NUFFIELD DEPARTMENT OF SURGICAL SCIENCES

UNIVERSITY OF OXFORD

NDS Student Symposium

Monday 1 July 2024

Richard Doll Building, Old Road Campus

NDS Student Symposium 2024
Richard Doll Building
Old Road Campus
Oxford
OX3 7LF

Main meeting: Richard Doll Lecture Theatre
Registration and refreshments: Richard Doll Foyer

Prize judges

Simon Buczacki
Claire Edwards
Anna Furmanski
Martin Gillies
Ashok Handa
Joanna Hester
Maria Kaiser
Ed O'Neill
Srinivasa Rao

Programme

9:30 Welcome - Professor Ian Mills and Professor Claire Edwards

9:40 – 10:15 ***Final Year talks Session 1*** ***Chair: Professor Ashok Handa***

9:40 Megan Bradbury

9:50 Selena Kim

10:00 Dennis Mazingi

10:10 Alex Sagar

10:20 Sarah Short

10:20 – 11:00 Break & Posters

11:00 – 11:40 ***Plenary Talk*** ***Chair: Professor Freddie Hamdy***

Prof. Simon Leedham, Nuffield Dept. Of Medicine, University of Oxford

Using spatial biology to quantitively map and understand cell interactions in colorectal cancer

11:40 – 12:10 ***Final Year talks Session 2*** ***Chair: Dr Letizia Lo Faro***

11:40 Oliver McCallion

11:50 Ann Ogbemudia

12:00 Aleksandra Ziubroniewicz

12:10 – 12:20 ***Snap Poster Presentations*** ***Chair: Dr Letizia Lo Faro***

12:20 – 13:30 Lunch & Posters

13:30 – 14:10 ***Final Year talks Session 3*** ***Chair: Dr Gurdeep Mannu***

13:30 Casey Rosso

13:40 Fatemeh Salimi

13:50 Rebecca Vaughan

14:00 Bingyuan Yang

14:10 – 14:30 Break

14:30 – 15:20 ***First Year talks*** ***Chair: Dr Sandy Fiegel***

14:30 Hannah Contreras

14:35 Mohamed Elzawahry

14:40 John Kellas

14:45 Farah Khan

14:50 Zexi Li

14:55 Hatem Sadik

15:00 Rumyana Smilevska

15:05 Yi Zhou

15:10 – 15:25 ***MSc talks*** ***Chair: Dr Anna Furmanski***

15:10 Madeline Carey

15:15 Romane Henninger

15:20 Jennifer van Heerden

15:25 – 15:30 Public Engagement in NDS, Louise King, Communications and Public Engagement Officer

15:30 – Bodleian Health Care Libraries, Hannah McGivern, Outreach Librarian

15:35 – 15:50 Prizes - Prof. Claire Edwards

Simon Leedham
Biography

Simon Leedham is a Professor of Molecular and Population Genetics and an Honorary Consultant Gastroenterologist at the University of Oxford. His research is into the morphogenic signalling pathways that control the intestinal stem cell in homeostasis, regeneration and cancer, and he has published more than 100 peer reviewed papers in journals that include Nature, Nature Medicine, Nature Genetics, Cell Stem Cell, Gastroenterology and Gut. Simon’s research has been recognised by the United European Gastroenterology Rising Star award in 2010, the British Society of Gastroenterology Francis Avery Jones research prize in 2015 and the CRUK Future Leaders prize in 2017.

Abstracts

Sophia Abusamra

Circulating tumour cell isolation and enrichment methodologies for investigation of prostate cancer metastasis
Sophia M. Abusamra, Daniele T. Cotton, Thineskrishna Anbarasan, Sandy Fiegel, Ahmed Alkhateeb, Wencheng Yin, Robert Barber, Edmond Walsh, Todd M. Morgan, Jason J. Davis, Ian G. Mills, Alastair D. Lamb, Claire M. Edwards

Circulating tumour cells (CTCs) are tumour cells that are shed from the primary tumour, intravasate into circulation, and have the potential to seed disease metastasis. Methods to enrich for CTCs often rely on immune-affinity techniques targeting EpCAM. Such methods may fail to capture CTCs that have downregulated EpCAM expression, for example as a result of the epithelial-to-mesenchymal transition (EMT). Multiplexed immune-affinity isolation and label-free enrichement methods offer the ability to capture CTCs independent of EpCAM expression alone. In this study, nanoparticle-mediated CTC isolation resulted in capture efficiencies ranging from 12.3%-61% for anti–EpCAM particles and 8.8%-42.3% for anti–PSMA particles. Label–free CTC enrichment recovered PC3-EGFP and LNCaP cells from whole blood with high capture efficiency (80.1% and 70.5%, respectively). Future work will include enrichment of CTCs from the blood of prostate cancer patients for ex vivo expansion and single—cell RNA sequencing.

Megan Bradbury

Soft tissue sarcomas (STS) are highly aggressive mesenchymal malignancies with poor prognosis, typically treated using surgery, radiotherapy, and systemic chemotherapy.
Several recent clinical studies have shown that High Intensity Focused Ultrasound (HIFU) to be safe and effective for the treatment of unresectable STS by inducing coagulative necrosis. HIFU has also been shown to encourage an immune response to the antigens and danger-associated molecular patterns (DAMPs) that are produced during ablation to bolster the response to treatment. However, the ability to pair HIFU with immunotherapy, such as anti-PD-L1, to induce a greater systemic response remains unexplored and holds great potential for improved treatment outcomes in the future.
The aims of this DPhil project are three-fold: (1) to characterise the baseline immune status of soft tissue sarcomas, (2) to investigate immune responses within a HIFU clinical trial, and (3) in vivo with immunotherapy.

