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2024 Florey Postgraduate Research Conference Abstracts

Faculty of Health and Medical Sciences

make history.

2024 18th Annual Florey Postgraduate Conference

About the Conference

The Florey Postgraduate Research Conference is a highlight in the Faculty of Health and Medical Sciences calendar. This year, the conference reaches its 18th year and will showcase some of the outstanding research activity occurring within the Faculty of Health and Medical Sciences.

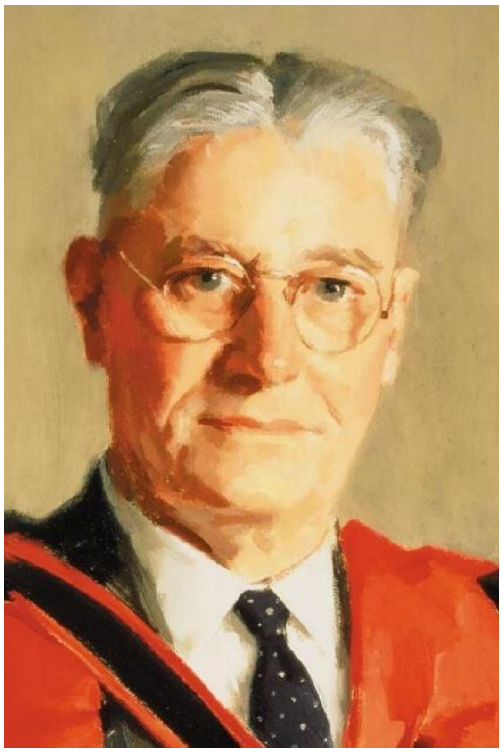
Higher Degree by Research (HDR) students are presented with this opportunity to discuss their research with fellow students, academics, industry partners and other major stakeholders of the University. Excellence in research will be recognised through the prizes and awards, supported by our highly regarded sponsors.

Attendees will also have an opportunity to hear from our distinguished speakers on “Preparation for life post PhD" during the professional development session.

This year, the conference will be held on Wednesday 3 July 2024 at the Adelaide Convention Centre, North Terrace.

Poster Presentations

Poster presentations will be judged over two sessions. Each presentation will be judged by a small research panel using specified criteria. The most outstanding presentations will be recognised through the awarding of prizes supported by our valued sponsors.



Lord Howard Florey

Florey Medical Research Foundation

Named after Lord Howard Florey, a University of Adelaide graduate who shared a Nobel Prize for his development of penicillin, the Florey Medical Research Foundation raises funds for postgraduate research scholarships and early-career postdoctoral research fellowships within the medical degree.

Lord Florey and his team of scientists changed the course of history when they developed penicillin into a life-saving antibiotic treatment. Today, through the Foundation that bears his name, his lifetime of achievement continues to inspire Adelaide students and researchers alike.

The Foundation is based within the Faculty of Health and Medical Sciences.

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Session 1

Poster presentations are held in the Panorama Ballroom, Upper Level of the Adelaide Convention Centre.

Students will be allowed **5 minutes** presentation time, with an additional **3 minutes** allocated for question-and-answer time with the assessors.

Poster presentations will be assessed according to the criteria below. Each assessor will provide a score out of 10 for each category.

- Quality and clarity of presentation and poster
- Scientific merit
- Quality of data/results/significance
- General understanding and ability to answer questions
- Overall poster rating

To encourage networking, collaboration, and the opportunity to meet with some of our major stakeholders and industry partners, all students are encouraged to attend both poster sessions.

Research Areas

Immunology and Infection

Neuroscience, Behaviour and Brain Health

Oral Health

Surgical and Health Systems Innovation

Immunology and Infection

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4	**Terence Ang** *Patterns of recurrence in idiopathic orbital myositis* Adelaide Medical School
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21	**Sintayehu Wondemagegn** *Staphylococcus aureus Exoproteins Disrupts the Nasal Epithelial Barrier: A Sharp Contrast to S. epidermidis and S. lugdunensis Isolated from the Same Niche* Adelaide Medical School
24	**Benjamin Young** *Precise mapping of disease progression in murine models of septic shock: A prerequisite to target validation of novel intensive care therapeutics.* Adelaide Medical School

Immunology and Infection

Poster Number: 1

Elevating protection against COVID19 with intranasal mRNA Vaccines

Zahraa Al-Delfi

Al-Delfi Z [1],Masavuli MG [1], Mekonnen ZA [1], Yeow AEL [1], Turville SG [2], Bull RA [3], Wang X[4], Zhao CX [4], Gowans EJ [1], Grubor-Bauk B [1]

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Introduction

Current COVID-19 vaccines reduce mortality and severe disease, but the emergence of SARS-CoV-2 variants and waning of vaccine-induced immunity resulted in reduced vaccine efficacy and increased rates of reinfection. It is estimated that ~10% of mild SARS-CoV-2 cases develop long COVID, a multi-system severe illness that occurs after infection. As such there is a major unmet need for vaccines that can block transmission, prevent breakthrough infections, and induce durable immunity. This has highlighted the necessity for development of intranasal vaccines (IN) to induce mucosal immunity to prevent viral replication and transmission. Studies have shown that intramuscular mRNA COVID-19 vaccines, such as those from Pfizer and Moderna, fail to induce strong mucosal immunity in the lung, while intranasal vaccination induce responses that are similar to the responses elicited by natural infection but not by intramuscular mRNA vaccination. In this study, the objective was to develop an mRNA version of our Omicron RBD COVID-19 DNA vaccine, which is in Phase 1 clinical trials and develop mRNA vaccines that encode conserved SARS-CoV-2 proteins to be delivered intranasally. Immunogenicity of our RBD COVID-19 DNA vaccine was evaluated in Balb/c mice, and it showed that the vaccine induced strong antibody and T cell responses. Importantly, live virus neutralisation showed that the vaccine can neutralise SARS-CoV-2 ancestral and variant strains.

Methodology

We developed Lipid nanoparticles (LNPs) that encapsulate pseudouridine (Ψ) modified Luciferase mRNA as a pilot study to assess the capacity of the LNPs to deliver mRNA to the nasal cavity and lung. The LNPs were formulated using a microfluidic mixing system and the LNPs were characterised and validated by Dynamic Light Scattering. We assessed tissue distribution of Ψ modified Luciferase mRNA encapsulated in two different LNP formulations (LNP1 and LNP2) by In Vivo Imaging System.

Results

Only luciferase mRNA encapsulated in LNP1 showed luciferase expression in the lung of Balb/c mice at 6- and 24-hours post-delivery, which shows that LNP1 is superior compared to LNP2 in delivering mRNA to the lung and nasal cavity.

Conclusion

The results suggests that LNP1 can be used to deliver the RBD mRNA vaccine to block SARS-CoV-2 transmission at the nasal mucosa and boost immune responses in individuals previously vaccinated against SARS-CoV-2.

Supervisors: Associate Professor Branka Grubor-Bauk, Dr Makutiro Masavuli, Dr Zelalem Addis Makonnen

Immunology and Infection

Poster Number: 4

Patterns of recurrence in idiopathic orbital myositis

Terence Ang

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Objective

To characterise patterns of disease recurrence in idiopathic orbital myositis (IOM).

Methods

Multi-centre retrospective study of IOM patients. Serial imaging was also analysed. Patients with incomplete clinical records and specific orbital myositis (e.g. thyroid-associated ophthalmopathy) were excluded.

Results

Thirty-three patients (Female: 18, mean age: 40.8±16.8-years-old) presenting between 2001 and 2023. Twelve (36.4%) patients had disease recurrence. There was no difference between age or gender predilection of patients with and without recurrence (P=0.107 and 0.469, respectively). There was no association between patients presenting with multiple EOM involvement, unilateral disease, anterior tendon sparing or lacrimal gland involvement with recurrence (P=0.328, 1.0, 0.630 and 0.686, respectively). Recurrence with single EOM involvement occurred in eight (66.7%) patients, and ten (83.3%) patients had recurrence involving different EOM(s) than on initial presentation. Seven (58.3%) patients had metachronous contralateral orbital involvement and one (8.3%) had simultaneous bilateral involvement. There was no association between age, gender, patients presenting initially with single EOM or lacrimal gland involvement with the development of contralateral orbital myositis (i.e. metachronous bilateral disease) (P= 0.777, 0.491, 0.109, and 0.236, respectively). Of the patients with a single acute episode, two (9.5%) patients experienced residual ocular symptoms, compared to four (33.3%) patients with recurrent disease (P=0.159).

Conclusion

This study summarises the patterns of recurrence in IOM. Recurrence was not associated with age, gender, multiple EOM involvement, bilateral disease, tendon-sparing or lacrimal gland involvement. Recurrence was observed in a heterogenous sample of patients and may frequently develop contralateral disease or involve different EOMs (i.e. ‘migratory’ disease).

Supervisor: Professor Dinesh Selva

Immunology and Infection

Poster Number: 7

Small scale sequencing to investigate rare Treg populations in long-COVID

Sarah Battersby

Battersby SM [1,2], Hope CM [1,2], Brown CY [1,2], Barry SC [1,2]

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[2] Molecular Immunology, Women's and Children's Hospital

Background and Aims

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can cause coronavirus disease 2019 (COVID-19). Post-acute COVID syndrome (PACS) disease, known to the general public as Long-COVID, involves persistent acute symptom(s) and/or delayed complications more than 4 weeks post infection (wpi) despite testing RT-PCR negative. SARS-CoV-2 causes global immune dysregulation during acute infection, impacting cells of the innate and adaptive arms of the immune system. In the adaptive arm, CD4+ T helper cells (Th) and regulatory T cells control the anti-viral immune response and tissue repair. Importantly, the roles and effects of regulatory T cells (Tregs) in COVID-19 pathology are still unclear, and, even less is known about the role of Tregs in long-COVID. Tregs (CD25+CD127lo) control immune responses by multiple mechanisms coordinated by the transcription factor Forkhead box P3 (FOXP3). Distinctive Tregs subsets, called T helper-like regulatory cells (ThR), specifically suppress their T helper cell (Th) counterparts and are thought to differentiate under the same conditions and express the same lineage specific transcription factor, in addition to FOXP3.

However, these ThR populations are rare in peripheral blood hence investigation of the transcriptome and function is difficult. Additionally, obtaining samples from those who suffered mild disease which led to long-COVID is very difficult, making the currently stored biobank a precious resource. These ThR populations are especially rare in those post COVID-19 who consequently have a lower proportion of ThR subsets of interest. These include ThR2, ThR22, and ThR2/22 who are thought to have roles in allergy and antibody responses, wound repair, and other functions. These subsets have also shown a decrease in FOXP3 levels in long-COVID individuals, potentially disrupting their regulation of immune responses. The ability to research these rare populations will further elucidate their roles in health and how, when they are altered, could affect disease.

Methodology and Results

Therefore, a new technique was developed to allow for sequencing of low numbers of ThR subsets. A FACS strategy was optimised to collect between 50-4500 cells which generated an average of 1-4ng of cDNA, sufficient for the downstream RNA-sequencing library

generation. This will be performed in a cohort of unvaccinated, uninfected healthy controls, and convalescents 16 weeks post mild COVID-19, with and without long-COVID.

Conclusion

Transcriptomic analysis of these rare subsets, from rare samples, could help to understand their roles in health, and therefore undercover potential mechanisms of disease or biomarkers of disease presence when they are altered.

Supervisors: Proessor Simon Barry, Dr Christopher Hope, Dr Cheryl Brown

Immunology and Infection

Poster Number: 10

Metagenomics or Metataxonomics: Best Practice Methods to Uncover the Truth of the Sinus Microbiome

Isabella Burdon

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[1] Adelaide Medical School, The University of Adelaide

[2] Basil Hetzel Institute

Background and Aims

Dysbiosis of the human microbiome has been linked to many chronic diseases including chronic rhinosinusitis (CRS). Advances in next generation sequencing have improved our ability to identify difficult-to-culture bacteria, many of which populate the sinuses. At present, the gold-standard method used by most researchers to analyse the sinonasal microbiome is 16s rRNA sequencing. However, despite following best practice, significant discrepancies in microbiome results are reported in the literature. Although differences in demographics, sample size, sampling techniques, library preparation and bioinformatic analysis may in part explain this, the reliability of 16s rRNA sequencing itself for sinus sample analysis is yet to be examined.

Methodology

This study creates the first sinus-relevant mock-community and uses this as a positive control to benchmark genomic methods of analysis for sinus microbiome study. Using linear regression models of the growth of 9 strains of bacteria commonly isolated in the sinuses, the mock community was assembled with equal proportions of each strain. Five different library preparation/sequencing methods were employed to generate 29 unique samples. Taxonomic profiles were generated with emu for the long read (LR) 16S datasets, dada2/SILVA for the short read (SR) 16s datasets and sourmash for the metagenomic datasets.

Results

Our work shows that 16s sequencing, the current gold standard method of analysing sinus microbiomes, produces unrecognisable results when compared to the ground truth; and that this distortion of results is both PCR-primer and species specific. 16S rRNA PCR amplification introduces excessive bias and thus, subsequent taxonomic profiling is misrepresentative of the input microbiome. This was consistent for SR and LR sequencing. By contrast, shotgun metagenomic sequencing (both SR and LR) was able to, repeatedly and accurately, recapitulate the taxonomic profile of the input mock community. When we

applied these methods to a patient sample, we saw a dramatic difference in the taxonomic profile of the microbiome, with shotgun sequencing revealing the dominance of Corynebacterium spp.

Conclusion

In order to reach meaningful conclusions that impact clinical practice and improve patient outcomes, we need reliable and robust methods. This work is the first to prove a validated sequencing workflow for sinus metagenomics.

Supervisors: Professor Alkis Psaltis, Professor PJ Wormald, Professor Sarah Vreugde

Immunology and Infection

Poster Number: 13

Can JAZF1 Enforce and Maintain iTreg Metabolic and Homeostasis?

Hannah Morgan

Morgan H [1], Shepherdson K [1] Wong Y [1], Sadlon T [2], Hope C [1], Brown C [1], Barry S [1,2]

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[2] Dept. Gastroenterology, Womens' and Childrens' Hospital

Background and Aims

Our immune system requires a balance between tolerance and reactivity to maintain health. Disruption of Treg mediated tolerance results in loss of immune homeostasis which drives immune mediated pathology. Administration of healthy Treg for autoimmune therapy can reinstate tolerance, however their rarity largely precludes their use for clinical therapy. Induced Tregs (iTregs) can be generated at the high cell numbers required for clinical use from naïve Tcells ex vivo. Unfortunately, iTreg are metabolically and therefore phenotypically unstable making them unsuitable for therapeutic use. Unravelling the molecular mechanisms that contribute to iTreg metabolic instability and identifying new, key modulators of iTreg fidelity has important implications for the treatment of autoimmunity.

Our lab mapped the regulatory network controlled by FOXP3, the major transcription factor of Treg, identifying transcription factors that reinforce Treg integrity. Here, we identified JAZF1. In deleting JAZF1 in Treg, we have shown that JAZF1 coordinates a stabilise Treg metabolism. Disruption of Treg metabolic program has been linked to the pathogenesis of several autoimmune disorders. Harmonising with this, our pathway analysis suggests that JAZF1 may protect against autoimmune diseases including IBD and T1D.

Hypothesis

Investigate if JAZF1 co-ordinates a metabolic transcriptional program to stabilise the Treg phenotype in human iTreg.

Aim 1. Examine FOXP3 and JAZF1 RNA expression in iTreg.

Aim 2. Confirm the suppressive capabilities of induced iTreg

Aim 3. Investigate the metabolic function reprogrammed in iTreg.

Methodology

iTregs were differentiated from naïve Tcells supplemented with IL-2,

IL-7, TGF-β, All-trans Retinoic Acid (ATRA) Rapamycin and CD3/CD28 expansion and activation beads

at a 1:1, Cell: Bead ratio. Treg and naive were activated with IL-2, IL-7 and expansion and activation beads at a 1:1, Cell: Bead ratio.

Expression of JAZF1 and FOXP3 expression was measured by qRT-PCR in iTreg, Treg and naïve Tconv.

In vitro unmatched donor MLR suppressor assays was carried out with iTregs and Tregs to determine the suppressive potency of iTregs, thus confirming their induction.

Metabolic function was measured by Seahorse Extracellular Flux Analyser as instructed by Aligent.

Results

Interestingly, while iTreg possess high FOXP3 RNA expression they have low JAZF1 RNA expression, compared to Tregs, which have high RNA expression of both.

Despite their high FOXP3, iTreg possess a lower suppressive potency compared to Treg at some ratios of (i)Treg:T Responders.

iTreg are metabolically dissimilar to Treg and Tconv, when transitioning from a resting to an activated state.

Conclusion

iTregs lack JAZF1 and this may be contributing to their metabolic and suppressive instability. Enforcing JAZF1 in iTreg may co-ordinate a Treg transcriptional program within them to stabilise their metabolic phenotype. This would provide a new potent and safe autoimmune therapy, and in particular, IBD. We propose the following experiments to address this:

- Transcriptome/epigenome and phenotypic/functional analysis of iTreg overexpressing JAZF1 compared with WT iTreg, Treg and Tconv to determine if JAZF1-iTreg repairs metabolic dysfunction of iTreg.
- Examine iTreg overexpressing JAZF1 restorative/protective effects in a colitis mouse model.
- Determine the ability of iTregs overexpressing JAZF1 to correct dysfunction in a paediatric IBD cohort.

Supervisors: Professor Simon Barry, Dr Cheryl Brown, Dr Chris Hope

Immunology and Infection

Poster Number: 18

A novel cocktail T-cell based zika virus DNA vaccine.

Ryan Santos

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[1] Viral Immunology Group, Discipline of Surgery, Basil Hetzel Institute for Translational Health Research, The University of Adelaide, Australia

Background and Aim

Zika virus (ZIKV) causes lifelong birth defects following infection in pregnancy, for which there is no available vaccine. Most ZIKV vaccines in development focus on the induction of neutralising antibodies (Nab) against the envelope (E) structural protein. Due to significant structural homology of the E protein between flaviviruses, vaccines that target the E antigen carry a risk of antibody-dependant enhancement of infection (ADE), which enhances virus entry and replication into host cells, resulting in more severe disease. Adaptive immune responses, specifically CD8+ T-cell responses preferentially target highly conserved non-structural (NS) proteins (such as NS1, 3 and 4) during natural ZIKV infection. NS proteins do not elicit NAbs and thus abrogate the risk of ADE, making them ideal vaccine targets.

Methodology

In this study, we developed DNA vaccines, pVAX-NS3 and pVAX-NS4 which we evaluated immunogenicity in mice. These DNA vaccines were generated through the cloning of codon optimised ZIKV NS3 and NS4 genes into an FDA approved pVAX mammalian expression vector. Subsequently, female BALB/c mice (n=7, 6-8 weeks old) were vaccinated intradermally three times at two-week intervals with 50ug of pVAX-NS3, pVAX-NS4 or pVAX control. Vaccine immunogenicity was assessed from mice using an in vivo fluorescent target array (FTA) assay and an ex vivo IFN-y ELISPOT. Mice splenocytes were stimulated with peptide pools of overlapping 13-15mer peptides which span over ZIKV NS3 (5 pools) or NS4 (2 pools). Furthermore, we developed a DNA vaccine encoding both NS3 and NS4 (pVAX-NS3/4) in combination with a DNA vaccine encoding secreted NS1 (pVAX-tpaNS1). pVAX-tpaNS1 has been extensively validated and shown to be highly immunogenic. We evaluated the protective efficacy of the combination vaccine through intradermally vaccinating female BALB/c mice (n=10, 6-8 weeks old, 3 doses, two-week intervals) following with a non-lethal ZIKV challenge of 100PFU ZIKV-PRVABC59. Sera from mice were collected on days 1, 2 and 3 post challenge and sampled for ZIKV viral titres using RT-qPCR.

Results

pVAX-NS3 and pVAX-NS4 demonstrated be highly immunogenic inducing strong NS3 and NS4-specific immune responses. From our FTA results we found significant NS3-specific CD8+ killing responses towards NS3 pools 1, 2 and 3 and CD4+ T-helper responses towards NS3 pools 1 and 5. IFN-y ELISPOT captured similar results with significant levels of NS3-specific IFN-y responses detected in NS3 vaccinated mice stimulated with NS3 pools 1, 2, 3 and 5. FTA analysis from NS4 vaccinated mice displayed significant CD8+ killing responses towards NS4 pools 1 and 2. However, no significant CD4+ T-helper responses were detected when compared to pVAX control. NS4-specific IFN-y responses were detected upon stimulation with NS4 pools 1 and 2. When protective efficacy was assessed, we found a significant reduction in ZIKV viral titres in all ZIKV DNA vaccinated groups on day 1 post challenge. With a greater reduction in ZIKV viral titres in the group administered with the combination vaccine.

Conclusion

Our data demonstrates that the inclusion of highly immunogenic vaccine targets such as NS3 and NS4 can increase protective efficacy against ZIKV. Further evaluation needs to be performed to determine if this cocktail vaccine is suitable to protect against vertical transmission and prevent testicular damage from ZIKV. Taken together our results have important implications for the development of protective and safe T-cell based ZIKV vaccines, that can abrogate the risk of ADE of flavivirus disease.

