Medical Research Council

UNIVERSITY OF OXFORD

Oxford-MRC Doctoral Training Partnership

Oxford-MRC DTP Symposium

June 24th, 2021

Programme

10:00 **Welcome – Professor Ester Hammond,** Director of Oxford-MRC DTP

10:10 **Peer supporters –** information on how they can help you!

10:15 Student Talks – Session 1 (Chair – Katarzyna Chwalenia)

Claire Blacklock – Center for Tropical Medicine and Global Health

"The social ties of hospital staff: a realist synthesis"

Karen Wendt – Department of Engineering Science

"Developing an enhanced transcranial magnetic stimulator"

Imran H. Yusuf – Nuffield Department of Clinical Neurosciences

"Gene therapy rescues cone and rod photoreceptor function in a pre-clinical model of CDHR1-associated retinal degeneration through restoration of outer segments"

11:15 **Coffee Break**

11:30 Student Talks – Session 2 (Chair – Athena Cavounidis)

Barnabas Williams – The Jenner Institute

"Investigation of the Plasmodium falciparum RH5-Interacting Protein (PfRIPR) as a blood-stage malaria vaccine target"

Cornelia Heuberger– Sir William Dunn School of Pathology

"Antigen presentation and T cell regulation by intestinal epithelial cells"

Caitlin O'Brien-Ball – MRC WIMM Human Immunology Unit, Radcliffe Dept of Medicine

"The Role of T-cell Receptor Expression and Signalling in Early Contact Formation by T Cells"

12:30 **Lunch Break**

13:15 Keynote Panel
Professor Catherine Green
Professor Theresa Lambe
Professor Sarah Gilbert
"Developing a vaccine during an ongoing pandemic"

14:15 3 Minute Research Competition (Chair – Jan Boehning)
Maisha Jabeen – Respiratory Medicine Unit
"Application of Modern Molecular Microbiological Techniques to Identify Treatable Chronic Bacterial Airway Infection in Severe Asthma"
Adam Bush – Institute of Biomedical Engineering, Department of Engineering Science
"Oxygen Microbubbles to Relieve Tissue Hypoxia in Cancer Therapy"
Sara Bandiera– Department of Physiology Anatomy and Genetics
"Characterization of the earliest thalamocortical interactions in the human fetal brain"
Alice Brankin – Experimental Medicine, NDM
"Predicting fluoroquinolone resistance in Mycobacterium tuberculosis"
Rishi Anand – Department of Physiology Anatomy and Genetics
"Glycine reduces evoked striatal dopamine release in a region-dependent manner"
Bethany Charlton – Nuffield Department of Medicine
"Immunological and genetic correlates of delayed HIV-1 disease"

Careers panel

15:00 **Dr Daniele Corridoni** – Group Leader at Kymab Ltd and Visiting Researcher at University of Oxford
"Translating precision immunology into novel therapeutics: drug discovery without borders"

15:25 **Dr Alison Murphy** – Senior Medical Writer at Oxford PharmaGenesis
"My journey from academia to medical communications"

15:50 **Conclusion and Prizes**

Student Talk Abstracts

Session 1

The social ties of hospital staff: a realist synthesis

Claire Blacklock, Amy Darwin, Mike English, Jacob McKnight, Lisa Hinton, Elinor Harriss, Geoff Wong

Center for Tropical Medicine and Global Health

Social ties influence access to and interpretation of information, and behavioural norms. It is unclear how social ties might be used to improve quality in multi-professional healthcare workplaces. Using realist synthesis, we develop explanatory theory to illuminate the details and significance of social ties in hospitals. Specifically: How, why, for whom, to what extent and in what context do the social ties of staff within a hospital influence quality of service delivery, including quality improvement? From a total of 75 included documents identified through a systematic literature search, data are extracted and analysed to identify emergent explanatory statements, from which 35 context-mechanism-outcome configurations are developed across four overarching theoretical domains: 1) social group, 2) hierarchy, 3) bridging distance, and 4) discourse. The relative social position of individual healthcare workers in hospitals is found to be a determinant of capital, influence, power and agency for change. Power to bring about change is inequitably and socially situated, and subject to specific contexts. These findings offer a lens through which to understand the details and importance of social ties in hospitals, and could help identify possible strategies for intervention to improve communication and distribution of influence and power, for quality improvement in hospitals.