Hannah Contreras

Birth defect registries play a pivotal role in understanding the prevalence, characteristics, and global variations of congenital anomalies. This rapid scoping review aims to comprehensively explore the landscape of cardiac, abdominal, digestive, and urogenital birth defect registries worldwide, focusing on the period from 2018 to 2024. With the overarching questions centered on the key characteristics, levels of implementation, and the influence of income classification on registry development, this review seeks to shed light on the effectiveness and functionality of these registries at a global scale.
The literature will be surveyed to provide an insightful overview of the availability, breadth, and depth of these registries. Furthermore, the review will delve into the key characteristics and levels of implementation of cardiac and gastrointestinal birth defect registries worldwide, emphasizing a comparative analysis among countries with distinct income levels to unveil variations in their development, comprehensiveness, and data quality.

Mohamed Elzawahry

Whole-organ pancreas transplantation (PTx) can treat patients with the most severe complications of diabetes. As it's related to significant morbidity, PTx is only offered to a small subset of such patients worldwide. The pancreas is particularly vulnerable to ischaemia/reperfusion injury (IRI) which plays a significant role in the associated morbidity, reflected in a high discard rate after retrieval.

Oxygenated hypothermic machine perfusion ($HMPO_2$) can provide the oxygen needed for normal mitochondrial function, flush-out metabolic products and maintain the microvasculature. $HMPO_2$ has demonstrated clinically significant benefits, in kidney and liver transplantation, in multicentre randomised controlled clinical trials. $HMPO_2$ was shown to be feasible experimentally in human pancreases.

The aims of my work are:

- Optimise the pre-clinical model for $HMPO_2$ of pancreas grafts.
- Test the feasibility of MRI in pancreas allograft pre-transplant assessment.
- Design and conduct a phase 1 clinical trial of pancreas $HMPO_2$ prior to transplantation.

John Kellas

This research examines patient and public involvement (PPI) in the medical imaging generative AI innovation pipeline, aiming to develop a critical appraisal framework to enhance the reporting of stakeholder engagement, project trustworthiness, and technology acceptance.
Initial exploratory research includes a review of stakeholder involvement frameworks, generative AI development frameworks, and standards for reporting PPI in medical imaging AI.
The current research plan comprises a scoping review, a NetZero AICT (green medical imaging generative AI) case study analysis, and a Delphi survey and interviews.
The research questions focus on the methods, materials, and outcomes of PPI, the documentation of this engagement in the literature, the frameworks and standards employed, and opportunities for improving reporting methodologies.
By addressing these questions, this study aims to create a framework that supports quality assurance and enhances transparency and trust in integrating generative AI into medical imaging.

Farah Khan

Upper limb, Lower limb fracture-related Pediatric Mortality and Morbidity in Low- and Middle-Income Countries: A Systematic Review.

One of the key factors of the impedance of the development of evidence-based interventions is the void in paediatric limb trauma research within low- and middle-income countries (LMICs). This causes a scarcity of data on epidemiology, treatment outcomes, and the long-term effects of limb injuries in children. Our systematic review attempts to close this gap by combining the available data on paediatric limb fractures in LMICs. Critical information about injury patterns, risk factors, treatment efficacy, and long-term consequences can be obtained from this review, which could help to create focused interventions and research goals. This analysis aims to improve outcomes and lower morbidity and mortality linked to limb injuries in LMIC settings by pinpointing areas for improvement in paediatric limb trauma care, instilling hope for better healthcare outcomes.

Jinseon (Selena) Kim

Prostate cancer (PCa) is the most common male cancer and has an ‘immune cold’ tumour microenvironment (TME), infiltrated by immunosuppressive tumour-associated macrophages and regulatory T cells (Tregs). High serum insulin-like growth factor 1 (IGF-1) is causally associated with risk of PCa development and lethality and has immunosuppressive functions in other disease models. We are investigating the hypothesis that IGF-1 contributes to an immunosuppressive TME, using PCa models and IGF-neutralising antibody xentuzumab. We found that, although PCa tumour growth in syngeneic mice was not suppressed, immunohistochemistry showed significantly increased total macrophage but reduced pro-tumorigenic M2 macrophage infiltration in xentuzumab-treated tumours. Flow cytometry *in vitro* revealed that xentuzumab reduced M2 macrophages by 60%, significantly increased cancer cell phagocytosis, and significantly enhanced CD8+ T cell functions. We are testing the clinical significance of these findings in samples from patients recruited to the WINGMEN clinical trial of xentuzumab pre-prostatectomy (NCT05110495).

Pierfrancesco Lapolla Losasso

Developing methods to characterise circulating biomarkers in Abdominal Aortic Aneurysms

Abdominal aortic aneurysms (AAAs) are abnormal expansions of the abdominal aorta, posing serious health risks if untreated, with a higher prevalence in men and those with a history of smoking or family incidence. Ruptured AAAs are emergencies with high mortality rates, highlighting the need for early detection and monitoring through regular ultrasound scans. Current surveillance methods lack personalized assessment, focusing mainly on aneurysm size and related factors.
To address this, I am developing methods to predict AAA growth by analysing protein biomarkers using novel mass spectroscopy (MS) techniques. This involves creating a labelled Quantitative Concatenated Standard (QconCAT) construct for absolute biomarker quantification in plasma samples from AAA patients. The QconCAT method offers higher accuracy and efficiency over traditional synthetic peptides. Additionally, I am refining the Gas Chromatography (GC-MS) technique to identify metabolic signatures unique to AAA, aiming to improve clinical outcomes through enhanced biomarker quantitation and personalized patient management.
Keywords — Abdominal Aortic Aneurysm – Growth

