Medical Research Council

UNIVERSITY OF OXFORD

Oxford-MRC Doctoral Training Partnership

Oxford-MRC DTP Symposium

16th June 2022

Programme

9.00 **Registration & Tea/Coffee**

9.30 **Welcome – Professor Ester Hammond,** Director of Oxford-MRC DTP

9.40 Student Talks – Session 1

Daan Paget – Department of Pharmacology
"Comparative and Integrated Analysis of Plasma Extracellular Vesicles Isolations Methods in Healthy Volunteers and Patients Following Myocardial Infarction"

Emily Carroll – Nuffield Department of Clinical Neurosciences
"Impairment of mitochondrial respiration and glycolysis in an mESC-MN model of ALS"

Verena Sarrazin –Department of Psychiatry
"Targeting negative affective biases in depression with non-invasive brain stimulation"

10.40 **Coffee Break**

10.50 Student Talks – Session 2

Romain Guyon – The Jenner Institute and the Institute of Biomedical Engineering
"Development of a single dose vaccine technology by delayed release using microfluidics"

Tomas Goncalves – Radcliffe Department of Medicine
"Induction of the Alternative Lengthening of Telomeres pathway by trapping of proteins on DNA"

Isaac Grennan – MRC Brain Network Dynamics Unit

"The coactivation of neurons in the prefrontal cortico-basal ganglia network distinguishes effort, reward and decision in a novel decision-making task"

11.50 '3MRC' (3-Minute Research Competition)

Wojciech Lason – Nuffield Department of Medicine
"Multiomic characterisation of changes to airway epithelium in SARS-CoV-2 infection and asthma"
Sophie Twigger – Department of Oncology and Department of Chemistry
"Design, synthesis, and validation of a reversible, fluorescent probe for measuring real time hypoxia"
Tehmina Bharucha - Department of Biochemistry
"Deep proteomics analysis of human cerebrospinal fluid in Japanese encephalitis virus infection"
Alice Evans – Department of Oncology
"Ex-vivo tumour slice culture for the optimisation of CAR-T cell therapy in pancreatic ductal adenocarcinoma"
Ruofan Connie Han – Nuffield Department of Clinical Neurosciences
"Developing CRISPR-Cas9 gRNA delivery strategies for the treatment of inherited retinal disease"
Anežka Macey-Dare – Department of Pharmacology
"Exploring the impact of patient-derived NMDAR NR1-specific IgG antibodies on the developing mouse striatum"

12.15 Keynote Lecture

Professor Sir Charles Godfray, Director of Oxford Martin School and Professor of Population Biology
"Science and policy: building the evidence base for better decision making"

13.00 **Lunch & Poster Presentations**

14.00 Careers Service Talk
Claire Chesworth, Careers Adviser, Oxford University Careers Service

14.30 Panel Discussion
"Insight into careers in biotech entrepreneurship and industry"
Claire Shingler, the Oxford BioEscalator
Loic Roux, Ochre Bio
Helena Meyer-Berg, SIRION Biotech GmbH

15.00 **Coffee Break**

15.15 Invited Speaker
Dr Tom Beattie, Programme Manager for Doctoral Training at the MRC
"From postdoc to programme manager: working for a research funder"

15.45 Invited Speaker
Dr Fiona Suttle, Oxford Sparks Lead
"Bringing science to you – an introduction to science communication and Oxford Sparks"

16.15 **Closing Remarks & Awards Ceremony**

16.30 **Drinks Reception**

Student Talk Abstracts

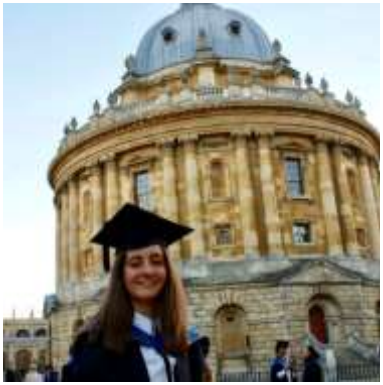
Session 1

Comparative and Integrated Analysis of Plasma Extracellular Vesicles Isolations Methods in Healthy Volunteers and Patients Following Myocardial Infarction

