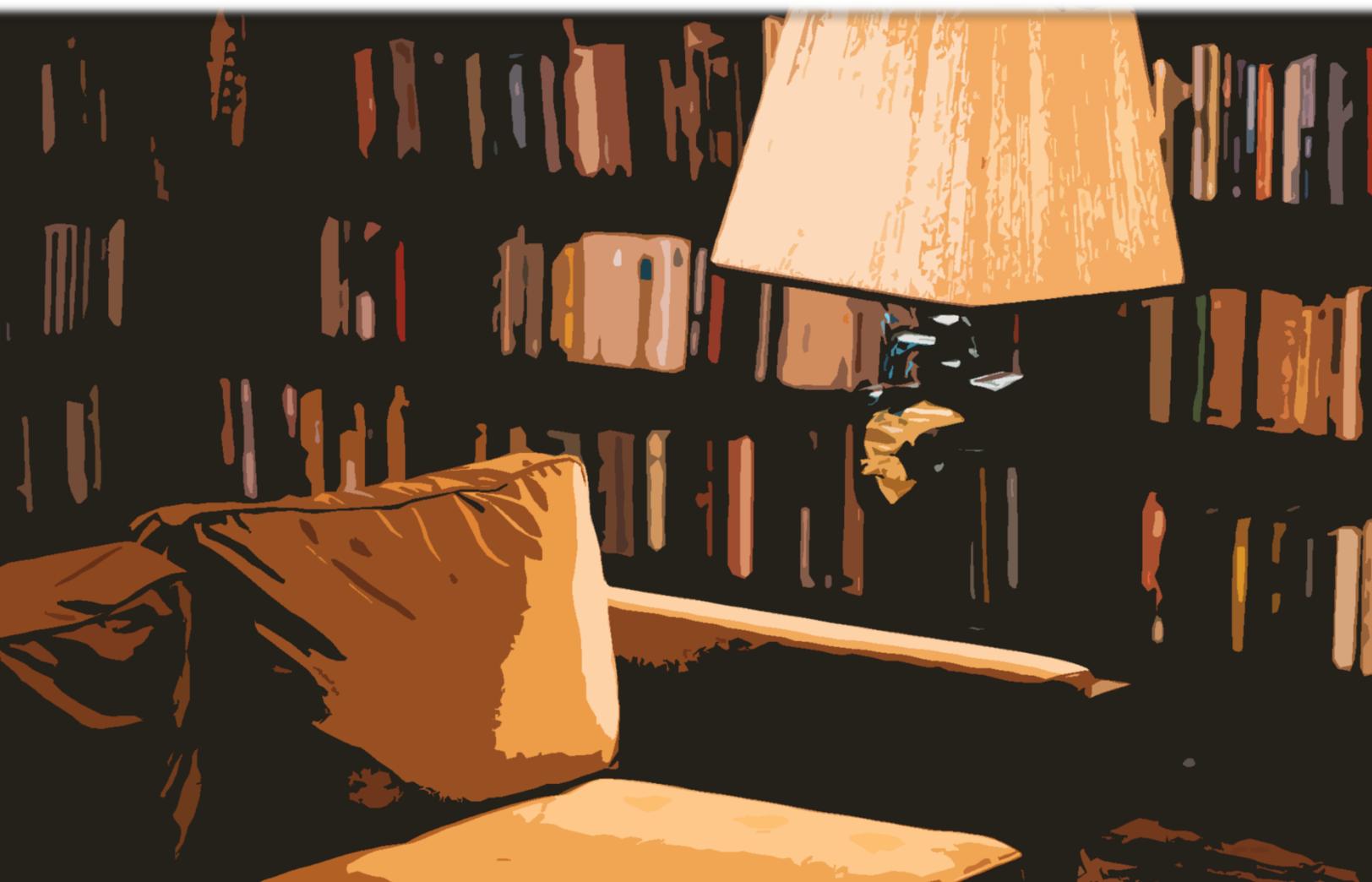


# ICAT Retreat 2022

## Abstract booklet



## Understanding the Immune Response to Influenza Vaccination in Patients with Haematological Disorders

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5. University College Cork

### Scientific abstract

#### *Background*

Infection with influenza virus is associated with significant morbidity and mortality in immunosuppressed patient populations. Vaccination remains the most effective prevention strategy, however vaccine response in those on immunosuppressive therapies for haematopoietic stem cell transplant, solid organ transplant and other biologic therapies is reduced and inconsistent compared to young, healthy members of the population. Furthermore, this patient cohort is frequently excluded from clinical trials evaluating vaccine responsiveness, and so outcomes cannot be extrapolated. Cellular immune response to vaccination has not been well studied and so its role is poorly understood

#### *Aims*

The aim of this study is to explore the immune function changes that occur following chemotherapy and haematopoietic stem cell transplant and to examine predictors of immune response to influenza vaccination in this cohort

1. To characterise humoral and cellular immune response that occurs following vaccination and examine the correlation between the two
2. To examine the patient and disease-specific factors that are associated with vaccine response
3. To explore the influence of other viral exposures

#### *Methods*

This study will be conducted as a single-site prospective observational study and will include adult patients who have undergone haematopoietic stem cell transplant at least 4 months prior to vaccine administration attending St James' Hospital, Dublin. Samples will be drawn at day 0, 7, 28 and 180 for whole blood and serum and analysed for antibody response including haemagglutinin inhibition titres, cellular immune response including CD4 and CD8 T cell response to influenza peptides, innate T cell responses, NK cell responses, and compared with healthy controls. The study will also characterise immune profile changes and their association with vaccine response, with a particular focus on CMV and EBV. Clinical outcomes will be assessed at study visits assessing for intervening episodes of influenza-like illness

#### *Impact*

The outcomes of this study will inform vaccination strategies and vaccine development in this population of at-risk patients

### Lay Summary

Medications used to treat certain medical conditions such as cancer, autoimmune and inflammatory conditions alter the function of the immune system leaving patients at higher risk of developing infection and complications of infection. Vaccines have been one of the most important advances made in medicine, protecting populations against developing infection or severe complications of infection. It is known however that patients receiving immunosuppressive medications do not respond to vaccines as well, or as consistently, as those with healthy immune systems. My research aims to characterise how patients receiving these medications respond to influenza vaccine. Influenza is a common, seasonal respiratory virus. It is a cause of significant morbidity and mortality worldwide, particularly in this patient group, and has potential to cause future pandemics. The results of this research will inform vaccination strategies for these patients in the future.

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Ellen Walsh

Positive feedback

Constructive feedback

Any other comments

## Why do kidney transplants fail so early in young people?

Michael Corr<sup>1</sup>, Gareth McKay<sup>1</sup>, Jane English<sup>2</sup>, Matt Griffin<sup>3</sup>, Peter Maxwell<sup>1</sup>

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### Scientific abstract

#### *Background*

The burden of End-Stage Kidney Disease in young people is severe. Renal transplantation is the gold-standard treatment. Recipients <30 years old have the best short-term outcomes following transplantation but paradoxically have the worst long-term graft survival rates. Why kidney transplant fail so early in young people is poorly understood.

#### *Aim*

To explore whether the difference in long-term kidney transplant outcomes between younger (< 30 years old) vs older (≥30 years old) recipients is associated with variations in epidemiological risk factors, proteomic profiles and subsets of immunological cell types.

#### *Objectives*

- 1.) Identify epidemiological factors associated with long-term kidney transplant outcomes and variation in these between younger and older recipients.
- 2.) Investigate variation in proteomic profiles between younger recipients with/without evidence of immunological injury and comparing with older recipients with/without evidence of immunological injury.
- 3.) Investigation of subset variance of T-regulatory, B-regulatory and natural killer cells between recipients <30 and ≥30 years old with functioning transplants.

#### *Methods*

Study-1: Data will be extracted from a prospective clinical database of renal transplant recipients. Statistical analysis will identify variation in transplant graft outcome and demographic associations with graft loss.

Study-2: Using the OLINK 384 inflammation platform, proteomic profiling of stored samples from young recipients with (n=50) and without (n=50) evidence of immunological injury will be performed. A control group of older recipients with (n=50) and without immunological injury (n=50) will enable cross-sectional comparisons to identify proteins associated with immunological injury in both age categories.

Study-3: Patients with functioning transplants will be recruited (n=25 <30 years old, n=25 ≥ 30 years old) to provide serum samples. High-dimensional multi-colour flow cytometry will enable subset analysis of T-regulatory, B-regulatory and Natural Killer cells identifying variation between younger and older recipients.

#### *Conclusion*

This study will assist in the understanding of why long-term outcomes in younger transplant recipients are poorer. The research may help identify ways of risk stratifying for immunologically mediated transplant loss.

### Lay Summary

Kidney transplantation is the best treatment for people with end-stage kidney disease; providing improved quality of life and much longer survival. Unfortunately, younger people appear to be at higher risk of losing their transplant; having a devastating impact on their health. It remains unclear why kidney transplants fail so early in young people.

The aims of my PhD are: 1.) Identify the reasons for kidney transplant loss in younger people and determine whether other details about their health can be linked to their increased risk of transplant loss. 2.) Use new technology to measure difference in proteins (proteomics) in transplant recipients to better understand their increased risk of transplant failure. 3.) Measure different types of cells that affect transplant outcomes to see if their expression varies between younger and older transplanted patients

I hope by better understanding why young people suffer from earlier transplant loss we will be able to improve their care and ultimately reduce transplant loss.

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Michael Corr

Positive feedback

Constructive feedback

Any other comments

**Elucidating the immunometabolic and genomic characteristics in young onset gastroesophageal cancers**

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3. Queens University Belfast, School of Medicine
4. Royal College of Surgeons, School of Pharmacy
5. Trinity Translational Medicine Institute
6. Trinity St James's Cancer Institute

**Scientific abstract***Background*

The incidence of gastroesophageal cancer (GC) is significantly rising in younger patients despite incidence declining overall. These patients present more frequently with advanced disease and an overall worse prognosis for reasons we do not fully understand. This is currently an acute unmet clinical need with current projections expecting incidence of early onset gastroesophageal cancer (EOGC) cases to increase significantly.

*Aims*

1. Identify the overall trends in incidence and outcomes in EOGC (<50 years at diagnosis), in an all-Ireland approach
2. Identify the genetic and molecular profiles that predominate in EOGC
3. Assess the immune metabolic profiles in normoxic and hypoxic tumours and evaluate whether manipulation of the hypoxic environment alters these processes in EOGC.

*Methods*

Aim 1 is a retrospective study looking at patient data over 2 decades (1999-2019) from the National Cancer Registry Ireland and Northern Ireland to create a whole Ireland map on incidence in EOGC as well as outcomes by survival, age subgroups (<50, 50-69 and >70), geographic location (North vs South) and socioeconomic status.

In Aim 2 we are going to interrogate publicly available genomic datasets for differential expression, mutational burden, and mutational signatures, specifically comparing differences by age subgroups as above.

Aim 3 is a prospective study where tumour biopsies will be cultured under normoxic/hypoxic conditions. We will measure their real time metabolic profiles, analyse their protein secretome and their immune profiles. Hypoxic tumour biopsies will be cultured with/without Oxygel (biocompatible thermoresponsive hydrogel) and we will measure metabolic and immune profiles.

*Discussion*

This project will increase our understanding of the underlying biological mechanisms driving the growing incidence of gastrointestinal cancers in young adults and will inform the development of new strategies for prevention, early detection and treatment.

**Lay Summary**

Gastrointestinal cancers are on the rise in people under 50 years of age. These patients tend to present with late-stage disease and have poorer outcomes than older patients for reasons we do not fully understand. This is an acute unmet clinical need with projections expecting the incidence of early gastric cancer cases to increase significantly. In this project, we will clarify if the incidence is rising in these patients on the entire island of Ireland. We will examine changes in DNA looking for differences compared to older adults. Lastly, we will look at biopsies in order to identify the characteristics of the microenvironment in these early-onset tumours. We will look at the metabolic (oxygenation status, energy and nutrient requirements) and immune profiles in these tumours. This project focuses on identifying genetic, immunologic and tumour characteristics in order to deliver new tools to improve the clinical management pathway for this young cancer cohort.

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Oana Deac

Positive feedback

Constructive feedback

Any other comments

**Linking structural changes to functional outcomes in non-arteritic anterior ischaemic optic neuropathies**

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2. Icahn School of Medicine, Mount Sinai Hospital, New York
3. Lambe Institute for Translational Research, University Hospital Galway
4. International Centre for Neuromorphic Systems, University of Western Sydney
5. School of Natural Sciences, University of Galway

**Scientific abstract**

Anterior ischaemic optic neuropathies (AION) result in devastating loss of vision for sufferers. Prognosis is highly variable. After 2 years approximately forty percent of patients with non-arteritic AION (NA-AION) will have improved to a variable extent, thirty percent will have had no improvement and thirty percent will have lost even more vision. However, we do not know which patients will fall into what category until the disease has run its course. As a result we are unable to appropriately assess the effect of our interventions. Furthermore, up to 25% of patients will develop sequential involvement of the other eye but we have no way of predicting who is at risk of this. Consequently, results of clinical trials to date have been underwhelming.