Supervisor: Associate Professor Branka Grubor-Bauk

Immunology and Infection

Poster Number: 21

Staphylococcus aureus Exoproteins Disrupts the Nasal Epithelial Barrier: A Sharp Contrast to S. epidermidis and S. lugdunensis Isolated from the Same Niche

Sintayehu Wondemagegn

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[2] The Department of Surgery - Otolaryngology-Head and Neck Surgery, University of Adelaide and the Basil Hetzel Institute for Translational Health Research

Background and Aims

The enigmatic interplay between the microbiome and chronic rhinosinusitis (CRS) pathophysiology persists as an area of ongoing investigation. S. aureus contributes to the recalcitrant forms of CRS. In addition, coagulase negative Staphylococcus (CoNS) are frequently isolated from the sinonasal cavity of CRS patients. However, the influence of different Staphylococcus species coexisting in the same niche of CRS patients on the inflammatory process remains unclear. The aim of this study was to explore the impact of exoproteins from these bacterial species on the mucosal barrier.

Methodology

Staphylococci species isolated from the sino-nasal niche in CRS and control patients were cultured in planktonic and biofilm forms, and exoproteins were extracted. Primary human nasal epithelial cells (HNECs) from CRSwNP patients were cultured at an air-liquid interface (ALI) and exposed to 20µg/ml of exoproteins or control. Barrier disruption and cytotoxicity were assessed by measuring the transepithelial electrical resistance (TEER), passage of fluorescein labelled dextrans and lactate dehydrogenase (LDH) levels. In addition, ELISA was employed to measure interleukin 6 levels.

Results

A total of 44 Staphylococcus species (22 S. aureus, 12 S. epidermidis, and 10 S. lugdunensis) were isolated from 22 CRS patients. The analysis of exoprotein effects from different strains of these bacteria within individual sinonasal niches showed distinct barrier disruption attributed to S. aureus, underlining strain-specific differences. Exoproteins (20µg/ml) obtained from both planktonic and biofilm forms of these bacteria were evaluated. Co-existence of S. aureus with S. epidermidis or S. lugdunensis, or simultaneous colonization of all three strains in nasal epithelia, exhibited variations in their ability to induce

barrier disruption, cytotoxicity, and paracellular permeability. Overall, damage to HNEC-ALI was found to be strain-specific, with S. aureus disrupting epithelial integrity, inducing cytotoxicity, and increasing paracellular permeability ($p < 0.005$). The application of exoproteins obtained from S. epidermidis and S. lugdunensis strains resulted in either mild or negligible effects on the HNECs barrier integrity, cell viability, and paracellular permeability. Conversely, S. lugdunensis induced a significant inflammatory response.

Conclusion

This study differentiated the various Staphylococcus spp in induction of barrier disruption. Unlike that of S. epidermidis and S. lugdunensis strains, various strains of S. aureus induce wide varied nasal epithelial cell barrier disruption and cell toxicity.

Supervisors: Professor Sarah Vreugde, Professor Alkis J. Psaltis, Dr Kevin Aaron Fenix

Immunology and Infection

Poster Number: 24

Precise mapping of disease progression in murine models of septic shock: A prerequisite to target validation of novel intensive care therapeutics.

Benjamin Young

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[5] Endocrine and Metabolic Unit and [6] Intensive Care Unit, The Royal Adelaide Hospital, SA, 5000

Background and Aims

Septic shock, concurrent with circulatory failure, has an unacceptably high 28-day mortality rate of 30-50% and an unmet need for new therapeutics beyond standard care. Murine models of sepsis are used to map the progression of septic shock but often use disparate and imprecise methods. We used arterial telemetry and determined plasma biomarkers of systems, organs, and inflammatory mediators to precisely characterise low and high-impact models of septic shock following cecal ligation and puncture (CLP).

Methodology

Fasted male C57BL/6 mice (8–10-week-old, N=104) underwent low- (12 mm ligated caecal pocket, single pass 21G puncture) or high impact-CLP (18 mm ligated pocket, dual-pass 21G puncture) to induce polymicrobial sepsis. Mice received 8-h subcutaneous fluid resuscitation (saline, for 168-h), analgesia (buprenorphine 0.1 mg/kg Q8-h for 48-h) and antibiotic (Enrofloxacin 10 mg/kg, Q8-h up to 168-h low-impact, once postoperative, high-impact) for 6 , 12-, 24-, 48-, 96-, and 168-h (N=6/time) until collection of cardiac blood to measure plasma biomarkers of inflammation, system- and organ-damage via ELISA or multiplex. A subset of 168 h mice were implanted with carotid artery telemetry 96-h prior to CLP to measure real-time arterial pressure, heart rate, and temperature; septic shock onset was defined by a 10% reduction in mean arterial pressure sustained for at least 10 mins (N=10-12/model).

Results

Seven-day mortality was 40% and 71% for low- and high-impact CLP, respectively, with septic shock onset after 5-6-h in 30% of low-impact and all high-impact CLP mice. Plasma lactate was unchanged in low-impact CLP but elevated from 48-h in high-impact CLP. Plasma cytokines (IL 6, IL-10, MIP-2, TNFα) and the glucocorticoid corticosterone peaked at 6-12-h in all mice, normalised at 48-h in low-impact CLP but remained elevated to 168-h in high-impact CLP. Liver (AST, ALT), renal (cystatin-C), and cardiac (troponin-I) damage markers were unchanged in low-impact CLP mice but peaked at 24-h and remained elevated at 168-h in high-impact CLP. Peak plasma corticosterone and low levels of its targeting carrier corticosteroid binding globulin (CBG, below 6 µg/mL) at 6-h correlated significantly with CLP mortality.

Conclusion

In summary, we have developed precise models of low- and high-impact sepsis in mice to map septic shock onset, disease progression and inflammatory, system and organ damage status. Reduced plasma CBG is a major determinant of preclinical and clinical mortality in septic shock and will be evaluated in these CLP models as a novel replacement therapy.

Supervisors: Associate Professor Richard Young, Professor David Torpy

Neuroscience, Behaviour and Brain Health

Poster Number	Abstract Details
27	**Marlon Blencowe** *Walking and Vision* School of Psychology
30	**Eleanor Bowley-Schubert** *Characterising the impact of pre-existing brainstem tau pathology on the development of cognitive deficits following a single mild traumatic brain injury* School of Biomedicine
31	**Ryan Dorrian** *Peripheral nerve stimulation via a novel, bio-adhesive graft-antenna to improve outcomes following traumatic spinal cord injury* School of Biomedicine
34	**Samantha Edwars** *Characterising synergistic effects of traumatic brain injury and pesticide exposure on the development of neurodegeneration in a novel rat model of disease* School of Biomedicine
37	**Nishadi Gamage** *Enhancing motor cortex plasticity and motor skill acquisition through theta-gamma transcranial alternating current stimulation (tACS) in healthy young and older adults.* School of Biomedicine
40	**Justin Krieg** *Comparing age-at-injury on the spatial distribution of diffuse axonal injury in a novel gyrencephalic ferret model of TBI.* School of Biomedicine
43	**Jane Morphett** *Enriched phenotype analysis: Tying Perineuronal net structures to high and low burrowers in isolated and enrichly housed rats.* School of Biomedicine
51	**Isaac Saywell** *Evaluating the prognostic utility of cognitive reserve and neuroimaging measures for predicting functional outcomes* School of Psychology
54	**Jacob Sevastidis** *Social Synchronising Primates: Prediction of Prosocial Behaviours can Uncover Inter Brain Neural Synchronisation in Primates.* School of Biomedicine
57	Benjamin Simmonds *Navigating Health Claims on Social Media: Reasoning from Consensus Quantity and Expertise* School of Psychology

60	**Shannon Stuckey** *The Role of Neuroinflammation in Delayed Neurodegeneration following Photothrombotic Stroke in Rats* School of Biomedicine
61	**Lucy Turner** *The Impact of Latencies Associated with Information Displays on Visuomotor Performance* School of Psychology

Neuroscience, Behaviour and Brain Health

Poster Number: 27

Walking and Vision

Marlon Blencowe

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[2] School of Biomedicine, The University of Adelaide

[3] Adelaide Medical School, The University of Adelaide

[4] Andy Thomas Centre for Space Resources, The University of Adelaide

[5] CNRS IRL Crossing

Background and Aims

Traditionally, researchers have studied contrast detection and motion direction discrimination while participants in head-fixed, seated participants. However, evidence from studies in non-human animals indicates that activation patterns in visual areas alter during locomotion. How visual perception changes in humans during locomotion remains unclear, with conflicting findings in the literature (Benjamin et al., 2018; Cao & Händel, 2018).

Methodology

To investigate changes in visual perception during locomotion in humans, we employed a within-subject design, examining contrast thresholds in 14 participants. We conducted a two-alternative forced-choice motion direction discrimination task while participants walked and while seated. During the walking phase, participants walked on a treadmill at a self-selected speed (0.97-1.3 meters per second) for 10-minute intervals. A vertical drifting Gabor stimulus was presented centrally (σ=0.375 degrees of visual angle), and participants had to determine its direction. We tested four spatial frequencies (0.5, 2, 8, and 16 cycles per degree) and two temporal frequencies (2 and 10 Hz) in combination. During both conditions participants also had their eye-movements tracked to ensure they maintained fixation.

Results

We analysed the results using a linear mixed effects model. We found small but significant differences in contrast sensitivity depending on spatial and temporal frequencies between the walking and sitting conditions. Notably, a significant sensitivity difference was found between sitting and walking at 10 Hz, primarily influenced by variations in the 2 cycles per degree condition, with no notable change at 2 Hz.

Conclusion

These findings suggest that there are spatial and temporal frequency dependent changes in human contrast perception during locomotion. We explore potential drivers behind these observed changes in humans.

Supervisors: Professor Anna Ma-Wyatt, Associate Professor Steven Wiederman, Associate Professor Dominic Thewlis

Neuroscience, Behaviour and Brain Health

Poster Number: 30

Characterising the impact of pre-existing brainstem tau pathology on the development of cognitive deficits following a single mild traumatic brain injury

Eleanor Bowley-Schubert

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Traumatic brain injury (TBI) is one of the environmental risk factors for the later development of neurodegenerative diseases, including Alzheimer's disease (AD). However, most people with a TBI do not develop neurodegeneration, instead a TBI may accelerate disease progression in those with pre-existing pathology. The locus coeruleus (LC) is well-documented to be the first site of tau pathology in AD and may be particularly susceptible to effects of TBI due to its high metabolic demand and anatomical location. This study aimed to examine the effect of pre-existing inflammatory-induced tau pathology within the LC on the development of cognitive deficits following a mild TBI. 10-week-old male Sprague-Dawley rats (n=15-16 per group) were randomly allocated to sham or LC injection and then to sham or diffuse TBI via the Marmarou weight drop model 7 days later. Three months following TBI rats underwent a behavioural battery to assess anxiety-like behaviour on the Elevated Plus Maze (EPM), cognition on the Barnes Maze and affective state via burrowing. Pre-existing inflammation within the LC prior to a TBI did not affect the development of cognitive deficits ($p=0.85$), anxiety-like behaviour on the EPM ($p=0.98$) or affective state assessed as burrowing behaviour ($p=0.67$). An overall main effect of injury was observed in latency to find the new escape box, with injured rats taking longer ($p<0.05$), with no affect of injury on anxiety ($p=0.76$) or affective state ($p=0.36$). Inflammation within the LC led to a significant decrease in burrowing behaviour ($p<0.05$), but no effect on any other measure. Future work will examine whether LC inflammation prior to TBI accelerates the spread of tau pathology and inflammation post-injury, given that the time-point is most likely too early to observe behavioural changes.

Supervisors: Associate Professor Frances Corrigan, Associate Professor Lyndsey Collins-Praino

Neuroscience, Behaviour and Brain Health

Poster Number: 31

Peripheral nerve stimulation via a novel, bio-adhesive graft-antenna to improve outcomes following traumatic spinal cord injury

Ryan Dorrian

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Background and Aims

Peripheral nerve stimulation (NS) represents a promising intervention for spinal cord injury (SCI), having demonstrated functional improvements and neuropathic pain relief. However, current NS devices are large, invasive, and incorporate complex circuitry. These factors risk device failure, restrict clinical applications and create access barriers. We have developed the graft antenna, a biodegradable device that facilitates wireless NS. While the graft antenna has not been utilised post-SCI, the device has successfully promoted regeneration following nerve transections. Similarly, NS may improve outcomes post-SCI by promoting tissue regeneration and modulating neuroinflammation. As such, we hypothesised that NS via the graft antenna would alleviate neuropathic pain and improve motor and bladder function post-SCI by modulating neuroinflammation and promoting tissue regeneration.

Methodology

Male Sprague Dawley rats (11 weeks old) were randomised into groups (naïve, sham, SCI-only, SCI + unilateral NS [US], SCI + bilateral NS [BS]), and endpoints (3 days/8 weeks post-SCI, n=9/group/timepoint). Graft-antenna's (US/BS) or an inactive adhesive (SCI-only) were implanted on the sciatic nerve one week before T10 SCI induction (200kdyne, Infinite Horizon). NS was administered immediately post-injury and weekly thereafter (1Hz, 1hr/antenna). Animals were assessed for neuropathic pain (von Frey, place-escape-avoidance-paradigm [PEAP]), motor function (BBB open-field, Horizontal Ladder), and bladder function (Void spot assay, retained urine weight).

Results

Preliminary results suggest the graft-antenna may alleviate neuropathic pain, with SCI-only animals exhibiting a lower foot withdrawal force (von Frey: -14.09% change from baseline) than NS animals (US: -3.26%, BS: 0.81%) and greater pain-avoidance behaviour (PEAP percentage time in white box: SCI = 32.06%, US = 7.72%, BS = 9.72%). However, NS did not improve motor (BBB score at the endpoint: SCI = 12.55, US = 13.19, BS = 13.63) or

bladder function (retained urine weight during first two-week post-SCI: SCI = 18.7g, US = 20.1g, BS = 16.8g). Statistical analysis will be completed when datasets are appropriately powered. Ongoing analysis evaluates potential mechanisms (neuroinflammation, tissue regeneration) via immunofluorescence and light-sheet microscopy.

Conclusions

The graft antenna offers smaller, simpler, less invasive NS and may represent a novel intervention for individuals who experience SCI-induced neuropathic pain.

Supervisors: Associate Professor Anna Leonard, Associate Professor Antonio Lauto, Dr Carolyn Berryman

Neuroscience, Behaviour and Brain Health

Poster Number: 34

Characterising synergistic effects of traumatic brain injury and pesticide exposure on the development of neurodegeneration in a novel rat model of disease

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Background and Aims

Traumatic Brain Injury (TBI) and exposure to pesticides have been independently associated with increased risk of developing Parkinson's Disease (PD). However, it is becoming increasingly clear that development of PD is complex and likely involves multiple factors. There are currently few preclinical models of neurodegeneration that reflect this, and thus elucidating mechanisms of disease pathogenesis presents considerable challenges. The aim of this study was to develop and characterise a novel "two-hit" model of PD combining TBI and low-level rotenone exposure, to induce underlying inflammation and dopaminergic neuronal loss in the Substantia Nigra prior to injury.

Methodology

8-10 week-old male Sprague-Dawley rats were randomly allocated to receive vehicle or rotenone treatment, and sham or TBI surgery (n=16 per group). Animals were subcutaneously injected with 2% DMSO or rotenone (1.5mg/kg) every 48 hours for 12 days, followed by a moderate-severe TBI using the Marmarou weight-drop model, or sham surgery, 24 hours after the final injection. Animals were tested on various motor and cognitive domains at 3-months post-TBI to assess the development of Parkinsonian symptoms.

Results

Gross motor function, involuntary movement, forelimb dexterity and grip strength were not significantly affected by injury or rotenone, or the two in combination. TBI significantly affected motor coordination, as assessed by faults on the beam walk ($p=0.0006$), and sensorimotor function, as assessed by step adjustments ($p=0.0055$), and time to removal ($p=0.026$) in the tape removal test, however there was no interaction with rotenone exposure. No difference in cognitive domains, including learning, motivation, motivation or impulsivity were observed as a result of injury, rotenone, or a combination of the two factors.

Conclusion

While a synergistic effect of TBI and rotenone exposure was not observed 3-months post-injury, deficits may emerge at a later time-point post-injury. Thus, further characterisation of our two-hit model is currently underway, including histological analysis of tissue collected 1-month post-injury and broad functional testing and histological analysis of tissue at 6-months post-injury, to assess chronic manifestations of disease.

Supervisors: Associate Professor Lyndsey Collins-Praino, Associate Professor Frances Corrigan

Neuroscience, Behaviour and Brain Health

Poster Number: 37

Enhancing motor cortex plasticity and motor skill acquisition through theta-gamma transcranial alternating current stimulation (tACS) in healthy young and older adults.

Nishadi Gamage

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Background and Aims

Theta-gamma transcranial alternating current stimulation (tACS) over primary motor cortex (M1) can improve motor skill acquisition in healthy young adults, but its effects on older adults are unknown. This study investigated the effects of theta-gamma tACS on use-dependent M1 plasticity and motor skill acquisition in young and older adults.

Methodology

18 young and 18 older healthy adults completed two experimental sessions in which high-definition theta-gamma (6-75 Hz) or sham tACS was applied over right M1 for 20 minutes during ballistic left thumb abduction motor training, with a post-training-performance block performed 1 hour after training. Transcranial magnetic stimulation (TMS) was applied to right M1 to assess changes in M1 excitability before and after training, with motor-evoked potentials (MEP) recorded from left abductor pollicis brevis used to assess changes in M1 excitability (use-dependent M1 plasticity) and short-interval intracortical inhibition (SICI).

Results

Following training, mean MEP amplitudes were significantly greater for theta-gamma tACS compared with sham for all participants ($P < 0.001$). However, the change in SICI was not different between tACS treatments ($P = 0.404$). Normalised thumb acceleration was significantly greater with theta-gamma tACS than sham throughout motor training in both age groups ($P < 0.001$). During post-training performance, thumb acceleration did not differ between tACS treatment ($P = 0.571$) or age groups ($P = 0.864$).

Conclusion

Theta-gamma tACS over M1 increases use-dependent plasticity and improves motor skill acquisition in young and older adults. These findings could have implications for improving motor function in age-related neurological conditions.

Supervisors: Associate Professor John Semmler, Associate Professor Mathew Piasecki, Dr George Opie, Prof Philip Atherton

Neuroscience, Behaviour and Brain Health

Poster Number: 40

Comparing age-at-injury on the spatial distribution of diffuse axonal injury in a novel gyrencephalic ferret model of TBI.

Justin Krieg

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Background and Aims

Diffuse axonal injury (DAI) drives most functional deficits following traumatic brain injury (TBI). Mechanical force causes biochemical and structural axonal changes which initiate secondary injury cascades, leading to ongoing axonal damage following injury. Given that the developing brain has higher water content and less myelination, age at time of injury may markedly alter the response of axons. Furthermore, not all components of the axon are affected, as even in the same location different axons may show different types of axonal pathology. As such, we sought to compare axonal injury following diffuse TBI in adult and paediatric ferrets, which have a human-like gyrencephalic brain.

Materials and Methods

TBI was induced using the CHIMERA (Closed-Head Injury Model for Engineered Rotational Acceleration), with adult males (6-9 months; 1.1-1.6kg) were allocated to sham or 22J (mild TBI) (n=5-7/group), and paediatric males (2-3 months; 400-600g) allocated into sham or 17J (n=5-6 group). The axonal response to injury was examined using ex-vivo diffusion tensor imaging (DTI), serum levels of the axonal protein neurofilament light (NF-L) and examination of the brain itself microscopically through a cyclic immunofluorescence protocol which allows for co-labelling of 6 different markers of DAI(Ankyrin, APP, Calpain, CASPR, NF-L, RMO-14).

Results

Histology analyses remain ongoing, however serum NF-L analysis showed no significant differences between sham and injured adult ferrets (61.71±35.76 pg/ml vs 30.18±13.31pg/ml, $p=0.14$). However, paediatric TBI animals had significantly higher serum NF-L (76.62±48.56 vs 15.10±6.79 pg/ml, $p<0.05$). Despite the increase in NFL, ex vivo DTI showed no appreciable differences with injury in paediatric ferrets, with comparable findings in adults.

Conclusion

This is the first description of serum NF-L following paediatric TBI (both clinically and pre-clinically). Although the study remains ongoing, early results highlight that serum NF-L may have differing utility with age-at-injury. Histological analysis will further clarify whether these findings are reflective of the full scope of DAI within the brain. Further research into DAI phenotypes can prompt for more targeted therapeutic interventions. Serum NF-L may be used to help inform injury severity and how age modulates this response is important for understanding treatment windows. Whilst in-vivo DTI can show DAI clinically, this may not translate ex-vivo, where formalin crosslinks interfere with tissue properties.

Supervisors: Associate Professor Frances Corrigan, Associate Professor Anna Leonard, Associate Professor Renee Turner

Neuroscience, Behaviour and Brain Health

Poster Number: 43

Enriched phenotype analysis: Tying Perineuronal net structures to high and low burrowers in isolated and enrichly housed rats.

