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ABSTRACT BOOK

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Thursday 28th November

Brian O'Mahony — Session 1, Pre-PhD

Title: Strategic Timing of Resistance Training to Guard Against Antipsychotic Induced Metabolic Syndrome (START GAAIMS)

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Scientific Abstract

Background

There is a growing health gap between individuals with enduring psychotic disorders and the general population, with the former group having a reduced life expectancy by nearly twenty years (Laursen et al, 2011). A major contributor to these lost years of life is the metabolic side effects of antipsychotic medication (Pillinger et al 2020). The mechanisms of this effect are multifactorial, with weight gain likely being primarily driven by the orexigenic effects of antipsychotics' H1 and 5-$HT2_a$ antagonism, leading to increased food consumption.

A caloric surplus enhances resistance training by increasing its effects on muscle strength and hypertrophy (Slater et al, 2019). Additionally, resistance training enhances skeletal muscle glucose regulation through the GLUT4 receptor, whose activity is itself downregulated by antipsychotic medication (Yaspelkis et al, 2006).

No study to date has investigated the effects of using a resistance training programme, in individuals taking antipsychotic medication, on building lean body mass. An especially important time to intervene is when the patient first commences on antipsychotic medication, as this time period carries the largest risk of weight gain.

Aims

1. Quantify the weight gain induced by different antipsychotics at given time-points.
2. Identify the effects of resistance training on the lean body mass and metabolic profile of individuals who are taking antipsychotic medication
3. Assess whether resistance training can ameliorate or reverse the biochemical effects of antipsychotic use on skeletal muscle
4. Identify barriers to implementing a resistance training programme in a cohort of patients recovering from a first episode of psychosis

Methods

Study 1: A systematic review to identify any non-pharmacological interventions to mitigate antipsychotic-induced weight gain

Study 2: Use of individual patient data from electronic healthcare databases and research papers to analyse the weight gain associated with different antipsychotic medications over time.

Study 3: A feasibility Randomised Control Trial to assess the use of resistance training on the metabolic profile of patients who have been newly prescribed antipsychotic medication

Study 4: Assess the biochemical mechanisms of resistance training and antipsychotic use on skeletal muscle

Study 5: A qualitative study of patients recovering from a first episode of psychosis, who participated in a resistance training programme

Impact

Should this intervention show promise, it would encourage funding towards facilitating use of resistance training in this patient cohort. It would also provide an insight into the mechanism of antipsychotic-induced weight gain. Lastly, exact quantification of weight gain for each antipsychotic will help to guide patient and clinician decision-making.

Lay Summary

Psychosis is a mental health condition where a person loses touch with reality. It affects how people think, feel, and understand the world around them. People who suffer from psychosis are prescribed medication called antipsychotics, which can cause weight gain in people who take them. Doctors and scientists are unsure the exact reasons why this happens, but these medications increase people's appetite. This leads them to eat more food and gain weight.

To get the most out of resistance training (or weightlifting), people benefit from eating more food. This helps the exercised muscles to recover better, helping them to become bigger and stronger.

We want to investigate whether the weight gain caused in someone who is taking antipsychotic medication can be made better by the person partaking in a resistance training programme. We believe that the increased appetite might even be turned into a positive, helping the person to gain strength and muscle, which is important in improving their quality of life, both now and in the future.

We also want to clarify how much weight gain people can expect to gain when they use antipsychotics, which might help doctors and patients to choose a medication that best suits them.

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Title: Molecular Approaches to Diagnosing and Managing Pulpitis in Equine hypsodont teeth ('DAMPEN')

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Scientific Abstract

Background

Pulpitis is a common disease in equine hypsodont teeth (EHT) that is traditionally managed by extraction[1,2]. Vital pulp treatment (VPT) is a conservative alternative that has been promoted recently in humans but is complicated in EHT by complex root canal systems and the lifelong juvenile state of eruption[3,4]. In order to improve VPT strategies and outcomes in diseased EHT it is critical to understand the molecular mechanisms of dental pulp cell (DPC) mineralisation and repair in comparison with both brachydont and human teeth. There is currently a lack of available information on this subject.

Aims

The overarching aim of this project is to investigate the pulpitic response in EHT to microbial challenge with the aim of identifying potential diagnostic therapeutic targets for use in regenerative VPT.

Methods

- To review the molecular characterization of pulpitis in equine teeth, highlighting current methodological issues as well as key mediators, pathways and focus areas for future research.
- To experimentally establish the molecular changes occurring in LPS stimulated primary DPCs from healthy EHT / brachydont teeth and compare with inflamed/ uninflamed DPCs from healthy human teeth, by using RNAseq analysis, candidate marker confirmation, bioinformatic analysis and proteomic array.
- To clinically characterise candidate mediators, molecules and pathways in inflamed EHT *ex vivo* by clinical collection of pulp tissue and teeth from veterinary clinics and abattoir by using gene/ protein expression, histology and immunohistochemistry.
- In combination with recombinant proteins (e.g. growth factors) and pharmacological inhibitors, siRNA knockdown to investigate the potential therapeutic benefits in inflamed equine DPCs of inhibiting key inflammatory mediators in pulpitis and repair as part of a topical VPT.

Impact

Understanding EHT pulpal inflammation and repair pathways will help to advance clinical equine endodontic diagnosis, regenerative treatment and horse welfare. From a ONE HEALTH perspective 'DAMPEN' may also act as a translational model to improve human VPT strategies.

Lay Summary

Dental decay is the main cause of inflammation, infection and toothache (called pulpitis). Pulpitis affects half the World's population[5,6]. Traditional treatment includes extraction and root canal treatment (RCT). RCT is technically challenging in horses' teeth and predisposes teeth to fracture[3,7]. Vital pulp treatment (VPT) preserves the cells in a tooth, while overcoming the limitations of RCT and is recommended in humans[8,9]. The centre of horses' cheek teeth contain dental pulp cells (DPCs). These cells contribute to repair and to a unique feature of horse's cheek teeth, their continual growth throughout life, a feature required for dietary reasons [4]. The mechanisms underlying inflammation and repair in horses' teeth is currently unknown. Within this study we plan to compare the response in human and horse teeth with a view to identifying targets and pathways that may benefit our understanding of the disease and improve our therapies in the future.

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Title: GLP-1 analogues reduce the incidence of endometrial cancer in an animal model

M Wilkinson[1], Karen Mulligan, Bruce Moran, Oleksii S. Rukhlenko, Eugene Kashdan Boris N. Kholodenko Aurelie Fabre, Janet Mc Cormack, Niall Docherty, Carel LeRoux, DJ Brennan[1,8*]

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Scientific Abstract

Background: GLP-1 analogues can stimulate apoptosis and autophagy in endometrial cancer cell lines. We sought to assess the effect of liraglutide on endometrial cancer development and local microenvironment in the BDII/HAN rat model.

Methods
38 BDII/Han rats were randomised into two groups at 12 months of age - a standard group (n=17) and a liraglutide + diet restriction group (n=21). Animals were sacrificed at 15 months of age and RNAseq, whole and phospho-proteomics performed on endometrial cancers and normal endometrium. Cell state transition assessment and regulation (cSTAR), analysis of transcriptomic, proteomic and phosphor-proteomic data was used to assess the mechanism of action of liraglutide on the endometrium.

Results
Liraglutide treatment caused a 15% weight loss and reduced incidence of endometrial cancer from 53% (9/17) in the standard group to 20% (4/20) in the intervention group, all of which were poorly differentiated serous, immune excluded cancers. cSTAR analysis demonstrated that Liraglutide upregulates transcription of numerous genes while their abundance at proteomic and phosphoproteomic levels are strongly downregulated and inhibits autophagy in normal endometrium. Liraglutide also inhibits estrogen signalling which in combination with inhibition of autophagy may support the development of serous cancers in an atrophic endometrium.

Conclusion
GLP-1 analogues reduce the rate of endometrial cancer in BDII/HAN rodent models however the cancers that developed in the liraglutide group were poorly differentiated, immune excluded serous cancers. Further data is required to establish the potential role of GLP-1 induced weight loss as an adjunctive treatment in endometrial cancer.

Margaret Brennan

Session 1, Pre-PhD

Title: Heat and adverse pregnancy outcomes: an individual participant data meta-analysis of harmonised cohorts and trials conducted in sub-Saharan Africa linked with geospatial data

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Scientific Abstract

Background

Climate change is one of the greatest threats to global health,[1] with rising temperatures leading to more frequent and intense heatwaves.[2] Pregnant women and babies have recently been identified as vulnerable to heat,[3] yet uncertainty remains about which aspects of heat exposure during pregnancy – cumulative dose, heatwaves or temperature fluctuations – are most harmful.[4] A limited number of pregnancy outcomes have been examined.[4] Threshold temperatures remain unknown, as are critical periods of vulnerability, high-risk groups and underlying mechanisms.[5]

Aim and objectives

This project aims to advance knowledge of the relationship between heat and clinical outcomes during pregnancy, and mechanisms that may mediate or moderate risks.

The specific objectives are as follows:

1. Examine the association between heat and perinatal mortality to identify risk thresholds, lagged effects and temporal trends.
2. Investigate whether hypertensive disorders of pregnancy and other maternal health disorders, contribute to the association between heat and adverse birth outcomes.
3. Assess whether timing of heat exposure during pregnancy differentially affects outcomes.
4. Examine the moderating role of other environmental factors such as air conditioning, housing type, air pollution and climate zone.
5. Quantify the proportion of adverse pregnancy outcomes attributable to heat.