Developing an enhanced transcranial magnetic stimulator

Karen Wendt, Majid Memarian Sorkhabi, Jacinta O'Shea, Hayriye Cagnan, Tim Denison

Department of Engineering Science

When a disorder such as depression cannot be adequately treated with pharmacotherapy, brain stimulation can be an effective alternative. Transcranial magnetic stimulation (TMS) is a non-invasive technique that uses magnetic pulses to modulate the nervous system. However, conventional TMS devices use analog circuitry and are restricted currently to a small set of stimulation waveforms and patterns which may limit their application. We are developing a novel TMS device which can generate magnetic pulses of arbitrary shapes and patterns using digital synthesis techniques. This new instrument will allow more flexibility in exploring and choosing stimulation parameters for TMS treatment while staying within safety limits for the stimulation. To validate the use of digitally-modulated pulses in TMS, we used computational modelling to estimate the effect that the digital pulses have on neurons as compared to conventional analog TMS pulses. The results show a high correlation between the neural responses to the digitally-modulated pulses and the conventional stimuli. In practice, the effects of TMS are more complex and may vary between individuals. Therefore, the next step will be to validate these results in human participants before expanding to novel pulse shapes and patterns and customising treatment through individual feedback from biomarkers.

Gene therapy rescues cone and rod photoreceptor function in a pre-clinical model of CDHR1-associated retinal degeneration through restoration of outer segments

Imran H. Yusuf, Michelle E. McClements, Robert E. MacLaren, Peter Charbel Issa

Nuffield Department of Clinical Neurosciences

Purpose: To evaluate the efficacy and safety of retinal gene therapy in a pre-clinical model of CDHR1-associated retinal degeneration – an untreatable, blinding disorder. Methods: Cdhr1-/- (n=28) and C57BL6J control mice (n=23) underwent paired sub-retinal injections of AAV8.GRK1.CDHR1 (1.5x108) and PBS vehicle control in the fellow eye. Dark- and light-adapted electroretinography (ERG) was undertaken at 2-monthly intervals and optical coherence tomography (OCT) retinal imaging at 6-monthly intervals to 12 months post-injection. Results: In Cdhr1-/- mice, AAV8.GRK1.CDHR1 rescued rod and cone photoreceptor function on dark-adapted (A-wave: $p<0.0001$ for all time points) and light-adapted ERG ($p<0.0001$ from 8 months post-injection) versus paired control eyes. The photoreceptor layer was preserved versus control eyes to 12-months post-injection (mean 70.2um versus 29.3um; $p<0.0001$). In C57BL6J mice, there was no difference in ERG responses at 12-months (A-wave, $p=0.052$; B-wave, $p=0.56$; Cone responses, $p=0.99$) or photoreceptor thickness measurements at 12 months between AAV and PBS-injected eyes ($p=0.58$). Conclusion: These data provide proof-of-principle of the efficacy and safety of CDHR1 gene therapy in a pre-clinical model of CDHR1-associated retinal degeneration. Rod and cone rescue occur through prevention of photoreceptor cell death and regeneration of photoreceptor outer segments. A follow-on clinical trial in patients with CDHR1-associated retinal degeneration is anticipated.