Zexi Li

Since digital pathology is rapidly developing, the advancement of artificial intelligence (AI) algorithms in pathology has led to the development of quality assessment (QA) tools for whole slide image (WSI) quality. Ensuring high image quality is crucial for accurate assessment in both research and clinical diagnosis, as it can significantly impact downstream treatments and AI model performance. My DPhil research focuses on quality assurance and AI safety, employing machine learning algorithms to maintain the quality of WSIs in both clinical workflows and AI model applications. The study is designed to be applicable across a wide range of tissue types, rather than being limited to specific cohorts. The primary outcome of this research is the creation of an automated real-time monitoring system, intended for use in both clinical and research settings, to enhance the reliability and effectiveness of histopathological analysis.

Catherine Lovegrove

Genetic variants associated with DGKD, CYP24A1, and SLC34A1 predisposing to increased risk of kidney stone disease via effects on serum calcium or phosphate concentrations

Catherine E Lovegrove*, Michelle Goldsworthy, Jeremy Haley,*
Diane Smesler, Fadil Hannan, Mohnish Suri, Omid Sadeghi-Alavijeh, Daniel Gale, David Carey, Michael V Holmes, RajeshThakker, Dominic Furniss, Sarah A Howles

Kidney stones (KS) are common, heritable, and associated with abnormalities of calcium and phosphate metabolism.
Using Mendelian randomisation and colocalisation we identified three variants predicted to increase KS risk via increased serum calcium or decreased serum phosphate (odds ratios for genomic regions=4.30-13.83 per 1 standard deviation alteration). These account for 11-19% of KS due to reduced calcium-sensing receptor (CaSR)-signal transduction, increased urinary phosphate excretion, and impaired 1,25-dihydroxyvitamin D inactivation via diacylglycerol kinase delta (*DGKD*), solute carrier family 34 member 1 (*SLC34A1*), and cytochrome P450 family 24 subfamily A member 1 (*CYP24A1*), respectively.
Drug-target Mendelian randomisation analyses revealed that targeting *CASR*, *DGKD*, or *CYP24A1* to decrease serum calcium, or *SLC34A1* to increase serum phosphate may reduce KS risk. *In-vitro* studies demonstrated that reduced DGKδ expression impairs CaSR-signal transduction and that positive CaSR-allosteric modulation ameliorates this effect.
These studies suggest that genotyping individuals with KS may facilitate personalised risk stratification and pharmacomodulation.

Dennis Mazingi

Background:
Unintentional injuries are a substantial portion of the global burden of disease. Despite significant progress in many countries, others, like Zimbabwe, still face a growing burden due to underdeveloped trauma systems.
Objective:
This study aims to support the reduction of injuries in Zimbabwe by employing a public health approach to injury prevention.
Methods:
Conducted a systematic review of trauma registry literature in Africa to inform the design of a surveillance system in Zimbabwe.
Qualitative Study: Assessed unique risk factors for childhood injury in Zimbabwe, explored patient journeys through the care continuum.
Prospective Observational Study of consecutive trauma admissions in major Zimbabwean hospitals.
Results:
The mixed-methods approach identified and quantified context-specific risk factors and provided key insights into trauma-systems, patient experiences, and surveillance.
Conclusions:
The study's findings are expected to guide the implementation of a prospective interventional phase in Zimbabwe. These insights will contribute to developing effective injury prevention strategies, thereby reducing injury-related morbidity and mortality in the country.

Oliver McCallion

Adoptive cell therapy (ACT) with autologous expanded regulatory T cells (Tregs) is a promising therapeutic strategy to enable immunosuppression minimisation in organ transplant recipients. The TWO study is the world’s largest phase II clinical trial of autologous polyclonal Treg ACT following living donor kidney transplantation currently being undertaken by our group in NDS. In Treg ACT treated patients there is interest in assessing the migration patterns of transferred Tregs and their impact on tissue alloresponses within the transplant. To achieve this aim, I am utilising cutting-edge in situ spatial transcriptomics and CITEseq to define the immune phenotype and repertoire within the transplant and to identify dominant therapeutic mechanisms following Treg ACT.

Azita Mellati

Investigation into the effect of GNE684 -a RIPK1 inhibitor- delivered during organ preservation in a porcine model of renal ischaemia-reperfusion injury

Necroptosis is a form of cell death that occurs during kidney ischaemia reperfusion injury which is an inevitable event in transplantation. Phosphorylation of receptor-interacting serine/threonine-protein kinase 1 (RIPK1) has a key role in the necroptosis pathway. The aim of this study is to assess the safety and efficacy of GNE684 -a RIPK1 inhibitor- in an ex-vivo model of kidney transplantation. We set out to investigate three models (n=6 kidney pairs in each) in which the organ preservation method used to deliver GNE684 differs: static cold storage (SCS, model 1), hypothermic machine perfusion (HMP, model 2) and normothermic machine perfusion (NMP, model 3). Following preservation, normothermic reperfusion with autologous whole blood is used as a surrogate for transplantation. Currently, perfusion experiments in model 1 and 2 have been completed and results suggest safety of GNE684 (assessed through perfusion parameters, metabolic activity, histology and injury markers) and effectiveness of SCS and HMP as platforms to deliver GNE684 during organ preservation (assessed through pharmacokinetics of GNE684). No effect of GNE684 on assessed cytokines and DAMPs (downstream of necroptosis pathway) has been observed, and phosphorylation of upstream regulator proteins (including RIPK1 as the main target) is currently being assessed.