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Background and Aims

Affective state (emotion) has influence over our behaviour and cognition. A negative affective state compromises health and immune response. The extracellular matrix, a lesser understood region of the brain, potentially provides mechanisms for change in mood states. Mood disorders, such as depression, associate with change in neuroplasticity. Perineuronal nets (PNNs), specialised structures of the extracellular matrix, have been linked to the mechanism of synaptic plasticity and dendritic spine arborisation. PNNs mostly surround parvalbumin neurons (PV) providing them neuroprotection and enabling their fast-spiking property; thereby PNNs may contribute to altered inhibitory signalling. The aim of this study was to induce a positive or negative affective state in rats through housing conditions, validate this with behavioural tests, and explore structural changes of PNNs in the rat brain.

Methods

Adult Sprague Dawley rats were housed singly isolated or caged together in enriched environments for 21 days (n=12 per group) to induce a shift in affective state. The enriched environment included large cage (1m x 1m x 2m), rotation of novelty items, and daily handling. Rat ultrasonic vocalisations were recorded during handling to investigate association with induced affective states. Isolated rats were not handled and had gnaw blocks as the only enrichment. Rats underwent basal, day 3 and day 21 trials of burrowing and sucrose preference. Brain tissue was analysed by immunofluorescent labelling of PNNs (Wisteria floribunda agglutinin) and parvalbumin inhibitory interneurons.

Results

Results of the burrowing task showed a change in behaviour was induced at day 3 ($p<0.0001$) and day 21 ($p=0.042$) (Mann Whitney U-test). For initial analysis, the top two high and low burrowers in each group were analysed for PNNs and PV in the anterior cingulate cortex as this region is involved in processing emotions and behaviour regulation. However, there was no significant difference found in PNN count, PV count or colocalization of PNN and PV within this region between these high and low burrower groups.

Conclusion

Limited research exists on functional causality of PNNs on behaviour and cognition. Day 3 showed the greatest change in behaviour so any molecular changes at this timepoint may have been missed or resumed by the 21 day timepoint when brains were collected for analysis. Alternatively, PNN may be altered by affective state changes in other brain regions. Further histological analysis of perineuronal nets on rats exposed to the same housing conditions (without behavioural testing) at the 3 day timepoint and in other brain regions will be undertaken.

Understanding the mechanistic neurobiology of affective state will enable therapeutic use of positive affective state to improve physical and mental treatment outcomes while fostering health and well-being.

Supervisors: Professor Mark Hutchinson, Dr Alexandra Whittaker

Neuroscience, Behaviour and Brain Health

Poster Number: 51

Evaluating the prognostic utility of cognitive reserve and neuroimaging measures for predicting functional outcomes

Isaac Saywell

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Background and Aims

Ageing is a heterogenous process, no one individual experiences identical functional changes as another, making forecasting trajectories quite difficult. Mapping prognosis becomes particularly even more challenging with neurological conditions like Parkinson's disease and traumatic brain injury. Mismatches in healthy ageing and neurodegenerative disease functional outcomes have been justified by the concept of cognitive reserve when there is no neuropathological explanation. There is evidence that some individuals can tolerate the effects of ageing or brain damage to maintain age-expected functionality because of different lifetime exposures. Proper evaluation of the putative effect of cognitive reserve on outcomes requires a proposed measure of cognitive reserve (e.g., socio-behavioural proxy or neuroimaging marker) and two other components: a measure of brain structure/pathology and of cognitive function. The influence of the CR proxy can only be validated by the latter two components to demonstrate a protective effect on cognition, at a given pathology level. Most studies investigating CR rarely consider the impact of brain structure/pathology on the relationship between CR and functional outcomes, thereby only establishing construct face validity, not its underlying neuroprotective effect. Currently, the degree of variability in outcomes that can be accurately attributed to CR, and not key anatomical features or other relevant factors associated with these outcomes, is unclear. CR neuroprotective effects that were derived from analyses that did not account for anatomy/pathology as possible confounders may be ill-informed. This study aimed to compare the predictive utility of several measures of brain function or structure against CR for different functional cognitive and motor outcomes.

Methodology

Seventy-five healthy individuals underwent an approximately one-hour long MRI brain scan, completed a questionnaire, neuropsychological testing, and a motor function examination. Brain measures were developed from several MRI sequences including, T1-weighted, T2-weighted fluid attenuated inversion recovery, diffusion-weighted, and resting-state functional

imaging techniques. CR was estimated using a validated socio-behavioural questionnaire and by using a verbal intelligence test. Different domains of both cognition and motor function were considered as functional outcomes. Correlation tests, principal component analyses, regression techniques and supervised machine learning algorithms were used to determine predictive utility of different MRI brain measures and CR factors.

Results

It is expected that anatomical brain measures extracted from MRI will correlate with both cognitive and motor function. CR is also expected to present significant associations with certain brain measures and outcome tests. Regression and machine learning techniques will be used to determine which CR and brain measures are more predictive of functional outcomes than others, thereby informing their predictive utility.

Conclusion

Results will have implications for future CR studies, potentially conveying whether measuring CR has value above and beyond using brain measures to estimate outcome trajectories. Under circumstances that CR's effect remains important for predicting certain outcomes then discoveries may inform which brain measures are important confounders to consider when determining the concept's neuroprotective effect. Importantly, findings will likely have implications for forecasting healthy ageing prognosis by providing a set of CR and brain measures that are most likely to have predictive utility for functional outcomes.

Supervisors: Dr Irina Baetu, Associate Professor Lyndsey Collins-Praino, Professor Mark Jenkinson

Neuroscience, Behaviour and Brain Health

Poster Number: 54

Social Synchronising Primates: Prediction of Prosocial Behaviours can Uncover Inter Brain Neural Synchronisation in Primates.

Jacob Sevastidis

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Prosocial co-operation has been critical for all evolution and survival on earth and has played a large part in shaping the neural, behavioural, and cultural sophistication of modern humans. A recent, neurological phenomenon termed inter-brain neural synchronisation (IBNS) has been shown to facilitate elevated efficacy of prosocial co-operation in mammals (humans, macaques, bats, and rats) & avians. A product of sociality, the selective pressures which motivated the development of IBNS throughout primate evolution have yet to be discovered; leaving its true purpose in humans a mystery. The current research aims to illuminate the presence of IBNS in primates (excluding the tribe hominini) to guide future research to specific primate populations which display prosocial behaviours theorised to facilitate IBNS based off human models. Further experimental research revealing the nature of IBNS in primates is critical to understanding the nature of this phenomenon in humans and human ancestors. Logit modelling utilising machine learning principles was used to create likelihood estimates which were converted into probability statistics of primate prosocial behaviours modelled with correlated social, ecological, morphological, and behavioural (SEMB) variables. Results indicated that prosocial behaviours of food-sharing, group foraging, consolation and coalition formation are all significantly predicted by select SEMB variables. This suggested the theoretical presence of IBNS in primate populations through comparative human models of prosociality, revealing similar recruitment of neural architecture and behavioural patterns that could precede IBNS in primates.

Supervisors: Dr Wenpeng You, Professor Maciej Henneberg, Dr Arjun Burlakoti, Dr Lance Storm

Neuroscience, Behaviour and Brain Health

Poster Number: 57

Navigating Health Claims on Social Media: Reasoning from Consensus Quantity and Expertise

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Background and Aims

The accessibility afforded by social media has abolished traditional barriers to the global proliferation of health information. To ascertain what is true, online reasoners rely on the judgements of others while considering certain indicators of reliability, such as their degree of consensus and their level of expertise. However, whether online reasoners respond to such indicators as simple heuristics or use them to make more complex assumptions about the possible information space remains unclear.

Methodology

We investigated this question by asking participants (N = 99) to rate their belief in a series of short health claims both before and after reading user responses. The degree of consensus among these users as well as their level of expertise was manipulated within-subjects.

Results

Results indicated a positive relationship between the persuasiveness of a consensus and its size, although with diminishing returns. We also identified a small expertise effect, wherein an expert consensus was marginally more persuasive than a non-expert consensus but displayed greater diminishing returns as its size grew.

Conclusion

This provides tentative evidence suggesting that people reason from consensus using more complex assumptions about the possible information space. Implications for these findings include better understanding the role that consensus plays in shifting belief in health claims, and the role that experts can play in aiding online reasoning.

Supervisors: Dr Rachel Stephens, Dr Keith Ransom

Neuroscience, Behaviour and Brain Health

Poster Number: 60

The Role of Neuroinflammation in Delayed Neurodegeneration following Photothrombotic Stroke in Rats

Shannon Stuckey

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Background

Many patients suffer long-term functional deficits following stroke. This is linked with delayed neuronal death in areas distal from the infarct site, termed secondary neurodegeneration (SND). Increasing evidence demonstrates neuroinflammation as a potential driver of SND, although, the current long-term implications of this are not understood. As such the aim of this study is to investigate the spatiotemporal profile of neuroinflammation and neurodegeneration, and associated functional changes, long-term following stroke.

Method

Male Sprague-Dawley rats (n=44/gp; 12-weeks) underwent photothrombotic stroke or sham surgery and were aged out to 12- or 15-months post-stroke where brain tissue and serum were collected (n=30 stroke; n=14 sham/gp). Prior to endpoint, motor outcomes (step test), anxiety (open field), and cognitive decline (Barnes maze) were assessed. Neuroinflammation was analysed using a cytokine/chemokine multiplex (Millipore). Data was analysed using three-way ANOVAs, with Tukey's post hoc test.

Results

Motor deficits were observed to be greater at 15-months post-stroke (D baseline -1.9±0.4steps/30cm) than 12-months (Dbaseline 0.07±0.4steps/30cm, p=0.0016). Unexpectedly, animals showed higher levels of anxiety (p=0.001), with excessive grooming, and cognitive decline (p=0.03), with longer time to the escape box, at 12-months (48.9±7.0secs; Dbaseline 48.8±8.8secs, for anxiety and cognition respectively) compared with 15-months post-stroke (6.6±10.7secs; Dbaseline 26.6±4.5secs, respectively). Within distal regions of the brain (thalamus and hippocampus) the levels of proinflammatory cytokines (IL-6, TNF-a, IL-12, IFN-g and MCP-1) were significantly decreased in the stroke groups ($p<0.05$) when compared to shams. Interestingly, in some select cytokines this decline was seen to be more significant in the 15-month post-stroke group, with multiple

comparison analysis showing significant differences ($p<0.05$) between 12- and 15-month post-stroke groups, as well as significant differences ($p<0.05$) between sham and stroke groups at 15-months. This is of particular interest, given that the levels of similar cytokines were in fact increased within the serum of both the 12- and 15-month post-stroke groups ($p<0.05$).

Conclusion

Our results show a progression in motor impairment between 12- and 15-months post-stroke. Conversely, animals showed improvements in cognition between 12- and 15-months. Interestingly, when investigating the underlying mechanisms, we observed decreased levels of inflammation in the thalamus (relay centre for motor function) and hippocampus (important for memory and learning) in both groups. This was surprising given our behavioural results, but may be a result of neural repair mechanisms in these regions or reflective of less immune cell activity due to tissue damage. Importantly, we did observe an increase in pro-inflammatory cytokines in the serum which we hypothesise is a biomarker of SND in other brain regions. Our observation of the change in anxiety like behaviour supports this hypothesis, as it is indicative of changes in the function of the amygdala. Given that we have observed changes both beyond the understood timeline and in known regions of SND, our study highlights the need for long term comprehensive analyses of SND in rats and potential targets for neuroprotective therapies. Further, our study has provided a number of peripheral markers that may be of use when identifying patients at risk of SND.

Supervisors: Associate Professor Renee Turner, Associate Professor Lyndsey Collins-Praino, Dr Rebecca Hood

Neuroscience, Behaviour and Brain Health

Poster Number: 61

The Impact of Latencies Associated with Information Displays on Visuomotor Performance

Lucy Turner

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Background and Aims

Humans use visual information to effectively interact with their environment, for example when grasping a cup or pressing an elevator button. But visual processing and the sensorimotor integration of this information takes time. Because of this, human action must take advantage of out-of-date information to complete these kinds of actions. Minor delays at any point in this process may be compensated for with predictive and intermittent control strategies. However, information displays including computer monitors and near-eye displays introduce an additional visual feedback delay due to sensing, computer processing, and display times. Research in manual tracking has shown that constant delays above 100ms result in tracking error (movement lag and overshoot) (Miall et al., 2000). Gradual adaptation to such delays has been shown to occur up to 200ms in an interception task (Camara et al., 2018). However, it is not well understood how sudden latency changes impact visuomotor performance on a manual tracking task. This project investigates tracking performance when there is a step change in visual feedback delay and characterises the smooth pursuit eye movements made throughout the task.

Materials and Methods

Participants completed a manual tracking task across two one-hour sessions. Participants controlled crosshairs presented on the screen using a mouse. The target moved along curvilinear trajectories and the participants were requited to align the cross hairs as accurately as possible to the moving target. A temporal delay was inserted between the mouse movement and the crosshair movement on the screen. In the first session, baseline performance was recorded using 5 constant latency conditions (100ms, 150ms, 200ms, 250ms, and 300ms) and a control condition with no latency. In the second session the latency of the cross hair either increased or decreased from the control condition (0ms) mid trial by one of four different latencies (150ms, 200ms 250ms, and 300ms). Participants' eye movements were recorded at 1000Hz using an Eyelink 1000. The centre of the crosshair

position was also recorded at 75Hz. Performance measures included tracking accuracy, lag and lead proportions, and return to baseline times.

Results

As the latency increased, participants tracked with less accuracy as evidenced by a significant increase in error across each condition. The time taken to correct for a movement error also significantly increased across the conditions. The proportion of time lagging the target was significantly different from control in each condition. However, there was not a significant change in lag proportion from 250ms to 300ms. A change in the crosshair delay lead to aftereffects in error and lag proportion.

Conclusion

The findings indicate that visual feedback delays, stemming from sensory and motor history, influence the control strategies employed in pursuit tracking tasks. These data provide insights into the impact of timing discrepancies on human visuomotor performance, with implications for developing human-centric design of such systems.

Supervisors: Professor Anna Ma-Wyatt, Associate Professor Steven Wiederman, Dr Jessica O'Rielly

Oral Health

Poster Number	Abstract Details
64	**Jamal Giri** *Development of soft tissue facial profile from age 7 to 17 years: a twin study* Adelaide Dental School
67	**Don Ketagoda** *Oral microbiome transplantation in rats induced with dental caries* Adelaide Dental School
70	**Qazi Farah Rashid** *Digital Shade Matching In Dentistry: A Systematic Review* Adelaide Dental School
73	**Manisha Tamrakar** *Association between Multimorbidity and Periodontitis in Older Adults: A network analysis* Adelaide Dental School

Oral Health

Poster Number: 64

Development of soft tissue facial profile from age 7 to 17 years: a twin study

Jamal Giri

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Background and Aims

While the role of genetic and environmental factors in the development of craniofacial morphology is well known, little is known about their relative contributions to the development of soft tissue facial profiles. This study aimed to partition the contribution of genetic and environmental factors in the phenotypic variation of the facial soft tissue profile and assess the temporal change in the contribution of these factors during facial development.

Methodology

Standardized facial profile photographs of 139 twin pairs (55 monozygotic and 84 dizygotic) were obtained from the archives of the Adelaide Dental School. Photographic analysis used 12 angular and 14 linear facial profile measurements during the mixed dentition (7-10 years) and the permanent dentition (12-17 years) stages. A genetic analysis was performed using a univariate structural equation model adhering to the normal assumptions of a twin model. A polynomial function was used to analyze the shape of the soft tissue facial profile.

Results

In the mixed dentition stage, the additive genetic (A) and unique environmental (E) model, AE model, was the most parsimonious in explaining the observed phenotypic variance for all 26 facial traits with the narrow-sense heritability estimates ranging between 0.38 to 0.79. In the permanent dentition, the AE model was the most parsimonious for 20 out of 26 variables, however, the variance of six facial traits particularly on the lower third of the face was best explained by the shared environmental and unique environmental factors. Furthermore, the soft tissue facial profile could be best described using a seventh-degree polynomial equation (adjusted $R^2 > 0.85$).

Conclusions

The soft tissue facial profile demonstrated dynamic genetic and environmental influences with a greater genetic influence during the mixed dentition years. However, there was evidence of increasing environmental influence on the lower third of the face during the early stages of the permanent dentition.

Supervisors: Professor Toby Hughes, Professor Alan Brook

Oral Health

Poster Number: 67

Oral microbiome transplantation in rats induced with dental caries

Don Ketagoda

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Background and Aims

Incredibly diverse microbial communities (microbiota) are now routinely studied throughout the human body in the context of health and disease. In the mouth, microbiota play key roles in all oral diseases, including dental caries. Oral Microbiome Transplantation (OMT) is an innovative concept of transferring health-associated oral microbes into the oral cavity of a diseased person. The purpose of this microbial transplant is to shift a state of oral dysbiosis to a stable ecological balance with the host immune system. This aims of this study are to assess the safety and the effectiveness of OMT in an in vivo rat caries model as a new method to treat dental caries and improve oral health.

Methodology

OMT inoculum was prepared by growing plaque from two healthy donors in 3D printed flow cells for 10 days. One half of the microbes were mixed with 2% carboxymethyl cellulose (CMC) at a 1:1 ratio and the remainder of the OMT inoculum was mixed with Streptococcus mutans at a 1:1 ratio. 48 Sprague Dawley rats were equally divided into 4 groups: 1)CMC 2) S. mutans 3)OMT 4)OMT+S. mutans.

Prior to inoculation all rats were subjected to a 0.1% chlorohexidine rinse and saline rinse. 100µL of the inoculum (CMC, S. mutans, OMT or OMT+S. mutans) was inoculated into each rat in the designated groups across 3 days. From the first inoculum day to the end of the experiment (day 12), the rats were fed x5 a day with NIH2000 diet. Oral swabs were taken from 6 selected rats before the chlorohexidine rinse (before transplant) and at the end of the experiment for 16S next generation sequencing and the data was analysed used QIIME2. Serum (ELISA for CRP), colon and caecum samples (H & E staining) were collected from the same rats at the end of the of the experiment. Rat jaws of each group were subjected to micro-CT scanning and scored for caries.

Results

There was no significant difference of the CRP levels and histological scores of all the groups when compared with each other. Beta diversity was significantly different between the oral microbiome before and after transplantation in group 3 and 4. Alpha diversity and taxonomic analysis showed that there was a significant difference (increase) in the number of bacterial species post-transplant in group 3 and 4 in comparison to the microbiome pre-transplant indicating a new hybrid microbiome has been formed ((PERMANOVA; pseduo-F=6.98; FDR correct p-value (q) = 0.027). Caries scores of the transplant groups (3,4) were significantly ($p<0.05$) lower than the non-transplant groups (1,2).

Conclusion

This study demonstrated the safety and efficacy of OMT using an in vivo rat caries model. The significant reduction in dental caries was via an OMT which showed a clinical reduction in caries due to the change in the oral microbiome. Additionally, this is the first instance in which a successful OMT has been done in vivo.

Key words: Oral Microbiome Transplant, DNA Sequencing, Micro-CT Scanning, in vivo

Supervisors: Associate Professor Peter Zilm, Dr Laura Weyrich

Oral Health

Poster Number: 70

Digital Shade Matching In Dentistry: A Systematic Review

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Background and Aims

The pursuit of aesthetic excellence in dentistry, shaped by societal trends and digital advancements, highlights the critical role of precise shade matching in restorative procedures. Although conventional methods are prevalent, challenges such as shade guide variability and subjective interpretation necessitate a re-evaluation in the face of emerging non-proximity digital instruments. The objectives were 1) to identify the non-proximity digital recording instruments used in dentistry for matching shades and the associated colour spaces, 2) to compare the clinical outcomes of non-proximity digital systems with spectrophotometers and conventional visual colour matching methods.

Methodology

Following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) protocols and keyword-based ‘Search Strings’ using Boolean Logic, the search was conducted across Scopus®, PubMed.gov, Web of ScienceTM from 20th August 2020 to 12th September 2020 with an update in March 2022 by two reviewers. Predefined exclusion and inclusion criteria were used for study selection and any disagreements between the raters were resolved and tested through a Cohen’s kappa calculator. To assess the risk of bias and methodological quality, the Joanna Briggs Critical Appraisal tool (JBI) and GRADEpro GDT were employed. The primary objective was to identify non-proximity digital instruments and their associated colour spaces utilized in dentistry, while the secondary goal was to compare the clinical outcomes of these instruments with available spectrophotometers or conventional colour matching methods. The PICO model and a 4-point Newcastle-Ottawa Scale served as the search strategy tools for obtaining relevant articles in relation to the secondary outcome.

Results

Eighty-five articles met the eligibility criteria, of which 33 articles were included in a PICO to facilitate clinical comparisons. Only 8% (n = 7/85) of articles were judged to be of high quality, 42% (n = 36/85) were of moderate, and the remaining were of low to very low quality.

Conclusion

Among the studies examined, 42% employed the CIELAB color space for their analysis. In controlled conditions, non-proximity digital instruments exhibited more consistent clinical outcomes when compared to conventional visual shade-matching methods. Furthermore, the efficacy of non-proximity digital instruments was discovered to be comparable to that of spectrophotometers and colorimeters.