One of the key areas of research in neuroscience is the elucidation of the relationships between structural changes and functional outcomes. In the eye it is made easier by being able to directly visualise tissues using techniques such as optical coherence tomography (OCT), fundal photography and angiography. Functional outcomes can be assessed using visual acuity, perimetry and contrast sensitivity.

This project aims to link objective, structural changes at the optic nerve head to functional visual outcomes and to explore how these relationships can be utilised to develop a predictive algorithm to determine clinical outcome.

*Objectives*

1. Develop new structure-function relationships via a machine learning approach and utilise these to sub-classify patients with NA-AION at presentation
2. Predict sequential involvement of fellow eye with NA-AION
3. Investigate the application of a novel OCT post-processing algorithm for improved feature resolution and characterisation at greater depths within the optic nerve head.

**Lay Summary**

NA-AION is a disease characterised by sudden, painless loss of vision. We know very little about the risk factors and mechanisms of this disease and what makes a person more likely to go on to develop it in their other eye as well.

Several trials have sought to explore potential therapies for this condition but they have suffered from an inability to correctly identify at presentation which patients were likely to get better naturally and which ones were going to have a poor prognosis.

Using artificial intelligence (AI), this project aims to relate the physical changes at the nerve to visual outcome so that:

- patients who are at risk of this disease can be identified at an earlier stage;
- patients who have one eye involvement and are likely to have sequential involvement of the other eye can be identified at an earlier stage;
- patients can be stratified based off their likely natural outcome at the time of presentation so that in the future the impact of therapies in clinical trials can be better delineated.

The final aspect of this project is to develop a new algorithm to analyse scans of the optic nerve to get a better insight into what is going on in the optic nerve during the course of these conditions.

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Brian Woods

Positive feedback

Constructive feedback

Any other comments

**Cognitive Impairment in People who are long-term Homeless: Evidence and Relationships (CIPHER)**

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3. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden
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5. School of Medicine, Trinity College Dublin, College Green, Dublin 2
6. St James’s Hospital, James’s Street, Dublin 8

**Scientific abstract***Background*

Social exclusion & poverty drive the accumulation of allostatic load and result in adverse health outcomes & increased mortality, with an established dose-response relationship. The homeless represent a section of society in whom the cumulative effects of allostatic load resulting from lifelong adversity and social exclusion are maximally seen. The Irish homeless population can serve as a model for assessing the effects of social exclusion on the brain. The average age of a homeless person in Ireland is 30.5, with an estimated prevalence of cognitive impairment (CI) of 42% and a median age at death of 44 for men and 36 for women. Studying the characteristics, associations and potential mechanisms of early CI in the homeless will provide information to inform local policy and practice and will further understanding of the effects of social exclusion on the brain.

*Hypothesis*

Social exclusion & homelessness, mediated by traumatic brain injury and drug addiction negatively impacts cognitive function, resulting in neurodegeneration & structural brain abnormalities.

*Aims*

- (1) To characterise the patterns of cognitive impairment in European Typology of Homelessness and Housing Exclusion (ETHOS) Category 1-3 homeless adults in Ireland.
- (2) To identify the associations of cognitive impairment in ETHOS Category 1-3 homeless adults in Ireland.
- (3) To suggest potential mechanisms driving cognitive impairment in ETHOS Category 1-3 homeless adults in Ireland.

*Methods*

A case-control study will be performed. Detailed demographic data will be collected & participants will be comprehensively neuropsychologically assessed to retrospectively identify associations of CI in the homeless & to characterise their cognitive deficits. Magnetic Resonance Imaging (MRI) will be performed to assess volumetrics and burden of white matter hyperintensities: potential neuroimaging associations of CI. To suggest a potential mechanism, serum biomarkers of neurodegeneration and blood brain barrier function using delayed-contrast enhanced MRI will be assessed.

*Impact*

This project will be the first to couple comprehensive neuropsychological assessment of a homeless population with structural MRI outcomes whilst assessing biomarkers of neurodegeneration & blood brain barrier integrity to suggest a potential mechanism.

**Lay Summary**

Social exclusion is a term used to describe the relegation of a person or group of people to the fringes of society. It is often driven by poverty and results in difficulties in accessing the opportunities and resources such as housing and healthcare that may otherwise be available to them. Social exclusion is associated with worse health outcomes and early death, with a dose-response relationship: the more socially excluded an individual is, the worse their outcomes. The homeless are a group of people in whom the effects of social exclusion are maximally seen, reflected in their high rates of chronic illness, cognitive impairment, and early death. I will perform a study comparing homeless individuals to healthy controls using neuropsychological tests, blood-based biomarker tests and MRI brain imaging. I aim to identify the pattern of cognitive impairment seen in this group, the associations of this impairment and to try to identify potential mechanisms driving this impairment. This information can then be used to inform health policy in Ireland and abroad, and to develop strategies to reduce health inequalities.

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Georgia Richard

Positive feedback

Constructive feedback

Any other comments

**Immune mediated factors in early (T1/T2) oral cancers and their impact on metastasis (The ADAPT study)**

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3. Department of Immunology, University of Pittsburgh, Pittsburgh, PA, USA.
4. Tumor Microenvironment Center, Hillman Cancer Center, University of Pittsburgh

**Scientific abstract***Background*

Early oral squamous cell carcinoma (OSCC) (T1/T2) is managed with primary surgery with curative intent but 24.4% of clinically NO OSCC have occult metastasis 12. Elective neck dissection is used frequently for pathological staging however it remains a significant challenge to preoperatively predict which patients have metastatic disease. In melanoma research, organised lymphoid structures, known as tertiary lymphoid structures (TLS) have been associated with a lower risk of recurrence 6. In early-stage OSCC cases that have TLS are associated with improved prognosis 3–5.

*Aims and Objectives*

This project aims to determine how immune mediated factors, in particular TLS affect metastatic potential in early (T1/T2) OSCC.

*Objectives:*

- 1) Describe the immune contexture in early (T1/T2) OSCC with/without occult metastasis, using histological assessment, multiplex immunofluorescence and spatial transcriptomics
- 2) Develop a novel pathological scoring metric to predict occult metastasis in early OSCC.
- 3) Create a reductionist in vitro assay to determine how OSCC influences B cell profiling.

*Methods*

Retrospective matched cohort study of early (T1/T2) OSCC over a 20-year period. Group 1- OSCC, T1-T2 cN0 at presentation + occult metastasis. Group 2 - OSCC T1-T2 cNo without metastasis. Archived FFPE tissue will be retrieved through Northern Ireland Biobank. Whole face sections will be used to assess histological characteristics and identify TLS and TILs. Create a tissue microarray to assess TLS and TIL composition using multiplex immunofluorescence (Vectra polaris) and spatial transcriptomics (GeoMx). A reductionist in vitro assay will be developed to determine how squamous cell carcinomas influence B cell profiling.

*Outcomes*

- 1) Provide a unique insight into how the presence and character of TLS differs in early (T1/T2) oral squamous cell carcinomas with/without occult metastasis.
- 2) Creation of a novel pathological scoring metric, combining histological features of early-stage OSCC with secondary immune parameters to determine metastatic potential.

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### Lay Summary

Small intra-oral cancers should be curable with surgery but nearly a quarter have spread into the neck at diagnosis. This spread is called metastasis and may not be detectable clinically, so operations are often extensive, requiring removal of lymph nodes from the neck. Side effects of surgery include scarring, even in the absence of metastasis. Immune cells in lymph nodes act to eliminate tumour cells; metastasis thus indicates a failure of local immune control. In some oral cancers organised groups of immune cells called tertiary lymphoid structures (TLS) can form; these have a better prognosis. In melanoma, tumours with TLS have a lower chance of recurrence. Our research seeks to explore the immune status of small oral cancers to determine if it is possible to identify which cases are more likely to have spread at that time of diagnosis, avoiding neck dissection in patients who are not at risk.

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Laura Graham

Positive feedback

Constructive feedback

Any other comments

**An implantable, Closed-Loop Antihypertensive Drug-Delivery Algorithm in Hypertension (The CLADDAGH study)**

James Curneen<sup>1</sup>, Conor Judge<sup>2</sup>, Sally Ann Cryan<sup>3</sup>, Delyth Graham<sup>4</sup>, Garry Duffy<sup>5</sup>

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2. School of Medicine, HRB Clinical Research Facility, University of Galway
3. School of Pharmacy, Royal College of Surgeons in Ireland, Dublin
4. School of Cardiovascular and Metabolic Health, University of Glasgow
5. Anatomy and Regenerative Medicine Institute (REMEDI), University of Galway

**Scientific abstract***Background*

The development of closed-loop systems for diabetes mellitus treatment is expected to lead to greater adherence and control and prevention of end-organ damage and adverse-effects.<sup>5</sup>

Given the wide variabilities in blood pressure (BP) physiology both between and within individuals with hypertension and challenges with adherence leading to an increased risk of cardiovascular events, a closed-loop system of blood pressure measurement feedback and dynamic antihypertensive release from an implantable device could lead to greater BP control and reduction in end-organ complications.

*Aims/Objectives*

1. Develop dose-response relationships between antihypertensive therapy and BP/heart rate response in animal models.
2. Leverage existing closed-loop technology models to design control algorithms for hypertension that will determine the dynamic dose release of the antihypertensive.
3. Test this control system in a simulated cardiovascular model of human physiology and in an animal model, using radiotelemetry measurement and subcutaneous implantable drug release.

*Methods*

(i) Angiotensin II-infused Sprague-Dawley rats and (ii) Spontaneous Hypertensive Rats (SHR) will serve as the animal models of hypertension. A dual chamber drug delivery reservoir will be subcutaneously implanted. Dose-response relationships will be determined with manual release of variable doses of eprosartan, based on mean arterial pressure (MAP) thresholds. Radiotelemetry will continuously measure BP and heart rate.

From this data, a control system for eprosartan release using a closed-loop design will be created, modifying an open-source automated insulin delivery algorithm, to integrate the new control system. It will optimise (i) regulating MAP close to the normotensive range (ii) minimising the aggressiveness of eprosartan administration to limit its excess accumulation.

This closed-loop system will be tested in SHR models, with outcomes assessing time in range of normotension as well as the pharmacokinetic profile and end-organ changes.

*Discussion*

The anticipated outcome of this research is development of a closed-loop system for antihypertensive release in animal models of hypertension, eventually translating this to first-in-human trials in the future.

**Lay Summary**

High blood pressure (hypertension) is one the main causes of ill health and death. Diet and exercise and antihypertensive medication taken by mouth is the main treatment option. Despite this, hypertension is poorly controlled.

A possible alternative is a device that is implanted under the skin, releasing antihypertensive drugs depending on what that individual's blood pressure is at a point in time using information from a wearable device such as a wristwatch as well as using technology to predict what the blood pressure readings will be. This technology is being used for diabetes management and could have significant benefits for people with hypertension.

My aim is to test this idea in experiments with rats that have hypertension, administering an antihypertensive and assessing the blood pressure response. Using this information, I will build a system that will automatically release an antihypertensive at a certain dose, depending on what the blood pressure is at that point in time.

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James Curneen

Positive feedback

Constructive feedback

Any other comments

## The Application of Machine Learning and Deep Learning Techniques to Diagnose and Differentiate Stroke Subtype in the Acute Phase.

Clodagh McDermott<sup>1</sup>, Martin J O'Donnell<sup>1,2</sup>, Catherine Mooney<sup>3</sup>

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2. HRB Clinical Research Facility, University of Galway
3. School of Computer Science, College of Science, University College Dublin

### Scientific abstract

#### *Background*

Stroke is a leading cause of death worldwide and leaves most survivors with permanent disability.<sup>1</sup> Stroke presents diagnostic challenges, which limits access to effective reperfusion therapies in the form of thrombolysis or endovascular thrombectomy (EVT). Currently, neuroimaging is required before any intervention. Delays to neuroimaging is a major reason for underuse of time-sensitive reperfusion therapies. What is clearly missing is an easier, faster method to distinguish ischaemic from haemorrhagic stroke, which would allow for point-of-care management.

#### *Aims and Objectives*

The primary objectives of this project are to develop a clinical prediction tool (CPT), utilising a combination of clinical features and non-invasive bedside investigations (vital signs and ECG), via supervised machine learning algorithms to diagnose stroke and differentiate into its subtypes i.e. intracranial haemorrhage (ICH), non-Large Vessel Occlusion ischaemic (non-LVO) stroke and Large Vessel Occlusion (LVO) ischaemic stroke.

#### *Methods*

Using data from the multi-centre case-control study INTERSTROKE<sup>2</sup>, we will develop, validate, and test supervised learning models for stroke identification and classification. We will investigate baseline demographics, symptoms, medical history, medications, examination findings, vital signs, and ECG, to generate the models. The model will calculate the predictive probability of haemorrhagic stroke, as well as subtype LVO ischaemic stroke, non-LVO ischaemic stroke and ICH. Cases and controls will be randomly allocated into derivation, validation, and test cohorts. Development and analyses will be conducted using R.