Daan Paget

Department of Pharmacology

Plasma extracellular vesicle (EV) number and composition are altered following myocardial infarction (MI), but to properly understand the significance of these changes it is essential to appreciate how the different isolation methods affect EV characteristics, proteome and sphingolipidome. Here, we compared plasma EV isolated from platelet-poor plasma from four healthy donors and six MI patients at presentation and 1-month post-MI using ultracentrifugation, polyethylene glycol precipitation, acoustic trapping, size-exclusion chromatography (SEC) or immunoaffinity capture. The isolated EV were evaluated by Nanoparticle Tracking Analysis, Western blot, transmission electron microscopy, an EV-protein array, untargeted proteomics (LC-MS/MS) and targeted sphingolipidomics (LC-MS/MS). The application of the five different plasma EV isolation methods in patients presenting with MI showed that the choice of plasma EV isolation method influenced the ability to distinguish elevations in plasma EV concentration following MI, enrichment of EV-cargo (EV-proteins and sphingolipidomics) and associations with the size of the infarct determined by cardiac magnetic resonance imaging 6 months-post-MI. Despite the selection bias imposed by each method, a core of EV associated proteins and lipids was detectable using all approaches. However, this study highlights how each isolation method comes with its own idiosyncrasies and makes the comparison of data acquired by different techniques in clinical studies problematic.



Impairment of mitochondrial respiration and glycolysis in an mESC-MN model of ALS

Emily Carroll

Nuffield Department of Clinical Neurosciences

Amyotrophic lateral sclerosis (ALS) is a fatal, neurodegenerative disorder for which there is currently no cure. Motor neurons in the brainstem and spinal cord are primarily affected, which demonstrate mislocalisation of a normally nuclear RNA-binding protein, TDP-43, to the cytoplasm. Dysregulation of cellular energy metabolism and exposure to oxidative stress have emerged as key players in the neurodegenerative process. Here, we investigate cellular energy metabolism in mutant TDP-43M337V mouse embryonic stem cell-derived motor neurons (mESC-MNs), in unstressed and oxidative stressed conditions, compared to controls. Subsequently, we examine the effects of a pro-survival drug on these phenotypes. Extracellular flux analysis revealed no differences in mitochondrial respiration or glycolysis in unstressed conditions, however following oxidative stress we observed a significant reduction in basal glycolysis, compensatory glycolysis and spare respiratory capacity in TDP-43M337V mESC-MNs relative to controls. Treatment with a pro-survival drug significantly increased cell viability and basal glycolysis, whilst significantly reducing basal respiration in TDP-43M337V mESC-MNs. Here we have identified metabolic dysregulation in TDP-43M337V mESC-MNs following oxidative stress. Treatment with a pro-survival drug leads to a significant increase in basal glycolysis accompanied by a significant decrease in basal respiration, suggesting this drug may induce neuroprotective effects through inducing a metabolic shift.

.

Targeting negative affective biases in depression with non-invasive brain stimulation

Verena Sarrazin

Department of Psychiatry

The development of non-invasive brain stimulation offers a new approach for the treatment of depression. Transcranial direct current stimulation (tDCS) has mild to moderate antidepressant effects. In clinical trials tDCS is typically applied at rest. However, tDCS has been shown to boost learning effects and might therefore be more effective if applied during a learning task. Since depression is characterised by a negative cognitive bias, the antidepressant effect of tDCS could be enhanced by combining it with a learning task designed to counter-act negative biases. In a proof-of-concept study in healthy participants (n=80), we found that bifrontal tDCS applied during a learning task increased learning from positive events which might be beneficial in depression treatment. In a follow-up study in individuals suffering from low mood (n=85), tDCS did not have this effect. However, we found that low mood was characterised by a lack of flexibility in using positive vs. negative information to optimise decision making. Our results indicate that tDCS might normalise this deficit. This finding is of potential clinical relevance since previous research suggests that negative biases in depression might be caused by a deficit in using positive vs. negative information in a flexible manner.