Methods

A two-stage individual participant data meta-analysis approach will be conducted using a harmonised dataset of sub-Saharan studies linked with environmental data, encompassing 26,000 women, with an additional 10 studies currently undergoing harmonisation. Distributed lag linear and non-linear time-series models,[6] case-crossover, and random forest methodologies will be applied. Attributable risk of heat will be calculated as per Intergovernmental Panel on Climate Change methodologies.

Conclusion

This study will advance understanding of the relationship between heat and adverse pregnancy outcomes, which may inform clinical and public health strategies aimed at managing heat-related risks and reduce harms to mothers and children in a changing climate.[5]

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Lay summary

Climate change is the one of the biggest global health challenges we face, and increasing temperatures are especially worrying. We've recently learned that pregnant women and their babies are more vulnerable to heat, but we don't fully understand how heat affects them. This research will help us understand what temperatures should be considered dangerous for pregnant women, how long pregnant women can spend in heat and which stages of pregnancy are the riskiest for heat exposure. Using big data gathered from numerous studies on pregnant women in sub-Saharan Africa, combined with environmental data, we aim to answer these important questions to help protect pregnant women and their babies in a warming world. We also aim to leverage this data to advocate for international action to prevent further climate change and safeguard maternal and child health into the future.

Nicholas Stefanovic

Session 2, Pre-PhD

Title: Investigating the Mechanisms of Impaired Bone Health in Adult Patients with Atopic Dermatitis

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Scientific Abstract

Background

Atopic dermatitis (AD) is the most common inflammatory skin disorder worldwide; it is associated with systemic comorbidities, including impaired bone health (osteopenia, osteoporosis, osteoporotic fractures).[1,2] Patients with AD are at least twice as likely to develop impaired bone health, compared to those without.[3] Mechanisms underpinning this epidemiologic association are unclear and may include:

1. Deleterious bone health impact of treating AD (and other atopic comorbidities, e.g. asthma) with glucocorticoids.
2. Deleterious bone health impact of chronic, systemic type 2 inflammation.
3. Impaired bone health due to sleep disruption and reduced physical activity as a result of chronic itch.

Aims and Objectives

1. Estimate prevalence of impaired bone health among AD patients in the UK Biobank prospective cohort, using bone mineral density (BMD) and trabecular bone score (TBS) methodology.[4]
2. Pharmacoepidemiological analysis of cumulative, multi-route glucocorticoid exposure in the above cohort, aiming to establish a threshold beyond which risk of impaired bone health increases.
3. Serum proteomics analysis investigating differential systemic inflammatory pathways in AD patients with and without impaired bone health.
4. Analysis of behavioural factor impact on impaired bone health in AD patients.

Methodology

My project will utilise the UK Biobank, a prospective cohort of 500,000 volunteers aged 40-60.[5] AD patients will be identified via one of five diagnostic codes and validated using linked prescription data.

1. Raw DEXA data will be used to derive BMD and TBS measures.
2. Linked prescription data will be used, and cluster analysis will be performed to stratify participants by cumulative glucocorticoid exposure and bone health outcomes.
3. Differential expression analysis of serum proteomics data in AD patients with impaired bone health vs. those without.
4. Derived accelerometry data will be used to cluster patients by sleep/physical activity metrics and bone health outcomes.

Confounders will be identified via systematic literature review at project outset. Regression modelling will be used to assess relative contribution of each of the above mechanisms.

Impact

Understanding key pathophysiologic mechanisms will identify optimal targets for intervention with a view to preventing impaired bone health in AD patients. The project aims to guide targeted AD therapy and minimise comorbidity at the population level.

Lay Summary

Eczema is the most common inflammatory skin disease worldwide. We are increasingly understanding that patients with eczema are more likely to develop osteopenia and osteoporosis- conditions whereby bones become brittle and are more prone to breaking. We do not understand exactly why this is, but it may be due to one of three mechanisms:

1. Patients with eczema are often treated with steroids, which may negatively impact their bone health.
2. Patients with eczema have high levels of inflammation in the skin and blood, which may affect bone health.
3. Patients with eczema are less likely to engage in physical exercise and experience sleep disruption due to chronic itch, which impacts their bone health.

My project aims to investigate these three theories, using the UK Biobank- a large database of 500,000 participants and their health data. By investigating how much each of the three possible mechanisms contributes to poor bone health in eczema patients, we can select the most appropriate avenue for intervention to ensure patients with eczema do not develop osteopenia and osteoporosis.

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Owen Killian

Session 2, Pre-PhD

Title: DANCE-FND: Deep learning Analysis of Neurophysiology and Computer vision methods in the Evaluation of Functional Neurology and Dystonia

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3. Trinity College Institute of Neuroscience, Trinity College Dublin

Scientific Abstract

Background:
Functional Movement Disorder, a common condition, is a brain network disorder affecting sensory processing. Dystonia, another common disorder, affects similar pathways. Both face frequent misdiagnosis, impacting prognosis and quality of life. Diagnosis typically relies on subjective clinical evaluations, while neurophysiological gold standards remain inaccessible. Emerging alternatives, like kinematic analysis and computer vision, are yet to be applied to these disorders. Investigating shared biophysical abnormalities may uncover diagnostic biomarkers or therapeutic targets.

Objectives:

1. Conduct kinematic and neurophysiological assessments (accelerometry, EMG, computer vision) during scoring tasks for Dystonia and FMD patients.
2. Evaluate sensory processing (Temporal Discrimination Threshold, TDT) and perceptual decision-making (PDM) in untreated Dystonia and FMD patients versus controls.
3. Reassess kinematics and PDM six weeks post-treatment (botulinum neurotoxin therapy for Dystonia; rehabilitation for FMD).
4. Analyze pre- and post-treatment changes in sensory processing, PDM, and kinematics to understand pathophysiology and treatment effects.

Methodology:

- Sensory Processing & Decision-Making Tasks: TDT tasks use VR to display asynchronously flashing lights, recording the stimulus interval first perceived as asynchronous. PDM tasks involve determining dot motion direction in dynamic Glass patterns, with accuracy and reaction times recorded pre- and post-treatment.
- Kinematic Analysis: The Delsys Trigno system, combining IMU sensors, EMG arrays, and 3D video, will capture movement tasks from clinical scales. Nuitrack API will process joint movements, while accelerometer, EMG, and movement data are time-locked and classified using Generalized Matrix Learning Vector Quantization.

This approach aims to advance understanding of Dystonia and FMD by identifying shared mechanisms and treatment impacts.

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Lay Summary

This research aims to improve how we diagnose and treat two common but complex movement disorders: Adult-Onset Isolated Focal Dystonia (AOIFD) and Functional Movement Disorder (FMD). Both conditions affect how we move and are often hard to diagnose correctly, which leads to delays in treatment and a lower quality of life for patients.

Currently, diagnosing these disorders relies on expert clinical judgment, but this can be inconsistent. Our study will explore new ways to diagnose and track these disorders using technology like accelerometers (to measure movement) and video analysis. We will also assess how patients respond to treatments such as botulinum toxin injections for AOIFD and rehabilitation for FMD.

Additionally, we'll investigate how patients with these disorders process sensory information and make decisions based on perception, as both conditions involve abnormal brain networks.

By comparing patients with healthy individuals, both before and after treatment, we hope to identify patterns that can lead to earlier, more accurate diagnoses and better treatment plans. Ultimately, this research could improve outcomes for people living with these challenging conditions.

Title: Carbapenemase-Producing Enterobacterales (CPE) Reduction through Innovative Solutions with Photodynamic Disinfection (CRISP)

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[2]Department of Clinical Microbiology, Royal College of Surgeons in Ireland
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Scientific Abstract

Background

Antimicrobial resistance (AMR) is a critical global health threat, projected to cause 8.22 million deaths annually by 2050. Environmental reservoirs, particularly in hospital water systems like sinks and showers, play a significant role in spreading resistant bacteria through direct contact or aerosolized droplets. However, traditional hospital disinfectants often fail to eliminate multi-drug-resistant Enterobacterales (MDR-E), and the lack of standardized disinfection protocols leaves facilities vulnerable to outbreaks.

Aims & Objectives

1. To compare the genomic diversity of MDR-E isolates from the built-environment between Irish human and small-companion animal hospitals
2. To compare the genomic diversity of MDR-E isolates from the built environment between Trinidadian human and small-companion animal hospitals
3. To compare the genomic diversity of MDR-E isolates from the hospital-built environment between Ireland and Trinidad
4. To assess the bactericidal activity of traditional and novel disinfection strategies - chlorine-containing compounds, sodium hypochlorite, acetic acid, hydrogen peroxide and photodynamic disinfection (PDD)
5. To assess the efficacy of traditional and novel disinfection strategies - chlorine-containing compounds, sodium hypochlorite, acetic acid, hydrogen peroxide and PDD – against biofilms

Methods

- A cross-sectional study in hospitals in Ireland and Trinidad will assess the genomic diversity of antimicrobial-resistant bacteria (CPE and ESBL) from sinks and drains. Swabs will be cultured on selective media, bacteria identified and resistance genes analysed using advanced genomic techniques.
- Data on antimicrobial use and infection prevention and control will be collected.
- Laboratory studies will test the effectiveness of disinfectants against planktonic bacteria and biofilms.

