Academic Session 1

9:30 AM – 10:30 PM

Keynote Speaker

Mapping the appetite circuitry in the human brain

Giles Yeo
Institute of Metabolic Science, University of Cambridge

Bio: Giles Yeo is now a Professor of Molecular Neuroendocrinology and programme leader at the MRC Metabolic Diseases Unit, Institute of Metabolic Science in Cambridge University. He graduated from University of California, Berkeley in Molecular and Cell Biology in 1994, after that he joined in the lab of Prof Sir Stephen O'Rahilly at University of Cambridge, working on the genetics of severe human obesity, and completed his PhD in 1997. In addition, he is a fellow of Wolfson College, and Honorary President of the British Dietetic Association. Giles is also an author and broadcaster, he has published two books, presented documentaries for the BBC, and hosts a podcast "Dr Giles Yeo Chews The Fat". He was appointed an MBE in the Queen's 2020 birthday honours for services to 'Research, Communication and Engagement'. Going back to the academic aspect, as an extraordinary scientist, his research focuses on the role of brain in control of body weight and influences of genes in regulating the feeding behaviours.

Short Talks

The National Prevalence of Eating Disorders in Children and Young People in England: a Public Health concern

Clara Faria
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Abstract: Since the Covid-19 pandemic, there have been growing concerns about an increase in the population prevalence of eating disorders in young people. This research was part of the fourth follow up to the 2017 Mental Health of Children and Young People (MHCYP) survey. Parents of 11 to 16 year olds and children and young people aged 11 to 25 years were asked to complete 5 screening questions from the Development and Well-Being Assessment (DAWBA) eating disorder module. Responses to these were used to determine if the child or young person 'screened positive' for possible eating problems. Those who screened positive were invited to complete the full DAWBA. A selection of those that screened negative were also invited to participate. A total of 1110 participants took part in the survey. In 2023, the prevalence of any eating disorder was 2.6% in 11 to 16 year olds (CI 2.2 - 4.6%), 12.5% in 17 to 19 year olds (CI 9.1 - 17.8%) and 5.9% in 20 to 25 year olds (CI 3.4 - 8.5%). The prevalence of any eating disorder in 2023 was 4 times higher in girls compared with boys for the age group 11 - 16 years olds; 4.3% (CI 3.6 - 7.8%) vs 1% (CI 0.0 - 2.3%) for boys. The same trend was observed in the 17 - 19 years old group with 20.8% (CI 14.3 - 29.2%) prevalence rates for girls vs 5.1% (CI 1.4 - 10.7%) for boys. Overall, these statistics show there was a dramatic increase in the prevalence of clinically impairing eating disorders among school aged children and young people in 2023.

Cell-type aware CRISPR editing outcomes prediction

Weizhong Zheng
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Abstract: The CRISPR-Cas system has revolutionized gene editing by enabling precise and efficient modifications, encompassing a wide range of applications, including gene activity modulation and the generation of model organisms. However, the inherent variability in CRISPR-induced DNA repair processes, influenced by sequence context and cell lines, poses a significant challenge in accurately predicting editing outcomes before conducting experiments. In this study, we introduce inDecay, a flexible system for predicting CRISPR editing outcomes. InDecay predicts the probability of a large number of editing outcomes derived from the target sequence, and incorporates cell-type-specific repair preferences through a multi-stage design. By utilizing informative and parameter-efficient features for each indel event, inDecay outperforms existing prediction methods across multiple evaluation measures, including identifying the most common DNA alterations and the overall occurrence of frameshift mutations. Furthermore,

inDecay exhibits superior few-shot learning capabilities when transferred to novel cell types. The unique features of inDecay establish it as a valuable tool for planning CRISPR editing experiments that require precise control over editing outcomes or for experiments conducted in previously unexplored cellular environments.

Academic Session 2

11:00 AM – 12:30 PM

Keynote Speaker

Biofabrication and 3D Bioprinting for Engineering Biology

Shery Huang
Department of Bioengineering, University of Cambridge

Bio: Dr Shery Huang is a University Lecturer in Bioengineering in the Department of Engineering and Director of Studies in Physics at Homerton College. Shery's group 'Biointerface', is driven by translational bioengineering research, focusing on 3D bioprinting and biofabrication for sustainability and healthcare.

Short Talks

PIG-S regulates the FOXA1/ERα/RXRα complex in breast cancer

Krysia Sadzikowska
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Abstract: Estrogen receptor α (ERα) positive breast cancer is the most common subtype of breast cancer, where ERα transcriptional programme activation drives disease progression. ERα is recruited to enhancer regions by the key lineage defining pioneer factor – FOXA1. There are highly efficient endocrine therapies targeting ERα signalling, however, a significant proportion of patients relapse due to emerging drug resistance. This creates a need for finding new ways of targeting drug resistant breast cancer by exploiting its persisting dependence on FOXA1, ERα and their cofactors. By coupling whole-genome CRISPR screening technology with a reporter system expressing FOXA1-fluorophore fusion, we identified a mild FOXA1 stabiliser – PIGS. PIGS is a poorly characterised protein reported to be involved in GPI anchor biosynthesis in the endoplasmic reticulum.

