeostasis. This contributes to the development of metabolic conditions such as type 2 diabetes and non-alcoholic fatty liver disease. While environmental factors such as physical inactivity and high-fat or sugar diets are risk factors for insulin resistance, genetic predisposition also plays a role. Genome-wide association studies (GWAS) of insulin resistance have been limited to small sample sizes due to the difficulty in obtaining gold-standard phenotypic measures, decreasing the power to detect genetic signals. Proxy measures of insulin resistance, which are available in larger cohorts, have been used instead. However, these traits show only a limited correlation with gold-standard measures so may capture non-specific signals.

To increase statistical power and specificity, we used Genomic Structural Equation Modelling (SEM) to model the shared genetic architecture between multiple insulin resistance proxy traits, including fasting insulin and HDL-C to triglyceride ratio. Genetic variant associations were then tested against this model, identifying 400 independent loci, which we mapped to 335 genes associated with insulin resistance. Further work will involve shortlisting candidate genes for follow-up studies in 3T3-L1 adipocytes to identify novel regulators of insulin resistance.

31 Verena G. Gautsch

DTP-MR, CRUK

Md Saiful Islam, Rimma Belotserkovskaya, Almudena Serrano-Benitez Olga Perisic, Roger L. William, Stephen P. Jackson

ATM is mutated in patients with Ataxia Telangiectasia (AT) and is also implicated in cancer. On the molecular level, ATM is one of the three key regulators of the Phosphatidylinositol 3-Kinase-Related Kinases (PIKK) family of the DNA damage response, acting as the primary kinase upon DNA double-strand breaks (DSBs) to coordinate repair through homologous recombination (HR) or non-homologous end joining (NHEJ). Its activation requires autophosphorylation and interaction with the MRN complex (MRE11, RAD50, NBS1) and leads to a conformational change. ATM activation induces cell-cycle arrest and, when sustained, can drive senescence or apoptosis. While ATM loss is well studied, the consequences of ATM (hyper-)activation remain poorly understood.

A structural ATM mutation was identified which appears to induce constitutive activation in vitro, bypassing MRN-dependent control. We aim to ascertain whether MRN-independent activity of the ATM mutant can be recapitulated in a cellular envionment. Because hyperactive ATM proved unstable under constitutive expression, we established an inducible system to enable controlled expression and mechanistic dissection. This approach provides temporal control of mutant ATM expression to study its activation mechanism and cellular impact. Understanding how ATM activation is structurally controlled may ultimately reveal new therapeutic opportunities.

Poster Presentations (Session 2)

32 Ty Kannegieter

PhD in Biological Sciences, MRC Toxicology Unit
Ty Kannegieter, Tomas Deingruber, Georgina Anderson, Mike Chapman, David Spring, James Thaventhiran

Agro-industrial chemicals (e.g. pesticides, surfactants, plasticizers) provide tremendous utility to modern society. However, some of these chemicals cause severe health consequences following acute and/or chronic exposure, with acute pesticide poisoning alone killing some 200,000 annually. There are limited interventions to prevent these toxic events beyond banning chemical use – which can itself have tremendous negative impacts on public health.

We propose that these the toxicities may be mollified at the patient level via use of immunotherapeutics. Predicated upon a rich literature of immunotherapies for substance use disorder (SUD), similar design methodologies may be applied to agro-industrial targets. To date, we have demonstrated the ability to elicit immune responses specific to 5 diverse toxic chemicals which hold tremendous significance to global agro-industrial production - 2,4D, Atrazine, Paraquat, DDT, and Chlorpyrifos. We provide overviews of immunotherapy design, development, and testing. Data ranges from structural confirmation of immunogens to a distributional "challenge trial" which models real-world toxicity in vivo.

Demonstration that diverse persistent organic pollutants can be targeted and mollified via immunotherapy use supports an expansion of what we, as an immunological community, see as a druggable target - helping broaden immunotherapeutic target selection past the biotic and viral towards more diverse targets.

33 Harry Messent

MRC mitochondrial biology unit
Harry Messent, Spencer Regan-Smith, Robbie Waddell and Judy Hirst

Respiratory complex I is a redox-driven proton pump crucial to oxidative phosphorylation in both mitochondria and bacteria. The mechanism by which the energy is harvested from the redox reaction and coupled to distal proton pumping is unknown. Using the genetically tractable Paracoccus denitrificans complex I as a model, we biochemically characterise the effect of mutations in the candidate hydrated proton transfer pathways of the E-channel. Including full quantitative determination of these mutations effect on the proton pumping stoichiometry of complex I, providing insights into the basis of long range energy coupling.

Poster Presentations (Session 2)

34 Shawn Han

MRC Biostatistics Unit
Shawn Han, Jessica Barrett, Eleanor Winpenny.