Impact

By prioritizing the development and implementation of effective evidence-based disinfection strategies and interventions, we can better safeguard hospitals against the spread of MDR-E and take a crucial step in the broader fight against AMR.

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Lay Summary

Some bacteria possess enzymes capable of breaking down antibiotics; and can share these enzymes amongst other bacteria spreading antibiotic resistance. The number of cases of multi-drug-resistant bacteria is steadily increasing, as well as the number of deaths. Hospital environments, particularly water systems such as sinks and showers, have been recognised as sources of these bacteria. Conventional disinfectants are used to limit the risk that drains may pose, but these multi-drug-resistant bacteria can survive these interventions by forming hard-to-remove communities in the drain pipework. Furthermore, there are no guidelines or standardised protocols to effectively deal with these bacteria in the hospital-built environment. Our study aims to explore the types of these bacteria found in the hospital-built environment and to investigate which disinfectant/s is/are most effective in removing them.

Effects of Cartilage Loading Conditions In Pseudo-Space Environments on Development, Adaptation and Repair (ECLIPSE)

Scientific Abstract

The effects of loading on articular cartilage plays such a crucial role in determining the final make-up of functional properties of articular cartilage caused by its unique structure. Articular cartilage has limited repair capacity during adulthood which is contrary to immature cartilage which has a capacity to self-repair guided by loading in a process of functional adaptation.

Growing access to space travel has prompted new questions around the potential negative effects of microgravity causing reduced loading on musculoskeletal tissues and articular cartilage. The impact of microgravity on the human musculoskeletal system is poorly understood with research limited to models that poorly reflect the biological complexity of articular cartilage in the joint environment.

This research will have wide reaching impacts such as achieving a better understanding of how loading in juveniles will affect long term cartilage development and subsequent health. This is also very relevant to foals and their subsequent training and racing careers, do periods of reduced loading following injury or box rest have any effects longer term? Furthermore, the development of this model will have applications for the study of other disease such as osteoporosis or fracture and soft tissue healing and guide rehabilitation following cartilage injury and repair procedures.

We are the first to propose a unique animal model in the goat that makes use of surgical unilateral claw removal that is clinically used as a therapeutic treatment for complex claw disease in bipedal animals and similarly the claw block application. The study will focus on the development and application of the caprine claw removal (C-CRM) and extension (C-CEM) models with 5 objectives:

1. To study the long-term effect of under- and over- loading during development from birth to puberty.
2. To study the long-term effect of under- and over-loading during adulthood.
3. To study the short-term effect of under- and over- loading and its recovery during adulthood.
4. To study the short-term effect of under- and over- loading during cartilage repair and the effects of reloading.
5. To study the long-term effect of under- and over- loading during cartilage repair.

Lay Summary

The function and long-lasting nature of cartilage is enabled by its complex, multi-layered structure and composition. When cartilage is damaged, due to injury or disease, the tissue does not heal well.

After birth, in both humans and animals, articular cartilage develops its distinctive and important complex structure. However, this process is not well understood. In particular, mechanical loading is thought to be important for healthy cartilage development, but the effects of absent or increased loading on the joint cartilage has not been investigated in depth.

The objectives of the project are to understand how loading of articular (joint) cartilage effects the complex cartilage characteristics during development from birth to adulthood, during adulthood and during repair of damaged cartilage.

The results of this project will benefit those involved in space travel now and in the future in addition to furthering the understanding of cartilage development and repair on earth allowing optimisation of the post treatment rehabilitation plans.

Discrimination of Ischemic versus Hemorrhagic Stroke type by Presenting Symptoms and Signs: A Systematic Review and Meta-Analysis

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Scientific Abstract

Background:
Valid discrimination of ischemic and hemorrhagic acute stroke relies exclusively on neuroimaging. The emergence of promising biomarkers presents an opportunity to reconsider diagnostic approaches that combine clinical assessment with biomarkers, prompting our systematic review of the diagnostic properties of clinical features of acute stroke in determining primary stroke subtype.

Methods:
We conducted a systematic review and meta-analysis according to the PRISMA statement. Eligibility criteria included (1) cohort, cross-sectional, case-control, randomised controlled trial, systematic review, or meta-analysis; (2) consecutive adult individuals with an acute ischemic or hemorrhagic stroke confirmed by neuroimaging; and (3) one or more acute stroke symptom(s)/sign(s) recorded by stroke subtype. A random-effects model was used to pool odds ratios.

Results:
A total of 58 studies, including 59 distinct populations (n=12,878,621; ischemic stroke=10,814,215; hemorrhagic stroke=2,064,406) were eligible. Mean age was 65.9±13.1 years and 44.9% were women. Clinical presenting symptoms and signs associated with a significantly higher odds of hemorrhagic stroke (compared to ischemic stroke) included coma (OR, 8.81 [95% CI, 5.02–15.49]), neck stiffness (OR, 5.21 [95% CI, 2.22–12.21]), vomiting (OR, 3.85 [95% CI, 2.67–5.57]), altered level of consciousness (OR, 3.48 [95% CI, 2.48–4.88]), headache (OR, 3.43 [95% CI, 2.55–4.62]), seizure (OR, 2.59 [95% CI, 1.67–4.03]), abnormal extensor plantar response (OR, 1.94 [95% CI, 1.24–3.04]) and vertigo/dizziness (OR, 1.32 [95% CI, 1.04–1.68]). Clinical symptoms/signs association with significantly lower odds of hemorrhagic stroke (i.e. higher risk of ischemic stroke) included symptom onset in morning time (OR, 0.41 [95% CI, 0.32– 0.54]), facial weakness (OR 0.66 [95% CI, 0.46–0.94]), hemiplegia (OR, 0.68 [95% CI, 0.50–0.92]), and ataxia (OR, 0.73 [95% CI, 0.61–0.86]).

Conclusions:
Our review reports substantive differences in prevalence of stroke symptoms/signs between ischemic and hemorrhagic stroke subtypes, encouraging further research to develop a standardized approach to measuring pre-test clinical probability.

Lay Summary

Differentiating an ischaemic (clot) from haemorrhagic (bleed) stroke quickly is vital as their treatments differ greatly. Currently, the only reliable way to tell the difference is through brain imaging. However, there is growing interest in exploring other methods to help make this diagnosis faster.
In our systematic review, we reviewed 58 studies to see if certain symptoms/signs can help distinguish between these two types of stroke. We found that certain features, like coma, neck stiffness, vomiting, confusion, headache, seizures, and dizziness, were more likely to occur in hemorrhagic stroke. Conversely, symptoms like waking up with symptoms, facial weakness, one-sided paralysis, and difficulty with coordination were more common in ischemic stroke.
Our findings suggest that specific symptoms could help make an initial assessment of the type of stroke a patient may have, even before imaging tests are available. This could lead to faster treatment decisions and potentially better outcomes for patients.

Why do kidney transplants fail so early in young people?

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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 two OLINK 384 inflammation platforms, 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. This analysis will be further supplemented with genome wide sequencing to enable genotype phenotype linking.

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.

Title: Understanding the Immune Response to Vaccination in Haematological Malignancy (UNIREV Study)

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Scientific Abstract

Background

Respiratory viruses are associated with significant morbidity and mortality in immunosuppressed patient populations. Complications include pneumonia, respiratory failure and superimposed bacterial infection. Vaccination remains the most effective prevention strategy against infection. However, vaccine effectiveness is reduced and inconsistent in those with altered immune system function as a result of haematopoietic stem cell transplant (HSCT) compared with young, healthy members of the population. Studies to date have shown inconsistent seroconversion and seroprotection rates in HSCT recipients. Correlation of findings with clinical outcomes is unclear. Furthermore, this cohort is frequently excluded from clinical trials evaluating vaccine responsiveness and so findings cannot be extrapolated. Vaccines against respiratory syncytial virus (RSV), have recently become available. RSV is a significant cause of morbidity and mortality among immunocompromised patients, however immune response in this cohort has not been assessed. This study evaluates the immune responses to influenza vaccination and (RSV) vaccine in a cohort of patients who have undergone allogeneic HSCT compared to a control population.

Methods

Patients who had undergone allogeneic stem cell transplantation for an indication of haematological malignancy were invited to participate. Volunteers without a history of immunosuppression or malignancy were also recruited. Participants received commercially available quadrivalent inactivated seasonal influenza vaccine for 2024/2025 and an AS_3-adjuvanted RSV vaccine as per the licensing criteria. Blood was drawn pre-vaccination and at 21-42 days post-vaccination. Whole blood was stimulated overnight with Influenza A and RSV antigens. Interferon-gamma and IL-2 production were measured. Peripheral blood mononuclear cells and serum samples were also stored for analysis.

Impact

This work provides insight into the immunological response to vaccinations against two important viral pathogens in immunocompromised hosts.

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 respond to vaccines in the post-transplant period including influenza vaccination and respiratory syncytial virus vaccination. There are common seasonal respiratory viruses. They cause significant morbidity and mortality worldwide, particularly in this patient group, with flu having potential to cause future pandemics. The results of this research will inform vaccination strategies for these patients in the future.