#### *Discussion*

The anticipated outcome of this research is the development a CPT, which could be incorporated into clinical practice in the pre-hospital setting. A CPT which identifies brain haemorrhage, with sensitivities and specificities comparable to the gold standard of CT, may make community thrombolysis possible. This CPT could also identify patients with probable LVO, leading to their direct transport to the closest EVT centre. Employing a combination diagnostic-modality approach in stroke has not previously been explored and could prove highly effective.

### Lay Summary

Stroke is a leading cause of acquired adult disability and death.<sup>1</sup> Stroke presents diagnostic challenges, which limits its access to effective therapies. This project will aim for novel machine learning techniques to diagnose stroke and classify it as a haemorrhagic (bleed) or ischaemic (clot) stroke. The ability to diagnose stroke and differentiate it into its subtypes at initial point-of-contact would allow for faster intervention with effective treatments as well as guide further management. The tool will be developed from pre-existing data collected during a multi-centre case-control study (INTERSTROKE) and will use information such as patient age, sex, medical history, current medications, onset of symptoms, symptoms present (headache, seizure, nausea/vomiting, speech disturbance, face weakness, arm weakness, leg weakness), vital signs (heart rate, blood pressure) and ECG. The aim is for this clinical tool to identify stroke type with a similar ability as the gold standard of CT brain imaging.

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Clodagh McDermott

Positive feedback

Constructive feedback

Any other comments

## **PREDiCt-MM: Investigation Of The Paracrine Roles of Extracellular Vesicle Derived Chemokines in Malignant Melanoma Progression**

SM Bollard<sup>1,2,3,4</sup>, C Casalou<sup>5</sup>, J Howard<sup>2,3</sup>, K O'Donnell<sup>1,4</sup>, K Wynne<sup>3</sup>, DJ Tobin<sup>5</sup>, P Kelly<sup>6</sup>, A McCann<sup>2,3</sup>, SM Potter<sup>1,2,3,4</sup>

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5. The Charles Institute of Dermatology, University College Dublin, Dublin 4
6. UCD School of Veterinary Medicine, University College Dublin, Dublin 4

### **Scientific abstract**

#### *Background*

Melanoma is an aggressive skin cancer, though our current prognostic indicators are crude resulting in a clinical unmet need. Naturally occurring canine malignant melanoma shows striking homologies with human disease, representing a valuable translational model. Extracellular vesicles (EVs) are tiny nanoparticles released by all cells, which play a role in melanoma progression. Chemokines have also been shown to play a role in melanoma progression, though the interactions between EVs and chemokines in melanoma has not been thoroughly studied. This project aims to investigate the paracrine role of extracellular vesicle-derived chemokines in the progression and metastasis of malignant melanoma, utilising a Comparative Oncology approach.

#### *Methods*

Plasma was collected from 36 patients diagnosed with primary and metastatic melanoma, and 13 healthy controls. EVs were isolated using Size Exclusion Chromatography prior to characterisation following the MISEV2018 guidelines. Proteomic analysis and a membrane-based chemokine array were used to identify potential EV-derived chemokines of interest. Potential chemokines of interest were then investigated in vitro using metastatic melanoma cell lines and normal dermal fibroblasts.

#### *Results*

Patients with melanoma had a significantly higher concentration of EVs/mL in comparison to healthy controls, though there was no significant difference in concentration between those with metastatic and primary melanoma. No significant difference was seen in the modal particle size, or EV protein concentration between groups. Proteomic and chemokine secretion analysis of the cargo of circulating EVs, melanoma cell lines and patient derived fibroblasts identified a potential role for CXCL8 in melanoma progression. In vitro CXCL8 was associated with a significant decrease in the secretion of melanoma cell line EVs, though did not alter melanoma cell proliferation or migration.

#### *Conclusion*

These results give insights into the mechanisms of EV-mediated paracrine signalling between cell populations in the melanoma tumour microenvironment and their correlation with EVs in the circulation of patients with melanoma.

### **Lay Summary**

Melanoma is an aggressive skin cancer. We know very little about how melanoma spreads through the body. Extracellular vesicles (EVs) are small packets that carry messages between cells and help cancer spread. This project will explore the role of these EVs in the spread of melanoma. We will undertake this on cells in the laboratory and in patient blood and tissue by studying humans and our companion animal, the dog.

Dogs develop melanoma like humans. Importantly melanoma in the dog can also spread through the body. In general, cancer in dogs spreads faster than in humans. This shorter disease will allow for results to be found in a shorter time. We will only use tissue samples from the dogs that have been taken as part of their normal treatment.

Our hope is that these approaches will give us better ways to predict the spread of melanoma in both humans and dogs.

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Stephanie Bollard

Positive feedback

Constructive feedback

Any other comments

## Effects of Age on Human Alveolar Macrophage Responses to SARS-CoV-2 Antigens

Conor Grant, Joe Keane, Mary O'Sullivan

### Scientific abstract

#### *Background*

Advanced age is the strongest risk factor for COVID-19 severity and mortality. Human alveolar macrophages (AMs) are likely the first professional immune cells to interact with SARS-CoV-2 during the earliest phase of natural infection. It is unknown if human AMs recognise SARS-CoV-2 antigens, which antigens are recognised, by which Toll-Like Receptors (TLR) and which cytokines are produced in response. It is also unknown if these cytokine responses differ by age.

#### *Methods*

Human AMs were retrieved from patients undergoing routine bronchoscopy at our hospital. The AMs were treated with blocking antibodies of TLR2, TLR4 or an isotype control for 1 hour and then stimulated with SARS-CoV-2 spike protein, envelope protein or unstimulated. LPS was used as a positive control. Supernatant was taken 24 hours post-stimulation and the concentration of IFN $\gamma$ , IL-6, IL-8, IL-1 $\beta$ , TNF $\alpha$ , IL-10 and IL-12p70 were measured using MSD multiplex assay. Cytokine responses were compared between AMs from patients aged older or younger than 75 years old.

#### *Results*

SARS-CoV-2 envelope protein, but not spike protein, induced cytokine secretion from human AMs, in particular IL-6, IL-1 $\beta$ , TNF $\alpha$ , IL-10 and IL-12p70. Blocking antibodies against TLR4 but not TLR2 reduced these cytokine responses. AMs from patients older than 75 had significantly higher IL-6, IL-1 $\beta$  and IL-10 secretion than younger patients.

#### *Conclusion*

In the earliest phase of SARS-CoV-2 infection, AMs from older patients likely produce significantly more IL-6, IL-1 $\beta$  and IL-10 following the recognition of SARS-CoV-2 envelope protein by TLR4. This early effect may partly explain the worse clinical trajectories followed by these older patients. The inclusion of envelope protein as an antigen in COVID-19 vaccines may improve their efficacy in older patients.

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Conor Grant

Positive feedback

Constructive feedback

Any other comments

**VAPRE: Exploring the Relapse Prodrome of ANCA associated Vasculitis**

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<sup>4</sup> Department of Mathematical Sciences, University of Durham

<sup>5</sup> Department of Statistics, Dublin Institute of Technology

**Scientific abstract***Background*

ANCA associated vasculitis (AAV) is an archetypal autoimmune disease, resulting in immune-mediated organ damage. It has a relapsing-remitting course, resulting in cumulative morbidity and mortality. Toxic immunosuppression used to induce and maintain remission is a double-edged sword; >80% experience adverse events. A key unmet need is personalisation of this treatment. Identifying and predicting disease relapse is a key initial step, but the precise triggers are unknown. Evidence suggests a complex interplay of polygenic genetic susceptibility, epigenetic influences and environmental triggers – the latter receiving the least attention to date.

*Aims*

We sought to

- i. identify >1 measurable environmental factors statistically associated with AAV relapse: ultraviolet B (UVB) is the initial exploratory variable, informed by our systematic review
- ii. create an algorithm to automate the identification of AAV relapse in real-world registry-based trials

*Methods*

The Rare Kidney Disease (RKD) Registry is an Irish national longitudinal, multi-centre, cohort study, which includes 663 patients with definite AAV. All patients were eligible for inclusion.

- i). An n-of-1 study design was used to examine the effect of UVB-derived exposure variables on relapse risk, using multi-level models (MLM).
- ii). Patient encounters (N=3387) were summarised using five objective variables. The probability of relapse was independently adjudicated for each encounter (ground truth). A MLM to accurately label an encounter was developed (trained) and internally validated (tested). R studio was used for all analyses.

*Results*

- i). Average vitamin D-UVB was negatively correlated (0.82, 0.70-0.99, p=0.04) with relapse risk, with a stronger effect when restricting to winter measurements (0.71, 0.57-0.89, p=0.002).
- ii). The MLM achieved an accuracy and AUC of 0.94 and 0.98 (95% CI 0.96-0.99), respectively.

*Conclusion*

- i). Avoidance of vitamin D deficiency may reduce relapse propensity in AAV.
- ii). A MLM performs well at identification of relapse, using objective, readily-accessible registry data.
- iii). This work formed the nidus of a large EU grant, to create a prediction algorithm for AAV relapse, using multiple parallel diverse data sources.

**Lay Summary**

ANCA vasculitis is a rare autoimmune disease, whereby the immune system is triggered to self-destruct – the systems normally primed to fight infection and cancer cells are incorrectly activated, resulting in organ destruction, such as kidney failure.

Like most autoimmune diseases, ANCA vasculitis goes through periods of remission (quiet) and relapse/flare (active). Half of patients will experience a flare over 5 years, resulting in cumulative tissue damage, due to the disease itself and the powerful medications required. Infection is an unwanted complication.

The exact cause of ANCA vasculitis, and indeed the triggers of relapse, have yet to be discovered. Evidence suggests there is a complex interaction between a person's genetic make-up and unknown environmental triggers. We aim to identify and explore these factors, such as the influence of ultraviolet light. We also aim to build a model to accurately identify relapse in disease registries. These missions will enable prediction of autoimmune disease risk and hence facilitate exploration of avoidance mechanisms and personalised treatment options.

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Jennifer Scott

Positive feedback

Constructive feedback

Any other comments

**Assessing Sleep in INFants with early-onset atopic Dermatitis by Longitudinal Evaluation (The SPINDLE study)**

O'Connor C<sup>1</sup>, Irvine A<sup>1,2</sup>, Murray D<sup>1</sup>, Hourihane J<sup>1,3</sup>, Murphy M<sup>4</sup>, Boylan G<sup>1</sup>

1 INFANT, University College Cork

2 Dermatology, CHI at Crumlin; Clinical Medicine, Trinity College Dublin

3 Paediatric Allergy, CHI at Temple St; Paediatrics, Royal College of Surgeons of Ireland, Dublin

4 Dermatology, South Infirmary Victoria University Hospital; Medicine, University College Cork

**Scientific abstract***Background*

Atopic dermatitis (AD) is associated with impaired quality of life and development of other atopic disease. Good sleep is essential to healthy neurodevelopment. Sleep in older children with severe AD is known to be disturbed, thought to be due to pruritus, inflammation, increased transepidermal water loss and alterations in circadian rhythm. Little is known about the impact of AD on sleep in the first year of life.

*Aim*

The aim of the project is to describe, in detail, the sleep architecture of infants with early-onset atopic dermatitis (AD), compared to controls, by using electroencephalogram (EEG) polysomnography, overnight actigraphy, and parental reporting.

*Methods*

Sleep quality and quantity is measured by sleep EEG at six-eight months, overnight movements with actigraphy at six-eight months and 12 months, and parent-reported data monthly between six and 12 months. AD severity, skin barrier assessment (transepidermal water loss and natural moisturising factor levels) and cutaneous cytokine analysis are assessed serially. Filaggrin mutational status is assessed in cases. Neurodevelopmental and behavioural assessment is performed at 18-20 months.

The primary outcome will be altered macrostructure of sleep (sleep diary and actigraphy), measured as decreased sleep efficiency and increased night time awakenings. The secondary outcomes will be altered microstructure of sleep, measured as sleep spindle power and power in REM and NREM sleep stages; and parental sleep quality and quality of life.

*Results*

To date, 57 controls (target achieved) and 29 cases (target 32) have been recruited. Preliminary data will be presented on parent-reported outcomes, sleep EEG, overnight actigraphy, and sleep diaries.

*Discussion*

This study will deeply characterise sleep measures in infants with early-onset AD. The results will augment knowledge of the aetiology of sleep disruption in AD and may provide evidence for enhanced therapeutic strategies.

**Lay Summary**

Eczema in children has become more common in recent years. It is strongly associated with other conditions such as food allergies and asthma, and psychological co-morbidity. There is huge cost to the Irish economy associated with the treatment of eczema and associated problems.

Sleep disturbance in early life can have profound consequences for growth and brain development. This study will focus on infants with early-onset eczema who are at high risk of developing sleep disturbance. Early sleep changes will be investigated using brainwave analysis (EEG), overnight movement recording, and sleep questionnaires. EEG changes related to sleep have never been investigated in babies with eczema. The study will also examine the structure and function of participants' skin and correlate these changes with sleep disruption.

