Medical Research Council

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

Tuesday, 11th November
Clare College, University of Cambridge

UNIVERSITY OF CAMBRIDGE

Schedule

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)
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)
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

Professor Julian Rayner

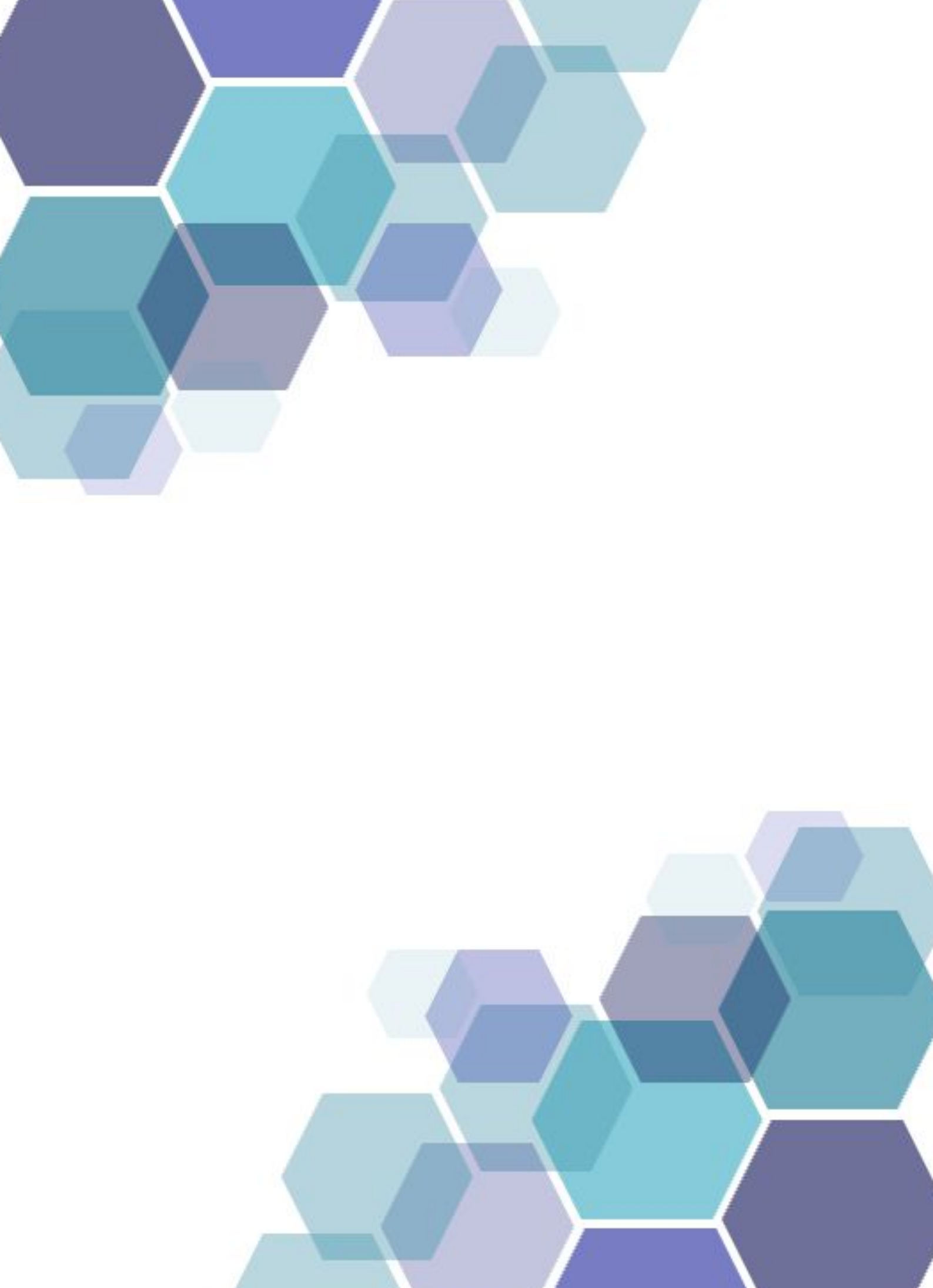
Associate Principal Scientist, AstraZeneca

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

After an undergraduate degree in Human Sciences at the University of Oxford and a PhD in Infectious Disease Epidemiology at the London School of Hygiene and Tropical Medicine, Caroline began her career at the Health Protection Agency and later held a position at the University of Bristol. In 2013, she moved to the University of Cambridge, joining the Disease Dynamics Unit in the Department of Veterinary Medicine. Her research programme is dedicated to understanding the epidemiology of vaccine-preventable diseases, with a major focus on meningococcal infection and studies conducted in both Europe and Africa; she also works on other pathogens including group B streptococcus, pneumococcus, and norovirus. She employs a diverse set of methodological approaches—from mathematical modelling and analysis of large databases to prospective field studies and health economics—to address research questions of direct relevance to immunisation policy. Strongly committed to capacity building and equitable global research partnerships, Caroline took on the role of Academic Director of Cambridge-Africa in 2018, leading a programme that supports African researchers and fosters mutually beneficial collaborations between Africa and Cambridge.



Student Talks (Session 1)

James Shonhard

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

Titile: 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

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 2)

1

Elizabeth McCall
MRC Unit, Epidemiology
E. McCall

Ultra processed foods and the NOVA classification system.

2

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)

3 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.

4 James Shonhard

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

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.

Poster Presentations (Session 2)

5 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.

6 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.

Poster Presentations (Session 2)

7

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.

8

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.

Poster Presentations (Session 2)

9

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.