Session 2

Development of a single dose vaccine technology by delayed release using microfluidics

Romain Guyon

The Jenner Institute and the Institute of Biomedical Engineering

The project is focused on the development of a new microfluidics-based technology for vaccine encapsulation to achieve delayed vaccine booster delivery through single-dose vaccination. Such a system would greatly improve vaccination compliance worldwide by removing the need for repeated injections. The encapsulation is achieved using a double emulsification microfluidics technique developed in our lab to produce uniform and reproducible particles containing a liquid vaccine core surrounded by a biodegradable shell capsule. The ability of the capsules to deliver a delayed vaccine release has been evaluated in vitro and in vivo in mice, using either fluorescent dextran as the model payload or the R21 malaria vaccine as proof of concept. Multiple capsule parameters have been tested to characterise the release mechanism and modulate the delay timescale. The potential use of the capsules in a single dose regimen against malaria has been evaluated in a challenge model in mice. The capsules demonstrated the ability to deliver the vaccine payload in vitro after a lag time that is influenced by different formulation parameters. Moreover, capsules given in a single dose regimen had the capacity to generate a higher immune response in vivo compared to non-encapsulated formulations.

Induction of the alternative lengthening of telomeres pathway by trapping of proteins on DNA

Tomas Goncalves

Radcliffe Department of Medicine

Telomere maintenance is a key hallmark of malignant cells and allows cancers to avoid senescence and programmed cell death. In some cancers, this is achieved through the alternative lengthening of telomeres (ALT) pathway, a break induced replication-mediated mechanism of telomere copying. Whilst loss of ATRX is a near universal feature of ALT-cancers, it is insufficient to induce the ALT-phenotype in isolation. As such, other genetic or epigenetic events must be necessary, but the exact nature of these events has remained elusive. Here, we report that trapping of proteins on DNA is a fundamental driving force behind induction of ALT in cells lacking ATRX. We demonstrate that protein-trapping chemotherapeutic agents induce ALT markers specifically in ATRX-null cells. Further, we show that formation of non-canonical DNA structures, such as G4s, act as a trap for proteins and stabilisation of these structures can lead to an ALT-phenotype. We show that this process is MUS81 dependent, providing evidence that trapped proteins lead to stalling of replication forks, with these forks being aberrantly processed in the absence of ATRX. Finally, we show that ALT-positive cells harbour a higher load of genome-wide trapped proteins, implicating these as the fundamental driving force behind ALT-biology in ATRX-deficient malignancies.

.

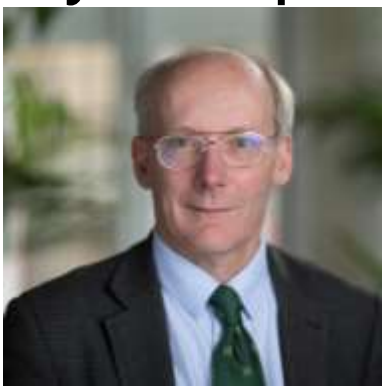
The coactivation of neurons in the prefrontal cortico-basal ganglia network distinguishes effort, reward and decision in a novel decision-making task

Isaac Grennan

MRC Brain Network Dynamics Unit

Levels of effort and reward associated with a given behaviour are encoded by diverse populations of neurons across the forebrain, but it is unclear how this information is integrated across these brain areas for decision-making. In this study, animals were trained to decide whether or not to run to the end of a linear track with varying numbers of obstacles, to receive rewards of different sizes. This task allowed reward and effort to be manipulated independently. Behavioural data (n = 13) confirmed that increasing reward and effort were associated with a higher and lower probability of accepting the reward-effort offer, respectively. Electrophysiological recordings were made simultaneously across the prefrontal cortico-basal ganglia network (medial orbitofrontal cortex, anterior cingulate cortex, ventral pallidum, striatum and subthalamic nucleus) as rats performed this task. A machine learning strategy was used to identify neurons across this network with a statistically significant tendency to coactivate over short timescales (neural ensembles) . The expression strengths of some identified coactivity patterns significantly distinguished the reward and effort offered to rats and/or their subsequent decisions on the task. The proportion of neurons in each structure that contributed to these ensembles was used to evaluate the contribution of different brain areas to reward and effort-based decisions. Coordinated activity across diverse populations of forebrain neurons may serve as a mechanism for encoding decision relevant information for effort-based decision making at the network level.