The results of this study will be used to help doctors guide parents in the management of their children's eczema and will help us develop better strategies for managing sleep disruption in eczema in future.

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Cathal O'Connor

Positive feedback

Constructive feedback

Any other comments

## Open Innovation for near-term artificial intelligence in Multiple Sclerosis Imaging

Brendan Kelly, Aonghus Lawlor, Ronan Killeen

UCD

### Scientific abstract

#### *Introduction*

Multiple sclerosis (MS) is a chronic demyelinating condition. MRI is the cornerstone of surveillance of patients with MS. The workload associated with medical imaging has greatly increased. However the number of radiologists has failed to keep pace with demand. Artificial intelligence (AI) has been suggested as a solution. Ethical considerations of the use of AI in medicine remains a subject of debate. Concurrently, the involvement of patients and the public in research (PPI) is becoming mandatory in the EU.

The goal of this research was to elucidate the important values for our relevant stakeholders, to give an overview of how the patient voice was implemented into our research planning, and to share preliminary results.

#### *Methods*

Open Innovation 2.0 methods were used to facilitate PPI in a proposed project that would use an AI model to aid assessment of radiologic change in people with multiple sclerosis. An ethical matrix workshop co-designed with a patient expert. The workshop yielded a survey which was disseminated to the professional societies of the relevant stakeholders.

Quantitative data were analysed using the Pingouin python package. Qualitative data were examined with word frequency analysis and analysed for themes with grounded theory with a patient expert.

#### *Results*

184 participants were included in the open innovation project.

Patients were hopeful that AI would work equally for all and facilitate more choice and access and achieve high performance, without causing deskilling or acting as the preeminent deciding factor, while remaining tailored to an individual without over generalisation, trustworthy understandable and secure.

We have incorporated these values into our research methodology. Preliminary results of our model show successful change detection with high levels of confidence and accuracy.

#### *Conclusion*

The Open Innovation paradigm provides a template for collaborative problem solving. The process provided practical methodologies to achieve patient centred outcomes.

### Lay Summary

Multiple Sclerosis (MS) is a condition affecting the brain and spinal cord. In MS the immune system attacks the nerves. This can be seen with Magnetic Resonance Imaging (MRI). People with MS get regular MRI scans but due to staff and resource shortages there can be delays in diagnosis.

Artificial Intelligence (AI) is a branch of computer science that allows machines to mimic human behaviour. AI might help to ease these shortages but there are associated ethical issues.

Before creating an AI model we asked of people with MS, doctors, nurses and computer scientists what values are important to them.

Patients were hopeful that AI would work equally for all, give more choice and access and achieve high performance, without acting as the preeminent deciding factor or over generalisation. It should also be trustworthy, understandable and secure.

We show successful results of our AI model while adhering to these principles.

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Brendan Kelly

Positive feedback

Constructive feedback

Any other comments

## Investigating novel therapeutic targets in JAK2 positive myeloproliferative neoplasms

### Scientific abstract

#### *Background*

Intrinsic activation of intracellular signalling cascades is a hallmark of myeloid malignancy. It is exemplified in the myeloproliferative neoplasms (MPN) in which activating mutations in JAK2, CALR and MPL drive downstream constitutive activation of JAK-STAT, MAPK and other signalling pathways. Networks of regulatory proteins provide positive and negative feedback to these signalling cascades and may offer therapeutic targets. UBASH3B is a histidine phosphatase which has been observed to regulate malignant myeloid haematopoiesis and support interferon signalling. UBASH3B expression is regulated by inhibition of JAK signalling and is differentially expressed in MPN.

#### *Methods*

UBASH3B KO clones were generated using a CRISPR-cas9 approach in JAK2 V617F positive UKE1 cells. Individual KO clones were established from single cell colonies and compared with the original parental population. Wildtype and mutant UBASH3B re-expression and over-expression models were generated with a lentiviral vector and individual clones established from single cell colonies. RNA-sequencing and phospho-proteomics were used to determine effects of KO.

#### *Results*

UBASH3B KO clones were consistent in demonstrating a significant downregulation of IFN pathways at both a protein and RNA level in the UKE1 cells. Consistent with this, these KO cells lost responsiveness to exogenous IFN. There was also a significant downregulation of genes related to megakaryocyte development and differentiation. Re-expression of UBASH3B did not rescue the original phenotype and whilst over-expression models showed some upregulation of platelet related genes, overall levels were lower than the original WT population. A computational approach has identified STAT1, STAT2 and GATA1 as likely drivers of the new phenotype observed.

#### *Conclusion*

Intrinsic activation of IFN signalling cascades and expression of megakaryocyte related genes are features of mutant stem cells in MPN. The gene specific effect of UBASH3B in regulating this phenotype as observed in the KO cell line is under further investigation with an alternative shRNA approach. This model allows molecular profiling at a transcription factor level and has identified STAT1, STAT2 and GATA1 as mediators of this phenotype and potential targets for therapeutic manipulation in MPN.

### Lay Summary

Myeloproliferative neoplasms (MPN) are a group of disorders of the bone marrow characterised by overproduction of red blood cells, platelets and/or bone marrow scarring. They are caused by changes to the genetic code of a number of important genes including the JAK2 gene. These disorders can reduce a patient's natural life expectancy and cause blood clots.

There has been some success using new therapies designed to block the action of abnormal JAK2 genes. These treatments help patients to feel better but the number of diseased cells is largely unchanged.

This study aims to improve our understanding of how the normal processes of cells are affected in MPN cells and to establish and test whether there are new targets for treatments using existing or new drugs that could be used alongside JAK2 blockers to improve their effectiveness.

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Graeme Greenfield

Positive feedback

Constructive feedback

Any other comments

## Subphenotypes in patients with severe acute respiratory failure requiring extracorporeal membrane oxygenation

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6. Division of Anaesthetics, Pain Medicine & Intensive Care, Department of Surgery & Cancer, Faculty of Medicine, Imperial College London, London, UK
7. Department of Critical Care, Imperial College Healthcare NHS Trust, London, UK
8. Department of Medicine, Division of Pulmonary, Critical Care, Allergy and Sleep Medicine; University of California San Francisco, San Francisco, CA
9. Department of Anesthesia, University of California San Francisco, San Francisco, CA

### Scientific abstract

#### *Introduction and Objectives*

Hyperinflammatory and hypoinflammatory subphenotypes have been identified in patients with the acute respiratory distress syndrome (ARDS) which consistently have different clinical characteristics, biomarker profiles and outcomes. These subphenotypes may not be specific to ARDS. Patients on veno-venous extracorporeal membrane oxygenation (VV ECMO) represent a distinct population in which subphenotypes have not been previously identified. The aim of this research was to identify if subphenotypes are present in a mixed cohort of patients with severe acute respiratory failure requiring VV ECMO.

#### *Methods*

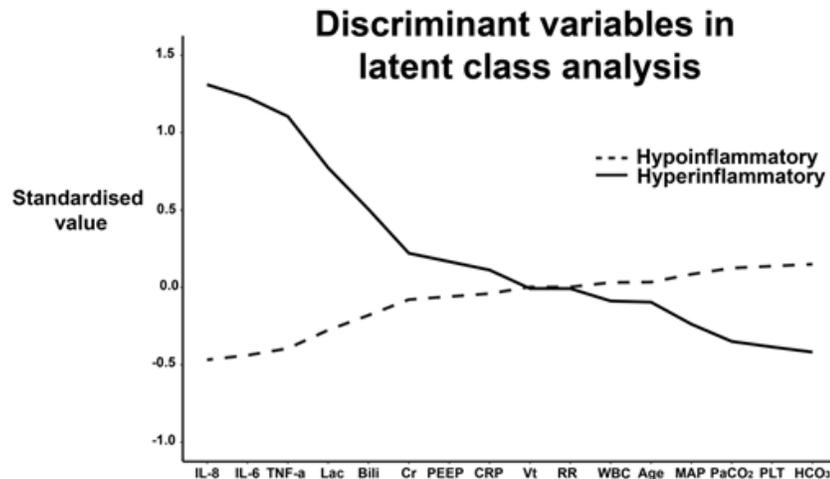
Adult patients requiring VV ECMO from a single centre in Regensburg, Germany were included. Clinical and ventilation data were recorded. The inflammatory cytokines IL-6, IL-8, and TNF- $\alpha$  were measured by ELISA from plasma taken immediately prior to initiation of ECMO. Latent class analysis (LCA) was used to identify subphenotypes and included both clinical and biomarker variables. Subphenotype association with hospital mortality was assessed.

#### *Results*

437 patients initiated on VV ECMO were included. The most common indications for ECMO were bacterial infection (41%), viral infection (15%), and post-operative (16%). Using LCA, a two-class model was the best fit ( $p < 0.001$ ). There were 322 (74%) patients in Class 1 and 115 patients in Class 2 (26%). Class 2 was characterised by higher cytokine concentrations, more metabolic acidosis, and more organ failure, consistent with the ARDS hyperinflammatory subphenotype. Patients with the hyperinflammatory subphenotype (Class 2) had worse hospital mortality (49% vs. 31%,  $p = 0.001$ ) than those with the hypoinflammatory subphenotype (Class 1). Discriminant variables in the LCA model are detailed in Figure 1.

#### *Conclusion*

Two subphenotypes were identified in patients with severe acute respiratory failure requiring ECMO, with characteristics similar to those previously identified in data from non-ECMO ARDS patients, including worse outcomes in the hyperinflammatory subphenotype. These subphenotypes could be targeted with precision medicine treatments in future trials of patients on VV ECMO.



**Figure 1:** Differences in the standardized values of each variable by subphenotype on the y-axis, with discriminant continuous variables along the x-axis. Variables are sorted based on degree of separation between classes from a maximum positive separation on the left (hyperinflammatory greater than hypoinflammatory) to a maximum negative separation on the right (hypoinflammatory greater than hyperinflammatory).

### Lay Summary

We do not have direct treatments for patients with acute respiratory distress syndrome (ARDS), which is common in intensive care and has a very high mortality. Two subgroups of ARDS patients have been identified that may respond differently to treatment. People in these subgroups likely have different inflammatory responses. These subgroups might be present in other syndromes and might be present in all intensive care patients with inflammation. We identified these subgroups in a large group of patients with and without ARDS who needed extracorporeal membrane oxygenation (ECMO) due to severe lung failure. ECMO is a highly specialised treatment that involves artificially adding oxygen to patients' blood and removing carbon dioxide using a machine. The subgroups have never before been identified in this group of patients. This finding means that precision treatments for the subgroups in ARDS could also be used in patients without ARDS and patients on ECMO.

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Kiran Reddy

Positive feedback

Constructive feedback

Any other comments

**Investigation of the impact of microbiome composition and immune activation in COVID-19 patients.**

Authors: Rachel MacCann<sup>1,2,3</sup>, Tarini Shankar Ghosh<sup>4</sup>, Alejandro Abner Garcia Leon<sup>3</sup>, Eoin R. Feeney,<sup>1,2</sup> Obada Younis<sup>5</sup>, Aoife G Cotter<sup>3,6</sup>, Eoghan de Barra<sup>7,8</sup>, Corinna Sadler<sup>9</sup>, Peter Doran<sup>1</sup>, Alan Landay, Paul W. O'Toole<sup>4</sup>, Patrick W. Mallon<sup>1,2,3</sup>, and , on behalf of the All Ireland Infectious Diseases cohort study

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<sup>10</sup> Department of Internal Medicine, Rush University, Chicago, Illinois, USA

**Scientific abstract***Background*

Systemic inflammation and innate immune activation are associated with COVID-19 disease severity. Progression to severe and critical COVID-19 is known to occur more frequently in older patients and those with higher BMI and specific comorbidities. Although alterations in gut microbiota are linked to systemic inflammation, the relationships between microbiome, inflammation and COVID-19 disease severity remain ill-defined.

*Aims*

In this study, our primary aim was to identify the interactions between gut microbiome compositions with systemic immune responses and correlate these interactions with COVID-19 disease severity.

*Methods*

To characterise these associations, we performed 16SrDNA analysis of stool samples in COVID-19 subjects to explore diversity and taxonomic repertoires and correlated these to circulating inflammatory biomarkers in matched plasma measured by bead-based ELISA and chemiluminescence. Hierarchical clustering on principal components analysis (PCA) identified biomarker-derived inflammatory clusters. Associations of microbial diversity and inflammatory biomarkers on maximal COVID-19 severity (mild, moderate v severe/critical) was explored using logistic regression and weighted gene correlation network analysis (WGCNA).

*Results*

Of 79 subjects, 58% were male and 88% were Caucasian with 36% of subjects experiencing mild disease, 22% moderate disease and 40% critical/severe. Of these subjects recruited only beta-diversity differed between the groups. Three distinct inflammatory clusters were identified from circulating biomarkers that then correlated with microbiome profiles and clinical outcomes using WGNA. These clusters related to specific clinical phenotypes with cluster 1 associated with upregulation of inflammatory markers, an older population and severe/critical disease outcomes. Cluster 2 can be described as an appropriately inflamed microbiome and cytokine cohort with an 'obesogenic' / cardiovascular risk profile and cluster 3, an uninflamed group, was a younger population associated with mild/ moderate disease outcomes.