Ann Ogbemudia

Using Normothermic Machine Perfusion to address the challenges of Beta Cell replacement
Supervisor: Professor Peter Friend

Casey Rosso

Connectonomic Target Optimization in Deep Brain Stimulation for Chronic Neuropathic Pain

Deep brain stimulation (DBS) is approved in the UK for chronic pain but not funded. DBS targets cortical and subcortical network hubs to restore neuronal circuits. Advances in imaging like rsfMRI and dMRI visualize these networks. Connectivity profiles from DBS electrodes can explain the efficacy of targets like the anterior cingulate cortex, sensory thalamus, and brainstem periaqueductal grey. This project uses retrospective neuroimaging analysis of 20 anterior cingulate cortex patients from the Oxford Functional Neurosurgery database, performing whole brain rsfMRI and dMRI tractography from DBS electrode VATs. Functional connectome fingerprint maps were created using data from the Brain Genomic Superstruct Project and correlated with patient outcomes. R-MAPS models predicted optimal connectivity profiles. Results will segment pain DBS targets and provide a predictive model for DBS outcomes, aiding researchers in optimizing DBS target location for chronic pain treatment.

Hatem Sadik

Controlled oxygenated rewarming of the liver prior to normothermic machine perfusion to attenuate ischaemia-reperfusion injury

Normothermic Machine Perfusion (NMP) of liver grafts is commonly used after cold storage to assess ‘transplantability’ and prolong preservation. However, rapid rewarming after hypothermia results in ischaemia-reperfusion injury and higher rates of biliary complications. A gradual transition from cold to warm perfusion may limit ischaemia-reperfusion injury. At low temperature blood causes microvascular occlusion, however, at body temperature an oxygen carrier is required. Previous studies testing this approach rely on artificial oxygen carriers or a perfusion pause to switch from acellular to blood-based perfusate. I have developed a novel protocol to allow a gradual transition from acellular cold perfusion to blood-based NMP without a pause. This protocol is being tested in porcine livers followed by human livers deemed not suitable for transplantation. This project will, if successful, lead directly to a clinical trial. It has the potential to increase access to vitally needed organs and change liver transplantation practice worldwide.

Alex Sagar

Extra-corporeal liver cross-circulation as liver support therapy

Effective temporary liver support does not exist for patients with acute or acute-on-chronic liver failure (ALF, ACLF).
Normothermic machine perfusion (NMP) is a technique of liver preservation, in which the liver is supplied with blood at body-temperature outside the body. In extra-corporeal liver cross-circulation (ELC), blood from the systemic circulation of a patient is treated by perfusion through a donor liver undergoing NMP.
ELC was assessed in a porcine model of ALF, induced by hepatic inflow devascularisation. All animals received intensive medical therapy including inotropic support. Intervention pigs ($n=6$) commenced ELC 1-hour post-devascularisation and remained connected until the experiment end at 25 hours post-devascularisation.
ELC effectively replaced native hepatic function, mitigating the biochemical and clinical hallmarks of ALF observed in control pigs ($n=6$).
The source of donor livers for clinical ELC may include declined human allografts or transgenic porcine xenografts. Subsequent work has assessed the feasibility of the latter through 48-hour xenoperfusion experiments.

Fatemeh Salimi

Our project, titled "Transcutaneous Stimulation of the Auriculotemporal Nerve for Treating Radiotherapy-Induced Xerostomia," addresses the significant issue of xerostomia following radiotherapy in head and neck cancer (HNC) patients. With HNC incidences increasing globally, and survival rates improving due to advancements in treatment like radiotherapy, managing treatment-related side effects such as xerostomia becomes crucial. Current interventions for xerostomia lack long-term effectiveness, prompting the need for innovative approaches.

Our research focuses on developing and validating a non-invasive transcutaneous electrical stimulation technique targeting the auriculotemporal nerve, responsible for saliva production. Through a series of experiments on healthy volunteers and computational modeling, we aim to demonstrate the feasibility and efficacy of our approach. While our preliminary results align with animal studies involving direct nerve stimulation, our method offers a less invasive alternative. This project seeks to pioneer a novel therapeutic strategy for alleviating radiotherapy-induced xerostomia, potentially enhancing patient outcomes and quality of life post-treatment.

Sarah Short

Vascularised composite allotransplantation (VCA) can offer functional and aesthetic restoration after significant tissue loss. Despite its potential, VCA recipients face significantly heightened rates of acute rejection compared to solid organ transplant recipients. The immunogenicity of skin, a common component of VCAs, is theorised to contribute to this apparent vulnerability to rejection. Due to small patient cohorts and limited clinical data, it remains unclear whether the skin component increases sensitisation or alters rejection mechanisms in this setting. To address this gap, we have analysed skin rejection in both preclinical and clinical samples to identify tissue-specific signatures of rejection, with the aim of identifying potentially targetable pathways. This DPhil project therefore encompasses three broad aims; characterising rejection within an immune-humanised mouse model (1), developing a novel model of vascularised skin rejection (2) and analysis of samples from both VCA recipients, and transplant patients that have received immunomodulatory therapy (3).