Supervisor: Associate Professor James Dudley

Oral Health

Poster Number: 73

Association between Multimorbidity and Periodontitis in Older Adults: A network analysis

Manisha Tamrakar

Tamrakar M [1], McCormick KM [1], Luzzi L [1], Mejia G [1]

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Background and Aims

Ageing, accompanied by an increased prevalence of multimorbidity, has become a global public health priority. Among the ageing population, periodontitis is also highly prevalent and linked with many chronic conditions. Despite this, it is not included in multimorbidity definitions or in prevalence estimates of multimorbidity. To address this, our study aims to reveal patterns and clusters of multimorbidity including periodontitis among older adults.

Methodology

This is study uses the baseline data of the South Australian Dental Longitudinal Study (1991-1992). A stratified random sample was used to collect data through household face-to-face interviews followed by periodontal examinations on 801 older adults aged 60 years and older from Adelaide and Mt. Gambier. Multimorbidity was defined as the presence of two or more chronic health conditions in the same individual at the same time. Information on ten medical conditions: asthma, chronic bronchitis, hypertension, heart attack, stroke, diabetes, arthritis, cataract, osteoporosis, and cancer were collected through questionnaires. For each, response options were: “Yes”, “No” and “Don’t know”, which was then categorised into binary variables coded 1= Yes and 0= Other than Yes. Periodontitis was defined according to the 2018 European Federation of Periodontology/American Academy of Periodontology classification (EFP/AAP). The EFP/AAP case definition consists of 4 stages; stages III and IV are based on tooth loss due to periodontitis. We grouped stage I and II in one category. To determine stage III and IV, six data sets were modelled based on the following assumptions: 100%, 70%, 60%, 50%, 30% and 0% tooth loss due to periodontitis. Exploratory graph analysis was performed on each data set using the walktrap algorithm, utilising Triangulated Maximally Filtered Graph (TMFG) to detect patterns of association between the multimorbidity and periodontitis variables.

Results

All participants were classified as periodontitis case according to AAP/EFP classification and the prevalence of multimorbidity being 56.55%. The network analysis showed varied communities of chronic conditions. Four of the ten conditions studied – heart attack, stroke, arthritis, and diabetes – showed positive associations with late-stage periodontitis. Heart

attack and stroke was positively associated to periodontitis in all models, whereas asthma and cataract did not show any direct associations with periodontitis.

Conclusion

The results showed conditional association between later-stage periodontitis and multimorbidity communities containing cardiovascular diseases. However, the number, direction and strength of associations varied with the proportion of missing teeth attributed to periodontal disease.

Supervisors: Dr Gloria Mejia Delgado, Dr Liana Luzzi

Oral Health

Poster Number: 73

Association between Multimorbidity and Periodontitis in Older Adults: A network analysis

Manisha Tamrakar

Tamrakar M [1], McCormick KM [1], Luzzi L [1], Mejia G [1]

[1] ARCPOH, Adelaide Dental School, The University of Adelaide

Background and Aims

Ageing, accompanied by an increased prevalence of multimorbidity, has become a global public health priority. Among the ageing population, periodontitis is also highly prevalent and linked with many chronic conditions. Despite this, it is not included in multimorbidity definitions or in prevalence estimates of multimorbidity. To address this, our study aims to reveal patterns and clusters of multimorbidity including periodontitis among older adults.

Methodology

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arthritis, and diabetes – showed positive associations with late-stage periodontitis. Heart attack and stroke was positively associated to periodontitis in all models, whereas asthma and cataract did not show any direct associations with periodontitis.

Conclusion

The results showed conditional association between later-stage periodontitis and multimorbidity communities containing cardiovascular diseases. However, the number, direction and strength of associations varied with the proportion of missing teeth attributed to periodontal disease.

Supervisors: Dr Gloria Mejia Delgado, Dr Liana Luzzi

Surgical and Health Systems Innovation

Poster Number	Abstract Details
78	**Chan Hee Cho** *Hip Implants with Evidence of Phased Introduction have Improved Survivorship at Long-Term Follow-up* Adelaide Medical School
81	**Taisha D'Apollonio** *Migration of Acetabular Components used in Revision Total Hip Arthroplasty is Twice that Observed in Primary Procedures* Adelaide Medical School
90	**Aaron Hammat** *Diagnosis and Treatment influence Hospital Costs of Revision Total Hip Arthroplasty: A Systematic Review and Meta-analysis* Adelaide Medical School
91	**Kasey Irwin** *Exploring Operating Room Staff Experience Related to The Design of Operating Room Spaces in Australia* Adelaide Nursing School
94	**Mia Majstorovic** *Surgeons' Views on the Barriers and Enablers to Bariatric Surgery* School of Psychology

Surgical and Health Systems Innovation

Poster Number: 78

Hip Implants with Evidence of Phased Introduction have Improved Survivorship at Long-Term Follow-up

Chan Hee Cho

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Aim

The aim of this study was to determine whether there was a difference in all cause revision rates between non-RSA-tested and RSA-tested acetabular components listed in national hip registries at 5- and 10-years follow-up. We hypothesised that RSA-tested acetabular components will have improved survivorship at 5- and 10-years follow up.

Methods

Data was collected from national arthroplasty registries that reported both 5-year and 10-year revision rate of individual acetabular component designs. A recent meta-analysis was used to identify RSA-tested acetabular component designs. A random-effects model was used to calculate the pooled revision rate at 5- and 10-years follow-up for non-RSA tested and RSA-tested acetabular components.

Results

There were 134 RSA-tested-acetabular component combinations of 28 acetabular component designs and 290 non-RSA-tested-acetabular component combinations of 97 acetabular component designs from 6 national registries analysed in the study. Mean all-cause revision rates at 5 years for RSA-tested and non-RSA-tested components were 2.8% (95% CI 2.6 to 3.0) and 3.7% (95% CI 3.5 to 3.9), with a mean difference of 0.8% favouring RSA-tested implants (95% CI 0.5 to 0.11). Mean all-cause revision rates at 10-years for RSA-tested and non-RSA-tested acetabular components were 4.9% (95% CI 4.5 to 5.2) and 6.8% (95% CI 6.5 to 7.2), with a mean difference of 1.7% in favour of RSA-tested acetabular components (95% CI 1.2 to 2.3).

Conclusion

RSA-tested acetabular components have significantly lower revision rates at both 5- and 10-years follow-up than non-RSA tested acetabular components. An improvement in revision rate of approximately 1.7% at 10 years represents a relative decrease of approximately 34% in revision burden during this period. This evidence further supports the use of RSA as an important surveillance tool in the stepwise introduction of new acetabular components to the orthopaedic market.

Supervisors: Dr Stuart Callary, Dr John Abrahams, Dr Bart Pijls

Surgical and Health Systems Innovation

Poster Number: 81

Migration of Acetabular Components used in Revision Total Hip Arthroplasty is Twice that Observed in Primary Procedures

Taisha D'Apollonio

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[2] Department of Orthopaedics and Trauma Royal Adelaide Hospital

[3] Department of Orthopaedics, Leiden University Medical Centre

Background/Aims

Early implant stability, measured by Radiostereometric Analysis (RSA), is a known surrogate of long-term implant survivorship for loosening. Despite improvements in the incidence of acetabular component loosening following Primary Total Hip Arthroplasty (pTHA), loosening remains a common complication following Revision (rTHA). This review aims to identify the early migration of, (1) implants used at rTHA procedures, (2) compared to pTHA.

Methods

A systematic review was conducted to identify RSA studies that measured the proximal migration of acetabular components used at rTHA. A recent review of RSA studies of acetabular components used at pTHA was used as a baseline comparator. The proximal migration at 2 years was extracted, pooled, and compared to the comparator studies using all component designs and then the same component designs in two independent comparisons to pTHA.

Results

15 implant designs (26 cohorts) were studied with RSA in rTHA cohort studies whilst 28 implant designs (83 cohorts) were studied with RSA in pTHA cohort studies. The migration of six acetabular component designs had been reported with RSA in eight rTHA cohorts. The pooled mean migration of the acetabular components used at rTHA at 2 years (0.38mm and 95CI 0.21 to 0.55) was twice that observed in pTHA (0.17mm and 95CI 0.13 to 0.21, p=0.0088). Cemented components had an increased probability of greater proximal migration at 2 years in rTHA studies and the comparator group. All rTHA cohort studies reported acetabular component migration greater than the acceptable thresholds and were considered at risk of requiring additional re-revision surgery.

Conclusion

Acetabular implant failure is commonly reported for rTHA cohorts, which is no fault of the component's design. There is a paucity of RSA studies within the current literature accurately measuring acetabular component migration in rTHA cohorts. This study highlights that acetabular implants used for rTHA cohorts migrate double that of pTHA cohorts utilising the same component. Notably, cemented rTHA components migrated more than cemented. Likely, the failures reported in rTHA cohorts are not directly reflective of the implant design as the same components have proven to be successful in pTHA cohorts. Acetabular defects, poor bone quality and inadequate initial fixation are among the major contributing factors that may influence the proximal migration of acetabular components used at rTHA.

Supervisors: Stuart Callary, Dr John Abrahams, Professor L. Bogdan Solomon

Surgical and Health Systems Innovation

Poster Number: 90

Diagnosis and Treatment influence Hospital Costs of Revision Total Hip Arthroplasty: A Systematic Review and Meta-analysis

Aaron Hammat

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[5] Wakefield Orthopaedic Clinic, Calvary Adelaide Hospital

[6] Department of Orthopaedics and Trauma, Royal Adelaide Hospital

Background and Aims

We conducted a systematic review and meta-analysis on the hospital costs of revision total hip arthroplasty (rTHA) by periprosthetic joint infection (PJI), periprosthetic fracture (PPF), aseptic loosening, and dislocation diagnoses. Additionally, this study aimed to synthesise the hospital costs of rTHA treatments by comparing them to two-stage PJI rTHA, one-stage PJI rTHA, and Open Reduction Internal Fixation (ORIF).

Methods

A systematic search of Pubmed, Embase and Scopus identified all studies reporting the hospital costs of rTHA. Screening, data extraction and risk of bias assessment were conducted. Reported

costs were adjusted for inflation to 2024 and converted to USD. The main diagnosis and treatment costs were pooled using a random effects model.

Results

Of the 852 publications, 38 were included in the systematic review, and 22 were included in the meta-analysis of cost by diagnoses. Mean costs of dislocation, aseptic loosening, PPF, and PJI rTHAs were $23,022, $34,920, $36,985, and $79,129, respectively. The mean cost of all 24 aseptic rTHA cohorts was $31,316. In 9 studies that directly compared PJI and aseptic rTHA cohorts, PJI revisions cost, on average, 2.1 times of aseptic revisions. Treating for PJI: Two-stage PJI revisions ($60,979) cost more than one-stage revisions ($39,676).

Conclusion

rTHA incurs substantial costs to hospitals and healthcare systems worldwide. Different costing structures across various health systems and lack of uniformity in study designs make it difficult to assign absolute costs to PJI rTHAs. Our systematic review confirmed that PJI rTHA hospital cost is, on average, 2.1 times of aseptic rTHAs across the published literature. Hospital costs of rTHA separated by diagnosis were incrementally increased from dislocation, aseptic loosening, PPF and periprosthetic joint infection. Two-stage rTHAs treating for PJI cost 54% more than one-stage PJI rTHAs.

Supervisors: Dr Stuart Callary, Dr Emmanuel Gnanamanickam, Professor Lucian Bogdan Solomon

Surgical and Health Systems Innovation

Poster Number: 91

Exploring Operating Room Staff Experience Related to The Design of Operating Room Spaces in Australia

Kasey Irwin

Irwin K [1], Donnelly F [1], Kelly J [1]

[1] Adelaide Nursing School, The University of Adelaide

Background and Aims

Operating Rooms (OR) are spaces where high-risk clinical care is provided, presenting complex challenges in patient care delivery due to evolving surgical needs and the involvement of multiple stakeholders (Sutherland-Fraser et al. 2022). Staff working within these spaces understand the complexities of surgical procedures and the technology used to provide safe care but may not be involved in built environment design planning. Research highlights the significant impact of OR layout on safety and performance outcomes, emphasising the importance of considering factors such as adjacencies, flow patterns, and staff movement (Bayramzadeh et al. 2018; Joseph et al. 2019; Jurewicz et al. 2020). However, there is a notable gap regarding staff inclusion in design and tools measuring engagement. This study aims to uncover factors influencing OR safety and function and examine the role of OR staff in design planning.

Methodology

This exploratory mixed-method sequential study (QUAL – Quant) (Creswell & Plano Clark 2017), involved semi-structured interviews and a focus group with 16 participants, including anaesthetists, surgeons, nurses, theatre technicians, and OR designers in 2021(Irwin, Donnelly & Kelly 2024).These findings led to a 21-item questionnaire distributed online to Australian OR staff and designers in 2023 to validate emergent theory. Previous research noted a lack of tools assessing healthcare environment quality, prompting the development of context-specific measures. The questionnaire focused on OR safety, function, and design participation, collecting 388 responses. Participants were asked to report their experience working within or designing OR spaces, ranked safety concerns and indicated agreement with qualitative concepts from the first study phase.

Results

Four core concerns of participants were analysed from qualitative data; Ensuring Engagement, Respect & collaboration, Foreseeing & Responding to Safety Concerns, Enhancing Design Planning to Minimise Internal & External Consequences, and Ambiguous Application of Standards. Initial quantitative analysis reveals that 69% of OR staff have not

participated in OR design planning processes, with surgeons being more involved compared to nurses and anaesthetists. Among engaged staff, participation in staff forums, reviewing floor plans, images, or simulations was common. Safety concerns, raised by 94% of engaged staff, were predominantly identified during floor plan, design image or simulation reviews. Qualitative findings support this, indicating that end users anticipate and aim to address safety concerns through design planning. The most important concern related to patient safety is access or proximity to support and essential items, while the most important concern related to staff was ergonomics aligning with qualitative findings. Overall, there is consistent agreement with qualitative statements, supporting validation of the developing theory related to the design of OR spaces in Australia.

Conclusion

Qualitative findings underscore the importance of staff engagement in anticipating and addressing safety concerns. Health professionals highlighted safety impacts related to patients and staff due to the built environment and emphasised the need for improved engagement, respect, and collaboration in design processes. Initial quantitative analysis reveals disparities in staff participation. OR staff raise safety concerns related to design proposals, emphasising the importance of addressing workflow challenges, minimising environmental risks, and ensuring staff and patient safety through comprehensive design planning. Addressing these concerns requires consideration of health professionals' lived experiences and overcoming hierarchical and cultural barriers to inclusive design. This research emphasises the importance of collaborative design processes in creating safer and more functional OR environments, informed by end users' insights.

Supervisors: Professor Frank Donnelly, Professor Janet Kelly

Surgical and Health Systems Innovation

Poster Number: 94

Surgeons' Views on the Barriers and Enablers to Bariatric Surgery

Mia Majstorovic

Majstorovic M [1], Chur-Hansen A [1], Andrews J [2,3], Burke A [1,4]

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[4] Psychology Department, The Central Adelaide Local Health Network

Background and Aims

Severe obesity is associated with significant physical, psychological, economic, and societal consequences. Bariatric surgery is an effective treatment for severe obesity, leading to substantial weight loss and enhancing health-related quality of life. Yet, the factors influencing who receives bariatric surgery remain poorly understood, particularly from the perspective of key healthcare professionals, such as bariatric surgeons. Thus, our qualitative study aimed to explore the views of bariatric surgeons on the barriers and facilitators to bariatric surgery.

Methodology

Sixteen bariatric surgeons or registrars from Australia and New Zealand participated in online interviews between April and September 2023. Interviews were conducted in English, and participants were aged 18 years or older. The data were analysed using qualitative content analysis.

Results

Five main categories were identified: patient-related factors, healthcare experiences and clinician-related factors, economic, governmental, and institutional factors, societal beliefs and attitudes towards obesity, bariatric surgery and bariatric surgeons, and bariatric surgery in the context of other treatments. Each category revealed various barriers and enablers to bariatric surgery.

Conclusions

Our findings underscored the significant role patients play in driving the decision for surgery and navigating healthcare complexities. Societal attitudes, including the stigma and normalisation of obesity, were identified as major barriers. Establishing rigorous guidelines, governance, and funding support for public bariatric surgery were discussed as crucial. Finally, the disregard for bariatric surgery relative to other treatments was highlighted, as was the role of other medications and surgeries in altering perceptions of bariatric surgery. This study provides policymakers and healthcare researchers/professionals with further research avenues as well as areas that could be improved in the healthcare system to ensure that progression to surgery is equitable.

Supervisors: Professor Anna Chur-Hansen, Professor Jane Andrews, Professor Anne Burke

Session 2

Poster presentations are held in the Panorama Ballroom, Upper Level of the Adelaide Convention Centre.

Students will be allowed **5 minutes** presentation time, with an additional **3 minutes** allocated for question-and-answer time with the assessors.

Poster presentations will be assessed according to the criteria below. Each assessor will provide a score out of 10 for each category.

- Quality and clarity of presentation and poster
- Scientific merit
- Quality of data/results/significance
- General understanding and ability to answer questions
- Overall poster rating

To encourage networking, collaboration, and the opportunity to meet with some of our major stakeholders and industry partners, all students are encouraged to attend both poster sessions.

Research Areas

Cancer Biology and Clinical Oncology

Indigenous Health and Health Equity

Innovative Therapeutics

Nutrition and Metabolic Health

Cancer Biology and Clinical Oncology

Poster Number	Abstract Details
2	**Dana Al Safadi** *Role of Androgen Receptor Signalling in Metastasis of Estrogen Receptor-Positive Breast Cancer Cells.* Adelaide Medical School
5	**Ahmed Aldoghachi** *Investigating the role of androgen receptors in bladder cancer* Adelaide Medical School
8	**Michael Antoniou** *How Cancer Associated Fibroblasts (CAFs) modify the stromal landscape to advance the malignant progression of breast cancer* Adelaide Medical School
11	**Sepideh Azizi** *Transforming Growth Factor Beta Upregulates Leukemic Stem Cell Marker CD123 to Prime Hematopoietic Progenitors for Pro-Inflammatory Granulopoiesis* Adelaide Medical School
14	**Maxim Buckley** *A Tale of Two Vesicles: Effects of CRLF2 p.F232C B-cell Acute Lymphoblastic Leukaemia Derived Microvesicle and Exosome Treatments on Ba/F3 Parental Cells* Adelaide Medical School
19	**Cate Cheney** *Antibiotic-induced ablation of gut microbiota in murine models of Acute Lymphoblastic Leukaemia results in variable patterns of leukaemic cell engraftment.* Adelaide Medical School
22	**Ez Aldeen Esawi** *Extracellular fatty acid induces loss of the canonical AR signaling pathway in prostate cancer.* SAiGENCI
25	**Bryan Gardam** *Dendritic Cell Defects in Patients and Mice with Brain Tumours* Adelaide Medical School
28	**Mohammad Ismail** *investigating ferroptosis as a metabolic vulnerability in SPOP mutant prostate cancer* SAiGENCI
32	**Sima Kianpour Rad** *Exploring the Impact of intracellular Staphylococcus aureus on Triple-Negative Breast Cancer Cell Proliferation, PD-L1 Expression, and Doxorubicin Accumulation* Adelaide Medical School

35	**Stephen Kinsey-Trotman** *Does tumour grade and ki67 have prognostic utility in male breast cancer? The results of two systematic reviews* Adelaide Medical School
38	**Julia Leeflang** *Harnessing Tumour Specific Evolution of Probiotic Bacteria to Engineer Next-Generation Bowel Cancer Treatments* Adelaide Medical School
41	**Runhao Li** *Modulation immunophenotypes in colorectal cancer liver metastasis via hepatotropic rAAV-SFRP5-RLuc gene therapy* Adelaide Medical School
44	**Caleb Lill** *Investigating the role of chemokine-like factor in paediatric B-ALL relapse* School of Biomedicine
46	**Jamshid Motalebzadeh** *The Biological Function of Tryptophan Metabolism in Triple Negative Breast Cancer: Implications for Immunotherapy* Adelaide Medical School
49	**Alex Pace** *A CRISPR-KO Whole Genome Screen Identifies Candidate Combinational Strategies for use with an Androgen Receptor Agonist to Kill Estrogen Receptor Positive Breast Cancer Cells"* School of Biomedicine
52	**Micaela Quinn** *Effectiveness and safety of bone-protective interventions to mitigate bone loss and skeletal-related events experienced by patients with non-metastatic breast cancer: a systematic review and meta-analysis* School of Biomedicine
55	**Ines Semendric** *Prevalence of cancer-related cognitive impairment in paediatric patients and survivors of non-CNS cancers: a systematic review and meta-analysis* School of Biomedicine
58	**Suzanna Shirazi** *Epigenetic regulation of skeletal stem cells during high fat/glucose mediated inhibition of bone formation.* School of Biomedicine
62	**Tharindie Silva** *A gastric cancer organoid platform to guide personalised chemotherapy for advanced disease patients.* Adelaide Medical School
65	**Mackenzie Skinner** *Effect of fixation and decalcification on the lipidome of bone marrow biopsies using mass spectrometry techniques.* School of Biomedicine

68	**Ashlee Thomson** *Improving Accuracy and Reducing Bias in Genomic Alignment for B-cell Acute Lymphoblastic Leukemia Patients: A Pan-Genome Graph Approach* School of Biomedicine
71	**Maliha Wajahat** *ZBTB16 is a critical mediator of androgen receptor-induced tumour suppression in ER-positive breast cancer.* Adelaide Medical School
74	**Fangmeinuo Wu** *Evaluating the Efficacy of Perhexiline and Cisplatin Combination Treatment in Head and Neck Cancer* Adelaide Medical School
76	**Jiarna Zerella** *Germline ERG haploinsufficiency defines a new syndrome with cytopenia and hematological malignancy predisposition* Adelaide Medical School

Cancer Biology and Clinical Oncology

Poster Number: 2

Role of Androgen Receptor Signalling in Metastasis of Estrogen Receptor-Positive Breast Cancer Cells.