In breast cancer patients, PIGS amplification is seen in 5% of cases and correlates with decreased survival. PIGS knock-down causes dramatic phenotypic and global transcriptional changes in breast cancer cells. Decreased cell proliferation is accompanied by downregulation of pathways related to cell cycle progression and estrogen response. By implementing proteomic approaches, we showed that PIGS primarily resides in the nucleus, where it interacts with chromatin associated factors. It is also able to modulate FOXA1 protein interactions with SWI/SNF complex components as well as other nuclear cofactors, notably RXRα – a member of the nuclear receptor family. Remarkably, PIGS knock-down results in a global decrease of RXRα chromatin binding. These results suggest that the non-canonical PIGS action in breast cancer and its effect on RXRα signalling can be potentially exploited in breast cancer therapy.

Fatty liver disease directly induces diastolic dysfunction

Guillaume Bidault
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Abstract: Heart failure with preserved ejection fraction (HFpEF) is independently associated with non-alcoholic fatty liver disease (NAFLD) in humans. However, the direct causality and the mechanisms underlying this association remain to be elucidated. In this study we induced NAFLD using liver-specific overexpression of PPARG2. We demonstrated in two independent models of HFpEF (TAC and L-NAME) that the development of hepatic steatosis, independently of other confounders, is associated with an exacerbation of diastolic dysfunction in vivo. We observed that NAFLD induces cardiac lipid deposition

and an unbalanced non-essential to essential fatty acid ratio, suggestive of an increase deposition of liver-derived de novo lipogenesis (DNL) lipids in the heart.

We therefore inhibited liver DNL by knocking-down SCAP, a key regulator of DNL, specifically in the liver (SCAP-LKO). We challenged WT and SCAP-LKO mice with western diet + L-NAME to induce hepatic steatosis and diastolic dysfunction. Inhibition of liver-DNL in SCAP-LKO mice protects against diastolic dysfunction. Mechanistically, using in vivo deuterium tracing, we demonstrated that inhibition of liver DNL reduces DNL-derived palmitate accumulation in the heart and hepatic DNL strongly correlates with the extent of diastolic dysfunction. Altogether, our data confirm that NAFLD directly worsens HFpEF and that liver DNL-derived lipids could link NAFLD and HFpEF.

Flash Talks

The Medical and Social Origin of British Pharmaceutical Regulations, 1963–1971

Peihang Marshall Li
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Abstract: The period from 1963 to 1970 was pivotal in the evolution of drug regulation in the United Kingdom, occurring amidst the global response to the thalidomide disaster. While the US responded with the Kefauver-Harris Drug Amendments to tighten drug approval processes, the UK took a different approach, establishing the Committee on Safety of Drugs (CSD) in 1963 under Sir Derrick Dunlop's leadership. This committee, later institutionalised by the Medicines Act of 1968, emphasised an elastic, efficient, and collaborative approach to drug regulation, contrasting with the more bureaucratic and adversarial model of the US FDA. Comparative studies of the US FDA and the UK drug control system have highlighted the UK's case for deregulation. This study challenges the common neoliberal interpretation of the UK's regulatory strategy as a simple market-versus-state dichotomy. By examining historical archives, including those of Dunlop and other public health officials, it is argued that the UK model can be better understood through the lens of the medical profession's social history. The profession played a key role in mediating the balance between state authority and medical autonomy, influencing the regulatory framework to prioritise collective medical interests and public health. Using field theory and critical rhetoric analysis, this research elucidates the social and historical underpinnings of the UK's drug regulation system, highlighting the important role of medical professions and social groups in shaping the health regulatory landscape that governs the pharmaceutical market today.

Identification of small-molecule modulators of the Integrated Stress Response (ISR)

Jiayi Zhu
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Abstract: The eIF2α kinase GCN2 rsponds to ribosome stalling by activating the integrated stress response (ISR). Mutations of EIF2AK4, which encodes GCN2, cause two aggressive subtypes of pulmonary hypertension: veno-occlusive disease and pulmonary capillary haemangiomatosis. With no effective treatment besides lung transplantation, new therapies are urgently needed. Approximately 40% of disease-associated mutations of GCN2 are missense, and we find several to be hypomorphic. We aim to develop small molecules to restore GCN2 activity for therapeutic benefit. The activities of 16 disease-associated GCN2 variants were characterised by a suite of computational and biochemical techniques. In parallel, a high throughput screen of a diverse library of small molecules was performed to identify novel GCN2 activators. Structure-activity studies were performed for lead compounds. GCN2 variants could be classified as functional (likely non-pathogenic), destabilised, hypomorphic, or kinase-dead. Hypomorphic variants underwent autophosphorylation but engaged only weakly with their substrate. A type $1\frac{1}{2}$ 'kinase inhibitor' was shown to activate several hypomorphic variants expressed in cells. We went on to identified novel GCN2 activators with low micromolar activities (EC50 $\approx 5\mu$M). Activation of disease-associated GCN2 variants is possible using small molecules and we are developing novel drug-like molecules for this purpose.