Rumyana Smilevska

Donor and recipient selection for pancreas transplantation - risk factors for pancreas graft survival

DPhil Student: Rumyana Smilevska
Supervisors: Prof. Peter Friend, Prof Simon Knight and Dr Martyn Hill

Pancreas transplantation (PT) is a highly effective treatment for selected diabetic patients. It restores euglycemia and HbA1c levels, improves patient survival, quality of life and diabetic-related complications. However, PT remains challenging due to pancreas sensitivity to ischemia, high discard rates, surgical complexity and morbidity. Therefore, an important risk-benefit balance is to be established.
The aims are to identify risk factors predicting graft survival in PT, to create a database detailing 20 years of PT in the Oxford Transplant Centre, to analyse risk factors for graft and recipient outcomes, to develop and validate a risk model to predict 5-year graft survival after PT.
This research will allow a better understanding and identification of risk factors associated with graft and patient survival in PT, identification of patients at high risk of graft failure, developing risk prediction model to guide decision-making, donor organ selection and acceptance, and facilitate communication between surgeons and patients.

Rebecca Vaughan

Understanding changes in the DCD kidney degradome associated with warm ischaemia

Warm ischaemia (WI) inherent to the deceased after circulatory death (DCD) donor pathway associates with poorer short- and long-term outcomes post kidney transplant. The molecular and pathophysiological implications of WI on the donor kidney are poorly understood. To investigate the effect of WI on DCD kidneys, the kidney degradome was profiled using specialised peptidomic and bioinformatic methods and validated using a human hypoxic kidney cell model. Prolonged WI was associated with increased degradation of cytoskeletal proteins and dysregulation to metabolic pathways specifically glucose associated processes. Protease activity was also variable with WI time. Legumain activity increased whilst Cathepsin-B expression decreased; these proteases modulate matrix protein expression maintaining proteostasis. Cathepsin-B and Legumain expression in hypoxic kidney cells varied with hypoxia duration and glucose concentration. This study highlighted pathophysiological changes associated with WI and elucidated metabolic changes in the kidney that could prove a valuable target for intervention.

Bingyuan Yang

Optimising laser lithotripsy

Introduction
Laser lithotripsy is one of the key modalities for treating urinary stone disease. Laser devices have evolved dramatically across the last 30 years alongside endoscopic urology as a whole. This research examines key parameters of modern laser efficacy and how they can be optimised for current and future lasers.
Methods
A reference Ho:YAG laser and thulium fibre laser were selected to represent current gold standard technology, as well as a prototype Ho:YAG laser. The parameters measured were ablation rate, stone retropulsion and resulting particle size. All experiments were performed in vitro for reproducibility.
Results
Results are presented for ablation rate, stone retropulsion and particle size using all 3 lasers. In addition, results for an integrated model are presented illustrating how these parameters change when constrained in a simulated kidney model.
Conclusions
While measuring ablation rate is well established, there is no standard method for measuring stone retropulsion. Understanding of particle size is also poor. We present an image-tracking based method for quantifying retropulsion, and a technique for accurately measuring particle size on the milligram scale. Performing ablation in a simulated kidney can significantly alter results, and the effect varies depending on the laser and pulse modulation.

Yi Zhou

Fibroblasts play a key role in driving colorectal cancer progression. Tumours that are rich in fibroblasts have poorer prognoses than tumours with low fibroblast content. In this project, I aim to study how intestinal epithelial cells communicate with their surrounding fibroblasts, and how this communication makes epithelial cells behave more like cancer stem cells, hence driving tumour growth.
Using cutting-edge technologies including gene engineering techniques and 3D patient-derived cell models optimised in the lab, we can reliably model what is happening in human tumours. Preliminary data I have generated indicates that fibroblasts induce changes in epithelial cells when they are grown together. Findings from this project will help identify key proteins that are involved in colorectal cancer progression and ultimately may lead to novel treatments that can benefit cancer patients.

Aleksandra Ziubroniewicz

Integrative analysis of multiomic cancer datasets, while challenging, could enable the discovery of meaningful disease subtypes and inform clinical decision making. Current methods for analysing multiomic datasets are inadequate and fail to sufficiently address the complexity, dimensionality, prevalence of missing data, and heterogeneities that characterise different omics outputs. This project focuses on the development of a novel, fully-interpretable, adversarially learned inference model for multiomic data analysis. Specifically, we propose a method that allows for the extraction of clustering-relevant binary latent features from multiomic data, even in scenarios wherein not all data sources are available for all patients.

Isabel Burn

Exploring the relationship between tenascin-C and eosinophils in a murine model of breast cancer

Student: Isabel Burn
Supervisors: Kim Midwood, Zofia Varyova

There is increasing evidence of the role of eosinophils in breast cancer, a myeloid-derived granulocyte implicated in the innate response to parasitic infection. However, their role in the tumour microenvironment is debated, with functional heterogeneity observed between different types and stages of cancer. Additionally, the interaction between eosinophils and the extracellular matrix component tenascin-C (TNC) has been poorly characterised within the breast cancer milieu. TNC is of clinical interest given its restricted expression in healthy tissue and significant upregulation in pathology, associated with poor prognosis in cancer.

This study used 2-3 month old wild-type FVB mice engrafted with the mammary cancer cell line NT193, engineered to express high or low levels of TNC (denoted TNC+ and TNC-) to investigate the behaviour of eosinophils compared to TNC expression. Tumours were harvested at day 7 and day 18 post-engraftment to examine changes in tumours over time. Flow cytometry was used to determine infiltration of eosinophils into tumours and assess their production in bone marrow; and their spatial relationship with TNC was explored through immunofluorescence staining of solid tumour tissue.