Feline oral Squamous cell carcinoma and the IMpact of toll-like receptors 2 and 4 and feline oral BActeria on tumour cell behaviour and growth (SIMBA)

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Scientific Abstract

Background

Feline oral squamous cell carcinoma (FOSCC) is a devastating disease of cats due to its invasive growth and lack of effective treatments. Its biologic behaviour is similar to human oral squamous cell carcinoma (HOSCC). In humans, periodontal disease has been established as a risk factor for HOSCC and various studies have investigated oral bacteria and toll-like receptors (TLRs) in this context. In cats, the contribution of oral inflammation to FOSCC progression remains unstudied, despite the high prevalence of periodontal disease in this species.

Aims and objectives

1. Compare the expression of TLR2 and TLR4 mRNA and the presence of eubacteria in tissue samples of FOSCC, inflamed feline gingival tissue (pyogenic granuloma/PG), and healthy gingival tissue (HGT).
2. Investigate whether exposure to feline oral Gram negative bacteria (*Porphyromonas gulae, Fusobacterium canifelinum*) causes FOSCC cell lines to attain a more malignant phenotype *in vitro*.
3. Evaluate the effect of feline oral bacteria on tumour phenotype (growth rate, invasion, angiogenesis) in an *in vivo* chick embryo xenograft model of FOSCC.

Methods

1: Twenty-two samples each of FOSCC and PG (archived biopsy specimens) and HGT (collected at postmortem) will be interrogated for the presence of a) TLR2 and TLR4 via RNA in-situ hybridisation (RNAscope) and b) eubacteria via fluorescent in-situ hybridisation (FISH).

2: Commercially-available FOSCC cell lines (SCCF2, SCCF3) will be cultured *in vitro* and exposed to clinical isolates of *P. gulae* and *F. canifelinum* obtained from feline oral swabs. The response of cell lines to bacteria will be assessed via cell migration, invasion, and proliferation assays and via RT-PCR, RNA-seq and ELISA for cytokine and TLR expression.

3: An *in vivo* chick embryo xenograft model model of FOSCC will be established and exposed to feline oral bacteria (*P. gulae, F. canifelinum*). Response to bacteria will be determined via quantitative and semi-quantitative assessment of tumour growth parameters (size, weight, depth of invasion) and of angiogenesis.

Impact

This study will enhance our understanding of the potential impact of periodontal disease on the progression of FOSCC. This will help inform future prevention strategies, diagnostic techniques and treatments, improving animal health and welfare. This will also highlight the potential importance of companion animals as natural models of disease in oncology research.

Lay summary

Feline oral squamous cell carcinoma (FOSCC) is the most common oral tumour of cats. It is usually incurable and affected animals are often euthanised at diagnosis. Periodontal disease (inflammation around the gums and teeth) may contribute to the development of a similar oral tumour in humans, but it is unknown if the same is true in cats. However, almost all cats develop periodontal disease as they age, so this possibility should be investigated.

This research project will investigate the potential link between feline periodontal disease and the progression of FOSCC. We will test FOSCC samples for bacteria and proteins that bacteria bind to. We will also grow tumour cells in the laboratory and stimulate them with feline oral bacteria, to investigate whether this causes the tumour cells to grow faster and become more invasive.

This will improve our understanding of why FOSCC develops, and help to guide vets in preventing and managing this condition in the future, thus improving animal health and welfare.

Characterisation of High-Risk Multiple Myeloma and An Exploration of CAR-Cellular Therapeutics in this Cohort (CHaRM-CAR)

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Scientific Abstract

Background
Multiple myeloma (MM) is an incurable haematological malignancy characterised by clonal proliferation of plasma cells in the bone marrow. There is a cohort of MM patients with High-Risk disease (HRMM) that predisposes them to a reduced therapeutic response and worse clinical outcomes, with a significantly lower 5-year overall survival (OS) rate, compared to standard-risk patients (40% vs. 82%).[1] The pivotal step in developing targeted treatment strategies and improving clinical outcomes for HRMM is to reliably and uniformly define this cohort. Established HR features include extramedullary disease (EMD) and specific cytogenetic abnormalities. However, current biomarkers and prognostic tools lack the precision needed for effective risk-adapted therapies.

Improved understanding of the bone marrow (BM) and immune microenvironment have facilitated the development of advanced therapies like Chimeric Antigen Receptor T-Cell (CAR-T) treatment, which demonstrates promising results in relapsed refractory MM.[2-3] However, despite eliciting therapeutic responses in patients with HR features, this cohort still face a significantly shorter OS post-treatment, demonstrating that current cellular therapies do not overcome the poor prognostic impact of HR disease.[4-5] Thus, the identification of specific targets for HRMM is essential for the development of advanced therapies which achieve durable clinical responses.

Methods
This project comprises two integrated streams aimed at identifying and evaluating specific therapeutic targets for cellular therapy in HR disease, as defined by standardised criteria. HRMM in this study is identified by a validated gene expression profile, *MMprofiler/SKY92* [6] and/or the presence of EMD. Genomic and transcriptomic profiling of the HR cohort aims to identify molecular drivers of HR disease and to inform the design of a CAR-based cellular therapy.

Interim Results
Preliminary results from genomic profiling of EMD patients (n=6) provides insight into potential driver gene mutations, variability in the mutational profile of primary versus relapse EMD, and the molecular heterogeneity between BM and EMD sites. Initial next steps include expanding the EMD cohort, molecular characterisation of HR patients identified on SKY92 testing, and the design of a CAR construct for evaluation in a humanised murine model of EMD.

Lay Summary

Multiple myeloma (MM) is an incurable blood cancer with a highly variable survival rate. The clinical outcomes for patients with MM have significantly improved in the most recent decade, resulting in an improved quality of life and prolonged survival for the majority of patients. However, there is variability regarding the duration of treatment response and overall survival. Specifically, there is a subset of patients who have high-risk disease, which result in a poor response to therapy and a shorter survival. The project aims to identify possible causes or characteristics of high-risk disease, at a molecular level, and to evaluate a novel cell-based therapy specifically targeting this entity, in a laboratory-setting.

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Introduction:
Hypertension remains a leading cause of cardiovascular morbidity and mortality globally, with blood pressure (BP) variability emerging as a contributor to cardiovascular risk.(1,2) The CLADDAGH (Closed-Loop Antihypertensive Drug-Delivery Algorithm in Hypertension) project aims to develop and test an implantable closed-loop antihypertensive drug-delivery system to manage hypertension and reduce BP variability, serving as a proof of concept for precision medicine in BP management.

Methods:
A two-phase experimental approach will be performed using stroke-prone spontaneously hypertensive rats. Phase 1 involves administering incremental doses of Esmolol hydrochloride via a subcutaneous pump, following a fixed oral dose of Amlodipine, to establish dose-response curves. Phase 2 will utilise proportional integral derivative (PID) algorithms derived from Phase 1 data to control the timing and dose of Esmolol release, optimising BP control and minimising variability (coefficient of variation), dependent on real-time BP and HR data.

Results:
Early results will facilitate development of PID algorithms that adjust Esmolol dosages based on real-time monitoring of BP and HR. These algorithms will initially be validated on an already existing BP dataset. The closed-loop system will be composed of: i) radiotelemetry measurement of BP and HR, that will communicate wirelessly with ii) a controller that contains the sets of algorithms, that will determine the timing and release of Esmolol via the iii) implantable, subcutaneous pump. A custom application will allow for review of live BP, HR and coefficient of variation values during the closed-loop system administration to monitor system responsiveness. Phase 2 of the study will test the closed-loop system in a stroke-prone spontaneously hypertensive rat model.

Conclusions:
The initial stages of the CLADDAGH project are focused on establishing a robust foundation for a closed-loop antihypertensive drug delivery system. Preliminary findings on algorithm development and real-time analysis of cardiovascular data will be presented, anticipating a proof-of-concept for managing hypertension and BP variability.

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Lay Summary

Hypertension, or high blood pressure, is a major cause of heart disease and stroke worldwide. Traditional treatment methods often can't respond quickly to changes in blood pressure, which is linked to cardiovascular risks. The CLADDAGH project aims to create a smart, implantable system to better control blood pressure by adjusting medication doses in real time. In our animal model, we will use an implant that continuously monitors blood pressure and heart rate, with the system delivering precise amounts of medication to keep blood pressure stable and to reduce variability. This research will initially test the system in rats with a similar high blood pressure condition, laying the groundwork for future applications in humans. If successful, the CLADDAGH project could offer a breakthrough in personalised hypertension management, making blood pressure control more precise and reducing health risks associated with sudden fluctuations.

ATLANTIS - Identification of AutoimmuniTy reversaL in ANca vasculiTIS

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Scientific Abstract

Background

ANCA associated vasculitis (AAV) is an archetypal autoimmune disease, resulting in immune-mediated organ damage. Immunosuppressive drugs (ISDs) have transformed AAV from a progressively fatal condition into chronic relapsing-remitting disease. However, infection post ISDs is now the primary cause of death among patients with autoimmune diseases. The greatest unmet need in AAV is to devise personalised strategies for precise tailoring of ISDs. ISDs could be reduced if it were possible to quantify relapse risk and to identify patients in whom treatment could be stopped safely.

