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Wessex Medical Research

Funding research to fight disease

The newsletter of WESSEX MEDICAL TRUST

Autumn 2024

The impact of our Innovation Grants

Chairman of Trustees, Professor Sir Charles George, writes:

During the past year we were assessed externally by the More Partnership Ltd who confirmed the importance of our Innovation Grants. Here are two examples:

Professor Sir John Iredale

Professor John Iredale became Knight Bachelor in the 2023 New Year Honours. Sir John graduated Bachelor of Medicine (with honours) from Southampton in 1985. After several posts in the NHS, he became a member of the liver research group and embarked on a career in research. He became a Medical Research Council (MRC) clinician scientist in 1994 and received his first grant from Wessex Medical Research in 1996 for *"An investigation into the regulation of scar forming cell numbers in liver fibrosis"*.

Sir John told us that *"for most researchers the toughest hurdle to overcome is securing the first grant. But that grant can be the launchpad for a lifetime of discovery"*.

Sir John's career progressed in Southampton with the award of a personal Chair and a second grant from WMR that enabled the employment of a research fellow and joint working with groups in Germany and the USA. This resulted in the publication of 3 papers in major journals. In 2009 he moved to Edinburgh as Director of the MRC Centre for inflammation research and became Dean of the medical school. He moved to Bristol as Pro Vice-Chancellor Health in 2015 and later served as interim Executive Chair of the Medical Research Council.

We send him our best wishes and congratulations on his many achievements which include Fellowship of the Royal Society of Edinburgh and Fellow of the Academy of Medical Sciences.

Professor Mark Cragg

In September 2024 I had the pleasure of seeing **Professor Mark Cragg** admitted to Fellowship of the Academy of Medical Sciences. Mark is Professor of Experimental Cancer Biology at Southampton's Centre for Cancer Immunology. His career began at the University of Bath where he gained a first class honours degree in Biochemistry. His course included two placements: one in Industry (Glaxo Wellcome) the other at Northeastern University in Boston. He moved to Southampton in 1994 to pursue a PhD in Immunology and Immunochemistry.

Supervised by Professor Martin Glennie, he focused on the B-lymphocyte antigen CD20 which became a therapeutic target for B-cell malignancies. In 2004 we awarded him an Innovation Grant for *"Transcriptional changes in lymphoma cells following anti-CD20 mAb"*. This helped him to *"learn how to write grants and formulate experimental plans"*. He then obtained a Fellowship from the Leukaemia Research Fund at the world-famous Andreas Strasser laboratory at the Walter and Eliza Hall Institute in Melbourne. He returned to Southampton in 2007 to start his own group in the School of Cancer Sciences. In 2018, alongside the other members of the Antibody and Vaccine Group, he took residence in the newly erected Centre for Cancer Immunology.

Although his research has several different strands he continues to analyse how the immune system interacts with cancer cells and leads to their destruction. He then seeks to translate these findings into better treatments for patients. Mark is also an advocate for the Centre's excellent PhD programme. Wessex Medical Research is proud to have provided joint funding with the Cancer Immunology Fund for six PhD studentships to date and I am pleased that the Trustees agreed to fund a seventh at their October 2024 meeting.

BUDGET October 2024—Inheritance Tax

REMEMBER: * If you give at least 10% of your net Estate to charity in your Will, you may qualify to pay IHT at the reduced rate of 36%.

* Gifts to charity during your lifetime may be set off against your Income Tax liability.

** You should always seek professional advice*

The toxicity of particulate emissions from road vehicles

In 2019 we awarded a PhD studentship of £100,000 to Dr Matthew Loxham in the Faculty of Medicine (as supervisor) for a project on "The toxicity of particulate emissions from braking systems—a potential role in idiopathic pulmonary fibrosis". *His former student—James Parkin—completed his studies and was awarded his PhD in the spring of 2024. The following is a summary of his findings:*

Dr James Parkin

Exposure to airborne fine particulate matter (PM) generated by cars has been associated with an increased risk of lung and heart diseases. While exhaust emissions are often discussed, these are decreasing due to technological improvements and the increasing use of battery-electric vehicles. However, so-called "non-exhaust" PM generated from the wear of road, tyre, and brakes remains, with brake wear being the main contributor.