The NIHR BioResource

Edmond Wood
NIHR BioResource National Coordinating Centre

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Abstract: The NIHR BioResource, hosted by the Dept. of Haematology and Dept. Public Health and Primary Care here at the University, is a unique resource for studying disease mechanisms and for investigating the links between genes, the environment, health and disease; enabling scientific discoveries as well as facilitating translational medicine for the benefit of patients. The BioResource is composed of more than 250,000 highly characterised patients with a common or rare disease, or healthy volunteers. Researchers can apply to access data and/or samples or to recall participants to take part in their research. Participant recall studies can be run from the BioResource Clinical Research Unit (S2) at Addenbrooke's hospital on the Cambridge Biomedical Campus. A BioResource presentation can cover the ways in which academic and industry researchers on campus and farther afield can work with the BioResource to deliver their research, and include case studies from over 300 publications we have supported.

Investigating the mechanism of ucoupling obesity from its metabolic complications

Ruoqi Du
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Abstract: TBC

Academic Session 3

14:00 AM – 15:00 PM

Keynote Speaker

Stemness within an involuting organ: implications for thymus regeneration
Paola Bonfanti
Francis Crick Institute
Bio: With a clinical background, Paula excels in her research in stem cells, greatly contributing to our understanding of immunity. Paula is now a senior research lead in the Francis Crick Institute, specializing in analyzing the bahavior of epithelial stem cells in the thymus gland. Beyond that, she has a global impact, setting her footsteps in Italy, USA, Switzerland and UK.

Short Talks

Autogramin-2, a sterol-derived synthetic compound, inhibits T cell integrins

Katharina Alice Patommel
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Abstract: Integrins are key regulators of T cell function, mediating adhesion, migration, immune synapse formation and TCR signalling, and are increasingly selected as targets for immunotherapy. Integrin affinity and avidity have been shown to be regulated by interactions with cholesterol stabilised lipid rafts, though the underlying biophysical mechanism governing this are not yet fully understood.

We hypothesise that perturbation of plasma membrane (PM) cholesterol should alter integrin mediated T cell adhesion and function, enabling study of the biophysical mechanisms underlying control of integrins by cholesterol in T cells. Here, I establish two PM cholesterol perturbation models using a sterol-derived synthetic compound (autogramin-2) targeting Aster A, an intracellular cholesterol transporter; and methyl-beta-cyclodextrin complexed cholesterol (MBCD-chol) to study the regulation of T cell integrins by PM cholesterol.

Increasing total PM cholesterol content with MβCD-chol altered neither integrin mediated adhesion nor anti-tumour cytotoxic killing capacity of T cells. Yet, perturbing PM cholesterol with autogramin-2 significantly reduced T cell adhesion and LFA-1 mediated immune cell function (T cell cytotoxic killing capacity, production of pro-inflammatory cytokines (TNF, IFN gamma) and upregulation of activation marker CD69 upon activation with anti-CD28 & anti-CD3). These results suggest that T cell integrins are regulated by PM cholesterol distribution rather than content.

The precise mechanism by which autogramin-2 inhibits T cell integrins, be it through inhibition of Aster A mediated transport of accessible cholesterol or through direct interference with the formation of integrin stabilising lipid rafts in the PM, is subject of further study."""

Transmembrane K+ gradients are essential for Chlamydia trachomatis differentiation

Rachel Weild
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Abstract: Transmembrane electrochemical gradients govern many aspects of microbial life. The temporal regulation of bacterial spore germination, parasite egress, and viral infection are influenced by potassium ion (K+) fluxes. Replicative Chlamydia trachomatis reticulate bodies (RB) accumulate K+ from the host cell while in intimate contact with the luminal face of the inclusion membrane and K+ dissipate from RB as this connection is lost and differentiation into EB occurs. Perturbing this K+ gradient early during the replicative phase promotes bacterial persistence. Here we examined the role of K+ later during the infection cycle. Using live-cell fluorescence confocal microscopy we demonstrate that as the inclusion expands, a subpopulation of RB maintain high intra-bacterial [K+] at the inclusion periphery, whereas most bacteria present at this stage, whether transitory intermediate bodies (IB) or EB exhibit low [K+]. When treated with the ionophore nigericin specifically in the mid-late cycle, we discovered that infectivity is disrupted, inclusions concomitantly vesiculate and 40% inclusions are ejected from the cell. Treatment with additional K+-targeting ionophores or K+-channel inhibitors abolish or significantly restrict infectivity, respectively. Transmission electron microscopy of infected cell sections following these treatments revealed a striking and significant reduction in the proportion of EB in the inclusion and a corresponding increase in the number of IB and stalled transitional RB-IB intermediates. These combined data reveal K+ as a key regulator of bacterial differentiation and infectivity across the infection cycle.

Sponsor Talk

Real World mouse models accelerate drug development

GemPharmaTech