Aims

The aim of this study is to quantify the immunological state in AAV remission and to identify factors that signify a return to normal, with re-establishment of tolerance to the relevant autoantigens, myeloperoxidase (MPO) or proteinase-3 (PR3).

The objectives are to:

1. Perform an in-depth comparison of the immune status of AAV patients in long-term remission off therapy (LTROT) with (a) patients with active disease, (b) patients with anti-GBM disease, a monophasic “one-hit” autoimmune disease, and (c) healthy controls.

2. Test whether the cluster of “tolerance markers” are present at various time points in the AAV disease course in LTROT patients.

3. Build a statistical model, incorporating a longitudinal dataset and the parameters identified above, and assess whether this identifies those remaining in remission when applied at the point of treatment discontinuation.

Methods

The RITA-Ireland Vasculitis RIV Registry and Biobank includes over 900 patients with vasculitis, approximately 50 meet LTROT criteria. This longitudinal dataset has serial biological samples obtained at diagnosis, remission and relapse (PBMC, serum, plasma, urine, DNA, Paxgene).

The experimental methods to define LTROT immune tolerance signature include high dimensional flow cytometry using stored PBMCs, including identification of antigen specific B cells (Aurora cytometer, proteomic screening (o-link), single cell RNA sequencing, PCR and measurement of Torque Teno Virus levels. Validation will be performed by testing international cohorts e.g. UCL, IDIBELL, Barcelona and Czech vasculitis biobank.

Impact

Tailored ISD use will benefit low-relapse-risk patients, enhance societal productivity, and reduce healthcare costs, patient/carer burden, and physician clinical time.

Lay Summary

Autoimmune disease affects 10% of adults, most of whom are women, and two of the top five medications with the highest cost globally are used to keep these recurring conditions in remission. These medications suppress the immune system, leaving the patient exposed to increased infection and cancer risk. Patients have highlighted a desire to tailor these treatments to each patient and to stop these medications where safe.

What is the aim of ATLANTIS?

ATLANTIS delivers a practical response to this challenge.

We aim to closely examine the immune system characteristics of patients who have infrequent disease flares by performing tests in laboratories. This may help us identify patients in which immunosuppressant medications can be stopped.

We use systemic vasculitis as a typical autoimmune disease to answer these questions.

The IMAGINE Study

Imaging Morphea: Advancements for DiaGnosis and INtensive Evaluation

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Scientific Abstract

Background

Morphea is a rare autoimmune disorder characterized by inflammation and sclerosis of the skin and soft tissues.[1] It has the potential to cause extreme disfigurement with both neurologic and ocular complications.[2,3] Once fibrosis is established, it becomes irreversible. Pathogenesis is poorly understood however vascular injury is thought to play a central role.

Morphea is difficult to diagnose and difficult to monitor, complicating management decisions. The Localised Scleroderma Cutaneous Assessment Tool (LoSCAT) score is the validated measure of morphea activity,[4] however objective measures are needed to accurately detect activity to drive treatment decisions. Techniques such as Multispectral imaging and Tissue Viability Imaging (TiVi) may provide enhanced insight into active inflammation within lesions, enabling a more precise assessment of disease activity. Accurate identification of disease activity and progression is essential to prevent diagnostic delays and inform treatment decisions.

This study aims to identify key markers of disease activity in morphea, with the goal of developing novel, non-invasive, robust, and quantifiable measures of disease activity to guide clinical care.

Primary Objective:

Describe the serial clinical assessment scores (classified by LoSCAT score), patient questionnaires, inflammatory cytokine (by tape stripping) and novel quantitative imaging (Multispectral, Tissue Viability Imaging [TiVi]) data in a large cohort of well-phenotyped patients with morphea.

Methods

This study is a detailed longitudinal observational analysis of a prospective national cohort of patients with morphea. Clinical assessment will include validated scoring methods (LoSCAT) and patient reported outcome measures. In this self-controlled study, multispectral imaging will be used to image lesional and non-lesional skin. Additionally, tape-stripping of skin will be performed to collect samples for local inflammatory cytokine analysis. A multimodal machine learning model will integrate these diverse data sources with the goal of accurately classifying active from inactive lesions.

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Lay Summary

Morphea is a scarring skin condition which appears subtle at first but can progress to deeper layers of skin, muscle, and bone. Once scarring takes hold it is permanent. Head and face involvement is disfiguring and can cause neurological problems including seizures.

Because morphea is subtle at first, it is hard to diagnose and even harder to monitor. It is essential for doctors to be able to tell when the disease is active, to determine when treatment is needed, helping to prevent further damage.

I plan to use specialized cameras which can “see” beneath the skin’s surface measuring blood and swelling in affected skin compared to healthy skin. By combining results from these tests using an artificial intelligence model, I aim to detect disease activity more accurately.

Automated retinal vascular analysis reveals response to acetazolamide in idiopathic intracranial hypertension

Brian Woods, David Szanto, Jui-Kai Wang, Asala Erekat, Lola Stern, Aaron Golden, Mona Garvin, Randy H Kardon and Mark J Kupersmith

Scientific Abstract

Purpose: Optic nerve head swelling due to Idiopathic Intracranial hypertension (IIH) is a dynamic process requiring accurate monitoring. Acetazolamide (ACZ) reduces cerebrospinal fluid (CSF) pressure and retinal venule diameter in patients with idiopathic intracranial hypertension (IIH). We used an automated vessel analysis approach to detect and quantify retinal vessel change with ACZ treatment.

Methods: Fundus photographs from 165 participants in an IIH treatment trial randomized to either ACZ or placebo alongside weight management were analysed from study entry to the six month outcome visit. Vessel analysis was performed using the Automorph pipeline. For each photo, average venule measurements were standardized based on arteriolar width.

Results: At study entry, mean venule diameter was 139µm +/-27µm. Participants treated with ACZ had more vein diameter reduction (-7.8µm, $p < 0.05$) than the placebo group (-2.0µm, $p = 0.42$) at 6 months. Arteriolar diameters increased at 2 months with ACZ (8.5µm, $p < 0.05$ Vs 2.8µm, $p = 0.14$). Standardizing venule measurement based on arteriolar width showed greater venule diameter reduction with ACZ from 1 month onward.

Conclusion: Response to ACZ can be detected and quantified in patients with IIH via automated analysis of fundus photographs. Retinal vascular analysis holds promise as a technique for non-invasively assessing response to treatment.

Overview:
Using the deep-learning based Automorph vascular analysis pipeline we analysed retinal vessel measurements in patients with idiopathic intracranial hypertension treated with acetazolamide (ACZ) versus weight management only. Venule diameter was shown to decrease with ACZ therapy. When venule measurements were standardized based on average arteriolar width within each photo, this difference between both treatment groups became apparent after just 1 month of treatment.

Chemical Adherence Testing in the Clinical Management of Hypertension: A Scoping Review

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Scientific Abstract

Introduction

Despite growing use, questions remain surrounding the utility, acceptability and feasibility of chemical adherence testing (CAT) as part of hypertension management in clinical practice.

This scoping review aimed to (i) identify and summarise studies using CAT in hypertension management, and (ii) describe and critically evaluate how CAT is currently being used in the clinical management of hypertension.

Methods

Peer-reviewed and published studies in English, reporting original research in any setting, with any study design, were included. Search concepts included hypertension, medication adherence, CAT, and their synonyms.

Searches were carried out using Ovid Medline, EMBASE, and PsycInfo (EBSCO), alongside manual searching of reference lists. Using Covidence software, we screened titles and abstracts, followed by full-text articles. Data from the included articles were tabulated and summarised.

Results

Of the 618 studies identified, 48 were included. Studies were mostly published in high-income countries, focussed on treatment-resistant hypertension in secondary or specialist healthcare settings, and usually observational in design. 7 studies reported adherence analyses within clinical trials for hypertension therapies. Few studies measured the impact that performing CAT has on clinical outcomes for patients, such as BP control . The use of theoretical frameworks to guide reporting was rare, and there was considerable variation in key terminology and definitions, most notably in the definition of adherence. Some studies consider a participant adherent only if there is 100% concordance between their prescribed and detected AHDs, and consider all other results to represent nonadherence, while others differentiate between categories such as 'partial' and 'complete' nonadherence, though the thresholds for these categories vary. Such discrepancies are a significant barrier to the development of a cumulative evidence base.

Conclusions

The current body of evidence demonstrates considerable variability in the approach to implementing CAT for hypertension management in clinical practice, and a paucity of randomised controlled trials to evaluate its impact. Future research could (i) adopt a cohesive theoretical framework including clear operational definitions to standardise the approach to this important topic; (ii) further explore the impact of CAT on clinical outcomes using RCTs.

Lay Summary

This review examines the use of chemical adherence testing (CAT) in managing high blood pressure, focusing on its effectiveness and how useful it is in clinical settings. CAT is a way to test people's blood or urine to see if they are truly taking their medications as prescribed. Researchers examined 618 studies, ultimately including 48 that met their criteria; these were mostly from high-income countries and were interested in treatment-resistant hypertension in specialized healthcare environments such as hospitals and specialist clinics. The findings reveal that adherence is defined and measured differently in different studies, with significant variations in terminology. For instance, some studies only consider patients adherent if their tests perfectly match prescribed medications, while others recognise varying degrees of nonadherence. Very few studies assessed the impact of CAT on patient outcomes like blood pressure control, and there is a notable absence of randomised controlled trials. The review suggests future research should standardize definitions and frameworks to better evaluate the effectiveness of CAT in hypertension management.