Preliminary data demonstrate that at the day 18 timepoint, fewer eosinophils infiltrate tumours as a proportion of total immune cells in TNC- tumours compared to TNC+ controls, whereas at day 7 no difference was observed. The levels of eosinophil production and maturation in bone marrow was not altered. Additionally, a significantly greater proportion of eosinophils were found on TNC tracks at day 18 compared to day 7 for the TNC- tumours, which was not reflected in TNC+ tumours. This suggests that knocking down TNC in mammary tumours results in reduced eosinophil infiltration into tumours, but greater localisation to the TNC tracks. Overall this study demonstrates an influential relationship between TNC and eosinophils in the progression of breast cancer, with potential prognostic value.

Madeline Carey

Madeline Carey, Peter Wing, Jiyeon Ha
CAMS Oxford Institute (COI)

BK virus (BKV) is a small dsDNA polyomavirus which ubiquitously infects approximately 90% of the human population. BKV primarily replicates in the renal tubular epithelia of the kidney, where infection is often asymptomatic in an immunocompetent host. However, when the immune system is compromised or suppressed, particularly in kidney-transplant patients, BKV infection can reactivate resulting in severe health complications. BKPyV-associated nephropathy (BKVAN) can lead to tubular interstitial damage and ureteral stenosis and is a leading cause of transplant rejection. The vascular architecture of the kidney coupled with significant heterogeneity in blood perfusion and oxygen consumption predisposes the organ to a significant variation in local oxygen tension, particularly between the inner and outer medulla. The hypoxia inducible factor (HIF) signalling axis is responsible for governing the cellular response to oxygen by coordinating transcriptional responses to promote cell adaptation to hypoxia. As BKV exhibits transient replication in the airway, the proposed high oxygen site of virus entry, yet persistently replicates in the reduced oxygen environment of the renal tubules, we hypothesised that HIF signalling may define this tropism. Culture of BKV-infected kidney cell lines in oxygen tensions comparable to renal physiology potentiated viral replication. Further, infection of kidney cells chronically overexpressing HIF augmented viral replication demonstrating a direct role for HIF in enhancing BKV replication. Importantly we noted that hypoxic culture promoted BKV replication in interferon (IFN) deficient cells but suppressed replication in cells with functional IFN signalling, highlighting an underappreciated interplay between HIF signalling and IFN regulation of BKV replication. These data highlight the importance of understanding the context of BKV replication and may support the development of novel therapeutics to address a serious clinical problem which currently lacks effective treatment.

Dingase Dula

Analysing the Impact of Aging on Antibody Responses to COVID-19 and Influenza Vaccine Immune Challenge

Dingase Dula[1], Khiyam Hussain[2], Charandeep Kaur[2], Jamie Fowler[2], Katrina Pollock[2]

1. Nuffield Department of Surgical Sciences, MSc in Integrated Immunology
2. Oxford Vaccine Group, Department of Paediatrics

Mouse models of aging have shown that reduced lymph node and splenic follicles, decreased expression of CXCL13 and CXCR5, and impaired B cell migration correlate with weak and short-lived antibody responses to vaccines. Understanding the molecular mechanisms of human aging can improve vaccine design. This study, part of the LEGACY03 trial, aimed to simultaneously assess serum IgG responses in adults receiving a COVID booster and seasonal influenza A and B vaccines. This observational, experimental, randomized, open-label study involved 15 healthy adults aged 18-45 and 5 adults aged ≥65 years. Participants received a single intramuscular dose of each vaccine at baseline, and serum anti-Wuhan spike IgG, anti-Darwin strain HA IgG, and anti-Phuket strain HA IgG were measured pre-vaccination and at 7, 14, 28, and 84 days post-vaccination. CMV serostatus was also determined at baseline. ELISAs followed the OVG protocol. NUNC ELISA plates coated with protein were incubated at 4°C overnight. Following washing with PBS Tween-20 and blocking with Blocker ™ Casein, serial dilutions of test and reference serum were added in triplicate and duplicate, respectively. Samples, standards, and controls were incubated for 2 hours. After washing, goat anti-Human IgG (γ-chain specific)-Alkaline Phosphatase antibody was added and incubated for 1 hour. Following another wash, p-nitrophenyl phosphate substrate was added, and plates were read in a microplate reader. Gen5 ELISA software measured optical densities at 405 nm and calculated antibody concentrations. Statistical analysis used GraphPad PRISM. CMV seroprevalence was 45%. Pre-vaccination differences between age groups were not observed, but post-vaccination IgG titres were consistently higher in younger adults. Peak titres occurred earlier in the younger cohort (Day 14) compared to the older cohort (Day 28). Antibody titres remained elevated at D84 in both age groups. Concurrent COVID-19 and influenza vaccination resulted in higher serum antibody responses in younger than older individuals.

Chiomah Ezeomah

New World Arenavirus Vaccine Development

Chiomah Ezeomah, Sarthak Sahoo, Rachel Anslow, Marie Lucienne, Lee Page, Manuel Gannon, Alex Sampson, Sagida Bibi, Daniel Wright, Teresa Lambe