Session 2

Investigation of the Plasmodium falciparum RH5-Interacting Protein (PfRIPR) as a blood-stage malaria vaccine target

Barnabas Williams, Simon Draper

The Jenner Institute

Plasmodium falciparum is the deadliest of the five Plasmodium species that cause malaria. Vaccines remain the most cost effective tool in the fight against infectious disease; however, an efficacious malaria vaccine is still not available. A vaccine against blood-stage malaria could prevent severe clinical malaria and complement naturally acquired immunity. The conserved antigen Plasmodium falciparum RH5 interacting protein (PfRIPR is a potential vaccine target however, very little is known about this large and complex protein. Rabbits were immunised with full length PfRIPR to generate anti-PfRIPR polyclonal antibody. A number of PfRIPR protein fragments which were used to reverse the inhibitory activity of this anti-PfRIPR polyclonal antibody. The identified neutralising epitopes of PfRIPR were used to immunise rats either as protein fragments with Matrix-M™ adjuvant or conjugated to Hepatitis B surface Antigen (HBsAg). The purified rabbit polyclonal antibody pool can effectively block the invasion of erythrocytes by P. falciparum with an average EC50 of 2.0mg/mL. Using antigen reversal, we determined that all of the neutralising epitopes are located on a small region of PfRIPR. Immunisation with this PfRIPR region lead to a four-fold improvement in antigen specific EC50 compared to the full-length protein.

Antigen presentation and T cell regulation by intestinal epithelial cells

Cornelia Heuberger, Dr Emily Thornton, Dr Fiona Powrie, Dr Kevin Maloy, Dr Johanna Pott

Sir William Dunn School of Pathology

A single layer of intestinal epithelial cells (IECs) separates the mucosal immune compartment from the microbiota present in the intestinal lumen. IECs help to maintain immune homeostasis and loss of epithelial barrier integrity may contribute to the breakdown of intestinal homeostasis observed in certain intestinal inflammatory disorders, such as inflammatory bowel diseases (IBD). This project aims to understand how antigen presentation by IECs contributes to intestinal homeostasis and intestinal inflammation. In agreement with previous findings, MHCII was expressed by IECs both in ex vivo stimulated organoids and in in vivo models of colitis. Mice lacking MHCII expression by IECs were generated (H2-Ab1VC). However, MHCII deficiency of colonic IECs had no discernible effects on the disease severity of colonic colitis models. The transfer of pathobiont specific T cells into pathobiont infected H2-Ab1VC mice and littermate controls showed increased development of antigen specific regulatory T cells in mice lacking IEC MHCII expression. We further developed an in vitro co-culture system of intestinal organoids and T cells and were able to show antigen specific activation of T cells by peptide:MHCII complexes presented by IECs. We will further investigate the role of antigen presentation by IECs in modulating these antigen specific T cell responses.

The Role of T-cell Receptor Expression and Signalling in Early Contact Formation by T Cells

Caitlin O'Brien-Ball, Dr. Simon Davis, Dr. Mafalda Santos

MRC WIMM Human Immunology Unit, Radcliffe Dept of Medicine

T cells require close physical contact with target cells to perform their effector functions. Recent imaging studies have shown that upon antigen recognition, initial small contacts rapidly transition to form a larger and more stable contact, eventually reorganising surface proteins to create the immune synapse. Despite extensive imaging of T cell-target cell contact formation, the mechanisms underlying the transition between these events are not well understood. By varying T-cell receptor (TCR) expression levels, and using a drug-sensitive variant of the kinase ZAP70, we uncoupled TCR binding from its signalling capacity, allowing us to study the effect of TCR number and signalling potency on the formation and regulation of early T-cell contacts. We find that initial adhesion to model target cell surfaces is independent of TCR signalling and expression, but that cell spreading requires TCR expression and ZAP70 kinase activity. Further, inhibition of TCR signalling, but not reductions in receptor expression, modulate the dynamics of initial microvillar-based T cell contacts, suggesting that very weak signalling may sustain the scanning functions of microvilli. These findings illustrate the complex interplay between passive and active events in establishing T-cell contacts with their targets.

Keynote Panel

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Developing a vaccine during an ongoing pandemic.