Dana Al Safadi

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Background and Aims

Breast cancer is the most common malignancy worldwide, accounting for 45% of total diagnosed cancer cases in females. More than two thirds of breast malignancies are estrogen receptor positive (ER+) and are treated with ER targeting endocrine therapy. Up to 50 % of patients develop resistance to endocrine therapy and relapse with metastatic disease, which contributes to 90% of breast cancer associated mortality. Our published data has shown that the androgen receptor (AR) plays a tumour suppressor role in ER+ breast cancer. The effect of AR signalling on cell motility and metastasis of ER+ cancer cells was not investigated in that study and is the aim of the current study.

Methodology

Using in vitro transwell migration assays, we measured the ability of BT474 cells, an ER+/AR+ breast cancer cell line, to migrate after activating AR with DHT (1-10 nM) for 24 hours or under vehicle control conditions. Expression of AR, ER and E-cadherin (ECAD) protein in BT474 cells with and without DHT treatment was quantified using Western blot. The chicken chorioallantoic membrane (CAM) assay was assessed as a potential model to evaluate in vivo invasion and metastasis of BT474 cells. IVIS imaging was used to detect metastatic BT474 cells labelled with an mKate fluorescence marker.

Results

Treatment with DHT (1-10nM) significantly reduced the in vitro migration of BT474 cells in comparison to vehicle controls. Relative to controls set at 100% average migration rate, the DHT-induced decline was 61% at 1nM DHT, 51% at 5nM DHT and 36.9% at 10 nM DHT with a significance of 0.01, 0.0005 and < 0.0001, respectively (One-way ANOVA). As expected, AR protein expression was upregulated following 24 hr treatment with 1, 5 and 10 nM DHT compared to vehicle control, but there was no effect on ER or ECAD expression. In a pilot CAM assay, fluorescence intensity was normalized to the signal detected from cells invading the CAM layer and 5 out of 8 chicken embryos had metastasis of BT474 cells to the liver at embryonic day 18 when seeded with 0.5 or 1.0x106 cells at embryonic day7.

Conclusion

Activation of AR with DHT significantly reduced the migration of BT474 cells in vitro, indicating inhibition of metastatic capacity. This was unlikely due to effects on ER or ECAD expression. We validated and optimized the CAM assay for in vivo assessment of BT474 invasion and metastasis. Ongoing experiments will assess whether DHT treatment can inhibit liver metastasis by BT474 cells in the CAM model.

Supervisors: Associate Professor Theresa Hickey, Professor Wayne Tilley, Dr Amy Dwyer

Cancer Biology and Clinical Oncology

Poster Number: 5

Investigating the role of androgen receptors in bladder cancer

Ahmed Aldoghachi

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Background and Aims

Though not traditionally considered a hormone-dependent cancer, bladder cancer is four times more common in males compared to females, prompting investigation into the role of the male sex determining hormone, androgen, and its cognate receptor in this disease. Evidence from prior experimental studies suggest that the androgen receptor (AR) plays an oncogenic role in bladder cancer by increasing cancer cell proliferation, migration, and invasion. Conversely, there are clinical studies indicating that AR expression in bladder cancer cohorts is positively correlated with low tumour grade and stage, suggesting a tumour suppressor role. The goal of this study is to resolve the role of AR in bladder cancer. To achieve this, we aim to characterise AR signalling more extensively in bladder cancer and determine the functional consequences of AR activation versus inhibition in bladder cancer cell line models.

Methodology

Western blotting and immunofluorescence analyses were used to determine the total protein expression and nuclear localization of AR and known AR target genes (SEC14L2, FKBP5) in three bladder cancer cell lines reported to be AR positive (UMUC3, T24, and TCCSUP). Cell proliferation and ATP-based viability was assessed using a Coulter Counter and Cell Titre Glow Assay, respectively, to determine the effect of AR agonists and AR antagonists. A colony formation assay was used to examine the ability of a single cell to regenerate a colony, indicative of tumour-forming capacity, following treatment with an AR agonist or antagonist. All experiments were carried out in 3 independent biological replicates and data was analysed using a one-way ANOVA.

Results

A low level of AR expression was detected by Western Blot in the UMUC3 cell line model, and no AR expression was detected in the T24 and TCCSUP models. In the AR-expressing UMUC3 cell line, treatment with the AR agonist 5α-dihydrotestosterone (DHT; 1nM; 48 hr) stabilised expression of AR in UMUC3 cells and induced expression of SEC14L2 but not FKBP5. Immunofluorescence analysis of UMUC3 bladder cancer cells demonstrated nuclear localisation of AR in a small sub-population of cells (~12% and ~18% upon treatment with

1nM DHT and 10nM, respectively). Neither AR agonists nor antagonists affected the proliferation, ATP content, or colony formation capacity of UMUC3 cells compared to the control group.

Conclusion

These findings refute previous studies that have reported AR expression in T24 and TCCSUP bladder cancer cell lines. Evidence of canonical AR signalling was observed in the UMUC3 cell line, albeit in a very small sub-population of cells, which likely explains a lack of a significant effect of AR modulating treatments on UMUC3 cell proliferation, viability, and colony formation capacity. Alternative cell line models and patient-derived models of bladder cancer including explants, xenografts, and organoids that retain AR expression are required to determine the functional role of AR in this disease.

Supervisors: Professor Wayne D Tilley, Associate Professor Theresa Hickey, Dr Amy R Dwyer

Cancer Biology and Clinical Oncology

Poster Number: 8

How Cancer Associated Fibroblasts (CAFs) modify the stromal landscape to advance the malignant progression of breast cancer

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Background and Aims

A recent paradigm shift in cancer research has proposed that the tumour microenvironment (TME), plays an important role in cancer progression. This idea has been supported by a large body of evidence from both experimental and clinical research in numerous cancer types, including breast cancer. Cancer associated fibroblasts (CAFs), a key component of the TME, actively support multiple facets of tumour development. The mammary cancer produced protein, CRELD2, has been recently identified as a key effector of CAF pro-tumorigenic phenotype.

Thus, the main objective of this study is to delineate specific molecular changes in CAFs that lead to tumour-enhancing modifications in the TME, creating a more aggressive breast tumour phenotype. This will be achieved through utilising a recently discovered CRELD2-CAF-extracellular matrix (ECM) axis as a handle to model and interrogate tumour-promoting CAF-mediated remodelling of the stromal compartment in breast cancer.

Methodology

We have utilised primary mammary CAFs and transgenic mouse models to address our experimental aims. Isolated from human breast cancer tumour biopsies and the PyMT-MMTV spontaneous breast cancer transgenic mouse model CAFs were evaluated for their pro-tumorigenic properties in optimised ex-vivo assays. In-silico analysis was undertaken to establish the relevance of our recent RNA-seq data on mouse mammary CAFs to human breast cancer. Novel proteins found to be expressed solely by CAFs within mammary tumours and not previously implicated in breast cancer pathobiology were selected and tested in cell-based functional analyses utilising a siRNA knock-down approach.

Results

Using a heterotypic adhesion assay, we found an increase in adhesion on the ECM produced by CRELD2-activated CAFs compared to untreated CAFs, in multiple cell types, including myeloid and epithelial cancer cells, and primary mouse and human lymphocytes.

These findings suggest the presence of ECM receptors that are common for numerous cancer types, that may be involved in ECM-related pro-tumorigenic alteration in the TME. Immunofluorescent analysis of actin dynamics of primary mouse mammary tumour cells allowed to attach to CRELD2-induced CAF secreted ECM, has also shown an increase in the ability of breast cancer cells to spread and migrate on the matrix in comparison to untreated CAFs. We have now shown that down-regulation of the matrix protein ECM2 is essential for adhesion of mammary tumour cells on the CAF-produced matrix.

Conclusion

In summary, we have established a strong link between novel, atypical for normal breast tissue CAF-produced ECM components and breast cancer adhesion and migratory potential. Further studies will now focus on determining specific biochemical properties of these proteins and their unique pro-tumorigenic role in breast cancer TME.

Supervisors: Associate Professor Daniel Thomas, Dr Marina Kochetkova, Associate Professor Theresa Hickey

Cancer Biology and Clinical Oncology

Poster Number: 11

Transforming Growth Factor Beta Upregulates Leukemic Stem Cell Marker CD123 to Prime Hematopoietic Progenitors for Pro-Inflammatory Granulopoiesis

Sepideh Azizi

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Background

Acute myeloid leukemia (AML) is a heterogeneous cancer and its earliest progenitors drive AML relapse after chemotherapy which accounts for a poor patient survival rate. The malignant myeloid blasts lose their capability to differentiated into mature hematopoietic lineages which leads to severe multi-lineage cytopenia. One of the unique immunophenotypic features of leukaemic myeloid blast is the aberrant expression of IL3Ra (CD123). The over-expression of IL3Ra has been observed in various type of haematological malignancy such as AML1,2, Myelodysplastic syndrome (MDS)3, CML4. In AML, relatively high expression of IL3Ra is detected on AML blasts, leukemic CD34+ progenitors (LSCP) and leukemic stem cells (LSC)5,6, whereas healthy non-leukemic progenitors have little to no IL3Rα expression. Little is known about the mechanism involved in over-expression of IL3Rα in AML and the possible advantage that it provides, if any, to LSC in AML relapse. During normal haematopoiesis, the IL3Rα, through mediating IL-3 signalling, is involved in the differentiation of HSC to multipotent and pluripotent cellular lineages as well as their proliferation. Under homeostatic conditions, the balance between the pro- and anti-inflammatory cytokines such as IL6 is maintained7. Recent studies however have shown that dysregulated cytokine secretion can contribute to AML blast survival and proliferation8. Given the potentially critical role of these primitive cells in perpetuating leukemic disease, we sought to investigate the molecular mechanism by which the over-expression of IL3Rα may be regulated in these early progenitors through specific stimulus.

Method

Time stimulation studies TGFβ family of ligand such TGFβ1, TGFβ2 and BMP4 in different AML cell lines and cord blood stem cells CD34+ via western blotting, qPCR and Flow cytometry.

Lentiviral-shRNA and siRNA knock down studies for Smad2 and Smad4.

CoIP Smad2 and Smad4 study to show complex formation.

ChIP Smad2 and Smad4 study to show enrichment of IL3Ra at promotor region IL3Ra.

Colony formation assay (CFU) study in complete cytokine Metho-cult to show the effect of upregulation of IL3Ra upon TGFβ1.

Results

To unravel the novel discovery of IL3Ra upregulation mediated by TGFβ1, western blotting and qPCR were performed in different time points and concentrations to harvest the critical time points and concentrations that upregulation occur. The critical time points then have been utilised to screen the upregulation of IL3Ra upon specific stimulus across 15 different cell lines and CD34+ from PBMC and cord blood by western blotting and flow cytometry. To recapitulate the phenomenon, the publicly available RNAseq data were used for comparison analysis between expression of stimulus and its responsive genes across defined AML patient samples versus healthy samples. Then regression analysis was performed to identify the significant of IL3Ra upregulation and TGFβ1 responsive gene. In addition, the correlation analysis between canonical protein downstream of stimulus and IL3Ra were performed in 15 different cell lines with western blotting to further confirm that TGFβ1 pathway is activated. shRNA knockdown performed on Smad2 and Smad4 to confirm the defined canonical pathway proteins are driven the IL3Ra upregulation, followed up by Smad4 and Smad2 CoIP complex confirmation upon TGFβ1 stimulation. Next, Smad2 and Smad4 ChIP-PCR analysis was performed to show the enrichment of Smad2 and Smad4 complex at enhancer region of IL3Ra gene. The colony formation assay was performed to evaluate transient exposure of CD34+ of cord blood to TGFβ1 derive CFU-GM formation. To further confirm this phenomenon is driven by IL3Ra upregulation upon TGFβ1, 7G3 blocking antibody were used to show CFU-GM colony in primary CD34+ only forms due to transient exposure to TGFβ1, which results in upregulation of IL3Ra.

Summary

Determining the underlying mechanisms that drive up-regulation of IL3Rα on AML blasts may facilitate a novel treatment option that could lead to improved leukemia clinical outcomes. Understanding the regulation mechanism harnessed by inflammatory cytokines such TGFβ1 in altering of IL3Rα expression level may also have implications to maintain the IL3Rα expression level in physiological condition.

Supervisors: Professor Angel Lopez, Professor Greg Goodall

Cancer Biology and Clinical Oncology

Poster Number: 14

A Tale of Two Vesicles: Effects of CRLF2 p.F232C B-cell Acute Lymphoblastic Leukaemia Derived Microvesicle and Exosome Treatments on Ba/F3 Parental Cells

Maxim Buckley

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Introduction

Cytokine Receptor-Like Factor 2 rearrangement (CRLF2r) occurs in ~5-10% of B-cell Acute Lymphoblastic Leukaemia patients. The CRLF2 p.F232C mutation results in overexpression and constitutive activation of the encoded thymic stromal lymphopoietin receptor (TSLPR). Extracellular vesicles (EVs) are lipid bodies produced by all cells. Microvesicles and exosomes, two distinct EV sub-populations, may be involved in leukaemic transformation, though investigation into EVs in a B-ALL context is limited. Microvesicles bud from the cell membrane and can facilitate direct horizontal receptor transfer. Exosomes are formed intracellularly in multi-vesicular bodies and carry cell specific micro RNAs and, in the context of cancer, potentially transformative genomic sequences. In general, both populations can carry a diverse array of nucleic acids, lipids, and proteins. Traditional theories of leukaemogenesis are defined by genomic alteration in a single cell and subsequent clonal proliferation. Microvesicles and exosomes offer the potential for horizontal transfer of leukaemogenic nucleic acids and proteins to non-transformed cells resulting in leukaemic transformation.

Methodology

EVs collected from an IL-3 independent Ba/F3 cell line expressing the CRLF2 p.F232C were purified via differential centrifugation. Parental Ba/F3 cells were treated daily with 5 µg/mL of either microvesicles or exosomes in the presence of IL-3 to mimic the bone marrow microenvironment. Fluorescence microscopy assessed microvesicle and exosome interactions with Parental Ba/F3 cells. Daily cell counts via Trypan Blue exclusion and CellTitre Glo ATP activity assay investigated the ability of microvesicles and exosomes to induce proliferation in Parental Ba/F3 cells. qPCR was used to quantify alterations in pro-

survival and pro-apoptosis gene expression and microvesicle and exosome mediated CRLF2 mRNA transfer.

Results

Both CRLF2 p.F232C-derived microvesicles and exosomes were sequestered into the Parental Ba/F3 cell cytoplasm. Microvesicles lost their characteristic vesicle shape upon uptake whereas exosomes remained spherical. A daily dose of 5 µg/mL of CRLF2 p.F232C-derived exosomes significantly induced cell growth in Parental Ba/F3 cells whereas a daily dose of 5 µg/mL CRLF2 p.F232C-derived microvesicles induced cell death in a dose dependent manner. Microvesicle and exosome treatments also resulted in changes in pro-apoptosis and pro-survival gene expression. Finally, both CRLF2 p.F232C-derived microvesicles and exosomes transferred the full-length CRLF2 mRNA to Parental Ba/F3 cells. Microvesicles transferred significantly more CRLF2 mRNA than exosomes, likely due to their larger size.

Conclusion

Here we demonstrate that microvesicles and exosomes interact with Parental Ba/F3 cells, affect their viability, alter pro-survival and pro-apoptosis gene expression, and horizontally transfer mRNA between cell-lines via both microvesicles and exosomes. Given these findings, microvesicles and exosomes may mediate leukaemogenesis of neighbouring non-leukaemic cells.

Supervisors: Professor Deborah L White, Dr Laura N Eadie

Cancer Biology and Clinical Oncology

Poster Number: 19

Antibiotic-induced ablation of gut microbiota in murine models of Acute Lymphoblastic Leukaemia results in variable patterns of leukaemic cell engraftment.

Cate Cheney

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Background & Aims

Emerging evidence supports gut microbiome immaturity as a contributing factor to Acute Lymphoblastic Leukaemia (ALL) development in childhood. Delayed maturation of the microbiome-immune interface in early life may arise due to various epidemiological factors. Here, we aimed to investigate the role of dysbiotic microbiota on the engraftment of ALL cells in a murine model.

Methods

Specific-pathogen-free six-week-old NSG mice were maintained on drinking water supplemented with ampicillin (1mg/mL) and neomycin (0.5mg/mL) (n=20) to deplete the gut microbiota, or regular water (control; n=20). Seventy-two hours later mice were injected with primary B-ALL blasts via tail vein from one of the following subtypes; NUP214::ABL1, DUX4::IGH, KMT2A::AFF1, P2RY8::CRLF2. Faecal samples were collected weekly and successful ablation of the gut microbiota was confirmed by 16s rRNA bacterial load qPCR. NUP214::ABL1 mice were humanely culled once %hCD45+ cells reached 15% in the blood of antibiotic animals. The remaining subtypes were humanely culled once %hCD45+ cells reached 50% in the peripheral blood of antibiotic-treated animals. Bone marrow, spleen, liver, colon, stomach and caecum were harvested and sectioned for histological analysis. Phenotyping of tissues was conducted via flow cytometry and statistical significance was analysed via unpaired T-test and 2-Way ANOVA.

Results

NUP214::ABL1 - The percentage of circulating hCD45+ cells reached a significant difference at day 43 post-injection in antibiotic-treated mice compared to controls (8.4% vs 1%, p=0.0113). Antibiotic-induced dysbiosis increased hCD45+ cells in the spleen (82.12% vs 54.34%, p=0.0002) and splenic weight (91 vs 60 mg, p=0.0087) compared to eubiotic controls. These observations were not recapitulated in the bone marrow or liver at this early time point.

P2RY8::CRLF2 - The percentage of circulating hCD45+ cells reached a significant difference at day 42 post-injection in antibiotic-treated mice compared to controls (26.4% vs 18.34%, p=0.0222), also displaying an increased splenic weight (356 vs 293 mg, p=0.0087) at study endpoint. The phenotypic profile of the leukaemic cells were similar across bone marrow, spleen and liver populations.

KMT2A::AFF1 – Percentages of circulating hCD45+ cells did not reach a significant difference at any time point before culling, however, the spleen size of antibiotic-treated mice was significantly smaller than eubiotic controls (69 vs 94 mg, p=0.0003), an inverse observation to NUP214::ABL1 and P2RY8::CRLF2 mice. No significant changes in the phenotypic profile of the leukaemic cells were observed across any organs.

DUX4::IGH – Percentages of circulating hCD45+ cells did not reach a significant difference at any time point before culling, nor were significant changes observed between organ weights, phenotypic profiles or survival (72 days).

Conclusion

A dysbiotic microbiota appears to accelerate leukaemic engraftment in mice harbouring blasts from NUP214::ABL1 and P2RY8::CRLF2 subtypes. Interestingly, effects appear restricted to the spleen with minimal changes in the bone marrow and liver between experimental groups. Repeated experimentation with leukaemic cells from varied patients within these subtypes is crucial to propose a subtype-specific response to gut microbiota ablation. Further investigation into the causal mechanism behind hCD45+ affinity for the spleen during dysbiosis is warranted to understand the role of gut microbiota composition in murine models of leukaemic engraftment.

Supervisors: Professor Deborah White, Dr Elyse Page, Professor David Yeung

Cancer Biology and Clinical Oncology

Poster Number: 22

Extracellular fatty acid induces loss of the canonical AR signaling pathway in prostate cancer.

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Introduction

Cancer cells are characterized by metabolic reprogramming and epigenetic modifications. A crosstalk between metabolism and epigenetic modifications that promotes cancer progression is well-established. The biological relevance of this phenomenon during the acquisition of therapy-resistant phenotypes in prostate cancer (PCa) is still largely unknown. Herein, we aim to study the influence of exogenous fatty acids on the epigenome and how this crosstalk affects androgen signaling and neuroendocrine markers in PCa.

Methods

Clinical data was used to study the relationship between fatty acid oxidation (FAO) genes and the progression of PCa. Further, we analyzed the public data set (GSE147877) to study the relation between FAO genes and ENZ treatment in PCa cell lines. Additionally, we treated LNCaP and MR42D cell lines with different fatty acids (FAs) and studied AR signaling and neuroendocrine progression.

Results

We analyzed RNAseq data for a cohort of 120 patients collected by our group at the point of initial diagnosis, subsequently tracking their progression to metastasis. The results identified FAO gene signature associated with clinical relapse in metastatic PCa patients. Furthermore, treating PCa cell lines with ENZ showed an increase in FAO gene expression and neuroendocrine markers. After that, we treated MR42D and LNCaP cell lines with medium or long-chain FAs showed an increase in total histone 3 acetylation and a decrease in the expression of the AR signaling pathway. In addition, the MR42D cell line showed a significant increase in the neuroendocrine marker NCAM1.