Keynote Speaker



Science and policy: building the evidence base for better decision making

Professor Sir Charles Godfray

Director of Oxford Martin School and Professor of Population Biology

Speaker Biography:

Charles Godfray is a population biologist with broad interests in science and the interplay of science and policy. He has spent his career at Oxford University and Imperial College and is currently Director of the Oxford Martin School and Professor of Population Biology at Oxford. His research has involved experimental and theoretical studies in population and community ecology, epidemiology and evolutionary biology. He is particularly interested in food security and chaired the UK Government Office of Science's Foresight project on the Future of Food and Farming and recently stepped down as chair of the UK's agricultural and environment (DEFRA) ministry's Science Advisory Council. He is a Fellow of the Royal Society and in 2017 was knighted for contributions to science and science advice to government.

Talk Summary:

In his talk he will do three things. First, he will briefly talk about his own career trajectory and how he became involved in providing science advice to policy makers. Second, he'll talk more broadly about how policy makers seek advice from the research community, focusing chiefly but not exclusively on the UK, and explore how people can become involved in this at all stages of their career. Lastly, he'll talk specifically about a very contentious area of policy in the UK, the control of bovine tuberculosis, which he hopes will illustrate some of the practicalities and challenges of working with government and other decision makers.

Panel Discussion

Insight into careers in biotech entrepreneurship and industry

Dr Claire Shingler, the Oxford BioEscalator
Dr Loic Roux, Ochre Bio
Dr Helena Meyer-Berg, SIRION Biotech GmbH

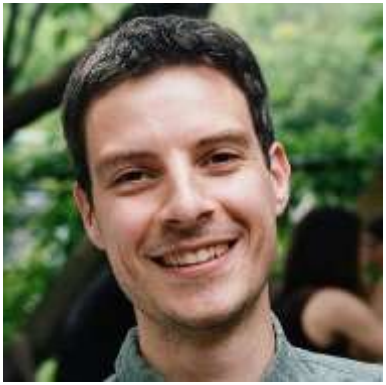
Dr Claire Shingler is the Business Manager of the Oxford BioEscalator, the University of Oxford's incubator for start-up and spin-out companies in the biomedical sciences. Claire is responsible for vetting and on-boarding new companies, the smooth running of the facility and the high level of support offered to enable tenant companies to grow quickly and move on. Claire took up the role as the BioEscalator opened in September 2018 and she and her team currently support 15 companies comprising approximately 100 staff. Part of the BioEscalator's value-added offering is a diverse curriculum of social and educational events designed to enhance tenants' networking opportunities and upskill their employees in a range of start-up oriented topics. Claire gained a first class degree in Chemistry from the University of York, an MPhil in Molecular and Cellular Biology from the University of Birmingham, and a PhD in Cancer Research from the University of Nottingham. She continued her PhD research as a postdoc in a joint venture start-up company at the University of Edinburgh. Claire's postdoctoral career

has focussed on multidisciplinary team management in the biomedical and university sector, initially as Head of Strategic Intelligence, leading a team producing a suite of business intelligence products at PharmaVentures, an Oxford-based pharmaceutical consultancy company. She then joined Oxford University where she has held roles in research- and departmental-management in the departments of Experimental Medicine and Oncology.

Dr Loïc Roux received his Ph.D in Medicinal Chemistry from Aix-Marseille University in France. His work focused on the development of new nucleotides pro-drugs against HIV focusing onthe phosphorus chemistry. He joined Prof. Khvorova'slab (UMass Med School, MA, USA) in 2018 working on the stabilization and delivery of fully chemically modified oligonucleotides and then Prof. Wood's lab (University of Oxford, UK) working on peptide-oligonucleotides conjugates for muscular degenerative diseases. After a position as principal scientist at PepGen Limited promoting a peptide delivery platform for nucleic acid delivery, he contributed to building and establishing NATA, a new UKRI initiative aiming to promote the development of nucleic acid therapeutics. He is now the Head of Lead Development in Ochre Bio, a Phenomics-led RNA medicines company developing the next-generation of RNA therapeutics for chronic liver diseases.

Dr Helena Meyer-Berg completed her studies in biochemistry at LMU Munich, and then pursued a DPhil in Medical Sciences at University of Oxford in the Gene Medicine Group headed by Prof Deborah Gill and Prof Steve Hyde. Helena received MRC DTP funding during her DPhil, including a supplementary funding award for a high cost training opportunity. She completed her studies on AAV-based gene therapy for a rare disease of the lung in October 2021 and started to work in industry the same year. Helena is now a full time employee of the rapidly growing SIRION Biotech GmbH in Munich, Germany where she manages innovation, marketing and client R&D projects within the AAV vector platform in a newly created department.