New World arenaviruses such as Junin, Machupo, Guanarito, Chapare, and Sabia viruses are etiological agents of hemorrhagic fevers with 15-50% case fatality rates and are potential bioterrorism agents. Candid#1 vaccine, approved for use against JUNV only in Argentina, is a live attenuated vaccine with a risk of reversion to wild-type capable of causing fatal illness in vaccinated individuals. There is therefore a need for an improved vaccine. Furthermore, it is essential to explore vaccine regimes that are cost-effective, ideally also cross-protective.
The glycoprotein complex of arenaviruses is the sole antigenic determinant associated with humoral immune responses on the virus' surface. Here, we have tested numerous vaccine regimens using viral-vectored or mRNA vaccine platforms that encode the GPC from these viruses.
Six mice per group were vaccinated as part of a prime-boost regime with ChAdOx1 or mRNA constructs encoding the GPC from Junin or Machupo. Additional multivalent constructs encoding the GPC from multiple New World arenaviruses were also tested. Serum samples were analyzed using enzyme linked immunosorbent assay (ELISA) to detect antibodies against Junin GPC.
A linear regression model was used to determine the IgG response level in each group. The data was not normally distributed, thus we performed a log10 transformation of IgG levels. Two-way ANOVA was used to assess the overall differences in IgG levels in each group. Pairwise comparisons were performed to evaluate the differences in IgG levels between pairs of vaccine candidates and p-values were adjusted for multiple comparisons by controlling for family-wise error rates using Tukey's method. Analysis was performed in R. The results show statistically significant differences in mean IgG levels specifically after prime-boost vaccination in ChAdOx1 Junin compared to ChAdOx1 controls ($p<0.001$) and mRNA Junin compared to mRNA controls ($p<0.001$).

Romane Henninger

Rheumatoid arthritis (RA) is a systemic autoimmune condition, in which immune cells infiltrate the synovial joints, especially in the hands, feet and knees, leading to swollen and painful joints. Stromal cells play a key role in driving RA pathogenesis. In particular, fibroblast-like synoviocytes aid immune cell recruitment and invade the surrounding cartilage and bone, causing irreversible damage.
RA has a predilection for particular anatomical sites: “inflammation-location”, exemplified by the joints of the hand. While the proximal interphalangeal (PIP) joints are susceptible to RA, the distal interphalangeal (DIP) joints are spared. Finding an explanation to this striking clinical observation might give insights into the pathogenesis of RA.
Single-cell RNA sequencing of embryonic finger joints previously identified a seminal population of PI16+ fibroblasts, enriched in PIP joints. Initial image analysis suggested that these cells occupy a unique spatial niche in the tendon near blood vessels. I developed a pipeline enabling robust characterisation of the spatial distribution and colocalization of cells on immunofluorescence images of healthy developing fingers. I compared different ways of extracting single cell data, and tailored a spatial statistics tool to the analysis of the structure of the joints. This confirmed the increased abundance of PI16 fibroblasts in the PIP joints, as well as the colocalization of PI16+ fibroblasts and blood vessels. The colocalization was stronger in the PIP joints. PI16 fibroblasts might interact more intimately with blood vessels at this site, potentially promoting vessel leakage and immune cell infiltration. In RA, tendon inflammation occurs early and may be involved in the initiation of the disease. Therefore, differential interactions between PI16 fibroblasts and blood vessels across the joint sites could explain their differential susceptibility to inflammation. Thus, our spatial analysis tool has characterised a cellular interaction that may prove important for the progression from early to established RA.

Andreas Huysman

T-cell activation kinetics and immune system ageing in type 2 diabetes

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The number of people living with type 2 diabetes (T2D) is rising globally. T2D increases the risk of infection-related morbidity and mortality. Studies on the immune system of people with T2D have demonstrated abnormalities in the function and metabolism of several immune cell populations but data on T cells is scarce. Recent studies have identified parallels between ageing and diabetes including an increase in senescent T cells in T2D. Understanding how T cells are affected by T2D is important in the context of designing vaccines, immunotherapy and other treatments for this population.
Unpublished data in our group shows impaired activation of T cells from T2D patients *in vitro*. In this study, we focus on exploring kinetics of activation, proliferation and nutrient transporter expression in T cells from people with and without T2D upon stimulation *in vitro*.
We have designed an in vitro stimulation protocol for T cells by culturing peripheral blood mononuclear cells (PBMC) with an optimised concentration of surface bound anti-CD3 and soluble anti-CD28 antibodies in order to polyclonally activate T cells. We then applied this protocol to PBMC from people with T2D and healthy age/sex matched controls and stimulated cells for up to 5 days. At the end of the stimulation period, cells were analysed by flow cytometry for markers of T cells subsets and expression of activation (CD69, CD25) and proliferation (Ki-67) markers and nutrient transporter (CD98, Glut1, CD36).
Furthermore, we will explore the expression of senescence markers, proportion of memory T cell subsets and recent thymic emigrants in diabetic and non-diabetic donors. The data will be integrated with available demographic and clinical parameters including age, sex, HbA1c and diabetes treatment to explore relationships to T cell function.

Julia Karjalainen

Visualising the formation of the nervous system and the interactions with mast cells in the developing lung.

Julia Karjalainen, Luca Verger, Franze Progatzky.

Mast cells (MCs) are tissue-resident immune cells that reside across all organs. While they are primarily known for their role in allergy and anaphylaxis, they have many unappreciated roles such as promoting angiogenesis, wound healing, protection against pathogens and interacting with the nervous system. Indeed, MCs and nerve fibers are closely aligned in many organs throughout the body where they have close functional relationships during health and disease.
Like macrophages, tissue resident MCs are formed during foetal development, as early as from the foetal yolk sac. The crucial roles of tissue-resident macrophages in development are already well characterised, as they support organogenesis, angiogenesis and neurogenesis. However, the developmental contribution of MCs remains still to be determined. Sharing similar ontogeny, could MCs also have important developmental functions as demonstrated by macrophages? Since MCs can interact with the nervous system during adulthood, similar functional relationships may occur during foetal development.
In this project, we employed cutting-edge optical tissue clearing and high-resolution 3D light-sheet imaging to study the murine lung neuroglial development across different in-utero and neonatal time points. The use of Sox10icreERT2:Rosa26tdTomato transgenic mouse which expresses the red fluorescence protein tdTomato in all lung Sox10-expressing glial cells allowed us to visualise the neuroglial network development and expansion. In addition, 2D confocal imaging with MC staining using fluorochrome-labelled antibodies was applied to demonstrate the anatomical positioning of lung MC in relation to the neuroglial network. Lastly, we quantified MC numbers at different timepoints of the developing lung using flow cytometry.
In summary, my project provides novel spatial and temporal insights into the development of the pulmonary neuroglial network in mice and in relation to MCs.