Conclusion

FAO signature gene expression is correlated with PCa progression. Also, the introduction of exogenous fatty acids leads to increased histone acetylation levels and enhances the neuroendocrine characteristics. We will trace the 13C labeled FA to confirm the carbon source of the acetyl groups. The chromatin changes will be studied through ATAC-seq, Hi-C, and ChIP-seq.

Supervisors: Dr Zeyad Nassar, Professor Lisa Butler

Cancer Biology and Clinical Oncology

Poster Number: 25

Dendritic Cell Defects in Patients and Mice with Brain Tumours

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Background and Aims

Glioblastoma is an aggressive form of brain tumour that is the leading cause of death from cancer in people under 40 in Australia and has a median survival of only 15 months from diagnosis. Glioblastoma has seen few advances in treatment for over 20 years, highlighting the urgent need for new treatments. Dendritic cells (DCs) are professional antigen-presenting cells required for priming and activating T cells and initiating effective immune-mediated tumour control. Several studies have reported reduced DCs in glioblastoma patients' peripheral blood compared to healthy controls, and a paucity of these cells within glioblastoma tumours. However, it is currently unclear which DC subsets are most affected or how this deficiency might be corrected. Here we aim to determine the affected DC subsets, and identify a murine model to replicate these results and investigate potential methods to restore DCs in glioblastoma patients.

Methodology

High-parameter flow cytometry and orthotopic murine models of glioblastoma

Results

We show a systemic reduction in DCs in glioblastoma patients' peripheral blood compared to healthy donors. We saw the most significant reduction in CD5+cDC2s, DC3s, and pDCs; notwithstanding, all subsets were reduced. Our investigation also identified changes in DC functional markers in both tumour and blood, including markers for antigen presentation and lymph node homing. We further identified that the systemic reduction of DCs was also found in other patients with primary and metastatic brain tumours, but not tumours outside the brain.

We then analysed DCs in orthotopic murine models of glioblastoma to evaluate their suitability as model systems. We evaluated multiple tissues from five syngeneic and two patient-derived xenograft models and found no significant difference in DC numbers between tumour-bearing and tumour-free mice in any model. However, the change in DC functional markers observed in brain tumour patients was best reflected in the syngeneic models, indicating that these are more suitable models for exploring treatments to expand and restore DC populations.

Conclusion

DCs are systemically reduced in patients with tumours in the brain. While the focus for our ongoing studies is the restorations and expansion of DCs in the murine models.

Supervisors: Associate Professor Lisa M Ebert, De Tessa Gargett, Professor Michael P Brown

Cancer Biology and Clinical Oncology

Poster Number: 28

investigating ferroptosis as a metabolic vulnerability in SPOP mutant prostate cancer

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Introduction

A SL interaction exists between two genes when a defect in either gene is not lethal but simultaneous perturbation of both genes results in cell death. Unlike traditional targeted therapies, SL therapies promote mutation indirect targeting by identifying an alternative SL target, which could be an oncogene, a DNA repair mechanism or a metabolism pathway. SPOP is one of the most frequently reported somatic mutations among prostate cancer (PCa) patients representing a biologically distinct subset of the disease with unique molecular characteristics such as overexpression of androgen receptor (AR) and AR regulated pathway. Here, we investigated the SPOP-mutant metabolic genotype and identified a novel SL interaction between SPOP and ferroptosis gene glutathione synthetase (GSS).

Methods

Mutation, copy number alteration, and mRNA expression data were analyzed from TCGA prostate adenocarcinoma database to identify SL candidates. The identified SL interaction was validated in vitro using siRNA techniques. The therapeutic potential of the identified interaction was evaluated using FDA-approved small molecule inhibitors.

Results

We identified SL interaction between SPOP and GSS gene which codes for glutathione synthetase enzyme. The glutathione plays crucial roles in lipid peroxides detoxifying. siRNA knockdown of SPOP was used to model SPOP loss-of-function in PCa cell lines. Cells were treated with ML210 and sorafenib as ferroptosis inducers. SPOP downregulation increased cellular reactive oxygen species (ROS) levels and malonaldehyde levels, suggesting heightened sensitivity to ferroptosis. Overexpression of ferroptosis-associated proteins, like glutathione peroxidase 4 (GPX4), indicated a compensatory adaptation to lipid peroxide accumulation in SPOP mutant cells. Cell viability assay confirmed increased sensitivity to ferroptosis inducers ML210 and sorafenib in SPOP-depleted PCa cells.

Conclusion

These findings suggest Sorafenib as a potential FDA-approved treatment option for SPOP mutant PCa. Overall, leveraging SL interactions between somatic alterations and metabolic vulnerabilities offers promising personalized treatment avenues in PCa.

Supervisors: Dr Zeyad Nassar, Associate Professor Daniel Thomas, Professor Lisa Butler

Cancer Biology and Clinical Oncology

Poster Number: 32

Exploring the Impact of intracellular Staphylococcus aureus on Triple-Negative Breast Cancer Cell Proliferation, PD-L1 Expression, and Doxorubicin Accumulation

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Background

Triple-negative breast cancer (TNBC) is characterized by its aggressive nature, limited treatment options, and poor prognosis. Recent clinical trials have shown that patients derive significant benefit from the addition of anti-PD-1 immunotherapy (pembrolizumab) to standard chemotherapy. However, little is known about what controls tumour immune cell infiltration and the regulation of PD-L1 expression. Gram-positive bacteria, including Staphylococcus aureus, are prevalent in breast tissues, and limited evidence suggests they may influence immune response and chemotherapy efficacy. S. aureus enhances PD-L1 expression in some cancer cells via interferon gamma and TLR2. Yet, its potential in combating drug resistance and regulating PD-L1 expression in TNBC remains unexplored.

Aim

To explore the impact of S. aureus on PD-L1 expression and doxorubicin chemotherapy accumulation within TNBC cells.

Methods

Internalization potential of fluorescent-labelled S. aureus at different multiplicities of infection (MOI) in TNBC cell lines, MDA-MB-468 (basal A-like), MDA-MB-231 (mesenchymal/ basal B-like/low E-cadherin), and MDA-MB-453 (luminal expressing androgen receptor) was evaluated using flow cytometry. Long-term effects (7 days) of bacterial infection on cell line proliferation and bacterial viability was determined by crystal violet staining and CFU measurements, respectively. Flow cytometry was employed to assess doxorubicin accumulation in bacteria-infected cells at different MOI. PD-L1 expression in response to

bacterial infection with and without interferon-gamma stimulation was determined using flow cytometry.

Results

TNBC cell lines displayed varying capacities for bacterial uptake and sensitivity to infection. At MOI of 50, both MDA-MB-231 and MDA-MB-468 achieved cell infection rates over 80%. Whilst MDA-MB-231 tolerated MOI >200, a MOI above 50 resulted in high toxicity for MDA-MB-468. Notably, MDA-MB-453 demonstrated Significantly lower capacity (30% with MOI=50) in bacterial uptake compared to the other two cell lines. Bacteria-induced antiproliferative activity was observed in MDA-MB-231 and MDA-MB-468 at MOI ≥200, while MDA-MB-453 required an MOI of 500. In MDA-MB-468, infection at a low MOI allowed for bacteria survival for 4 days, whilst at both high and low MOI, bacteria survived for up to 4 days in MDA-MB-231 without causing significant host toxicity. However, with an MOI of 200, bacteria could survive in MDA-MB-453 for only 2 days. Overall, bacterial viability declined over time, with MDA-MB-231 cells demonstrating the highest capacity to sustain the bacteria. Co-treatment with interferon-gamma significantly increased PD-L1 expression in MDA-MB-468 cells (fold-change of 9 and 35 after 24 and 48 hours, respectively), with a modest ~2-fold increase in MDA-MB-231, indicating the involvement of interferon-gamma-mediated mechanisms in these cells. PD-L1 expression remained unchanged in MDA-MB-453. Doxorubicin accumulation increased slightly in all cell lines following bacterial infection, with MDA-MB-468 cells showing the highest increase (4-fold), followed by MDA-MB-231 (1.6-fold) and MDA-MB-453 (1.2-fold).

Conclusion

These findings provide valuable insights into the potential role of bacteria and interferon-gamma in regulating PD-L1 expression in TNBC, which may have implications for the development of novel immunotherapeutic strategies. Furthermore, our study suggests that bacterial infection may contribute to enhanced chemotherapy accumulation and drug response, underscoring the multifaceted interactions between the tumour microenvironment and therapeutic outcomes in TNBC.

Supervisors: Dr Eric Smith, Associate Professor Wendy Ingman, Associate Professor Amanda R. Townsend

Cancer Biology and Clinical Oncology

Poster Number: 35

Does tumour grade and ki67 have prognostic utility in male breast cancer? The results of two systematic reviews

Stephen Kinsey-Trotman

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Background & Aims

Prognostic indicators of survival are poorly defined in male breast cancer. Two early validated indicators in female breast cancer, tumour grade and ki67 expression, have reported conflicting results in male populations. This research aimed to systematically review the literature on tumour grade and ki67 in relation to survival outcomes in male breast cancer patients following surgery.

Methodology

A systematic review was completed to determine the clinical question: Does tumour grade influence male breast cancer survival following surgery? A second review was undertaken to determine if an association between tumour ki67 expression and overall survival exists in male breast cancer. Both reviews were prospectively registered. Medline, EMBASE, Central and grey literature sources were searched in accordance with PRISMA criteria by three reviewers. Meta-analysis was undertaken where appropriate, in each review.

Results

A total of fifteen observational type studies were included in the first review with eight included in a meta-analysis. A significant association between tumour grade and breast cancer specific survival was most evident with regard to grade III tumours with a significant relationship in 9 out of 11 studies (lower grades as the reference). In the second review of ki67 expression in male breast cancer, a total of fourteen studies met inclusion criteria for data extraction. A minority of papers demonstrated a statistically significant association between ki67 and overall survival. Pooled analysis of this data did not reach statistical significance.

Conclusion

The review findings imply tumour grade has prognostic utility for disease survival in male breast cancer. The frequent reporting of grade II (intermediate) tumours in male datasets, together with the reliance on observational data from contributory studies remain significant limitations. A durable association between male breast tumour ki67 expression and overall survival was not demonstrated and remains limited by threshold setpoint variability across studies.

Supervisors: Associate Professor Wendy Ingman, Dr Pallave Dasari

Cancer Biology and Clinical Oncology

Poster Number: 38

Harnessing Tumour Specific Evolution of Probiotic Bacteria to Engineer Next-Generation Bowel Cancer Treatments

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Background and Aims

Colorectal cancer (CRC) is the second-leading cause of cancer-related deaths in Australia, claiming over 5000 lives annually. Conventional treatment strategies, inducing surgical resection, chemotherapy, radiotherapy, and immunotherapy, often have toxic side effects and are ineffective against recurrent and metastatic disease. As such, there is incentive to develop alternative treatment strategies.

One such alternative is live bacterial therapeutics, facilitated by the existence of bacteria that preferentially colonise tumour tissue. Importantly, advancements in synthetic biology have enhanced bacterial genetic engineering capabilities, allowing for the development of programmable ‘micro factories’ for drug delivery that have improved tumour specificity, and the capacity for environment sensing, therapeutic synthesis, and biocontainment. However, bacteria have notoriously rapid evolution, yet it is currently unknown how bacteria evolve within the tumour microenvironment. Characterising bacterial adaption to tumours can aid in the understanding of how to engineer chassis with improved tumour-homing capabilities by highlighting the genetic changes that beget optimised colonisation.

This project aims to characterise the tumour-specific evolution of engineered Escherichia coli Nissle 1917 (EcN) in a mouse CRC model.

Methodology

Mice were orthotopically injected with syngeneic mouse CRC organoids to induce tumour formation within the colon. Once tumours reached ideal size, mice were orally administered with EcN engineered to be bioluminescent for bacterial biodistribution assessment. The bacteria were harvested from colonised tumours two weeks post-infection, expanded in culture, then readministered into the next cohort of tumour-bearing mice, for a total of five passages. Whole genome sequencing will be performed on the initial strain and EcN isolated from each passage to identify genomic changes.

Results

Across all five passages, the EcN retained their tumour-specific colonisation capabilities. Unexpectedly, the tumour colonisation rate experienced an oscillating pattern, where it began at 44% for cohort 1 (7/16 tumours across four mice), then jumped to 87% (13/15 tumours, eight mice), then dropped to 50% (6/12 tumours, four mice), before rising to 78% (7/9, five mice), and finally finishing at 44% (4/9, three mice).

Conclusions

This observed behaviour highlights the variation in bacterial evolution and colonisation, and ideally, whole genome sequencing of EcN from each cohort will reveal a genomic mechanism that can be exploited to engineer stronger and more robust tumour-colonising capabilities. Despite these variations in tumour colonisation, it has remained specific to this tissue across all five passages, which thus highlights the safety of this strain as a potential therapeutic option for CRC.

Supervisors: Associate Professor Susan Woods, Dr Josephine Wright

Cancer Biology and Clinical Oncology

Poster Number: 41

Modulation immunophenotypes in colorectal cancer liver metastasis via hepatotropic rAAV-SFRP5-RLuc gene therapy

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Background and Aims

Colorectal cancer liver metastasis (CRLM) is the primary driver of mortality. Hyperactivation of the Wnt signalling pathway is observed in 70%-80% of colorectal cancer (CRC) cases, contributing to alterations in the immunophenotype within tumour microenvironment (TME), notably characterized by a T-cell desert. Secreted frizzled related protein 5 (SFRP5) serves as an antagonist of this pathway. Elevated plasma SFRP5 levels correlated with extended overall survival (OS) and disease-free survival (DFS) among stage II-III CRC patients, emphasizing its potential clinical significance as a prognostic biomarker. Additionally, reduced plasma SFRP5 correlates with CRLM. Recombinant adeno-associated virus (rAAV) gene therapies have recently been approved for human use due to its minimal pathogenicity and sustained gene expression. This study aimed to develop a hepatotropic rAAV viral vector for SFRP5 overexpression in mouse liver and assess its impact on the immunophenotypes of established CRLM in a mouse model via ultrasound-guided intrahepatic injection.

Methodology

Codon-optimized murine Sfrp5 and Renilla luciferase reporter (RLuc) were cloned into the multiple cloning site of a rAAV expression vector, yielding the SFRP5-RLuc expression plasmid. This plasmid, along with other viral plasmids, was co-transfected into HEK292T packaging cells to generate rAAV-SFRP5-RLuc. Simultaneously, a control viral vector (rAAV-RLuc) containing only the Renilla luciferase reporter gene was produced. Purified rAAV-SFRP5-RLuc was quantified using quantitative polymerase chain reaction (qPCR) and transduced into Hepa1-6 mouse cells in vitro. SFRP5 expression was confirmed through immunofluorescence (IF), western blot, and enzyme-linked immunosorbent assay (ELISA)

on conditioned media. Functional SFRP5 and RLuc expression were validated using TOP-flash assays for Wnt signalling and luciferase activity assays, respectively. In vivo, firefly luciferase (FLuc) labelled syngeneic MC-38 mouse colon cells (MC38-TGL) were injected directly into the livers of C57BL/6 mice using minimally invasive ultrasound-guided intrahepatic injection to establish an orthotopic CRLM model. Mice were treated with rAAV-SFRP5-RLuc or rAAV-RLuc, and tumour growth and rAAV expression were monitored using bioluminescence imaging (BLI) for FLuc and RLuc, respectively. An 18-color spectral flow cytometry panel was designed to explore the immunophenotypes of liver tumours and adjacent tissues.

Results

Compared to rAAV-RLuc, significant upregulation of SFRP5 expression in Hepa1-6 mouse cells transfected with rAAV-SFRP5-RLuc was confirmed by immunofluorescence (IF), western blot, and enzyme-linked immunosorbent assay (ELISA). Moreover, TOP-flash assays demonstrated that expressed SFRP5 effectively inhibited the canonical Wnt signalling pathway activated by Wnt3a. Bioluminescence imaging (BLI) results confirmed the specific expression of rAAV-SFRP5-RLuc in mouse liver. Intriguingly, 18-color spectral flow cytometry revealed a significant increase in T lymphocyte infiltration, particularly CD8+ T cells, upon SFRP5 overexpression.

Conclusion

In conclusion, a functional rAAV-SFRP5-RLuc has been engineered and validated. It significantly increased the infiltration of CD8+ T cells, and ongoing studies are exploring the mechanism of rAAV-SRFP5-RLuc gene therapy.

Supervisors: Dr Eric Smith, Professor Timothy Price, Dr Kevin Fenix

Cancer Biology and Clinical Oncology

Poster Number: 44

Investigating the role of chemokine-like factor in paediatric B-ALL relapse

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Introduction

B-cell acute lymphoblastic leukaemia (B-ALL) is the most common childhood cancer. While patient outcomes are generally favourable, approximately 15% of patients will relapse with extremely poor prognosis. We have associated high chemokine-like factor (CKLF) expression at diagnosis with increased relapse risk, however its functional role in B-ALL remains unexplored.

Methods

REH cells (a B-ALL cell line) overexpressing CKLF, or an empty vector (EV) control, were transplanted into immunodeficient NSG mice (n=7-8/group) and tumour burden within the bone marrow (BM) assessed by flow cytometry. In vivo proliferation was assessed by measuring retention of a fluorescent membrane dye (DiD) 7 days after injection into the tibia. CKLF-targeting shRNAs (and non-targeting control) downstream of a doxycycline (dox)–inducible promoter were expressed in REH cells, and dox-inducible CKLF knockdown in vitro and in vivo confirmed by RT-qPCR. ALL-PDX were subsequently transduced with CKLF-shRNAs and in vivo CKLF knockdown and BM tumour burden will be assessed following addition of dox (2mg/mL) to drinking water.

Results

CKLF overexpression in REH cells resulted in a 42% reduction ($P<0.05$) in BM tumour burden. REH-CKLF cells displayed a 27% increase in DiD MFI ($P<0.01$) compared with REH-EV cells in vivo, indicating a reduced proliferative capacity. CKLF knockdown following dox induction in REH cells was confirmed in vitro and in vivo, with a 91% and 65% reduction in CKLF mRNA expression respectively ($P<0.01$). ALL-PDX expressing dox-inducible CKLF shRNAs were successfully generated and effect of CKLF knockdown on B-ALL engraftment in vivo determined.

Conclusion

Overexpression studies show CKLF decreases proliferation of B-ALL cells and reduces tumour burden in vivo. We have successfully generated an inducible knockdown system in ALL-PDX that will allow us to investigate if CKLF knockdown will enhance chemotherapy response and/or prolong event-free survival, thereby highlighting CKLF as a potential therapeutic target to limit relapse in paediatric B-ALL.

Supervisors: Dr Jaqueline Noll, Dr Stephen Fitter, Professor Andrew Zannettino

Cancer Biology and Clinical Oncology

Poster Number: 46

The Biological Function of Tryptophan Metabolism in Triple Negative Breast Cancer: Implications for Immunotherapy

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Background and Aims

Research into novel treatment approaches for triple-negative breast cancer (TNBC) is highly prioritized due to its aggressive nature and the limited options currently available for TNBC treatment. The challenge in treating TNBC lies in the absence of well-defined molecular targets that are available in other breast cancer subtypes. However, emerging studies indicate differences in the metabolic pathways associated with TNBC development and progression compared to other breast cancer subtypes, including unique metabolic adaptations that support their rapid growth. Here we established a comprehensive study on breast cancer to find a unique metabolic pathway in TNBC as promising target for cancer treatment.

Methodology

To screen the metabolic pathways involved in TNBC, we used samples available in the available RNA-Seq datasets, GSE58135 and GSE160549. Totally, 46 ER+ tumour, 103 TNBC tumour samples, and 21 normal samples adjacent to TNBC tumours were downloaded from these datasets. Then, metabolic genes were filtered based on gene ontology analysed using the KEGG database. Based on the TCGA-BRCA dataset, genes with higher rate of DNA amplification in breast cancer patients were filtered. We employed real-time qPCR and western blot to confirm the gene expression in TNBC cell lines, BT549 and MDA-MB157, compared to the luminal cell line, T47D. Furthermore, targeted metabolomics and flux analysis were performed using 13C11 isotope by LC-MS Agilent Q-TOF system. Moreover, shRNA and CRISPR-Cas9 techniques were leveraged to elucidate the value of candidate genes as promising targets for TNBC treatment.

Results

Based on the data mining part of our study we found that TNBC tumour samples tend to increase the expression of genes involved in tryptophan to kynurenine metabolism compared to luminal and normal breast samples. Our in-silico data analysis showed higher levels of tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) genes expression and DNA amplification. We found the optimum concentration of tryptophan for

TNBC cell lines is approximately 100µM. Interestingly, the expression of TDO and IDO is higher in TNBC cell lines compared to luminal. We also confirmed that IFN-γ which is known as an inflammatory response suppressor, increases the expression levels of three tryptophan dioxygenase enzymes, especially IDO1 in TNBC cell lines. Furthermore, we found higher concentration of kynurenine in IFN-γ treated cell lines compared to untreated ones. Tryptophan flux analysis showed TNBC cells use one carbon of tryptophan for purines and creatine synthesis through one-carbon metabolic pathway.