Professor Catherine Green
Professor Theresa Lambe
Professor Sarah Gilbert

The COVID-19 vaccine developed by the University of Oxford and AstraZeneca is authorised in over 100 countries and is the most used COVID-19 vaccine world-wide. We are thrilled to present a Keynote panel including Oxford University's very own Catherine Green, Theresa Lambe and Sarah Gilbert, who have been instrumental in the unprecedentedly fast development and rollout of the vaccine.

Sarah Gilbert is the Saïd Professor of Vaccinology at the Jenner Institue and co-founder of Vaccitech. Her research interests include the development of vaccines for malaria, influenza, and emerging diseases. She was recently awarded a damehood in recognition of her instrumental efforts in the development of the AZD1222 COVID-19 vaccine during the ongoing pandemic.

Theresa Lambe is an associate Professor at the Jenner Institute. Her group focuses on emerging pathogens, including Ebola, Influenza and Coronaviruses. In recognition of her integral efforts in the development of the AZD1222 COVID-19 vaccine, she was recently awarded an OBE.

Catherine Green is an associate Professor at the Wellcome Centre for Human Genetics. She heads the Clinical Biomanufacturing Facility at the Nuffield Department of Medicine. In recognition of her instrumental efforts in the development of the AZD1222 COVID-19 vaccine, she was recently awarded an OBE.

Invited Speaker

Translating precision immunology into novel therapeutics: drug discovery without borders

Dr. Daniele Corridoni

Group Leader at Kymab Ltd

Dr. Daniele Corridoni has worked in academia and recently in industry. Daniele started his Ph.D. in Immunology at University of L'Aquila (Italy) that he completed it at Case Western Reserve University in Cleveland (USA), where he remained for a Post-Doctoral Fellowship. After six years in USA, he moved to UK to continue his research at University of Oxford. He contributed to define how dysregulation of the innate immune bacterial sensor NOD2, the strongest Crohn's disease susceptibility gene, leads to impaired bacterial clearance, incorrect regulation of pro-inflammatory cytokines and impaired CD8+ T cell responses, contributing to trigger inflammation. A more recent focus of his work is the characterization of intestinal immune cells employing multi-modal single-cell technologies. This led to the first unbiased characterization of different subpopulations of intestinal CD8+ T cells and to define which of those may contribute to inflammatory bowel disease. Daniele while is still affiliated with University of Oxford, is now a Group Leader at Kymab, the first Sanger Institute spin out and now a Clinical stage Biopharmaceutical company located in Cambridge. In April 2021, Kymab was acquired by Sanofi, helping to build on Sanofi's global leading presence in Immunology. Daniele in his current position aims to contribute to improving drug discovery for immune-mediated diseases by strengthening collaborations between academia and industry and the diversity this can bring.

Invited Speaker

My journey from academia to medical communications

Dr. Alison Murphy

Senior Medical Writer
at Oxford PharmaGenesis

Alison's educational background is in immunology with a focus on host–pathogen interactions. After completing a PhD in immunology at Trinity College Dublin, she undertook postdoctoral research at the University of Oxford. Throughout her academic research, Alison contributed to science communication events at festivals and primary schools, which she found very rewarding and motivated her to explore communication-based roles. Alison is now a Senior Medical Writer at Oxford PharmaGenesis, an independent, award-winning HealthScience consultancy, and develops scientific publications and materials for clients in the healthcare sector.

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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

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MRC Harwell Institute is at the international forefront of the use of mammalian models to study genetics and human disease.

MRC Harwell Institute is an international research centre at the forefront of the use of mammalian models to study genetics and human diseases. Located on the Harwell Campus, just south of Oxford, it is nestled amongst a vibrant community of leading science organisations. We aim to advance medicine through cutting-edge research into the genetic basis of disease. Our research programmes span an entire lifetime, from embryonic development to diseases of ageing.

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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.

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