Sacha Moore

Investigating sexual dimorphisms of differential matrix expression in inflammatory disease.

Males and females exhibit different prevalences of inflammatory diseases due to various factors, including genetic disparities, hormonal influences, and behavioural patterns.
Previous research from our laboratory has revealed that expression of tenascin-C (TNC), an extracellular matrix (ECM) protein elevated in inflammatory conditions such as rheumatoid arthritis (RA), differs between sexes. The ECM, a complex network of molecules produced by synovial fibroblasts, regulates cellular behaviour and tissue homeostasis, by dictating macrophage phenotype and activation status. This project aims to uncover whether matrix gene expression on the X and Y chromosomes, and hormonal regulation of transcription, contributes to inflammatory diseases and to assess how estrogen impacts levels of ECM proteins in synovial fibroblasts.
Bioinformatic analyses identified a subset of matrix genes associated with sex chromosomes, shedding light on the genetic basis of sex-specific disease mechanisms. Bioinformatics of estrogen response elements (ERE) highlighted a large proportion of estrogen responsive matrix. We further mapped these EREs to the promoter region of TNC gene, providing insights into how estrogen directly regulated TNC expression. In parallel, the effects of estrogen on matrisomal gene expression were quantified by RT-qPCR unveiling modulation of ECM proteins in synovial fibroblasts from synovial sarcoma and RA patients. Further, levels TNC were quantified in conditioned media from these cells using ELISA targeting the FN-IIIB domain. To understand the broader impact of the hormone-instructed matrix on immune phenotypes, fibroblast-macrophage co-cultures provided insights into the interplay between hormonal signals and immune regulation in the matrix environment. Elucidating the mechanisms underlying these sexual dimorphisms in ECM expression could offer new perspectives into the differential susceptibility to inflammatory conditions and inform personalised therapeutic approaches.

Jennifer van Heerden

The role of matrix metalloproteinase inhibition on the interleukin-5 mediated activation of eosinophils in T2-high asthma

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Eosinophils contribute significantly to airway inflammation and exacerbation in Type 2-high bronchial asthma, with interleukin-5 (IL-5) the key cytokine mediating eosinophil priming, activation, and survival. Matrix metalloproteinases (MMPs) have been reported to be increased in eosinophilic asthma and have been implicated in the pathogenesis of severe asthma by mediating airway remodelling. However, the role and significance of MMPs in the IL-5-mediated eosinophil activation and functioning is still poorly defined. In this study we used GM6001, a broad-spectrum MMP inhibitor, to assess the effect of *in vitro* MMP inhibition on the activation and functions of peripheral blood eosinophils from patients with eosinophilic asthma. We found that GM6001 prevented the morphological changes associated with eosinophil activation, reduced the release of eosinophil granule protein, and inhibited eosinophil migration induced by IL-5. However, GM6001 did not alter the IL-5-induced reduction of eosinophil apoptosis. In addition, we found that GM6001 blocked the activation of eosinophils by the other beta common chain cytokines including IL-3 and granulocyte-macrophage colony stimulating factor (GM-CSF), preventing the downregulation of CD62L, a marker of eosinophil activation. In conclusion, MMP inhibition prevents the activation, chemotaxis and degranulation of eosinophils, suggesting an integral role of MMPs in eosinophil priming and functional capacity. A better understanding of the relationship between MMPs and eosinophil activation may provide insight into future therapeutic targets and biomarkers in eosinophilic asthma.

Ziyue Yuan

Hepatitis B virus (HBV) is a major health problem with more than 250 million cases worldwide and 880,000 deaths per year from end-stage liver diseases including cirrhosis and hepatocellular carcinoma. As a hepatotropic virus, HBV exploits the tolerant environment in the liver to sustain a persistent chronic hepatitis B (CHB). The replication dynamics of HBV within the liver exhibit both spatial and temporal variability across different stages of the disease, but little is known about the intrahepatic processes behind it. We postulate this diversity reflects localized resistance mechanisms, both hepatocyte-intrinsic and mediated by liver-resident immune cells. Spatial transcriptomics, in contrast to bulk and single-cell sequencing studies that lack architecture information, offers a promising approach to studying the gene expression patterns between HBV-infected hepatocytes and the surrounding environment. Leveraging GeoMx Nanostring Digital Spatial Profiler (DSP), we profiled hepatocellular and hepatic microenvironment changes in response to CHB in 14 human liver biopsies. Our multiplex immunofluorescence staining showed heterogeneous HBV core and surface antigen expressions across the cohort, manifesting in both the cellular and subcellular levels. Ongoing work is focusing on characterizing the feature biological pathways, transcriptomic signatures and cellular composition in these samples, and our research aims to provide new insights into transcriptional landscapes of persistent HBV infection and to uncover the mechanisms underlying insufficient immune responses, a crucial step for advancing towards curative therapies.