Michael Gilligan

Session 1: Final year ICAT Fellows

Synaptic neural antibodies may be rapidly identified using proteomic assays in patients with 'seronegative' autoimmune neurologic disorders

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Scientific Abstract

Background

In the past 20 years, the number of neural antibodies has increased dramatically; however, as many as 50% of cases remain seronegative. The 5th most common neural antibody identified by TIFA in clinical practice is unclassified (target unknown). Identifying each analyte through traditional methods is a lengthy, years-long process; however, techniques such as protein microarray and phage-display immunoprecipitation sequencing (PhIP-Seq) have the potential to rapidly unmask antigen targets.

Methods

October 2022-September 2023, 258 patient specimens (133 serums; 125 CSFs) meeting criteria for unclassified neural-restricted synaptic antibodies by TIFA were screened using protein microarray and PhIP-Seq. Top ranking candidate antigens (top neural antigens, paired hits) were validated by dual-staining confocal microscopy, and ≥1 protein-specific assay (recombinant-protein western blot and cell-based assay). Clinical information was reviewed.

Results

Thirteen novel autoantibodies were identified among 25 patients. Fourteen patients were female; median age, 67 years (range, 11-86). Clinical syndromes were: encephalitis, 8; brainstem encephalitis, 2; encephalomyelitis, 3; cerebellar degeneration, 3; longitudinally extensive transverse myelitis, 2; sensory neuronopathy, 1; peripheral neuropathy, 4; and movement disorder, 2. Among 22 patients with data available, 13 (59%) had abnormal MRI findings (inflammatory-appearing T2 signal change [4], atrophy of cerebellum/cerebrum [6], longitudinally extensive cord hyperintensity with contrast enhancement [2], leptomeningeal enhancement [2], cranial nerve contrast enhancement [1], cerebral metastases [1]). In 11 patients with CSF data available, 9 (81%) had inflammatory CSF findings (pleocytosis, 7 [median 7.5 cells, range 7-294]; elevated IgG index or synthesis rate, 4; CSF-exclusive oligoclonal bands, 4). Six patients had a cancer detected (lung cancer, 3 [adenocarcinoma, 2; unknown histology, 1]; other, 3) Of 20 patients with outcome data available, 6 patients improved following treatment; 3 improved spontaneously.

Conclusion: Unclassified neural antibodies are frequently observed in patients with autoimmune neurologic disorders and novel antigenic targets may be rapidly identified using proteomic assays.

Lay Summary

Autoimmune encephalopathies are disorders which occur when the body's immune system attacks the brain.

Doctors are guided by the specific antibody associated with the patient's symptoms as it provides information on the natural course of the disorder, the treatment needed and which cancer (if any) to screen for. For many patients the associated neural antibody is not known and discovering these antibodies helps doctors in making the right diagnosis and choosing the correct treatment.

Using novel molecular tools, we have demonstrated that such neural antibodies can be rapidly discovered and subsequently confirmed as being specific to the patient's autoimmune neurologic disorder. In our study we report 13 novel neural antibodies among 25 patients with autoimmune neurologic disorders.

ImPRINT: Identifying and Predicting Intellectual Difficulties in Childhood

Scientific Abstract

Background
Approximately 16% of children will have cognitive ability substantially below that of the average child population. Around 2% will meet the criteria for an intellectual developmental disorder, but a much larger proportion will have cognitive ability that lies between what is considered an intellectual developmental disorder and what is considered typical cognitive ability. Low cognitive ability in childhood is associated with adverse adult outcomes in education, occupation, health, and social mobility. Less is known about the effect low cognitive ability has on childhood outcomes. Early intervention can improve cognitive outcomes for at risk children but, correctly implemented, is resource intensive. Increased risk can be due to a myriad of biological, psychological, and social risk factors. The challenge we face is predicting at an individual level, using accurate and scalable methods, who the highest risk infants are. The aim of this PhD is to explore the impact of low cognitive ability on outcomes in childhood and to examine current and alternative methods of early identification of children at risk of low cognitive ability in childhood.

This PhD consists of five studies which use data from the Baseline Birth Cohort, the Growing Up in Ireland Cohort, and the Swedish Neonatal Registry. Specifically the objectives of these five studies are to:

1) Investigate the predictive value of the Ages and Stages Questionnaire in late infancy for identifying children with low cognitive ability at age 5.
2) Examine the effect of low cognitive ability on emotional-behavioural function in childhood
3) Examine the effect of low cognitive ability on the early experience of education
4) Investigate whether perinatal data can be used in a predictive algorithm to identify children at risk of later low cognitive ability in the general population.
5) Investigate whether perinatal data can be used in a predictive algorithm to identify infants at risk of later low cognitive ability in a very preterm population.

Lay Summary

Children with low cognitive ability have cognitive ability that is substantially below that of the average population. Early developmental screening may not unearth these difficulties. At school, as tasks become more complex and children are compared to their typically developing peers, their difficulties may be uncovered. Unfortunately, a child may have to consistently fail the tasks ahead of them for many years before they are considered for formal educational assessment. This repeated failure may have implications on their emotional-behavioural development, their relationship with education, and on their mental health. This research will investigate whether children at risk of low cognitive ability could be identified earlier. The research will use large datasets which have collected information on the pregnancy, the delivery, the parents, the socio-demographic background, and the child. We will aim to combine this information using statistical methods to identify high risk children.

Enhancing the neoadjuvant treatment of rectal cancer by targeting Inhibitor of Apoptosis Proteins (IAPs)

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Scientific Abstract

Introduction

Of the ~50,000 cases of bowel cancer diagnosed in Ireland and the UK annually, one third occur in the rectum. Total Neoadjuvant Therapy (TNT) is a standard of care option for locally advanced rectal cancer and involves a sequence of (chemo)radiotherapy and systemic chemotherapy prior to surgery. Multiple benefits of TNT have been reported including a greater chance of avoiding an operation in the event of a complete response as well as improvements in rates of local and distant disease recurrence. However, despite TNT, most patients will still require significant surgery and approximately 25% will relapse within 3 years leading to death in most cases.

A potential strategy to improve the effectiveness of TNT is to increase the rate of cell death (apoptosis) induced by radiation and chemotherapy. Inhibitor of Apoptosis Proteins (IAPs) are frequently upregulated in rectal tumours and correlate with poorer responses to neoadjuvant therapy and a worse prognosis overall. Interestingly, intra-tumoral bacteria such as Fusobacterium nucleatum can also increase IAP expression and convey therapy resistance. Therefore, incorporating a small molecule IAP antagonist into the TNT paradigm might improve tumour regression and survival rates, at least in a subset of patients.

Methods

The clinically relevant dual antagonist of cIAP1/2 and XIAP, tolinapant, was combined with different radiation and chemotherapy schedules in two- and three-dimensional in vitro models including the APC, KRAS and p53 mutant rectal cancer-specific cell lines, SW837 and SW1463. Live cell imaging (Incucyte), viability assays (CellTiterGlo), Annexin V Propidium Iodide flow cytometry and Western Blotting were performed to investigate the impact of IAP inhibition on proliferation and apoptosis. Short interfering RNA was used to investigate the molecular mechanism of tolinapant. Several subspecies of F.nucleatum were grown anaerobically and cocultured with cancer cell lines and THP1 monocytes.

Results

Tolinapant enhanced apoptosis in all radiation schedules explored including single fraction (5 Gy), short-course (5 x 5 Gy) and chemo-radiation (5 x 2 Gy plus 5-fluorouracil). These effects were more pronounced in the presence of exogenous Tumour Necrosis Factor alpha (TNFa) and when cIAP1 or XIAP were knocked down. Tolinapant/TNFa increased the cytotoxicity of chemotherapy and reduced the formation of 5FU drug-tolerant persister cells. Finally, F.nucleatum infection increased the proliferation of colorectal cancer cells and elevated cIAP2 expression whilst supernatant from F.nucleatum-infected monocytes enhanced the effect of tolinapant in a TNFa-dependent manner.

Conclusion

This preclinical work suggests that antagonizing IAPs with tolinapant could enhance radiation- and chemotherapy-induced apoptosis in the total neoadjuvant management of rectal cancer. Tumours that are rich in TNFa, for example, those with abundant F.nucleatum may be more susceptible to this approach. An in vivo xenograft efficacy study is ongoing.

Lay Summary

- Bowel cancer that starts in the back passage is known as rectal cancer.
- It is common: 15,000 people are diagnosed with rectal cancer every year in Ireland and the UK.
- The treatment of rectal cancer involves a course of radiotherapy, and in some cases chemotherapy, before surgery. This can reduce the risk of cancer returning at the site of the surgery and elsewhere.
- About 1 in 5 patients experience a complete response to radiotherapy and chemotherapy – in other words there is no cancer remaining after the treatment. In some of these cases a patient might not need surgery at all.
- Unfortunately, most patients do not experience a complete response because of resistance to radiotherapy and/or chemotherapy. Therefore, new drugs are necessary to improve these treatments.
- In this research, a new drug, called tolinapant, was shown to improve the effects of radiotherapy and chemotherapy in laboratory models of rectal cancer.
- This might form the basis of a clinical trial to test whether giving patients tolinapant whilst they undergo radiotherapy and chemotherapy for rectal cancer, might lead to more complete responses, less surgery and a lower risk of cancer returning.