Conclusion

TNBCs are associated with increase in the expression of tryptophan dioxygenases. TNBC cell lines use tryptophan to generate kynurenine and the one-carbon metabolic pathway compounds. IFN-γ affects the expression of tryptophan dioxygenases in TNBC cells and increases the flux of tryptophan metabolism. Consequently, the concentration of kynurenine, purines, and creatine increase inside the cells.

Supervisors: Dr Daniel Thomas, Dr Theresa Hickey, Professor Stan Gronthos

Cancer Biology and Clinical Oncology

Poster Number: 49

A CRISPR-KO Whole Genome Screen Identifies Candidate Combinational Strategies for use with an Androgen Receptor Agonist to Kill Estrogen Receptor Positive Breast Cancer Cells"

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Background & Aims

Current standard of care therapies for estrogen receptor (ER) positive (ER+) breast cancer involve suppressing ER function or preventing the conversion of testosterone to estradiol (E2). Resistance to ER targeting therapies is common and although other pathway inhibitors (e.g., CDK4/6 inhibitors) have activity, alternative treatments are needed to improve disease outcome. To this end, we have demonstrated that agonist activation of the androgen receptor (AR) durably suppresses growth of ER+ breast cancer cells.

Methodology

However, as AR agonism is cytostatic, it likely will not result in durable tumour regression. Hence, this study aimed to define pathways that synergise with AR agonism to enhance killing of ER+ tumour cells. An unbiased whole-genome wide CRISPR knockout screen using the Brunello library was performed in T-47D ER+ AR+ breast cancer cells to identify genes that when depleted, enhanced death of T47D cell lines in combination with an AR agonist (5α– dihydrotestosterone, n = 4 biological replicates).

Results

The CRISPR-KO screen identified 26 significantly depleted and 13 enriched gene targets with DHT treatment. This included well characterised regulators of hormone receptor activity (NCOR1, CARM1) as well as novel factors that may regulate response to AR (MEN1, TFAP2C). Pathway analysis using the METASCAPE platform identified synergism of AR activation with disruption of lipid metabolism or regulation of mTORC1. Druggable gene candidates (SREBF1, SLC3A2, MEN1), will be further tested using small molecule inhibitors with clinical efficacy for ability to induce cell death in vitro and in patient derived xenograft models of ER+ breast cancer

Conclusion

This project identified several candidate druggable targets that may provide greater efficacy in the treatment of ER+ breast cancer in combination with AR agonists compared to ER-targeting therapies. Our study has potential to identify novel strategies that can reduce mortality of ER+ breast cancer and improve quality-of-life of patients undergoing breast cancer treatments.

Supervisors: Dr Amy Dwyer, Professor Wayne Tilley, Associate Professor Theresa Hickey

Cancer Biology and Clinical Oncology

Poster Number: 52

Effectiveness and safety of bone-protective interventions to mitigate bone loss and skeletal-related events experienced by patients with non-metastatic breast cancer: a systematic review and meta-analysis

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Background and Aims

Patients receiving antineoplastic treatment for breast cancer are well-known to experience accelerated bone loss, a phenomenon termed cancer treatment-induced bone loss (CTIBL), and associated skeletal-related events (SREs), defined as radiation to bone, pathological fracture, spinal cord compression, bone pain and orthopaedic surgery. A range of bone-protective interventions that aim to mitigate bone loss and subsequent SREs, such as bisphosphonates and denosumab, have been clinically approved for use in this patient population. However, the effectiveness and safety of these interventions in the setting of CTIBL in non-metastatic breast cancer remains inconclusive. This research aims to evaluate the effectiveness and safety of bone-protective interventions used to mitigate bone loss and SREs, specifically pathological fractures, experienced by patients receiving antineoplastic treatment for non-metastatic breast cancer.

Methodology

This systematic review considers studies investigating the use of bone-protective interventions, specifically bisphosphonates (alendronate, clodronate, ibandronate, pamidronate, risedronate and zoledronate), denosumab, and calcium and vitamin D supplementation, to mitigate bone loss and SREs. Studies featuring patients aged ≥18 years undergoing mono- or combination antineoplastic therapy for non-metastatic breast cancer were considered. Pre- and post-menopausal patients within both the hospital and community setting were considered in this review. Both experimental and quasi-experimental studies, as well as analytical observational studies were included, whilst preclinical studies and reviews were excluded. A comprehensive search was undertaken using MEDLINE/PubMed, Embase, Emcare, CINAHL, Cochrane Central Register of Controlled Trials and Google Scholar, with grey literature also systematically searched. Reference lists of included studies were manually searched for eligible studies. In accordance with Joanna Briggs Institute methodology, studies were screened by title and abstract and then full-text, before being critically appraised by two independent reviewers, with any disagreements resolved by the inclusion of an additional reviewer. Data was then extracted and is currently being

synthesised, with findings to be presented in a meta-analysis or narrative review depending on study heterogeneity. The protocol for this systematic review is registered in PROSPERO (CRD 42022379983).

Results

A total of 14,726 papers were identified through database, clinical trial registry, and grey literature searches. Following the removal of duplicates, 5,857 papers were screened by title and abstract, with 240 papers being retrieved and screened by full text. Following this, 88 papers were considered eligible according to the inclusion criteria and were included in the systematic review. Included studies were then critically appraised and data was extracted, in preparation for data synthesis and meta-analysis, which is currently underway.

Conclusion

The skeletal morbidity experienced by patients with breast cancer will continue to rise with increasing survivorship rates, hence, understanding the effectiveness and safety of bone-protective interventions used in this patient population is critical. This research will provide an assessment of the level of evidence for the effectiveness and safety of the bone-protective interventions used in the non-metastatic breast cancer setting to mitigate CTIBL and associated SREs. Further, it will contribute to the growing body of knowledge regarding the importance of bone health in the supportive cancer care setting, thereby enhancing clinical decision making.

Supervisors: Associate Professor Tania Crotti, Professor Joanne Bowen, Dr Bonnie Williams

Cancer Biology and Clinical Oncology

Poster Number: 55

Prevalence of cancer-related cognitive impairment in paediatric patients and survivors of non-CNS cancers: a systematic review and meta-analysis

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Background and Aims

Advances in the detection and treatment of cancer has aided in achieving a 5-year survival rate of 85-90% in childhood cancers. With a growing survivorship population, issues of survivorship have risen to the fore. In particular, neurocognitive toxicity is a common sequela of cancer and its treatment, with suggestions that 40-60% of children who are childhood cancer survivors may experience cognitive impairment, known as cancer-related cognitive impairment (CRCI), with a consequent impact on their quality of life. CNS cancers and CNS-directed therapy are considered the greatest risk factor for this; however, impairment has also been evidenced in non-CNS cancers, pre- and post- non-CNS treatment. Current evidence demonstrates that CRCI in children with non-CNS involvement corresponds to lower IQ, difficulty multi-tasking, and impaired school performance. Despite initial findings, there has been no formal assimilation of evidence using systematic techniques to report estimates in paediatric populations, or to identify the influence of cancer , treatment, and patient variables. Thus, this review aims to address this gap and investigate the prevalence of CRCI in paediatric patients and survivors of non-CNS cancers. An additional focus will be on subgroup analyses, where available, to investigate how individual factors may influence and contribute to prevalence.

Methodology

A comprehensive search was conducted using PubMed via MEDLINE, Scopus, PsycINFO via OvidSP, and CINAHL via EBSCOhost to identify relevant full-text peer-reviewed publications. Studies were considered for review if they met the following criteria: (1) Children (0-18 years) who have had any non-CNS cancer, during or following any therapeutic modality, and adults who had cancer as a child were considered, and (2) prevalence of cognitive impairment assessed by self-report or formal neurocognitive testing. Two independent reviewers screened studies for title, abstract and full-text and undertook data extraction. Included studies were assessed for methodological quality via the JBI

checklist for prevalence studies. Simple proportional meta-analyses were performed using PERSyst, and Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess and present certainty in the evidence. This review was conducted in accordance with the JBI methodology for systematic reviews of prevalence and incidence and PRISMA 2020 guidelines and has been registered with PROSPERO (CRD42022321930).

Results

A total of twenty-nine studies met the eligibility criteria and were included. Preliminary findings will be presented, with a focus on simple proportional meta-analyses on full-scale IQ (FSIQ), verbal/vocabulary IQ (VIQ), and performance/nonverbal IQ (PIQ) with subgroups focussed on cancer type, CNS- versus non-CNS directed therapy, time since cessation of treatment, time since diagnosis, and outcome impairment severity, where available.

Conclusion

Establishing and understanding the prevalence of CRCI following childhood cancer will help inform survivorship strategies and provide impetus for provision of dedicated supports, such as rehabilitation and additional assistance for patients on school return.

Supervisors: Associate Professor Lyndsey E. Collins-Praino, Associate Professor Alexandra Whittaker

Cancer Biology and Clinical Oncology

Poster Number: 58

Epigenetic regulation of skeletal stem cells during high fat/glucose mediated inhibition of bone formation.

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Introduction

Individuals with type 2 diabetes are at higher risk of osteoporosis and major bone fractures independent of their body mass index (BMI). Bone marrow derived mesenchymal stem/ stromal cells (BMSC) derived from these patients exhibit reduced osteogenic potential and increased cell death. Currently, it is not known how high fat/glucose levels can suppress BMSC osteogenic differentiation potential. We propose that diet impacts epigenetic regulators in BMSC. The present project examined the epigenetic mechanisms regulating BMSC dysfunction in response to high fat/glucose to identify targets for reversing high fat-mediated bone loss. We hypothesize that high fat/glucose levels lead to changes in BMSC epigenetic gene expression patterns that cause compromised bone formation, which increases the likely hood of developing osteoporosis. Ten-eleven translocation (Tet) family is a group of DNA demethylases, able to convert 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC), an epigenetic marker in osteogenesis.

Methods and Results

Our studies have shown that TET2 is essential in driving the differentiation of bone forming osteoblasts and high glucose level inhibits the expression of TET1 and TET2. Furthermore, human BMSC grown in high glucose conditions were found to display increased level of cell death, senescence and oxidative stress, associated with decreasing cellular proliferation potential compared to BMSC cultured in regular growth media. High glucose levels were also shown to drive the differentiation of BMSC towards lipid forming adipocytes at the expense of mineral forming osteoblasts. Furthermore, metabolomics analysis of human BMSC showed a significant difference in metabolite status of the cells grown under high glucose conditions compared to normal glucose. To observe the effects of Tet molecules on bone formation in vivo, we generated a double Tet1/Tet2 knockout mouse in the mesenchymal lineage using a Prx1: Cre driver mouse. The results found that Prx1:Cre Tet1/Tet2 double knock out mice fed on high fat diet showed increased body fat and glucose tolerance and decreased bone density compared to Prx1:Cre control mice on the same diet.

Conclusion

Understanding the role of epigenetic regulators in hyperglycaemic conditions will help to identify solutions to battle bone loss seen in diseases such as diabetes and osteoporosis. Given that epigenetic marks can be reversed by pharmacological inhibitors and altered via changes in diet and lifestyle, these targets are of unique therapeutic importance.

Supervisors: Professor Stan Gronthos, Dr Dimitrios Cakouros

Cancer Biology and Clinical Oncology

Poster Number: 62

A gastric cancer organoid platform to guide personalised chemotherapy for advanced disease patients.

Tharindie Silva

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Background and Aims

Gastric cancer (GC) is a challenging disease with a 5-year survival rate of <6% in advanced disease stages. This poor response is due to late diagnosis and tumour heterogeneity, suggesting potential improvements can be made with precision medicine. Patient-derived organoids (PDOs) are an emerging pre-clinical model that has shown promising results in selecting individualised treatment for cancer patients. This has been extensively tested in colorectal cancer, although very few similar studies have been undertaken for GC with a limited number of chemotherapeutics tested. We thus hypothesised that genomics combined with functional, PDO drug testing could be used to guide precision medicine for GC patients in a clinically useful time window. We aimed to culture GC PDOs from more than 60% of the samples, and perform genomic sequencing, and drug testing using standard care, and alternative chemotherapeutics to evaluate the efficacy of PDOs in treatment prediction.

Methodology

Tumour tissue samples were obtained when consented GC patients underwent endoscopy, laparoscopy, or tumour resection (HREC/16/SAC/344). The tumours were cultured as organoids and expanded. Haematoxylin and Eosin (H&E), and immunohistochemical staining were performed on organoids and patient tumour tissue. In vitro, drug testing was performed using standard care chemotherapeutic drugs FLOT (fluorouracil, leucovorin, oxaliplatin, docetaxel), FOLFIRI (fluorouracil, leucovorin, irinotecan)/ FOLFOX (fluorouracil, leucovorin, oxaliplatin) and alternate treatments (gemcitabine, doxorubicin, mitomycin C, cisplatin). Cell viability was determined by whole-well ATP quantification using Cell Titer-Glo 2.0 (Promega) and normalized to vehicle-only controls. PDO response to the chemotherapeutics was correlated to the patient's clinical response to neoadjuvant chemotherapy using CT/PET scans.

Results

Thirty-eight tumour samples were collected from 22 patients, with multiple samples from certain patients at different time points. GC organoids with varying morphologies and growth characteristics were established in 68% (15/22) of patients within 2-5 weeks. Five samples were discarded due to contamination and two organoid lines underwent growth arrest. Immunohistochemistry showed similar characteristics to the corresponding patient tumour tissue. Varying half maximal inhibitory concentrations (IC50) were recorded in ten organoid lines treated with standard care and alternative chemotherapeutics. The specificity between the PDO response, and the patient's clinical response to neoadjuvant chemotherapy was 60%.

Conclusion

To date, the process of establishing GC organoids has been promising with a high culture success rate of >60%. PDOs demonstrated the heterogeneity of GC tumours through varying morphologies and growth characteristics. The varying IC50 values of PDOs further indicated the heterogeneity in response to chemotherapeutics and the potential importance of individualised treatments in GC. PDOs recapitulated many patient responses in the clinic, thus shows promise as a reliable model to guide precision medicine. We have expanded recruitment to also include junctional and distal oesophageal cancers to increase sample numbers and enable conclusions based on a wider variety of disease presentations and greater sample numbers. Overall, we have developed a GC biobank that has the potential to be effective in guiding predictability of drug responses in advanced GC patients.

Supervisors: Associate Professor Susan Woods, Dr Josephine Wright

Cancer Biology and Clinical Oncology

Poster Number: 65

Effect of fixation and decalcification on the lipidome of bone marrow biopsies using mass spectrometry techniques.

Mackenzie Skinner

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Background and Aims

Matrix-assisted laser desorption/ionisation mass spectrometry imaging (MALDI-MSI) provides the ability to study spatial metabolic changes and has been successfully applied to soft tissues to assess lipid content. However, use of MALDI-MSI in bone samples has been limited, due to difficulty sectioning the heterogeneous tissue. To maintain morphology, samples must be processed using fixation and decalcification. While fixation is known to affect lipid signal, few studies have investigated the effect of decalcification on the lipidome. We sought to characterise the changes in lipid signal and distribution induced by both fixation and decalcification, using liquid chromatography mass spectrometry (LC-MS) and MALDI-MSI of sheep bone biopsies, investigating their suitability for spatial lipidomics.

Methodology

Bone marrow biopsies were obtained from a sheep pelvis (n=18). Sample preparation included: 1) 24h fixation with 4% paraformaldehyde (PFA), followed by decalcification for 14 days in 10% ethylenediaminetetraacetic acid (n=6); 2) decalcification only (n=6), or 3) immediate snap freezing (undecalcified) (n=6). For LC-MS, samples were homogenised using a Precellys-24 in MK28-R tubes (Bertin Technologies, France). Protein was quantitated using a Nanodrop-8000, and lipid extraction performed on 100□g. Samples were run on a Xevo-G2XS-QTOF in negative ion mode (Waters, USA). Data was processed using Skyline, peaks identified according to retention time, with reference to known internal standards. For MALDI-MSI, samples were embedded in 8% gelatin and frozen (-80□C). Cryosections were mounted on indium tin-oxide slides, washed with ammonium formate, and matrix sublimation was performed with 2,5-dihydroxybenzoic acid, or norharmane. MSI

data was acquired on a timsTOF fleX□, and processed with SCiLS Lab 2023a (Bruker, Germany). Statistical analysis was conducted using GraphPad Prism.

Results

Percent contribution of each lipid class to total lipid content detected by LC-MS was calculated for each preparation method. This revealed significant loss of phosphatidylethanolamine (PE) lipids with PFA fixation and decalcification (0.6%), and decalcification only (2.8%), compared to undecalcified samples (9.8%). Percentage of sphingomyelins (SM) was significantly increased in PFA-fixed (28.2%), and decalcified samples (29.2%), compared to undecalcified (17.0%). A total of 34 lipids were identified as significantly different between groups (*$p<0.05$, two-Way ANOVA, post-hoc Tukey's test). Of 36 annotated PE lipids detected, 12 significantly decreased with PFA fixation, and 9 with decalcification only, compared to undecalcified samples. A significant increase in 3 SM lipids was found upon fixation and decalcification. In PFA-fixed samples, 5 phosphatidylcholine lipids were significantly increased relative to independent decalcification. MALDI images confirmed these relative changes in signal. The fixed and decalcified samples showed better section integrity, and no delocalisation of lipids.

Conclusion

Sample preparation appears to have a significant effect on the lipid signal obtained through LC-MS and MALDI-MSI. Consistent with previous studies, a reduction in amine-containing lipids was seen upon PFA fixation. Interestingly, our results also indicate this effect is present with decalcification, independent of fixation. Processed samples provided greater morphological integrity for imaging and maintained lipid distributions seen in undecalcified samples. However, despite challenges sectioning undecalcified bone samples, alternative methods should be considered in the context of metabolic studies, to avoid chemical modification.

Supervisors: Dr Melissa Cantley, Dr Kate Vandyke, Dr Paul Trim, Professor Andrew Zannettino

Cancer Biology and Clinical Oncology

Poster Number: 68

Improving Accuracy and Reducing Bias in Genomic Alignment for B-cell Acute Lymphoblastic Leukemia Patients: A Pan-Genome Graph Approach

Ashlee Thomson

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Background and Aims

A current limitation of traditional genome analysis workflows is the use of a linear reference genome for sequence alignment which is made mostly from European ancestry individuals and does not capture the unique genomic variation contained within global populations. Aligning sequencing reads to this linear reference genome requires bioinformatic tools to adjust for discrepancies between sequencing reads and the reference, potentially leading to "reference bias". This bias is intensified when handling data with substantial genomic variability, as seen in B-cell acute lymphoblastic leukemia (B-ALL) patients. We aimed to build a B-ALL-specific pan-genome graph that incorporates clinically significant genomic alterations, to enhance alignment precision and eliminate reference bias.

Methodology

Using the GRCh38 reference genome as a base, we constructed a pan-genome graph using the Variation Graph (VG) toolkit that contains 7278 genomic alterations identified in B-ALL patients as listed in the Catalogue of Somatic Mutations In Cancer. We integrated genome annotations into the graph to facilitate exon and splice junction identification. To analyse mapping performance, we aligned Illumina paired-end RNA sequencing data from 10 B-ALL patients to both the spliced pan-genome graph using VG's mapping function and to the GRCh38 linear reference genome using STAR aligner as a comparison.

Results

Preliminary mapping results demonstrate that on average, 98.35% of paired-end sequencing reads map to the pan-genome graph compared to an average of 95.47% which map to the linear reference. This difference represents ~4 million paired-end sequencing reads. We also see an increase in the reporting of genomic insertions and deletions larger than 10 base pairs.

Conclusion

This spliced pan-genome graph is effective and comparable to the linear reference genome when aligning B-ALL patient sequencing reads. Further analysis will involve expanding mapping metric analysis and investigating the specific variations detected.

Supervisors: Professor Deborah White, Associate Professor James Breen, Professor David Yeung

Cancer Biology and Clinical Oncology

Poster Number: 71

ZBTB16 is a critical mediator of androgen receptor-induced tumour suppression in ER-positive breast cancer.

Maliha Wajahat

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Background and Aim

Breast cancer is the most commonly diagnosed cancer in Australia, with 70-80% being estrogen receptor-positive (ER+) and treated with ER-targeted therapies. While initially effective, these therapies are not curative and often debilitating, highlighting a critical need for new approaches. Recent studies demonstrated that the androgen receptor (AR) and progesterone receptor (PR) act as tumour suppressors in ER+ breast cancers by inhibiting ER-driven tumour growth. However, the critical downstream target genes mediating their tumour suppressor activity and potential overlap between AR and PR are unknown.

Methodology

Using available DNA binding (ChIP-seq) and gene expression (RNA-seq) data from ER+ breast cancer models, we identified ZBTB16 as a target gene commonly regulated by AR and PR, and a candidate mediator of their tumour suppressor activity. AR and PR bind to a hormone regulatory element (HRE) within intron 3 of ZBTB16, associated with an active gene enhancer signal (H3K27ac ChIP-seq). To validate ZBTB16's role, we employed CRISPR gene editing to delete a ~182 bp region within the intron 3 HRE in ER+ breast cancer cells (T-47D), generating clonal lines with and without this deletion.