*Conclusion*

This study uncovers new insights into the role of host and microbial factors in COVID-19 severity through differentiated biomarker and microbiome-defined clusters.

**Lay Summary**

Inflammation is seen in COVID-19 disease, with worse inflammation seen in those with severe disease. Severe disease is more often seen in the elderly and those with underlying medical conditions. The gut is an important site of inflammation in COVID-19 and how the bacteria in the gut, called the gut microbiome, is linked to inflammation in the body in COVID-19 disease is beginning to be understood. In this study of 79 people with COVID-19, we looked at inflammation markers from blood samples and extracted DNA from stool samples to examine which bacteria species can be found on the gut. We found three different groups, or patterns, of inflammation that linked these inflammation markers to different bacteria profiles. Groups 2 and 3 were associated with a milder COVID-19 disease and had a higher BMI, whereas Group 1 was associated with more severe COVID-19 disease. This study shows a link between patterns of inflammation in the blood, the gut and COVID-19 disease severity.

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Rachel MacCann

Positive feedback

Constructive feedback

Any other comments

## Computed tomography lung parenchymal descriptions in routine radiological reporting have diagnostic and prognostic utility in patients with idiopathic pulmonary arterial hypertension and pulmonary hypertension associated with lung disease

Krit Dwivedi<sup>\*1,4</sup>, Robin Condliffe<sup>2\*</sup>, Michael Sharkey<sup>3,4</sup>, Robert Lewis<sup>2</sup>, Samer Alabed<sup>1,4</sup>, Smitha Rajaram<sup>4</sup>, Catherine Hill<sup>4</sup>, Laura Saunders<sup>1</sup>, Peter Metherall<sup>3,4</sup>, Faisal Alandejani<sup>1</sup>, Dheyaa Alkhanfar<sup>1</sup>, Jim M Wild<sup>1</sup>, Haiping Lu<sup>5</sup>, David G Kiely<sup>1,2†</sup> and Andrew J Swift<sup>1,3,4†</sup>.

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2 - Pulmonary Vascular Disease Unit, Royal Hallamshire Hospitals, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK S10 2JF.

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4- Department of Radiology, Sheffield Teaching Hospitals NHS Trust, Sheffield S5 7AU

5 - Department of Computer Science, University of Sheffield, Sheffield S1 4DP.

### Scientific abstract

#### *Purpose*

Pulmonary hypertension (PH) is a heterogeneous, incurable condition with untreated survival poorer than most cancers. Patients presenting with CT features of both PH and lung disease pose a diagnostic dilemma between two phenotypes - idiopathic pulmonary arterial hypertension (IPAH) and PH secondary to chronic lung disease (PH-CLD). Accurate phenotyping is vital as it informs treatment, management and prognosis. Only patients with IPAH are eligible for PAH therapeutic agents, which significantly improve survival. The prognostic significance of commonly identified CT lung parenchymal patterns is unknown.

#### *Methods*

All patients with IPAH or PH-CLD between Feb 2001 - Jan 2019 were identified in a specialist tertiary PH referral centre using the ASPIRE (Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre) registry. CT scans performed within one year prior to diagnosis were termed 'incident'. All scans and reports were analysed blinded to clinical data. CT reports were searched using a regular expression string-search for 6 CT features - emphysema, ground glass (GG), centrilobular ground glass (CGG), consolidation and fibrosis. Results were manually validated to ensure they represented true positives. Multivariate regression analysis was performed adjusting for known significant predictors of age, gender and mean pulmonary arterial pressure.

#### *Results*

Cohort included 660 consecutive incident patients (335 IPAH, 325 PH-CLD) over 18 years. Honeycombing (HR 2.79), fibrosis (HR 2.09) and emphysema (HR 2.04) were significant ( $p < 0.05$ ) adverse predictors of increased mortality. GG (HR 0.54) and CGG (HR 0.55) were significant ( $p < 0.05$ ) protectors. CGG (HR 0.61,  $p = 0.02$ ), fibrosis (HR 1.58,  $p < 0.001$ ) and emphysema (HR 1.51,  $p < 0.001$ ) remained significant at multivariate analysis.

#### *Conclusion*

This study demonstrates commonly encountered lung CT patterns prognosticating PH patients with lung disease and being imaging biomarkers for mortality. Presence of emphysema and fibrosis predict poor survival. Ground glass change, including centrilobular ground glass change, predicts better survival, as these more likely represent patients with IPAH.

### Lay Summary

Pulmonary Hypertension (PH) is a condition where there is high blood pressure in the pulmonary arteries. There are many different diseases which can give you PH. In patients who have both PH and some mild lung disease (like emphysema or early lung fibrosis), the cause of the disease cannot confidently be diagnosed. The diagnosis is between two forms of PH - Idiopathic Pulmonary Arterial Hypertension (IPAH) and PH secondary to chronic lung disease (PH-CLD). There is a big difference in prognosis between the two forms, and only those diagnosed as IPAH qualify for new specialist drugs which can improve survival.

All patients suspected of PH have a chest CT scan. My research looks into if we can use this CT scan to more confidently predict the patient prognosis. My results show that there are indeed imaging signs which can help with this, providing both diagnostic and prognostic information.

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**Krit Dwivedi**

Positive feedback

Constructive feedback

Any other comments

**LGI1-antibody encephalitis: From bedside to bench**Kelly MJ<sup>1,2,3</sup>, Zhao M<sup>3</sup>, Wagner B<sup>3</sup>, Cavalleri GL<sup>4</sup>, Henshall D<sup>5</sup>, Delanty N<sup>2,5</sup>, Irani SR<sup>3</sup><sup>1</sup> School of Medicine, RCSI<sup>2</sup> Department of Neurology, Beaumont Hospital<sup>3</sup> Nuffield Dept of Clinical Neuroscience, Oxford University<sup>4</sup> School of Pharmacy and Biomolecular Sciences, RCSI<sup>5</sup> Dept of Molecular Physiology and Neuroscience, RCSI**Scientific abstract***Background*

Leucine-rich Glioma-Inactivated 1 (LGI1) receptor-antibody (ab) encephalitis is one of the most common forms of autoimmune encephalitis. Typical presentations include cognitive impairment, disturbance of consciousness, and seizures. With appropriate immunotherapy, outcomes are considered good in almost 90% of cases. However, these long-term outcomes are based on crude functional measures such as the modified Rankin Scale (mRS) and fail to recognise more subtle effects on cognitive function, mood and fatigue which occur in over 1/3 of patients<sup>1</sup>. Furthermore, there are small but challenging cohorts of patients who experience relapse or persistence of seizures.

Activated intrathecal B-cells and intrathecal antibody synthesis likely contribute to the pathogenesis of LGI1-ab encephalitis<sup>2</sup>, but it is not known how long this persists, whether antibodies remain pathogenic with affinity maturation, and how this influences long-term outcomes and treatment response. We outline a comprehensive project which combines analyses of both clinical phenotypes and the underlying pathophysiology of this complex illness.

*Aim*

To comprehensively phenotype clinical outcomes using patient-centred measures in people with LGI1-ab encephalitis, and correlate outcomes with intrathecal immunophenotypes and monoclonal antibody characterisation.

*Methods*

Study participants undergo deep clinical phenotyping through a series of validated questionnaires and semi-structured interview. This includes measures of cognition, fatigue, sleep, pain, quality-of-life and carer-burden. Participants undergo sampling of blood +/- cerebrospinal fluid (CSF) for biomarker analysis. CSF antibody-secreting cells (ASCs) and B-cells undergo single-cell fluorescence-activated cell sorting (FACS). Recombinant monoclonal antibodies (mAbs) can then be cloned from B-cell receptor RNA using transcriptionally-active PCR and analysed for LGI1-specificity and binding-affinity.

*Results and conclusion*

13 participants +/- family members/caregivers have been interviewed to date. We demonstrate proof-of-concept of a high throughput method of producing recombinant mAb from single ASCs in CSF for further characterisation.

**Lay Summary**

Autoimmune encephalitis is an inflammatory disease of the brain. This means the body's own immune system attacks the brain tissue by producing proteins called 'antibodies' (abs), potentially leading to seizures and dementia. One of the most commonly found antibodies targets a protein in the brain known as LGI1.

Treatment involves medications which suppress the immune system. While most patients with LGI1-ab encephalitis recover with treatment, many continue to experience effects on their thinking, mood and energy levels. This can have a significant impact on their quality-of-life and on their families and caregivers. Furthermore, a small group of patients will either not recover despite treatment, or experience relapse.

In this project we will study the immune systems of people who have experience LGI1-ab encephalitis by isolating the cells that produce antibodies from their spinal fluid. This allows us to study individual antibodies closely. We combine this with detailed analysis of the symptoms that people with this illness consider most troublesome, including mood, memory and quality-of-life. We aim to find out what impact the characteristics of antibodies have on these symptoms. This may help to direct future treatments for autoimmune encephalitis.

1. Binks, S.N.M., et al. Residual Fatigue and Cognitive Deficits in Patients After Leucine-Rich Glioma-Inactivated 1 Antibody Encephalitis. *JAMA neurology* 78, 617-619 (2021).

2. Lehmann-Horn, K., et al. Intrathecal B-cell activation in LGI1 antibody encephalitis. *Neurol Neuroimmunol Neuroinflamm* 7(2020).

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Mark Kelly

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**MEchanisms of hypercoagulability in MyeloProlifeRative nEoplaSmS – The EMPRESS Study**

Sarah Kelliher<sup>1,2,3</sup>, Kathleen Bennett<sup>4</sup>, Mary Frances McMullin<sup>5</sup>, Patricia Maguire<sup>2,6</sup>, Fionnuala Ní Áinle<sup>1,2,3,7</sup>, Barry Kevane<sup>1,2,3</sup>

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2. SPHERE Research Group, Conway Institute, University College Dublin
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4. Division of Population Health Sciences, Royal College of Surgeons of Ireland, Dublin
5. Department of Haematology, Centre for Medical Education, Queens University Belfast
6. School of Biomolecular and Biomedical Science, University College Dublin
7. Department of Haematology, Rotunda Hospital, Dublin

**Scientific abstract***Background*

Thrombosis and microvascular dysfunction are defining features associated with Myeloproliferative Neoplasms (MPN). The interplay between haemostatic and pro-inflammatory pathway activity ('thrombo-inflammation') has emerged as a source of hypercoagulability in MPN. Platelets are mediators of thrombo-inflammation in other disease states and may be effectors of pro-inflammatory/pro-coagulant activity in MPN.

*Aim*

To determine if differences exist in the pattern of platelet protein expression in patients with MPN compared to healthy donors.

*Methods*

62 patients (ET, n=38; PV, n=24) and 9 healthy volunteers were recruited. Differential proteomic signatures were established using label-free quantification mass spectrometry. Platelet lysate proteins were digested using the PreOmics kit and analysed in a Bruker TimsTOF mass spectrometer connected to a EvoSep liquid chromatography system. Identified peptides were searched against a human FASTA using MaxQuant.

Proteins identified in a minimum of 70% of samples in at least one group were included. Differences in protein expression were determined using an unpaired t-test with a false discovery rate of 5% and a minimal fold change of 0.1; p-values below 0.05 were considered significant.

*Results*

In MPN platelet lysates, 49 proteins were differentially expressed in comparison to controls ( $p < 0.05$ ), including increased expression of markers of platelet activity. Bioinformatical analysis revealed a cohort of mitochondrial, cytoskeletal & ribosomal proteins as well as potential effectors of thrombopoiesis and thrombo-inflammation which were upregulated in the MPN cohort. Strikingly, protein disulfide-isomerase (PDI, a member of the thioredoxin superfamily of redox proteins) was increased in MPN lysates. Plasma levels of PDI have been shown to be increased in MPN and are associated with thrombotic risk.

*Conclusions*

In this pilot study our preliminary analysis suggests the platelet proteome is altered in MPN. We have demonstrated an activated platelet phenotype with over expression of known procoagulant proteins. Additional proteomic analysis is ongoing and may provide additional insights into MPN pathobiology.

**Lay Summary**

Myeloproliferative Neoplasms (MPNs) are chronic blood diseases characterised by increased numbers of circulating blood cells, arising due to an acquired genetic mutation affecting the bone marrow. Blood clots in the arterial and venous systems occur in up to 30% of patients with MPN and represent the greatest risk to their life expectancy and quality of life. Hyperactive platelets appear to contribute to the mechanism of clotting in these diseases; however, the precise mechanisms are unknown. Platelets contain granules, the contents of which are released into the circulation upon activation. Platelets are essential for blood coagulation however it is also known that via the protein signals carried in their granules, that they also play an important role in several inflammatory diseases. We have shown that protein disulfide-isomerase is increased in the platelets of patients with MPN compared to healthy volunteers. This protein has previously been associated with blood clot risk in other studies. Further platelet protein analysis is ongoing.