The RolE oF Androgen excess in MUscle Energy MetaboLism in Women with PolyCystic Ovary Syndrome: The REFUEL PCOS study

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Background: Polycystic ovary syndrome (PCOS) affects approximately 10% of women globally and is increasingly recognised for its metabolic complications beyond reproductive health. Androgen excess, a hallmark of PCOS, is linked to insulin resistance, type 2 diabetes, and lipid accumulation in non-adipose tissues, particularly skeletal muscle. However, the specific mechanisms through which androgens influence metabolic dysfunction in PCOS are poorly understood.

Objective: This study aims to elucidate how androgen excess disrupts skeletal muscle mitochondrial function and lipid droplet dynamics, contributing to the metabolic phenotype observed in PCOS.

Methods: The REFUEL study combines in vivo and in vitro approaches to assess the role of androgens in skeletal muscle energy metabolism. In vivo, stable isotope tracer techniques evaluate whole-body fatty acid oxidation pre- and post-androgen receptor blockade in women with PCOS. In vitro, primary skeletal muscle cells are treated with androgen ligands, and mitochondrial function and lipid droplet biology are analysed using high-content screening and confocal microscopy. Additionally, ex vivo live cell imaging of mitochondrial networks in muscle biopsies provides high-resolution insights into mitochondrial morphology and function under androgen influence.

Results: Preliminary findings in vitro reveal that androgen excess is associated with significant alterations in lipid droplet morphology and mitochondrial function, with distinct changes in lipid droplet size. Alterations in lipid accumulation and mitochondrial dynamics suggest a potential pathway through which androgen excess may promote metabolic disturbances in PCOS.

Conclusion: This study aims to provide potential insights into the mechanistic links between androgen excess and skeletal muscle metabolic dysfunction in PCOS, highlighting lipid droplet and mitochondrial alterations as key mediators.

OF MICE AND PREMS: COMPARING PROTEOMIC TRANSITION IN A HUMAN AND MURINE COHORT

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Background

Numerous biological changes occur in the hours and days after preterm birth. Whilst the physiological and anatomical changes have been reasonably well described, the molecular changes which accompany these are poorly understood. We sought to describe proteomic changes in the first 3 days of life in both preterm infants and C57bl/6 mouse pups. To examine how these changes compare to adults, a cohort of adult mice were also sampled and compared with pup data.

Methods: Platelet poor plasma from preterm infants (<30 weeks) on day of life 1 (n=10) and day of life 3 (n=10) collected as part of the EVENT study was enriched for extracellular vesicles (EVs) using ultracentrifugation and proteomic analysis was performed using Bruker TIMStof platform and a Data Dependent Acquisition (DDA) mode for identification of peptide peaks. Washed platelets from mice on day of life 1 (n=3 litters, 6-8 individuals per litter), Day of life 3 (n=3 litters, 6-8 individuals) and adult mice (n=3) were prepared and proteomic analysis performed on Thermofisher Astral Orbitrap platform with Data Independent Acquisition.

Results: 212 proteins were identified in the human neonatal cohort. 6 proteins were differentially expressed in a manner which was likely statistically and biologically significant (Fold Change >0.5, corrected p-value <0.05). Mouse platelets represented a more abundant source of proteins with 4839 proteins identified. No significant differences existed between mouse pup samples on day 1 or day 3, however large differences existed between both day 1 and day 3 pup samples and adult mouse samples with overexpression of proteins associated with transcription in neonatal versus adult samples.

Conclusions: Limited proteomic change occurs in the first days of life in premature infants and neonatal mice. Large changes can be demonstrated between adults and neonatal samples. The timing of proteomic changes has yet to be fully elucidated.

Title: The B cell immunobiology underlying clinical phenotypes in LGI1-antibody encephalitis

Mark Kelly

Scientific Abstract

LGI1-antibody encephalitis (LGI1-Ab-E) is a common form of autoimmune encephalitis (AE), characterised by antibodies targeting neuronal surface protein LGI1, leading to seizures, cognitive impairment and behavioural change. Despite responding to immunotherapy (IT), long-term sequelae persist in most patients. Much remains unknown around the intrathecal immune process driving the illness and how best it should be targeted therapeutically. This translational research study addresses knowledge gaps in both the clinical management and pathophysiologic understanding of LGI1-Ab-E.

WP1: MRI characteristics of LGI1- and CASPR2-antibody encephalitis
In this cross-sectional, retrospective observational study of participants with LGI1/CASPR2-Ab-E, viral encephalitis, or CJD, 192 brain MRIs were evaluated for pre-defined features (discovery cohort; n = 87). Findings were then validated in an independent cohort (n = 105).
T2/FLAIR hyperintensities confined to the temporal lobes, without diffusion restriction or contrast enhancement, robustly distinguished LGI1/CASPR2-Ab-E from key differential diagnoses. This can assist clinical decision making in expediting diagnosis and treatment.

WP2: Patient reported outcomes in LGI1-Ab-E
To more accurately measure the persistent long-term symptoms of LGI1-Ab-E, we designed a disease-specific patient-reported outcome measure (PROM), in a participant-driven mixed-methods study of 66 participants. The result is a reliable and sensitive method to establish symptom burden in people with LGI1-Ab-E, both in clinical practice and trials.

WP3: The intrathecal B cell immunorepertoire of LGI1-Ab-E
LGI1-Ab-E is characterised acutely by an intrathecal clonal expansion of LGI1-specific B and antibody-secreting cells. It is not known how long these clones persist in response to IT. Here we characterise the B cell immunorepertoire of CSF from 11 patients with LGI1-Ab-E at different stages of illness; from pre-treatment to convalescence.
Flow cytometry and single B cell receptor sequencing demonstrate a rapid depletion of ASCs, gradual depletion of B cells and non-preservation of clonotypes after IT initiation. This could have important implications for targeting treatment of LGI1-Ab-E.

Lay Abstract

Autoimmune encephalitis (AE) is an inflammatory disease of the brain. This means the body's own immune system attacks the brain tissue by producing proteins called 'antibodies', potentially leading to seizures and dementia. Treatment involves medications which suppress the immune system. Despite treatment, symptoms may continue for years, especially if the illness is not recognised and treated early.

We have conducted a series of studies to learn more about a type of AE called LGI1-antibody encephalitis (LGI1-Ab-E):

1. We identified signs of the illness visible on MRI scans to help distinguish LGI1-Ab-E from similar illnesses.
2. We interviewed people with a history of LGI1-Ab-E to design a questionnaire that can accurately measure the symptoms most important to them so that, in future, treatments can be designed to target these symptoms.
3. We collected spinal fluid from people with a history of LGI1-Ab-E to investigate how the immune system is driving their illness.

Title: Invasive Group A Streptococcus: changing EPidemiology and Optimising Management (iGAS-EPitOMe)

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Scientific Abstract

Background

Group A Streptococcus (GAS) causes over 500,000 deaths annually[1]. In 2023, Ireland saw a fivefold increase in invasive GAS (iGAS) cases[2], a global trend with unclear causes[3]. In the absence of a vaccine, treatment relies on antimicrobials and adjuvant immune-modulatory therapies, though the effectiveness and clinical use of these adjuvants vary widely.

Primary Aim

Investigate the molecular epidemiology of iGAS in Ireland using laboratory and clinical data

Secondary Aims

- Identify genomic markers that correlate with severity, complications and outcomes in iGAS cases
- Evaluate the role of intravenous immunoglobulin (IVIG) use in iGAS treatment
- Investigate the efficacy of clindamycin as an anti-toxin agent in clindamycin-resistant GAS isolates

Methods

Study 1: An observational study using clinical data from the Health Protection Surveillance Centre (HPSC) and isolate data from the Irish Meningitis and Sepsis Reference Laboratory (IMSRL). Statistical and bioinformatic analysis will be employed to establish the molecular epidemiology, genomic diversity and emerging lineages of iGAS in Ireland and how this compares internationally.

Study 2: An observational study which will build upon the dataset from Study 1 to determine if genomic markers correlate with iGAS severity, complications, and outcomes. Genomic analysis will include genome assembly, read mapping and phylodynamic analysis, conducted in collaboration with Dr. Mark Davies at the University of Melbourne.

Study 3: A systematic review and meta-analysis to assess the impact of adjunctive IVIG therapy on mortality in iGAS infections, using data from MEDLINE, EMBASE, and Web of Science. The primary measure will be the risk ratio for death at 30 days.

Study 4: A laboratory-based study using an *in vitro* human whole blood model of streptococcal toxic shock syndrome to establish if the anti-toxin effect of clindamycin therapy is maintained in clindamycin-resistant GAS isolates. This will be completed at the Murdoch Children's Research Institute at the University of Melbourne.

Conclusion

My PhD addresses the significant surge in iGAS cases, which increased fivefold in Ireland in 2023 and has been mirrored globally. By focusing on the evolution of GAS and optimising treatment strategies, this work aims to enhance patient outcomes and inform responses to this pressing public health concern in the absence of a vaccine.