Invited Speakers



From postdoc to programme manager: working for a research funder

Dr Tom Beattie

Programme Manager for Doctoral Training at the MRC

Speaker Biography:

Tom completed his PhD in biochemistry at the University of Oxford before moving to Montreal for postdoctoral work at McGill University. After completing his postdoc, Tom decided to move out of academia and returned to the UK to work in a science communication role at the medical research charity Breast Cancer Now. After three years in various roles, he joined the MRC in September 2020, where he is Programme Manager for Doctoral Training.

Bringing science to you – an introduction to science communication and Oxford Sparks

Dr Fiona Suttle

Lead of Oxford Sparks

Speaker Biography:

Fiona is responsible for managing Oxford Sparks - the University's platform for digital science engagement, which shares and promotes the cutting-edge research taking place within MPLS and across the wider University. In addition to the 'Big Questions' podcast, Oxford Sparks produces live-action videos, including 'micro-documentaries' and short videos for social media. Prior to this role, Fiona carried out a DPhil in the University's Department of Zoology, examining the impacts of anthropogenic stressors (such as climate change and the krill fishery) on populations of penguins on the Antarctic Peninsula and surrounding Southern Ocean region. As part of this research, she was heavily involved with the Penguin Watch citizen science project, and is a keen advocate for the use of citizen science as a public engagement tool.

Talk Summary:

What is science communication? Why is it important, and how can you get involved? In this talk, Fiona will discuss some of the motivations behind 'public engagement with research', and present some of the options available to those wishing to pursue it (either as a career, or alongside full-time research). She will provide an overview of Oxford Sparks – the University's online science engagement platform – and explain how you can get involved in their content creation or 'Sparks Ambassador' scheme.

Poster Presentations

Posters will be displayed over the lunch break, please take the time to go and hear about your fellow students' work.

1. **Derivation and validation of risk scores for cardiovascular disease in Chinese adults.** Jacqueline Murphy.
2. **The effects of angiotensin-II antagonists on hippocampal processing.** Lorika Shkreli.
3. **Single cell RNA sequencing of cryopreserved human renal transplant core biopsies: a feasibility and optimisation study.** Oliver McCallion.
4. **Adipocyte autophagy in chronic inflammatory disease.** Klara Piletic.
5. **Frailty and risk of incident cardiovascular disease in a prospective study of 0.5 million Chinese adults.** Dani Kim.
6. **Characterization of the earliest thalamocortical interactions in the human fetal brain.** Sara Bandiera.
7. **Guiding Perception by Memories of Multi-Timescales.** Dongyu Gong.
8. **The role of astrocytes in Parkinson's disease pathogenesis in specific GBA N370S patient iPSC-derived neuro-glial co-cultures.** Naroa Ibarra-Aizpurua.
9. **Mice with a genetic loss of the vesicular glutamate transporter vGLUT3 targeted to 5-HT neurons show putative anhedonia and reduced reward sensitivity.** Luisa Sophie Gullino.
10. **Investigating mechanisms of zeta-globin gene silencing.** Susannah Holliman.
11. **Using 23Na sensitivity profiles to accelerate hyperpolarized 13C 2D Chemical Shift Imaging (CSI) with a flexible array coil.** Ayaka Shinozaki.
12. **Investigating the Role of Inflammation in Pancreatic Cancer**. Constantinos Demetriou.
13. **Characterising the role of coding polymorphisms in the function of TBX15 in adipogenesis and fat distribution.** Louisa Zolkiewski.
14. **The neural correlates of inhibitory control in infancy: a functional near-infrared spectroscopy study.** Abigail Fiske.
15. **Multi-omics comparison of plasma extracellular vesicle isolation methods.** Daan Paget.
16. **The activity, function and exploitability of tumour-reactive CD8+T-cells in malignant pleural effusion (MPE).** Delaney Dominey-Foy.
17. **Exploring the association between the immune response and heart regeneration in Astyanax mexicanus.** Esra Sengul.
18. **How can pilot trial progression criteria help researchers do better randomised trials?** Katie Mellor.
19. **Regeneration of the cardiac conduction system.** Judy R. Sayers.
20. **Oxford Brain Health Centre database: characterisation of the first 150 patients.** Jasmine Blane.