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Sarah Kelliher

Positive feedback

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**ENHANCED VON WILLEBRAND FACTOR CLEARANCE IN LOW VWF PATHOGENESIS - LIMITATIONS OF VWF PROPEPTIDE:ANTIGEN RATIO AND CLINICAL SIGNIFICANCE**

Dearbhla Doherty<sup>1,2</sup>, Michelle Lavin<sup>1,2</sup>, Mary Byrne<sup>1</sup>, Margaret Nolan<sup>1</sup>, Jamie M. O'Sullivan<sup>2</sup>, Kevin Ryan<sup>1</sup>, Niamh M. O'Connell<sup>1</sup>, Sandra L. Haberichter<sup>3,4,5</sup>, Pamela A. Christopherson<sup>3</sup>, Jorge Di Paola<sup>6</sup>, Paula D. James<sup>7</sup> and James S. O'Donnell<sup>1,2,8</sup> on behalf of the Zimmerman Program Investigators.

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<sup>2</sup> Irish Centre for Vascular Biology, School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland, Dublin 2, Ireland.

<sup>3</sup> Diagnostic Laboratories and Blood Research Institute, Versiti, Milwaukee, Wisconsin, USA.

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<sup>7</sup> Department of Medicine, Queen's University, Kingston, Ontario, Canada.

<sup>8</sup> National Children's Research Centre, Our Lady's Children's Hospital Crumlin, Dublin, Ireland.

**Scientific abstract***Introduction*

Increased von Willebrand factor (VWF) clearance plays a role in the pathogenesis of Type 2 von Willebrand disease (VWD) and Type 1 VWD with levels <30 IU/dL. However, the pathological mechanisms involved in mild to moderate reductions in plasma VWF:Ag (30-50 IU/dL range; Low VWF) remain poorly understood. The gold standard for detection of enhanced VWF clearance is a desmopressin (DDAVP) trial. The VWF propeptide to antigen ratio (VWFpp/VWF:Ag) has been proposed as an alternate test for identifying enhanced clearance. We investigated the hypothesis that enhanced VWF clearance may contribute to Low VWF pathobiology and modulate bleeding phenotype.

*Methods*

Patients with low VWF levels (30-50 IU/dL) were recruited to the LoVIC study. DDAVP was administered and blood samples drawn at baseline, 1 and 4 hours. Enhanced clearance was defined as plasma VWF:Ag fall-off >30% from peak at 4 hours. VWF propeptide levels were determined by ELISA. Bleeding phenotype was assessed using a validated Bleeding Assessment Tool.

*Results & Discussion*

75 patients within the cohort underwent DDAVP trial. 20% (15/75) demonstrated significantly enhanced VWF clearance. Patients with fast clearance had significantly higher increments in plasma VWF:Ag at 1 hour than those with normal clearance (median 3.84 vs 2.89-fold,  $p < 0.0001$ ), suggesting intact endothelial stores that could be released upon stimulation. Moreover, peak VWF:Ag response at 1 hour strongly correlated with 4-hour fall-off rates ( $r = 0.70$ ,  $p < 0.0001$ ).

Importantly from a clinical perspective, enhanced VWF clearance was seen following DDAVP but did not affect the VWFpp/VWF:Ag ratio, which had a sensitivity for identifying enhanced clearance of just 13%.

Finally, VWF response to DDAVP was significantly associated with bleeding score ( $\beta = -1.39$ , 95%CI -2.54:-0.23), adjusted for age and sex. We hypothesize that bleeding phenotype is less severe in Low VWF patients with enhanced clearance pathophysiology because they have intact endothelial stores that can be utilized to respond to haemostatic challenge.

**Lay Summary**

von Willebrand Factor (VWF) is a protein that is important for blood clotting. Cells that line blood vessel walls, called "endothelial cells", make VWF. Some people have slightly low levels of VWF and experience bleeding. These patients have a condition called 'Low VWF'. However, we don't know why most of these patients have low levels. Low levels of VWF in blood can be either due to problems with production of VWF in endothelial cells, or due to VWF being removed, or "cleared", too quickly from the blood. We administered a drug called DDAVP to patients to stimulate their endothelial cells to release VWF and then tracked how quickly VWF was cleared from their blood. We found that 20% of our patients cleared VWF quicker than normal individuals. Interestingly, patients who had low VWF levels because they cleared VWF too quickly experienced less bleeding than patients who didn't produce enough VWF.

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Dearbhla Doherty

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## Extracellular Vesicle proteomic analysis can demonstrate biological differences between preterm and term infants during extrauterine transition

Daniel O'Reilly<sup>1,2</sup>, Claire Murphy<sup>1,2,3</sup>, Luisa Weiss<sup>1</sup>, Fionnuala Ní Áinle<sup>1,4,5</sup>, Naomi Mc Callion<sup>2,3</sup>, Patricia Maguire<sup>1</sup>

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2. Department of Paediatrics, Rotunda Hospital, Dublin 1
3. Department of Paediatrics, Royal College of Surgeons in Ireland, Dublin 2
4. Department of Haematology, Mater Misericordiae University Hospital, Dublin 7
5. Department of Haematology, Rotunda Hospital, Dublin 1

### Scientific abstract

The Extracellular Vesicles in Early preterm Neonates and Thrombin generation study (EVENT) was a prospective, observational study which sought to establish the roles of i) extracellular vesicles (EVs) and ii) thrombin generation in neonatal haemostasis and extrauterine transition. As part of this study platelet poor plasma (PPP) was generated from term (>37 weeks corrected gestational age) and preterm infants (<31 weeks corrected gestational age). Four groups of infants from the EVENT cohort were analysed as follows preterm day 1 (n=10), preterm day 3 (n=10), term day 1 (n=5) and term day 3 (n=5).

An EV fraction was enriched using a sucrose cushion ultracentrifugation protocol and presence of EVs was confirmed by Tumour Susceptibility Gene 101 protein (TSG101) on western blotting.

A commercially available sample preparation kit (Preomics iST-BCT (Preomics GMBH, Germany)) was used for tandem mass spectrometry (MS/MS). 209 proteins were identified in at least 50% of the subjects from one of the four groups (Term, Preterm, Day 1 and Day 3). These were analysed using Euclidean distance to cluster using the Pheatmap package in R (R foundation for statistical computing, Vienna, Austria).

EV proteomics alone could reliably differentiate preterm from term infants using these methods. Analysis limited to proteins regarded as “significantly” different by Perseus analysis software (n=74 proteins) could still distinguish preterm from term infants. Infants did not cluster according to day of life, preeclampsia during pregnancy or the eventual development of BPD.

EV proteomics may offer new insights into the differing biology of transition between preterm and term infants. Future work will seek to elucidate the precise mechanisms underpinning the different proteomic profiles in these two groups.

### Lay Summary

Around 10% of all babies globally are born too soon. While our ability to care for these preterm babies has improved in the last number of decades their long term health is still different from babies who are born around their due date.

The EVENT study (Extracellular Vesicles in Early preterm Neonates and Thrombin generation study) was a study conducted to see what roles small particles in the blood called extracellular vesicles (EVs) may have as preterm babies adapt to life outside of the womb. Here we describe that the contents of these particles differ between term and preterm infants.

We hope this will help us understand why we see long term differences between these babies and may show us strategies to improve their outcomes.

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Daniel O'Reilly

Positive feedback

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4ward North PhD Academy Fellow

## Targeting miR-21 to inhibit the inflammatory response following ischaemic kidney injury

Emily K Glover<sup>1</sup>, Gary Reynolds<sup>1</sup>, Laura Denby<sup>2</sup>, Simi Ali<sup>1</sup>, Rachel Lennon<sup>3</sup>, Neil S Sheerin<sup>1</sup>

1. Translational and Clinical Research Institute, Newcastle University, UK
2. Centre for Cardiovascular Sciences, University of Edinburgh, UK
3. Division of Cell Matrix Biology and Regenerative Medicine, University of Manchester, UK

### Scientific abstract

#### *Background*

Kidney transplantation is the optimum renal replacement therapy in kidney failure and imbalance between organ supply and demand results in death on the waiting list. There is therefore a drive to increase the quality and availability of donor organs. One approach is to target the damage incurred from ischaemia during retrieval, transportation and during reperfusion. As key regulators of cellular processes, microRNAs are a potential target to modulate kidney injury pathways. miR-21 plays a role in ischaemia-reperfusion injury in kidneys and I hypothesise that blocking this microRNA with anti-miR-21 will be protective.

#### *Aims*

To test my hypothesis, I will investigate:

- The mechanism of cellular uptake of anti-miR into tubular epithelial cells
- The effects of miR-21 on gene transcription and translation
- The impact of anti-miR-21 on apoptosis
- If anti-miR-21 is protective against ischaemia-reperfusion injury in ex-vivo kidneys and so assess if miR-21 is a useful therapeutic target in transplantation

#### *Methods*

I will investigate my aims first through administration of anti-miR21 to proximal tubular epithelial cells isolated from human kidneys. I will then progress to administer anti-miR-21 to ex-vivo human kidneys during normothermic machine perfusion. To assess the impact of miR-21 blockade I will measure kidney injury markers, physiological and biochemical parameters of kidney perfusion and function, perform histological assessment of kidney injury and measure apoptosis. RNA-Seq and unbiased, global proteomics will be used to determine the effect of ischaemia-reperfusion and anti-miR-21 on gene expression in ex-vivo and cell culture models, thus elucidating its mechanism of action.

#### *Conclusion*

This project aims to further define the role of miR-21 in kidney ischaemia-reperfusion injury and the effects of its blockade. In doing so, I hope to identify strategies to improve donor organ quality and therefore the available pool for transplantation.

### Lay Summary

If a person's kidneys stop working, it is called kidney failure. Without treatment, kidney failure shortens a person's life. A kidney transplant is the best treatment to replace kidney function. Many kidney transplants come from people who have died. These kidneys have low oxygen levels when the donor is dying and whilst the kidneys are being transported. Kidneys that are without oxygen for longer stop working sooner meaning the patient will need another kidney transplant. I am investigating whether we can reduce the injury that happens from low oxygen levels by using a treatment called anti-miR21. This targets a key regulator of the injury process. If we can reduce the injury in the transplanted kidneys, they could last longer so people would need a new transplant less soon. This would be better for the patient and also shorten the transplant waiting list.

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Emily Glover

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**Seronegative autoimmune encephalopathies: biomarker characterisation and deep phenotyping**

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1. St Vincent's University Hospital, Department of Neurology
2. Neuroimmunology Laboratory, Mayo Clinic, Rochester, Minnesota, USA

**Scientific abstract***Background*

Autoimmune encephalopathies represent a body of treatable, brain disorders for which neural autoantibody biomarkers have existed since 2004. The rate of discovery of novel neural antibodies has grown dramatically since 2004 with an average of one-to-two antibody-mediated CNS disorders defined annually. Predictably, autoimmune encephalitis has trebled in incidence in the past twenty years. However, multiple epidemiological studies have demonstrated that half of all cases remain seronegative. Defining IgG biomarkers of seronegative autoimmune encephalopathy has important diagnostic, therapeutic, and prognostic significance. There is therefore a critical and unmet need to identify biomarkers in seronegative autoimmune encephalopathies.

*Aims*

- Identify disease-specific novel IgG biomarkers in seronegative autoimmune encephalopathies
- Assess molecular validity of novel autoimmune encephalopathy IgG biomarkers
- Deep phenotype and cohort seronegative autoimmune encephalopathies clinically and paraclinically

*Methods*

The patient cohort consists of 100 confirmed autoimmune encephalopathy patient CSFs and serums which have an immunofluorescence staining pattern that resembles anti-amphiphysin autoimmunity, but which are negative for this antibody on cell-based assay. Specimens in which neural IgG reactivity is confirmed via tissue immunohistochemistry will be evaluated by proteome microarray, testing those with identical patterns of tissue staining side-by-side, and alongside controls. Microarrays will each contain 15, 889 of the 19, 613 canonical human proteins (81%) in recombinant form. Verification of microarray results will be performed using Phage-library display immunoprecipitation sequencing. Novel biomarkers identified will be validated using established antigen-specific methods such as cell-based assay. Clinical and paraclinical data including MRI, EEG, serology and CSF results will be evaluated and compared to those of controls to assess for differentiated phenotypes.

*Conclusion*

We expect disease-specific IgG biomarkers to be characterised in patients with seronegative autoimmune encephalopathy, leading to the definition of novel immune-mediated CNS disorders with distinct clinical phenotypes.

**Lay Summary**

Autoimmune encephalopathies are recently-described disorders which occur when the body's immune system attacks the brain. They occur when antibodies (proteins developed as a response to a foreign entity, usually infection or a tumour) are created and provoke an immune attack on the brain or spinal cord.

Recognising and diagnosing these conditions is important as early treatment improves the chances of a full recovery. In some cases, these conditions can be associated with an underlying cancer; in other cases no cancer is found but long-term immune treatment is needed. Doctors are guided by the type of antibody causing the patient's symptoms as this gives the doctor information on the treatment needed and which cancer to seek.