The goal of this PhD project was to conduct an in-depth study of PM generated from four different types of brake pads, which aimed to determine how toxic it is compared to other vehicle-derived PM types, including road wear, and diesel exhaust PM. The original plan was to generate these particles in house, and the first part of my integrated PhD included work relating to this in the National Centre for Advanced Tribology within the Faculty of Engineering. Unfortunately, when my PhD was due to start after this initial MRes year, in September 2020, access to this lab was not possible because of COVID restrictions, and waiting for availability would have delayed the project. Therefore, PM from various brake wear, road wear, and engine exhaust samples were sourced from collaborators at the Dutch National Institute for Public Health and the Environment (RIVM).

Using a cell line model of the alveolar epithelium, it was found that the toxicity of the PM types depended on the source, with dust from non-asbestos organic and ceramic brake pads proving more potent in terms of inducing pro-inflammatory responses and other markers of toxicity than diesel exhaust PM. Analytical chemistry techniques were used to elucidate the composition of the different PM types, which identified that the composition of each type was unique, but similarities were identified with brake wear generated from non-asbestos organic, and ceramic brake pads with both containing the highest concentrations of copper, zirconium, and barium. Further experiments using chelating agents with various metal-binding specificities indicated that the copper content within these PM types was responsible for driving some of the toxicity, suggesting that the reduction of copper content within these brake pads could prove a potential mitigation strategy, while further analytical chemistry work showed that copper was able to accumulate within the exposed cells. Finally, a relatively novel effect of PM exposure, in the form of a hypoxia response, was studied, whereby exposed cells appear to respond to brake wear PM as if they are deficient in oxygen, with a resulting alteration in their metabolic phenotype.

Taken together, this research suggests that brake wear PM may be a potential source of adverse health effects from vehicle emissions, even when diesel-powered cars are phased out. It also suggests that certain brake pads may generate PM which poses more of a risk to health, and therefore that there is a need to better understand how braking systems can be designed to mitigate potential adverse health effects.

This work has already been presented at a range of national and international conferences, including:

- *British Association for Lung Research summer meeting (15-minute talk, 2021)*
- *European Respiratory Society Lung Science Conference (Poster, 2022)*
- *Public Health England UKHSA Annual UK Research Review (15-minute talk, 2022)*
- *European Respiratory Society International Congress Barcelona (One 5 minute talk, one 10 minute talk, 2022—won prize for best oral presentation in the session)*
- *Inhaled Particles and NanOEH Conference 2023 (15 minute talk, 2023—won prize for best oral presentation by a PhD student)*
- *University of Southampton Faculty of Medicine Conference (2021, 2022, 2023—won prizes for best oral presentation, best pitch presentation and best poster)*

Innovation Grants

This year, we have been able to make six Innovation Grants, each of up to £20,000, to early career researchers. Details of the recipients and their particular research projects are set out below.

Dr Triana Amen

Faculty of Environmental and Life Sciences

"Molecular regulation of peroxisome formation and function in Peroxisome Biogenesis Disorders."

This project aims to unravel how mutations in these tiny structures causes severe brain damage in children.

Dr Giorgia Chiodin

Faculty of Medicine

"Investigating the consequences of immunoglobulin variable region N-glycosylation in Burkitt lymphoma (BL)."

The study will use computational and biochemical techniques to diagnose and improve the treatment of this aggressive disease.

Dr Ben Gaastra

Faculty of Medicine

"The sphingosine-1-phosphate signalling pathway and outcome after aneurysmal subarachnoid haemorrhage (SAH)."

SAH is often fatal but survivors can suffer life-changing disability. SIP may be critical to the outcome of a SAH. Levels of SIP will be measured in the cerebrospinal fluid taken from 140 SAH patients and correlated with their outcomes.

Dr Carmen Jacob

Faculty of Medicine

"Haemolysis in Multiple Sclerosis (HIMS) pilot study."