Lay Summary

Group A streptococcus (GAS) is a germ which can be found in the throat and on the skin of healthy people causing no harm. When it does cause infection, it usually causes a mild illness such as a “strep throat” or a minor skin infection. Much less commonly GAS can cause serious, life-threatening infections. Invasive GAS (iGAS) is an infection where GAS is found in parts of the body that should usually be germ-free such as in the bloodstream. In Ireland, since October 2022, iGAS infections have occurred more often than expected and no-one understands why. Our study aims to discover why this sudden increase has happened. We will be looking at the GAS germ in more detail using special DNA tests. We aim to discover if new and/or specific types of GAS are circulating in Ireland recently. We will also look at how good some of the treatments for iGAS are such as immunoglobulin and an antibiotic called clindamycin. To do this we will read and summarise all the research published about immunoglobulin treatment and we will also investigate if the antibiotic clindamycin stops GAS from producing toxins by doing laboratory testing ourselves.

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Interrogation of Overlapping Mechanisms of Epileptogenesis and GliomAgenesis in Human Brain Tumours (OMEGA)

Healy, Vincent. O'Connor, Kate. Sweeney, Kieron. Cunningham, Mark.

Scientific Abstract

The OMEGA project aims to understand overlapping mechanisms of epileptogenesis and gliomagenesis in human brain tumours.

Brain tumour related epilepsy is debilitating and common, occurring in up to 100% of low grade and >60% of high grade gliomas.[1–4] Brain tumours are increasing in incidence globally, and lead youth cancer mortality in many countries including the US and UK.[5–8]

An emerging focus has developed, to understand shared mechanisms for seizure generation (epileptogenesis) and glioma growth (gliomagenesis), increasingly appreciated as 'two sides of the same coin'.[9–13] However, there remain many unknowns.

This project will utilise human tissue from the National Neurosurgery Centre to determine overlapping mechanisms of epileptogenesis and gliomagenesis via multimodal analysis including neuropathology, immunohistochemistry, electrophysiology and proteomics. Samples will include epileptogenic and non-epileptogenic i) high grade gliomas and ii) low grade gliomas, in addition to iii) LEATs (long-term epilepsy associated tumours). Both tumour and peritumoural samples will be independently analysed to understand the role of the peritumoural region and tumour microenvironment. A focus will be placed on brain tumour subtypes, recently recharacterized by the WHO 2021 Brain Tumour Classification, which particularly acknowledges IDH mutant status. This analysis will inform mechanistic and animal model studies, towards developing therapeutics directed towards both processes.

As an exploratory and novel analysis, this multidisciplinary, cross-institutional project may contribute much to our understanding of glioma and glioma-related seizures.

Lay Summary

This research aims to understand how seizures are caused by brain tumours.

Glioma is the most common form of brain cancer. Quite often, the first sign of a glioma is a seizure. Seizures are a disabling quality of life issue for patients. Currently, there are no specific treatments specifically designed to treat brain tumour related epilepsy. In addition, we do not have a complete understanding of how brain tumour growth contributes to seizures, or how seizures contribute to brain tumour growth. We believe that these processes are connected and fuel one another.

Using human brain tumour samples from consented patients in the National Neurosurgery Centre in Beaumont Hospital, we will apply advanced methods to understand the overlapping processes of brain tumour growth and the generation of seizures. We hope to gather new information to design targeted treatments for brain tumour related epilepsy.

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

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Scientific Abstract

Background
The incidence of gastroesophageal cancer (GC) is rising significantly in younger patients despite incidence declining overall. These patients present with more advanced disease, are resistant to treatment and display 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 under normoxic and hypoxic tumours and evaluate whether manipulation of the hypoxic environment with treatments alter these biological 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 interrogating 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 are cultured under normoxic/hypoxic conditions and real time metabolic profiles, inflammatory secretions and immune cell biology assessed prior and after treatments with oxygen carries and immunotherapies.

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. In the presentation we will update and discuss preliminary results from the retrospective study in Aim 1.

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.

Cognitive Impairment in People who are experiencing long-term Homelessness: Evidence and Relationships (CIPHER): Public and Patient Involvement Strategy.

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Scientific Abstract

Background

Social exclusion and poverty result in adverse health outcomes and increased mortality in people experiencing homelessness (PEH). Evidence suggests that PEH acquire significant cognitive impairment (CI) at higher rates and at a younger age than the general population, however this has not been investigated in Ireland, and the mechanisms driving this are unknown. The CIPHER study aims to identify the characteristics, associations and potential mechanisms of acquired CI in PEH, and will provide information to inform policy and practice nationally and internationally.

Public and Patient Involvement (PPI) is an important component of high-quality clinical research. PPI is crucial in research in socially excluded groups, including PEH, to minimise the power imbalance between researcher and participant, and to ensure that research is relevant, accessible and feasible.

Aim

The aim of PPI in CIPHER is to consult, collaborate with, and co-produce research with PPI contributors with lived experience of homelessness, throughout the research process, to foster trust and maximise study inclusivity, relevance, applicability, and feasibility.

Methods

A PPI group with lived experience of homelessness was created. A general and study-specific information leaflet for PPI contributors with lived experience of homelessness, based on INVOLVE Guidance, was created and disseminated to inform contributors about the role of PPI in research. The study design incorporated regular, subsidised meetings with this group.

Results

3 PPI consultations have been held to date: prior to research proposal submission, prior to the CIPHER pilot study, and following completion of the pilot. This has significantly informed the study design, recruitment posters & study materials.

Plan for further involvement

The PPI contributors are collaborating with the research team as lay contacts for study participants, to facilitate peer-to-peer discussion of the study when desired by potential participants. Co-production of a research paper on the recruitment and retention of PEH in observational research has commenced. Continued PPI consultation is planned at the completion of recruitment and following data analysis to assist with interpretation of the results and to steer plans for their dissemination.

Lay Summary

The CIPHER study is being carried out to look at problems with thinking and memory that people experiencing homelessness develop over the course of their lives. In order to make this research as relevant and acceptable as possible to its potential participants (people experiencing homelessness), a strategy to include public and patient involvement in this research has been designed. This will ensure that people with lived experience of homelessness can have their say about how the research is going to be conducted and what to do with its results. So far three meetings with people with lived experience of homelessness have been held, and this has influenced the design of the study and the study materials that will be given to participants. A plan for more meetings has been made to make sure that the voices of people with lived experience continue to influence the CIPHER study until it is completed & its results have been disseminated.

Are higher levels of cardiovascular stiffness the reason why more females develop HFpEF?

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Scientific Abstract

Importance Sex-related cardiovascular (CV) stiffness may contribute to the observed higher proportion of heart failure with preserved ejection fraction (HFpEF) in females than males.

Objective: To compare measures of CV and the associated risk of progression of left ventricular dysfunction or heart failure in female versus male participants who are at-risk of HF or with pre-heart failure (Stage A and B HF respectively).

Design, setting and participants: This is a post-hoc analysis of the STOP-HF (St Vincent's Screening TO Prevent Heart Failure) trial with extended follow-up. Participants with CV risk factors were classified as at-risk for HF or having pre-HF at baseline. None had symptomatic HF (Stage C). We compared measures of cardiac and vascular stiffness as well as relevant biomarkers between sexes at baseline and the associated risk of heart failure (HF) progression.

Results: Of 1248 patients (median age 66.2 [58.2;72.9] years, 609 (48.8%) female), 411 (33.0%) were classified as having pre-HF. Female participants were less likely to have diabetes, atrial fibrillation or coronary artery disease than males, and had lower systolic blood pressure (SBP), lower pulse pressure (PP) and higher LDL-cholesterol. Despite lower SBP and PP, females showed evidence of higher left ventricular (LV) filling pressures, more cardiac and vascular stiffness, greater systemic vascular resistance and lower arterial compliance than males. Females also had higher levels of biomarkers associated with fibro-inflammation (B-Type Natriuretic Peptide and Galectin-3) and lower levels of high sensitivity troponin I (a marker of cardiac injury). Female participants were more likely than males to have progression of asymptomatic LV dysfunction, or new symptomatic HF (n=119 (19.6%)) over 5.58 [3.57;8.27] years of follow-up than males (n=92 (14.5%), adjusted OR 1.51 [1.10; 2.06], p=0.009). Most cases of progression were due to worsening LV diastolic function associated with a preserved ejection fraction (EF).

Conclusions: Asymptomatic female participants at-risk for or with pre-HF more frequently had elevated filling pressures and elevated markers of cardiovascular stiffness/resistance, despite lower cardiovascular and metabolic risk than males. Females were more likely to develop progression of LV dysfunction over follow-up, predominantly due to worsening diastolic function with preserved EF.

Lay Summary

1 in 8 females will develop Heart Failure with Preserved Ejection Fraction (HFpEF) during their lifetime and have a 2.8-fold increased risk compared to males. There is very limited treatment for HFpEF and so prevention is key. We undertook a study which found novel mechanisms of increased stiffness and resistance in the heart and blood vessels of females when we compared them to males. We also looked at proteins in the blood which are related to the risk of heart failure and found differences between the sexes. Finally, we found females were at a 1.5-fold increased risk compared to their male counterparts of worsening structural or functional changes in the heart or the development of symptoms of heart failure over the study period of 5.6 years. These insights could provide new targets to help prevent HFpEF in females.