However, half of all cases do not have an antibody detected in the blood or spinal fluid. We believe that these patients have antibodies that have not yet been discovered. These antibodies, if discovered, may provide doctors with important information on what cancers are associated with this antibody and which treatment options are best suited for individual patients.

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Michael Gilligan

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## Randomised controlled trials of antihypertensive therapy: does exclusion of orthostatic hypotension alter treatment effect? A systematic review and meta-analysis

### Scientific abstract

#### *Background and Purpose*

Management of antihypertensive therapy is challenging in patients with symptomatic orthostatic hypotension, a population often excluded from randomised controlled trials of antihypertensive therapy. In this systematic review and meta-analysis, we sought to determine whether the association of antihypertensive therapy and adverse events (e.g. falls, syncope), differed among trials that included or excluded patients with orthostatic hypotension.

#### *Methods*

We performed a systematic review and meta-analysis of randomised controlled trials comparing blood pressure lowering medications to placebo, or different blood pressure targets on falls or syncope outcomes and cardiovascular events. A random-effects meta-analysis was used to estimate a pooled treatment-effect overall in subgroups of trials which excluded patients with orthostatic hypotension and trials which did not exclude patients with orthostatic hypotension, and tested P for interaction. The primary outcome was fall events.

#### *Results*

46 trials were included, of which 18 trials excluded orthostatic hypotension and 28 trials did not. The incidence of hypotension was significantly lower in trials that excluded participants with orthostatic hypotension (1.3% versus 6.2%,  $P < 0.001$ ) but not incidences of falls (4.8% v 8.8%;  $P = 0.40$ ) or syncope (1.5% v 1.8%;  $P = 0.67$ ). Antihypertensive therapy was not associated with an increased risk of falls in trials that excluded (OR 1.00, 95% CI; 0.89-1.13) or included (OR 1.02, 95% CI; 0.88-1.18) participants with orthostatic hypotension ( $P$  for interaction=0.90).

#### *Conclusion*

The exclusion of patients with orthostatic hypotension does not appear to affect the relative risk estimates for falls and syncope in antihypertensive trials.

### Lay Summary

The management of hypertension (high blood pressure) and orthostatic hypotension (low blood pressure on standing) is challenging. These two conditions commonly co-exist, however some trials of anti-hypertensive medications did not include individuals with both conditions. The objective of our study was to compare rates of adverse events (side effects) in trials which excluded individuals with orthostatic hypotension, compared to trials which did not exclude individuals with orthostatic hypotension. We found that the exclusion of people with orthostatic hypotension did not significantly alter safety effects (e.g. falls/fracture), however the number of hypotension (low blood pressure) and falls events was lower in trials which excluded individuals with orthostatic hypotension.

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## Catriona Reddin

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## Feeding Outcomes and Influencing Factors in Infants with Hypoxic Ischaemic Encephalopathy: A Mixed-Methods Study

Sarah Edney<sup>1</sup>, Lindsay Pennington<sup>1</sup>, Anna Basu<sup>1</sup>, Judith Rankin<sup>1</sup>, Farag Shuweidhi<sup>2</sup>

1. Population Health Sciences Institute, Newcastle University
2. School of Medicine, University of Leeds

### Scientific abstract

#### *Background*

Hypoxic ischaemic encephalopathy (HIE) is a brain injury occurring in the perinatal period. It is the most common form of neonatal brain injury in term-born infants, occurring in 3 per 1,000 live births. Many children with HIE develop lifelong neurodisabilities, including cerebral palsy and feeding disorders. At present there are no reliable data on the epidemiology or impact of HIE-related feeding disorders. This impedes parent counselling, intervention development, and the design of robust cohort and intervention studies.

#### *Aims*

- Determine the prevalence, characteristics, outcomes, and impact of HIE-related feeding disorders
- Identify factors associated with positive and negative feeding outcomes in young children with HIE, including modifiable factors to be harnessed in intervention development

#### *Methods*

Convergent mixed methods design.

#### *Quantitative*

1. Retrospective National Neonatal Research Database analysis: Records for approximately 10,000 infants with HIE will be analysed to determine the prevalence and factors predictive of feeding disorders at the point of discharge from the neonatal unit.
2. Prospective longitudinal cohort study: 70 infants will be recruited from neonatal units around the UK. Prospective feeding outcomes data will be collected at 1, 3, 7, and 12 months old, including outcomes for breastfeeding and lactation, enteral feeding, feeding disorder symptoms, and impact on the family.

Data will be analysed using risk and odds ratios, longitudinal logistic regression modelling, and survival analysis.

#### *Qualitative*

Parents of preschool aged children with HIE will be purposively sampled and interviewed about the impact of and what they feel has influenced their child's feeding outcomes.

Data will be analysed using Braun and Clarke's (2022) thematic analysis methods.

#### *Impact*

This study will provide HIE-related feeding disorder epidemiology data and identify modifiable factors that influence feeding outcomes. Findings will inform clinical decision-making, parent-counselling, health service planning, intervention development, and provide baseline statistics and feasibility considerations for future cohort and intervention studies.

### Lay Summary

Hypoxic ischaemic encephalopathy (HIE) is a brain injury that occurs around the time of birth due to a lack of oxygen. HIE is the most common form of brain injury in term-born infants and many children with HIE develop lifelong neurodisabilities, including cerebral palsy and feeding disorders. At present, not enough is known about HIE-related feeding disorders to provide parents with reliable information about their child's future or to develop effective feeding interventions. This study will use the National Neonatal Research Database, data from parent questionnaires over the first year of life, and parent interviews to determine which factors make positive and negative differences to feeding outcomes after HIE. These findings will facilitate information sharing with parents, enable clinicians to proactively provide support and therapies for high-risk infants and their families, and will provide essential baseline data for future large-scale cohort and intervention studies.

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Sarah Edney

Positive feedback

Constructive feedback

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**Characterising patients with chronic spontaneous urticaria that do not respond to omalizumab**K Ridge<sup>1</sup>, B Moran<sup>2</sup>, C O' Farrelly<sup>2</sup>, N Conlon<sup>1</sup><sup>1</sup>School of Medicine, Trinity College Dublin<sup>2</sup>School of Biochemistry and Immunology, Trinity College Dublin**Scientific abstract***Background*

There is a growing body of evidence to suggest that patients with chronic spontaneous urticaria (CSU) who do not respond to, or are slow to respond to omalizumab, represent a specific phenotype of disease known as type iib autoimmune CSU. It has been posited that these patients are more likely to have a low serum IgE, the presence of thyroid autoantibodies and positive basophil testing. However none of these measurements in isolation perfectly predict treatment response.

Identifying subtypes of urticaria at an early stage of disease may better equip clinicians to choose the most effective treatment for individual patients when they need it most. There are also important economic considerations in prescribing expensive medications to all patients with antihistamine refractory CSU, as our understanding of this condition evolves. Importantly, it is becoming clear that emerging treatments for urticaria including ligelizumab and femibrutinib, may be more effective in patients with type iib autoimmune CSU. This study assesses mast cell progenitors in peripheral blood of patients with CSU and compares responders to omalizumab therapy vs non- responders to omalizumab therapy.

*Methods*

Participants were individuals with antihistamine refractory CSUA listed for omalizumab over the age of 18. Responders were defined as patients with a Urticaria Control Test (UCT) of 12 or higher after 90 days on omalizumab. Non-responders were defined as patients with a UCT of 11 or lower after 90 days on omalizumab. Blood samples were collected from participants. PBMCs were isolated from fresh blood samples. Flow cytometry was used to identify cells which were negative for CD4, CD8, CD19 and CD14 and positive for CD34, CD13, CD117 and Fcε-R1.

*Results*

Eighteen individuals with CSU met the criteria for analysis. Ten participants were deemed 'responders'. Eight participants were deemed 'non-responders'. Individuals who responded to omalizumab had higher numbers of circulating mast cell progenitors when compared with individuals who did not respond to omalizumab ( $p = 0.0081$ ).

*Conclusions*

Preliminary results suggest that patients with chronic spontaneous urticaria with improved urticaria symptomatology within 90 days of starting omalizumab therapy have significantly higher numbers of circulating mast cell progenitors in their peripheral blood. This assay may be used as a contributory tool in identifying subtypes of urticaria that respond differently to anti IgE therapy.

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Katie Ridge

Positive feedback

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**Topical steroids stimulate T cell-dependent melanoma growth control**

Charles H. Earnshaw<sup>1</sup>, Agrin Moeini, Shih-Chieh Chiang, Eduardo Bonavita, Charlotte R. Bell, Maria Koufaki, Christopher E. M. Griffiths & Santiago Zelenay

1. Department of Cancer Inflammation & Immunity, Cancer Research UK Manchester Institute, University of Manchester, SK10 4TG, UK

**Scientific abstract**

Melanoma is the deadliest form of skin cancer. Treatment with immune checkpoint blockade (ICB) has transformed outcomes. However, half of melanoma patients do not derive long-term benefit and many face toxicities. Side-effects of ICB are typically managed by systemic or topical treatment with steroids, widely known for their immunosuppressive effects. Our lab recently showed that combining steroids with ICB improves outcomes in certain preclinical cancer models. Thus, understanding the dual role of steroids in cancer progression, and their effect on the tumour immune microenvironment, is critical.

In an intradermal murine melanoma model unresponsive to ICB, we found that topical, but not systemic, steroid treatment significantly impairs tumour growth. Intriguingly, this effect was lost in Rag1<sup>-/-</sup> mice or in mice depleted of CD8<sup>+</sup> T cells, uncovering a key role for T cells in steroid induced tumour growth control. CRISPR knockout of the glucocorticoid receptor in tumour cells abrogates this effect, suggesting glucocorticoids act directly on tumour cells to stimulate anti-tumour immunity. Analysis of TCGA data shows melanoma patients with high steroid receptor expression have better overall survival, and increased cytotoxic lymphocyte infiltration.

Ongoing work aims to characterise the local and systemic molecular and cellular effects of topical steroid treatment, and to investigate their relevance in human melanoma. Given the widespread use of steroids in patients receiving ICB, these unexpected findings may have significant clinical impact.

**Lay Summary**

Melanoma is the deadliest form of skin cancer, and the fifth most common cancer in the UK. Only half of patients with advanced melanoma survive for five years, meaning there is a significant need to improve treatment outcomes. We set out to assess whether cream-based treatments, used widely in the treatment of a range of skin diseases but not melanoma, could improve the immune response to mouse models of melanoma. We discovered that topical steroids, a medication often given to reduce the activity of the immune system, were able to reduce melanoma growth in mice. Unexpectedly, this effect required the presence of immune cells. Therefore, it appears that steroids have the potential to improve immune responses to melanoma. The precise reasons for this response, and the potential ways that this finding could be used in the clinic, are being investigated.

**Scientific abstract**

Polycystic ovary syndrome (PCOS) is a prevalent disorder affecting 10% of women, and is defined by androgen excess (AE). PCOS is associated with severe metabolic health consequences across the entire life course of women. There is a two-fold increased risk of type 2 diabetes mellitus and nonalcoholic fatty liver disease, as well as emerging evidence of increased incidence of cardiovascular disease. There are no disease-specific therapies to mitigate or treat metabolic risk in women with PCOS. This is consistently highlighted as the priority concern amongst PCOS patient advocacy groups.

Skeletal muscle is an important site of energy metabolism; increasingly it is suspected that skeletal muscle energy balance is adversely impacted by androgens, thereby driving metabolic complications. To take this theory forward, we want to investigate the effects of androgens on muscle energy metabolism. We will perform in-dept metabolic phenotyping in women with PCOS before and after androgen receptor blockade for 28 days. In addition, we will be using a gold standard technique to see how women with PCOS metabolise fat and other nutrients by measuring markers in blood and breath samples after a breakfast test meal. Using an in vitro approach, we will carry out experiments to define the impact of androgens on human skeletal muscle biology. Taken together this research will increase our understanding of the complex relationships between AE and metabolic disease in women with PCOS.

Our research study has 3 aims:

1. To identify differences in the non-targeted serum metabolome and skeletal muscle proteome at baseline in women with and without PCOS
2. To understand the impact of androgen receptor (AR) blockade on muscle energy metabolism in vivo in women with PCOS through measurement of whole-body fatty acid oxidation changes
3. In vitro characterisation of the impact of androgens on human skeletal muscle morphology and proteogenomics

**Lay Summary**

Polycystic ovary syndrome (PCOS) affects 10% of all women, usually co-existing with high levels of sex hormones called androgens (e.g. testosterone). Women with PCOS are at increased risk of metabolic complications such as diabetes. However, very little is understood about how androgen excess may drive the metabolic complications observed in women with PCOS.

To understand the role of androgens further, we will perform detailed metabolic testing (by way of bloods and muscle biopsies) in women with PCOS and in healthy women to identify any differences. A subset of women with PCOS will take tablets for 28 days that block the action of testosterone. We will take breath, muscle, and blood samples before and after the tablets to see if we can observe changes in how the body and skeletal muscle metabolises energy and fats. Additionally, we will be performing energy metabolism experiments on skeletal muscle cells to complement the other projects.