Sleep health plays a vital role in physical and mental well-being, yet its developmental trajectories remain insufficiently characterised. In the first year of my PhD, I investigated longitudinal sleep patterns using the Understanding Society dataset, deriving a composite sleep disturbance score from four survey waves. Several clustering frameworks were compared, with particular focus on Latent Class Growth Analysis (LCGA), Latent Class Mixed-Effects Models (LCMM) and Longitudinal Hierarchical clustering. The LCMM approach identified three distinct sleep trajectory classes, which were subsequently evaluated against mental health outcomes in the final survey wave. Regression analyses confirmed significant associations between sleep class membership and later mental health indicators, supporting the relevance of sleep trajectories as early markers of risk. These findings also demonstrate both the utility and limitations of current model-based approaches, particularly in handling ordinal and multidimensional sleep indicators. Building on this foundation, the next stage of my work will focus on methodological development: specifically, extending hierarchical clustering frameworks to accommodate longitudinal ordinal outcomes. The mathematical formulation for this extension has been established, and forthcoming work will implement the method in software and apply it to understanding society and Raine datasets.

35 Jillian Riveros

MRC mitochondrial biology unit
Jillian K. Riveros, John Suberu , Robin Antrobus, Michael P Murphy

Thermal proteome profiling (TPP) is a technique that measures protein changes that occur due to proteins interacting with other molecules through the use of multiplexed mass spectrometry-based proteomics in combination with a thermal shift assay. TPP relies on a protein's ability to denature and aggregate when exposed to heat. Samples are exposed to a range of temperatures typically between 37°C to 64°C which allows proteins to aggregate. By removing the aggregated proteins and running proteomics on the remaining peptides, we can identify a protein's thermal stability curve before and after interacting with another molecule. TPP has been used to study small molecules-, metabolites-, and protein-to-protein interaction changes typically in intact cells. In this work, we have optimized TPP for investigating protein changes in isolated, intact, liver mitochondria from rats.

Poster Presentations (Session 2)

36   Meghna Birla

MRC Metabolic Diseases Unit, Institute of Metabolic Science
Meghna Birla, Olivia J. Conway, Lisa M, Breckels, Satish Patel, David B. Savage, Kathryn S. Lilley, Daniel J. Fazakerley.

Adipocytes are central to whole-body energy homeostasis, storing energy, in the form of triglycerides (TGs), which can be released via lipolysis during energetic demand. This process is tightly regulated by hormonal cues; insulin suppresses lipolysis in the fed state, and β-adrenergic signalling activates it during fasting by promoting the activation of lipases including Adipose Triglyceride Lipase (ATGL) and Hormone Sensitive Lipase (HSL). A key regulatory mechanism for these enzymes is their subcellular localisation. The translocation of these lipases to the lipid droplet is essential for TG hydrolysis. Despite this, the broader spatial proteomic remodelling in adipocytes following insulin or β3-adrenergic stimulation remains largely unexplored. To address this, we applied LOPIT-DC (Localisation of Organelle Proteins by Isotopic Tagging after Differential UltraCentrifugation), a quantitative subcellular spatial proteomics method, to map subcellular protein localisation changes in adipocytes under insulin stimulated ("fed") and β3-adrenergic receptor agonist CL316,243 (CL)-stimulated ("fasted") conditions. Building on prior work with insulin-stimulated adipocytes, we now extend this work to systemically identify proteins that redistribute under β3-adrenergic stimulation. Our dataset captured thousands of proteins, including both previously characterised and novel regulators, that undergo significant subcellular redistribution in response to β3-adrenergic signalling. These proteins of interest were prioritised by their tissue-enrichment, association with clinical traits, and potential metabolic roles, yielding a focused list for downstream functional investigation. We will next validate CL-dependent movement via imaging, perform siRNA knockdown screens and functional assays to assess their roles in adipocyte response to β3-adrenergic signalling such as activation of lipolysis. Among these hits, here we are investigating SLC25A34, a member of the mitochondrial solute carrier family, as a dynamic and atypically localised protein.

This is the first application of an unbiased whole-cell spatial proteomics approach to map the dynamic subcellular landscape of adipocytes during β3-adrenergic signalling activation. The findings will reveal novel insights into β3-adrenergic signalling regulated responses and open up new avenues for understanding adipocyte function in metabolic health and disease.

37   Ali Beladi

MRC IMS
Ali Beladi, Thomas Brown, Lucy Davis, Isabelle Scerri, David Savage, Yann Ravussin, Clemence Blouet

In normal physiology, the body actively defends against acute increases in body weight by adjusting hunger and metabolism, maintaining weight at a set point, known as the body's set point. However, this regulation is impaired in obesity, and the underpinning mechanisms are unclear. Here, using two models of obesity (acute vs. chronic), we demonstrate that the median eminence, a circumventricular organ of the hypothalamus, exhibits structural plasticity upon release from the obesogenic treatment, in a paradigm-dependent manner. Firstly, in a chronic high-fat feeding model where body weight set point regulation is impaired, we found a decrease in WFA immunolabeling upon switching from a high-fat diet to a chow diet, suggesting perineuronal net remodelling. In contrast, in an acute model of overfeeding-induced obesity, where body weight set point regulation is maintained, we found a decrease in the myelin marker MBP, upon interruption of overfeeding via gastric lipid infusion, suggesting myelin remodelling occurring in the median eminence. Taken together, this work suggests that the mechanism of feeding, be it chronic or acute, may determine the mechanism by which plasticity occurs in the median eminence. In a wider context, shedding light on the mechanisms behind the body weight set point and guiding further investigation.