Red Blood Cells (RBC's) contain Haemoglobin (Hb) but if this pigment is liberated it can be harmful to nerve cells. This study will test whether RBC's from patients with MS are prone to leak Hb when they are exposed to mechanical stress.

Dr Nela Nikolic

Faculty of Environmental and Life Sciences

"Phage therapy to treat urinary tract infections."

Many urinary tract infections are caused by antibiotic-resistant bacteria. The use of phages (bacterial viruses) offers a promising alternative. In this project we will challenge a collection of bacterial strains with different types of phages to determine their efficacy.

Dr Bonnie Ng

Faculty of Medicine

"Using single cell RNA sequencing and proteomics to uncover novel immunotherapeutic targets for implantation disorders."

For a successful outcome the embryo must implant in the lining of the womb. Otherwise miscarriage can result. Uterine natural killer cells are important in this process. So, they will be studied in women both with and without a history of recurrent miscarriages.

PhD Studentships

We are pleased to report that in the Spring of 2024 we were able to award four PhD studentships. The students have now been recruited and began their studies on October 2024. Details of the projects are as follows:

"Spatial Transcriptomic Analysis of Immune Cell: Cancer Cell Interactions in a 3D Lymph Node Model."

Patients who become resistant to current therapy for either chronic lymphocytic leukaemia or non-Hodgkin lymphoma have a poor survival. Their lymph nodes are the critical tissue in which cancerous cells survive, proliferate and become resistant to attack by the body's immune system. This problem will be studied in samples taken from patients using cutting edge laboratory techniques to identify the best way of overcoming resistance.

Principal supervisor **Dr Matthew Blunt,** *Senior Research Fellow, Cancer Sciences*

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ASSOCIATION OF MEDICAL RESEARCH CHARITIES

We are proud to be a member of the Association of Medical Research Charities and our last regular Peer Review Audit took place in 2020.

amrc
PEER REVIEW AUDIT
2020

"Establishing 3D culture model systems to study how Inflammation subverts control of cell fate during carcinogenesis."

Epithelial cells provide a first-line of defence against viruses and bacteria. They respond by producing interferon which limits viral replication and mobilises the immune system. However, chronic inflammation increases the risk of cancers developing through ways that are not yet clear. The research will use cellular models to study how uncontrolled signals from interferon can corrupt the differentiation of tissues and may trigger the development of cancer.

Principal supervisor **Professor Tim Fenton**
Associate Professor in Cancer Biology

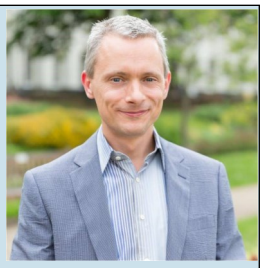
"Investigating human T cell development in lymph nodes"

Special white blood cells called T cells are important for fighting infections and for storing memory of previous infections. However, poorly controlled T cell responses can lead to the production of autoimmune diseases including Multiple Sclerosis and Inflammatory Bowel Disease. The project will investigate how disease-causing T cells differentiate in human lymph nodes removed during surgery. Comparisons will be made between normal nodes and ones from patients with Crohn's disease and between T cells circulating in the blood with those in lymph nodes.

Principal supervisor **Dr Emily Gwyer Findlay**
Associate Professor in Biomedical Sciences

Jointly funded with Rosetrees Trust.

"Fatigue risk management in healthcare: a wake-up call."



Fatigue amongst healthcare professionals presents a risk to both staff and patient safety. Pressures on staffing and workload coupled with working long hours and nights create fatigue in front-line practitioners. Tired people make mistakes and a significant number of practitioners have had crashes or near-misses when driving home from night shifts. We need to know more about clinical errors caused by fatigue. A survey of clinicians will be carried out to assess the issue and data will be collected from wearable devices to examine both actual fatigue and sleep patterns.

Principal supervisor **Professor Mark Young**
Professor of Human Factors in Transport

Jointly funded with a Tizard grant.

Hope
FUNDING RESEARCH FIGHTING DISEASE for Guernsey

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