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Leanne Cussen

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## Enhancing chemotherapy efficacy in *Fusobacterium nucleatum* infected, mesenchymal subtype colorectal cancer using a novel Inhibitor of Apoptosis Protein antagonist, tolinapant

Timothy O'Brien<sup>1</sup>, Vicky Coyle<sup>2</sup>, Daniel Longley<sup>2</sup>

1. Medical Oncology SpR, University Hospital Waterford
2. Patrick G Johnson Centre for Cancer Research, Queen's University Belfast

### Scientific abstract

#### Background

Colorectal cancer (CRC) is a common cause of cancer death in the UK and Ireland responsible for approximately 17,000 deaths annually.(1, 2) It is a heterogenous disease that may be classified into Consensus Molecular Subtypes (CMS1-4) based on gene expression and morphology.(3) The mesenchymal subtype (CMS4) represents approximately 25% of all CRC and is associated with the highest risk of relapse and lowest overall survival.

Recent work from Longley and collaborators showed that mesenchymal CRC infected with the bacterium *Fusobacterium nucleatum* (*Fn*) has a particularly poor prognosis.(4) This may be due to the ability of *Fn* to increase tumour resistance to chemotherapy through suppression of apoptosis.(5)

Tolinapant, a second generation IAP antagonist, has demonstrated safety and tolerability in phase 1 clinical trials in advanced solid tumours and lymphoma.(6) Preclinical studies have indicated activity against CRC cell lines and a phase 1 clinical trial of chemotherapy combined with tolinapant in metastatic colorectal cancer is in progress.

#### Aims & objectives

This PhD aims to provide preclinical evidence that targeting the anti-apoptotic effects of *Fn* using a clinically relevant Inhibitor of Apoptosis Protein (IAP) antagonist, tolinapant, can sensitise mesenchymal, *Fn*-infected CRC to chemotherapy.

The main objectives are to demonstrate this effect in human CRC cell co-cultures and more complex murine organoid and *in vivo* models.

#### Methods

1. Human spheroid *in vitro* co-culture models – generating spheroids from commercially available CRC cell lines, co-culturing with *Fn* and treating with chemotherapy, tolinapant or combination.
2. Murine *in vitro* organoid models – co-culturing CMS4-specific murine organoids with *Fn* and treating with chemotherapy, tolinapant or a combination.
3. *In vivo* CMS4 specific murine model – co-culturing organoids with *Fn* before injection into the submucosa of mouse colons and treating with chemotherapy, tolinapant or a combination.

#### Analysis

Conventional techniques including Western blotting, light microscopy, cell viability assays, cytokine ELISA as well as the innovative CellDIVE platform, a multiplexed immunofluorescence technique.

#### Impact

This PhD seeks to provide rationale for human trials of tolinapant in combination with chemotherapy in patients with *Fn*-infected, mesenchymal-subtype CRC, offering a potential therapeutic option in an aggressive disease with a poor prognosis.

### Lay summary

Bowel cancer is the 2<sup>nd</sup> and 3<sup>rd</sup> most common cause of death from cancer in Ireland and the UK, respectively. Chemotherapy is used to reduce relapse (stage 3 disease) and to prolong life (stage 4 disease). It works by damaging the DNA (genetic code) of cancer cells causing them to die by a process called apoptosis. Unfortunately, cancer cells can find ways of avoiding apoptosis and therefore become resistant to chemotherapy. This can lead to a recurrence of the cancer (relapse) and frequently death.

There are different subtypes of bowel cancer which behave differently depending on the DNA within the cancer cells. About a quarter of patients with bowel cancer have a subtype called mesenchymal, which is particularly aggressive – it has the highest rate of relapse and lowest survival. Recently, researchers at the Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, found that this subtype of bowel cancer is twice as likely to relapse when infected with a bacteria called *Fusobacterium nucleatum*. Other researchers have shown that these bacteria can help bowel cancer cells to resist chemotherapy and avoid apoptosis.

A new drug, tolinapant, can switch on apoptosis when cell DNA is damaged by chemotherapy. This project will investigate whether tolinapant can increase the ability of chemotherapy to kill the mesenchymal subtype bowel cancer cells and counteract the effects of *Fusobacterium*.

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Timothy O'Brien

Positive feedback

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## Determining novel receptor signalling pathways in T cells in health and cancer

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2. Division of Immunology, Immunity to Infection, and Respiratory Medicine, University of Manchester
3. Division of Pathology and Data Analytics, University of Leeds.
4. Lydia Becker Institute of Immunology and Inflammation, University of Manchester

### Scientific abstract

#### *Background*

The Ladbury Group has proposed that signalling mechanisms that are initiated by receptor tyrosine kinases (RTK) are described by two tiers: Tier 1 (RTK activity-dependent) and Tier 2 (proline-rich motif-SH3 domain driven). In the absence of the 'on-off switch' provided by tyrosine phosphorylation in Tier 1 signalling, Tier 2 signal transduction is solely dependent on relative concentrations of SH3 domain-containing proteins in competitive binding to proline-rich motifs. Tier 2 signalling is normally involved in cell homeostasis but in aberrant conditions can lead to cancer in epithelial cells. This proposal explores the role of Tier 2 signal transduction in immune cells, particularly T cells.

#### *Aims*

1. Identify interactions between receptors on T cells that contain proline-rich motifs and SH3 domain-containing proteins using a discovery approach to screening.
2. Characterise the effect of these interactions on the phenotypic behaviour of T cells and downstream signalling cascades.

#### *Methods*

- Biotin-tagged peptides containing proline-rich motifs from sequences on T cell receptors will be used to screen for interacting SH3 domain-containing proteins from serum-starved Jurkat cell lysates.
- An orthogonal high throughput screen with SH3 domain-containing proteins will be utilised.
- Changes in cell behaviour will be observed by knocking down identified SH3 domain-containing proteins or mutating the proline-rich motif on the relevant T cell receptors.
- Results will be validated in primary T cells and downstream signalling pathways characterised.

#### *Results*

- Initial western blotting experiments show pulldown of Grb2, Nck, Src, PLC $\gamma$ 1 and Lck using a CD3 $\epsilon$  peptide sequence with proline-rich motifs (and a scrambled sequence as control).
- Initial silver staining showed differential band expression between CD3epsilon peptide lane and scrambled sequence.
- Experiments with CD2, CD28 and CTLA4 are planned.

#### *Conclusion*

This study will be the first to explore the role of Tier 2 signalling in T cells and its relevance in cancer.

### Lay Summary

There is a large literature on the inner functioning of the building blocks of life: i.e. the cell, underlying disease states such as cancer. Although we have a good understanding of how some of these mechanisms in certain cell types (epithelial cells) cause human cancer, such as lung and ovarian cancer, there is more work needed to understand how these signalling mechanisms function in cells of the immune system, particularly in the human body's fight against cancer. We seek to understand through primary laboratory work how a novel signalling mechanism identified as being associated with cancer in epithelial cells could also be functioning in cells of the immune system, including in the context of how the immune system responds to disease states such as cancer. This would open up new ways of enhancing the body's defences against cancer.

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Debamita Bhattacharjee

Positive feedback

Constructive feedback

Any other comments

## Significant costs associated with investigation and treatment of apparent treatment-resistant hypertension in a specialist multidisciplinary clinic.

### Scientific abstract

#### *Objectives*

Hypertension represents the greatest burden of non-communicable disease associated morbidity and mortality globally. There is a high rate of medication non-adherence amongst patients with hypertension, which may be a source of unnecessary hospital use and costs in already budget constrained health systems. This study reports on the cost of providing care in a multidisciplinary hypertension clinic staffed by nephrologist, endocrinologist and cardiologist which manages patients with suspected secondary hypertension and hypertension which has proven difficult to control in primary care. Specialist clinics of this type are not commonplace and little evidence exists about on their cost and budget impact. The aim of this study is to provide the evidence required to inform policy and planning for care pathways relating to hypertension.

#### *Methods*

A cost-analysis, from a healthcare provider perspective, using micro-costing methods, was conducted to estimate the direct implementation costs of existing standard practice for the care pathway of patients attending the multidisciplinary hypertension clinic. 65 patients originally recruited for a study of medication adherence in hypertension were included in the sample.

#### *Results*

The total care-pathway cost per patient, taking into account clinic visits, clinical reviews, investigations and MDT discussion, was estimated to be €2964, on average. For the patient subgroups, the average cost was €5001 for patients diagnosed with primary aldosteronism and €1400 for patients diagnosed with essential hypertension.

#### *Conclusions*

There is significant cost associated with providing specialised hypertension care for patients with apparent treatment-resistant hypertension. Given the high rates of non-adherence in this population, it is likely that some of this cost could be avoided with better detection and management of medication adherence in this challenging population. Future studies should consider the cost-effectiveness of this or similar models of care by exploring the benefit to patients and the wider healthcare context of providing care of this type.

### Lay Summary

Hypertension (high blood pressure) is a common health problem that contributes to several serious health complications such as heart attack, stroke and kidney disease. Hypertension can usually be controlled with medication, but many people do not take hypertension medication as prescribed (this is called medication adherence). This may mean that the health service spends time and money testing and treating hypertension that appears to be uncontrolled when in fact the problem is that patients may not have taken their medication as prescribed.

By calculating the cost of staff time and every item required to run the clinic and provide all of the appropriate follow-up care to patients who attend the clinic, we calculated the cost to the health service of running this clinic. It costs €2964 on average to see a person in this clinic. This research will allow us to consider the cost-effectiveness of the care we provide and plan to provide healthcare services as appropriate.

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Louise Rabbitt

Positive feedback

Constructive feedback

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## The role of respiratory mucosal tissue resident memory T cells in protective immunity to *Bordetella Pertussis* in humans

K. McCarthy, R. McLoughlin, K.H.G. Mills

School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Ireland

### Scientific abstract

#### *Background*

The objective of the study is to investigate if tissue resident memory T (TRM) cells specific for *Bordetella pertussis* are present in human respiratory mucosal tissues and to determine the impact of immunisation with acellular pertussis (aP) or whole cell pertussis (wP) vaccines in childhood on the frequency of *B. pertussis*-specific TRM cells.

#### *Methods*

Techniques to isolate mononuclear cells and identify antigen-specific TRM in human tonsil, nasal and airway epithelial tissue have been developed and optimised. Adults who received wP and aP vaccination in childhood were recruited to compare tissue and blood antigen-specific TRM frequency and function. In different recruited cohorts tonsil, blood, nasal or airway epithelial mononuclear cells were isolated and cultured with *B. pertussis* antigens and antigen-specific cytokine producing TRM cells were quantified by flow cytometry.

#### *Results*

We identified IFN- $\gamma$  and/or IL-17-producing CD69+CD103- and CD69+CD013+ CD4+ TRM cells in human tonsil, nasal and airway tissue, but not in peripheral blood. These cells were expanded by culture with sonicated *B. pertussis* (SBP). Adults who received wP vaccine during routine childhood immunisation had significantly more *B. pertussis*-specific IFN- $\gamma$  producing TRM in tonsil tissue than aP vaccinated individuals ( $p < 0.05$ ). Building on this finding, we similarly identified that wP vaccine induces significantly more *B. pertussis*-specific IL-17 producing TRM in nasal tissue. Furthermore, airway *B. pertussis*-specific TRM have been identified and persist for decades following primary immunisation.

#### *Conclusion*

Our study demonstrates that immunisation with wP but not aP vaccines in childhood induces a population of antigen specific-cytokine producing TRM cells in respiratory mucosal tissues that persist up to 30 years following initial vaccination. In the murine model, these cells in the nose and lung have been associated with protection against infection following *B. pertussis* aerosol challenge. Immunisation strategies that aim to generate a population of protective TRM cells at mucosal site of infection are therefore more likely to induce more effective and sustained protective immunity in humans.

### Lay Summary

*Bordetella pertussis* is a bacteria that causes whooping cough, a serious illness in young children. Vaccines are available to protect us against whooping cough, which we know produce strong immune responses in the blood. New findings from animal research studies have shown the importance of immune responses in the parts of the body where the bacteria first enters; the lining of the nose and lungs. We do not know if current vaccines cause immune responses in the nose and lung in humans or what this tells us about how well the vaccine protects us from the disease. In this study, people who received different types of whooping cough vaccines as children donated blood and tissue samples. We compared the types of immune cells in these samples and how these cells respond when they encounter *B. pertussis* bacteria again. People who received an older vaccine type; "whole cell vaccine", had stronger immune responses in the nose and tonsil that people who received the current vaccine; "acellular vaccine". This finding might help to explain why there has been an increase in whooping cough cases in recent years. Developing a new, safe whooping cough vaccine that causes strong protection in the nose and lung as well as the blood may be helpful to curb the spread of whooping cough and protect vulnerable babies who have not received all of their immunisations yet.

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Karen McCarthy

Positive feedback

Constructive feedback

Any other comments