2022 Symposium Prizes

Student Talks

First prize - £200

Second prize - £100

Selected by judges (Prof. Ester Hammond and panel)

3 Minute Thesis Competition

Judges pick - £100

Audiences pick - £100

Poster Presentations

Top 3 - £50 each

Selected by delegate votes

Thank you to our sponsors

Organising Committee:

Jasmine Reese
Alissa Hummer
Bethan O'Connor
Gina Wren
Jan Boehning
Magda Mareckova

Aga Bush
Christopher Higham

Biogen

Biogen believes that no other disease area holds as much need or as much promise for medical breakthrough as neuroscience. Our focus on neuroscience, our deep scientific expertise and our courage to take risks makes us leaders in the research and development of medicines to transform neuroscience to benefit society.

www.biogen.com

IMMUNOCORE

Immunocore is a leading T cell receptor (TCR) biotechnology company, focused on delivering first-in-class biological therapies that have the potential to transform the lives of people with serious diseases. Our most advanced therapeutic programmes are focused on oncology, and we also have programmes in infectious and autoimmune diseases.

LinkedIn and Twitter
@Immunocore

Magstim® is a British-based medical device manufacturer and leading supplier of Transcranial Magnetic Stimulation (TMS) equipment, coils and complete packages used for both Magstim TMS therapy and neuromodulation research.

Magstim TMS Therapy for depression is an effective, non-invasive, outpatient treatment, with few known adverse effects.

Magstim's technology has been used in more TMS research studies worldwide than any other manufacturer and Magstim's product range provides users with the versatility and capability needed for a wide range of research applications.

With representation in over 70 countries and systems in more than 90 countries worldwide, Magstim is proud to be The Brains Behind TMS™.

"*The day I began treatment was one of the best days of my life.*"
- Bridget, TMS patient

"*I feel like a new person and my family says that they are glad to finally have 'me' back.*"
- Kathy, TMS patient

"[TMS Therapy] gives me the opportunity to actually live my life for the first time."
- Rob, TMS patient

www.magstim.com

MRC | Harwell

@MRCHarwell

MRC Molecular Haematology Unit

UNIVERSITY OF OXFORD

MRC Molecular Haematology Unit (MRC MHU) aims to understand how mature blood cells are normally made from stem cells and how this is perturbed in common blood disorders. Ultimately, their purpose is to improve the prognosis of patients with inherited and acquired blood disease.

The Unit includes 14 research teams with over 100 scientists who share a common interest in understanding the process by which multipotential haemopoietic stem cells become committed and differentiate into the highly specialised cells found in the peripheral blood (red cells, granulocytes, lymphocytes and platelets). They also study how these processes are perturbed in acquired and inherited blood diseases such as thalassaemia, myelodysplasia and leukaemia.

The Medical Research Council Population Health Research Unit (MRC PHRU) generates and disseminates reliable evidence from randomised trials and genetic or classical epidemiological studies that lead to practical methods of avoiding premature death and disability, or to an understanding of disease mechanisms.

The Unit has a particular focus on cardiovascular and metabolic diseases, including diabetes mellitus and chronic kidney disease. It has facilitated some of the world's largest and most informative observational studies and randomised trials.

MRC PHRU is part of the Clinical Trial Service Unit & Epidemiological Studies Unit in the Nuffield Department of Population Health. For further information, please visit:

https://www.mrc-phru.ox.ac.uk/

Vertex is a global biotechnology company that invests in scientific innovation to create medicines for people with serious diseases. The company has three approved medicines in the UK that treat the underlying cause of cystic fibrosis (CF) – a rare, life-threatening genetic disease — and has several ongoing clinical and research programs in CF. Beyond CF, Vertex has a robust pipeline of investigational medicines in other serious diseases where it has deep insight into causal human biology, such as sickle cell disease, beta thalassemia, pain, alpha-1 antitrypsin deficiency, Duchenne muscular dystrophy and APOL1-mediated kidney disease.

https://www.vrtxpharma.co.uk