Results

Utilizing the single-cell sorting technique we generated 23 clones of T-47D ZBTB16 intron 3 HRE knockout (KO). ChIP-PCR confirmed the loss of AR and PR binding at the intron 3 ZBTB16 HRE in clonal lines. Deletion of the HRE resulted in diminished androgen-induced ZBTB16 expression at both mRNA and protein levels across multiple cell line clones. However, PR activation could still induce ZBTB16 expression in the clones, albeit to a lower level compared to the parental line. Proliferative responses to estrogen (E2), androgen (DHT), and progesterone (P4) were characterized via live-cell imaging and a Coulter counter. E2 induced proliferation of mutant clones to a greater extent compared to the parental line and non-mutant clones. The tumour suppressive activity mediated via AR but

not PR was lost in the mutant clones. Further analysis suggested that sustained regulation of ZBTB16 by PR could occur via alternative regulatory elements. qPCR analysis revealed that with the loss of the ZBTB16 intron 3 HRE, AR activation not only lost its ability to regulate the expression of ZBTB16 but also failed to regulate the expression of some of its other target genes, such as FKBP51, and SEC14L2. RNA-seq analysis further corroborated these findings where activated AR failed to regulate the expression of its known target genes including SEC14L2, UGT2B11, UGT2B28, and SGK1 in clonal lines compared to the parental line. Gene set enrichment analysis (GSEA) further showed that AR failed to regulate or regulated to a lesser extent the expression of pathways critical for its growth inhibitory effects, such as the hallmark androgen response, cholesterol homeostasis, and hallmark glycolysis pathways in clonal lines compared to the parental line.

Conclusion

Deletion of the HRE within ZBTB16 intron 3 results in loss of AR but not PR tumour suppressive action in ER+ breast cancer cells. These findings suggest ZBTB16 is a candidate mediator of AR-induced tumour suppressor activity and a potential biomarker for monitoring AR agonist drug response in ER+ breast cancer.

Supervisors: Dr Amy Dwyer, Associate Professor Theresa Hickey, Professor Wayne Tilley

Cancer Biology and Clinical Oncology

Poster Number: 74

Evaluating the Efficacy of Perhexiline and Cisplatin Combination Treatment in Head and Neck Cancer

Fangmeinuo Wu

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Background and Aim

Cisplatin, a platinum-based chemotherapy, is commonly used clinically for recurrent or metastatic head and neck cancer (HNC) patients, but its utility is limited by toxicity and therapeutic resistance. Recent studies suggest that alterations in expression of fatty acid metabolism-related genes are associated with cisplatin resistance. Perhexiline, an anti-anginal drug, inhibits the mitochondrial enzymes carnitine palmitoyl transferase (CPT)-1 and -2, thereby inhibiting fatty acid β-oxidation (FAO). Additionally, pre-clinical in-vitro and in-vivo studies have revealed that perhexiline possesses anti-tumoural effects on multiple cancer types, either as monotherapy or in combination with standard chemotherapeutics. However, the potential of perhexiline to treat HNC remains unknown. The overall objective of this project is to determine if cisplatin alters the metabolic dependency and flexibility of fatty acid metabolism in HNC cell lines, thereby considering the possibility of perhexiline as adjuvant therapy.

Methodology

Human Papilloma Virus (HPV) status of HNC cell lines, SCC1, SCC47, FADU, and BIRC16 was determined by endpoint PCR. Drug sensitivity was determined by the half maximal inhibitory concentration (IC50) calculated from crystal violet assay. CPT isoforms transcript expression was determined by real-time quantitative PCR. Synergy between perhexiline and cisplatin was determined using the Zero Interaction Potency analysis method.

Results

Compared to HPV-positive cell line SCC47, CPT1A expression was significantly higher ($p<0.001$) in HPV-negative cell lines (FADU: 4.7-fold, SCC1: 3.0-fold, BICR16: 2.8-fold), while CPT1C was significantly lower ($p<0.001$) (FADU: 100-fold, SCC1: 6.7-fold, BICR16: 250-fold). Cisplatin IC50 for SCC1, FADU, SCC47 and BICR16 was 2.0μM (95%CI: 1.8-2.2), 3.2μM (3.0-3.4), 6.0μM (5.0-7.5), 8.3 μM (7.7-9.0), respectively. Treatment with 0.0975μM cisplatin did not alter proliferation, but decreased CPT1B and CPT1C transcript expression in all cell lines, except CPT1B in FADU.. In contrast, the IC50 concentration increased the expression of CPT1A and CPT1B isoforms in SCC1, only that of CPT1B in SCC47, and only CPT1C in FADU and BICR16. Cisplatin did not alter CPT2 expression at any concentration tested. The morphology of HNC cell lines changed after treatment with IC50 concentration of cisplatin, with apoptotic cells observed in SCC1 and senescence cells in others. Drug synergy analysis suggested that the combination of perhexiline with cisplatin was synergistic for SCC1 (ZIP-score 2.41, p=1.73e-19), but not for BICR16 (-3.54, p=2.41e-07) FADU (-5.79, p=7e-115) and SCC47 (-8.85, p=2.89e-160).

Conclusion

This study highlights that cisplatin alters CPT isoforms expression in a concentration and cell line dependent manner. Further, it demonstrates the anti-tumoral potential of perhexiline in HNC cell lines by inducing apoptosis. The combination of perhexiline with cisplatin shows potential synergism in certain HNC cell lines. These findings support the exploration of perhexiline as a beneficial treatment for a subset of HNC. Future investigations include measuring specific metabolic dependencies and flexibility after cisplatin and correlating these metabolic phenotypes to efficacy of perhexiline treatment.

Supervisors: Dr Eric Smith, Dr Kevin Fenix, Dr Yoko Tomita

Cancer Biology and Clinical Oncology

Poster Number: 76

Germline ERG haploinsufficiency defines a new syndrome with cytopenia and hematological malignancy predisposition

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Background and Aims

There remain gaps in our knowledge of hereditary and sporadic causes of haematological malignancy (HM) and bone marrow failure (BMF) that prevent optimal diagnosis, disease surveillance and treatment. Here we report the discovery of ERG as a novel predisposition gene for BMF and HM. ERG is a known oncogene, typically via gene-fusions, leading to dysregulated ERG overexpression in blood and solid cancers. We identified a germline ERG ETS domain variant p.Y373C segregating with thrombocytopenia in a mother, who progressed to AML (27 yr) and then therapy-related MDS (35 yr), and in her 2 sons. All three showed copy neutral loss of heterozygosity of all or part of chromosome 21q, including the ERG locus, with the oldest son showing at least 2 somatic genetic rescue (SGR) events. ERG, a highly constrained gene (LOEUF <0.33), is critical for definitive haematopoiesis, adult hematopoietic stem cell (HSC) function and platelet maintenance.

Methodology

Through global collaborations, we have identified a further 15 heterozygous variants in the ERG gene, 13 of which are missense and 2 truncating variants, in 17 individuals with cytopenia and/or HM (mainly myeloid) or lymphedema. We have functionally characterized 19 ERG variants, 12 potentially pathogenic, 1 known mouse pathogenic variant and 3 population controls using transcriptional transactivation, DNA-binding and/or nuclear localisation in vitro assays. Using a selection of variants, we used ex vivo models of ERG overexpression in mouse foetal liver cells in tissue culture (cytokine-independence), a mouse transplant assay to further elucidate the function of these variants.

Results

Onset of haematological symptoms ranged from birth to 38 years for truncating and constrained ETS domain variants. We functionally characterised 19 ERG variants, demonstrating that most ETS domain missense variants displayed loss-of-function (LOF) characteristics disrupting transcriptional transactivation, DNA-binding and/or nuclear localisation in vitro. Robust data from models of ERG overexpression in mouse foetal liver cells, and a mouse transplant assay, were concordant with ETS domain missense variants being LOF. Together, these data provide clinical, in vitro and ex vivo functional studies implicating LOF variants in haematological disease predisposition.

Conclusion

Our results demonstrate that germline ERG variants predispose to diverse cytopenia, BMF and HM in both children and adults. The natural history of this new syndrome will require careful identification of germline lesions with additional longitudinal studies in more patients and families needed. ERG adds to a growing list of genes whose unregulated expression contributes to HM and other cancers. Identification of causal germline ERG variants like those outlined in this study, has direct clinical implications for patient and family management including diagnosis, counselling, surveillance and treatment strategies such as selection of bone marrow transplant donors and potential for targeted therapies including gene and cell therapy.

Supervisors: Professor Hamish Scott, Associate Professor Chris Hahn, Dr Catherine Carmichael

Indigenous Health and Health Equity

Poster Number	Abstract Details
79	**Negin Mirzaei Damabi** *Comparative Analysis of Sexual Dysfunction Prevalence: A National Survey among Women from Migrant, Refugee, and Australian Backgrounds* School of Public Health

Indigenous Health and Health Equity

Poster Number: 79

Comparative Analysis of Sexual Dysfunction Prevalence: A National Survey among Women from Migrant, Refugee, and Australian Backgrounds

Negin Mirzaei Damabi

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Background and Aims

Australia is a vibrant multicultural nation that hosts one of the largest and most diverse migrant and refugee populations globally. This substantial presence of migrant and refugee communities highlights the importance of understanding their unique health needs, including sexual and reproductive health. Female sexual dysfunction (FSD) is a prevalent issue that can significantly impact an individual's overall quality of life and well-being. Pleasurable and safe sexual experiences, free from coercion, discrimination, and violence, constitute a fundamental aspect of sexual health and are recognized as influential predictors of happiness, life satisfaction. However, there is a lack of comprehensive evidence on the prevalence and factors associated with FSD among migrant and refugee women in Australia.

This study aimed to explore the prevalence of FSD among women from migrant and refugee backgrounds originating from low and middle-income countries (LMICs) and currently residing in Australia. Additionally, it sought to compare the prevalence of FSD within this group to the prevalence observed in the mainstream Australian population and examine potential socio-demographic factors associated with FSD.

Methodology

This study employed a cross-sectional, quantitative research design involving a national survey conducted across Australia. The target populations consist of two groups of reproductive-aged women: one comprising individuals from migrant and refugee backgrounds originating from LMICs, and the other comprising Australian women.

Participants were recruited through Qualtrics, an online survey platform, using quota sampling to ensure representation from both target groups. The validated Female Sexual Function Index (FSFI) was used to assess FSD across various domains, including desire,

arousal, lubrication, orgasm, satisfaction, and pain. Additionally, a demographic questionnaire collected relevant socio-demographic information from participants.

The data will be analysed using descriptive statistics, chi-square tests, and logistic regression analyses to determine the prevalence of FSD, compare prevalence rates between the migrant/refugee and mainstream groups, and examine the relationship between socio-demographic factors and FSD.

Results

The study has been initiated, and data collection through the Qualtrics online survey platform is currently finished. We have successfully received responses. The data has undergone thorough cleaning and quality control processes to ensure its integrity and reliability. We are currently analysing the data set, and the final results, including prevalence estimates, group comparisons, and analyses of associated socio-demographic factors, will be available and presented at the time of the conference.

Conclusion

This pioneering study holds immense significance as it sheds light on the often-overlooked area of FSD among migrant and refugee women in Australia. The findings will contribute to a comprehensive understanding of the complex intersections between migration experiences, cultural norms, and sexual well-being. The insights gained will inform culturally sensitive approaches to healthcare delivery, particularly in the realm of sexual and reproductive health services. This study has the potential to pave the way for further research and dialogue, fostering a deeper exploration of the lived experiences, concerns, and preferences of migrant and refugee women regarding sexual function and pleasure, ultimately promoting their overall well-being and quality of life.

Supervisors: Associate Professor Zohra Lassi, Dr Mumtaz Begum, Dr Jodie Avery

Innovative Therapeutics

Poster Number	Abstract Details
82	**Ryan Lee** *Developing CRISPR Therapies correcting Duchenne Muscular Dystrophy by targeting exon 45* School of Biomedicine
85	**Anna Li** *Matching stem cells and gut microbes: a pilot preclinical study on donor-matched faecal microbiota transplantation for Graft versus Host Disease* School of Biomedicine
88	**Caleb Lushington** *Advancing Prime Editing systems to perform efficient and precise custom genome edits* School of Biomedicine
92	**Sadia Munir** *Assessing the utility of the transient vasculature-modifying agent, LCRF-0006, in a novel pre-clinical model of bortezomib-induced peripheral neuropathy to improve treatment outcomes in multiple myeloma* School of Biomedicine

Innovative Therapeutics

Poster Number: 82

Developing CRISPR Therapies correcting Duchenne Muscular Dystrophy by targeting exon 45

Ryan Lee

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Background and Aims

CRISPR-Cas9 gene editing is site-specific and programmable due to its guide RNA (gRNA) directed activity. Therefore, it holds great potential for the therapeutic correction of monogenic disorders. Duchenne Muscular Dystrophy (DMD) is a universally fatal monogenic disorder characterised by progressive muscular weakness. It is mostly associated with frameshifting large deletions within the X-linked DMD gene which disrupt Dystrophin expression. The permanence of CRISPR-Cas9 gene editing distinguishes it as a promising alternative to current DMD treatments, which require lifelong administration. CRISPR-based DMD therapies have the potential to restore the expression of an internally truncated yet functional Dystrophin, either through exon skipping or reframing.

Despite being the most well-characterised CRISPR-Cas9 system, the inability to package gRNA and Streptococcus pyogenes Cas9 (SpCas9) within a single Adeno-associated virus (AAV) vectors limit its efficiency in vivo. The smaller size of Staphylococcus aureus Cas9 (SaCas9) allows for single-AAV delivery. This allows SaCas9 therapies to be administered with a twofold dosage compared to SpCas9, thus holding more promise for clinical translation. SaCas9 strategies targeting exon 45 of the human DMD (hDMD) gene have yet to be reported on. These strategies would be directly applicable to 9% of DMD patients, such as those harbouring exon 44 deletions (Δ44). Thus, we aim to investigate them in vitro.

Materials and Methods

Through paired SpCas9 activity, we generated an exon Δ44 DMD cell line from wildtype immortalised human myoblast obtained from a collaborator. This model allows for the screening of SaCas9-gRNA candidates which efficiently skip or reframe exon 45. Candidates were cloned into SaCas9-expressing vectors and delivered to our model through nucleofection. Editing efficiency was defined by the degree of intended editing through Next-Generation Sequencing (NGS) of target DNA amplicons.

Results

Here, we present a Δ44 DMD model with Dystrophin disruption confirmed via Western blotting. The intended deletion was also validated at the gDNA and RNA level via PCR. Using this model, several promising candidates were identified. Upon GFP selection for gRNA uptake, these candidates demonstrated up to 97% on-target editing. The single-nucleotide resolution of NGS technology also enabled bioinformatic forecast of Dystrophin restoration, with up to 42% of therapeutic reframing and 16% of therapeutic exon-skipping being reported.

In future, these forecasts will be validated through qPCR and Western blotting respectively. Additionally, a GUIDE-seq assay, which assesses genome-wide off-target editing activity, will also be conducted on our most promising candidates before advancing them towards in vivo testing in transgenic mice models harbouring hDMD.

Conclusion

We generated a human myoblast DMD model harbouring Δ44 and upon model validation, performed a preliminary efficiency screen of SaCas9 candidates targeting exon 45. Several promising strategies were identified and will be brought forward for further efficacy testing and off-target analysis.

Supervisors: Dr Fatwa Adikusuma, Professor Paul Thomas

Innovative Therapeutics

Poster Number: 85

Matching stem cells and gut microbes: a pilot preclinical study on donor-matched faecal microbiota transplantation for Graft versus Host Disease

Anna Li

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Background/Aim

Faecal microbiota transplantation (FMT) is increasingly recognised as a viable therapy for GvHD, inducing remission in ~40% of cases. However, FMT for GvHD has only been investigated with 3rd party (donor) FMT which fails to recognise the intimate relationship that exists between the immune system and microbiota within an individual. Hence, in the setting of allogeneic-HSCT, we hypothesise matching stem cell and fecal donors, i.e. “donor-matching”, will optimise the compatibility between donor-derived immune cells and the unique microbiome it is primed for, thereby improving FMT’s efficacy for GvHD. This pilot study aimed to explore the effect of donor-matched FMT in a preclinical model of GvHD.

Methodology

A MHC-matched, minor-histocompatibility antigen mismatched model of GvHD (LP/J [H2kb] → C57BL/6 [H2kb]) using busulfan and cyclophosphamide conditioning was established in N=10 male C57BL/6 mice (Riesner 2016). C57BL/6 mice were confirmed for engraftment and monitored for GvHD using an established clinical scoring system before randomisation into experimental groups; saline/control (n=3), 3rd-party FMT (n=3), donor-matched FMT (n=4). Caecal contents from stem cell donor LP/J mice or unrelated C57BL/6 mice were used to prepare FMT for the donor-matched and 3rd-party FMTs, respectively. 3× 200ul FMT was administered to GvHD positive mice via oral gavage. Mice were followed for 3 weeks post FMT (+54 days post allo-HSCT). Key outcomes for GvHD were change in body weight and GvHD score.

Results

Donor-matched FMT induced a significant increase in body weight 18 days after compared control mice (P=0.03, 95% CI [0.5918, 13.33]) and 3rd party-FMT mice (P=0.02, 95% CI [-14.06, -1.326]). This was in parallel to a significant decrease in GvHD clinical scores compared to saline/control mice (P= 0.03, 95% CI [-3.756, -0.1610]).

Conclusion

Donor-matched FMT appears to be more effective in controlling murine GvHD compared to 3rd party (donor) FMT. Although promising, cautious interpretation is required given preliminary nature of data.

Supervisors: Dr Hannah Wardill, Dr Feargal Ryan, Associate Professor Daniel Thomas

Innovative Therapeutics

Poster Number: 88

Advancing Prime Editing systems to perform efficient and precise custom genome edits

Caleb Lushington

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Background and Aims

Correcting disease-causing genetic mutations holds promise for treating monogenic disorders at their source. The widely used CRISPR genome editing system offers a means to introduce non-specific genomic alterations which can alleviate pathology in a fraction of genetic diseases. However, existing CRISPR systems often struggle to restore mutations to their normal, healthy state, limiting their applicability in most diseases. Prime Editing (PE) has emerged as a novel CRISPR-based approach, enabling custom recoding of genetic sequences by leveraging a repair template to modify targeted DNA regions. Whilst this technique offers the ability to restore mutations back to healthy wildtype sequence, its efficiency in diverse cell types in vitro and in vivo is limited. We hypothesised that consolidating essential PE components into a single plasmid (referred to as PEA1), inducing double-stranded DNA cleavage (PE-nuclease), and integrating additional signals for nuclear localisation (NLS) or DNA Modifying Proteins (DMP) could enhance PE's efficiency.

Methodology

To investigate this hypothesis, we engineered modifications to PE constructs through rational protein design, aiming to accommodate all PE components within a singular plasmid, activate dual DNA cleavage mechanisms, and incorporate factors that enhance editing efficacy. These modified PE systems were introduced into HEK293T, K562, and HeLa cells via lipofection in triplicate, followed by puromycin selection to isolate successfully transfected cells. Subsequent extraction of genomic DNA allowed for quantification of editing outcomes through next-generation sequencing, with statistical analysis conducted using GraphPad Prism.

Results

Our findings revealed that PEA1-mediated gene editing in HEK293T cells achieved remarkable efficiency, with precise custom editing rates reaching up to 95%. Conversely, editing in K562 and HeLa cells exhibited comparatively lower rates. Introducing a PE-

nuclease to induce double-strand DNA breaks increased PE initiation in K562 and HeLa cells but also led to unintended insertions. The addition of NLS further increased editing activity, whilst addition of DMP improved edit precision in K562 and HeLa cells.

Conclusion

In conclusion, the combination of single-plasmid delivery, double-strand DNA cutting nuclease, and additional NLS or DMP factors significantly improved the efficiency and precision of PE in cell culture models. These advancements provide invaluable tools for generating genetic models and developing therapeutic interventions.

Supervisors: Professor Paul Thomas, Dr Fatwa Adikusuma

Innovative Therapeutics

Poster Number: 92

Assessing the utility of the transient vasculature-modifying agent, LCRF-0006, in a novel pre-clinical model of bortezomib-induced peripheral neuropathy to improve treatment outcomes in multiple myeloma

Sadia Munir

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Background and Aims

High-dose bortezomib therapy is integral to the success of treating the haematological cancer multiple myeloma. However, peripheral neuropathy is a major dose-limiting toxicity necessitating dose reduction, increasing the risk of disease relapse. Bortezomib-induced peripheral neuropathy (BIPN) is characterised by pain and sensory loss in hands and feet, altered proprioception and, in some cases, muscle weakness. Selectively increasing drug delivery to sites of tumour represents a potential strategy to reduce drug side effects. The aim of this project is to (1) develop a clinically relevant mouse model of BIPN and (2) investigate the utility of a small molecule, LCRF-0006, that transiently increases blood vessel permeability, to increase the anti-tumour effectiveness of low-dose bortezomib without inducing side effects.

Methodology

For myeloma tumour studies, C57BL/KaLwRij mice bearing orthotopic 5TGM1-luc cell (expressing luciferase and GFP) tumours were treated i.v. with high-dose (1mg/kg) or low-dose (0.5mg/kg) bortezomib, the combination of LCRF-0006 (100mg/kg, i/p) and low-dose bortezomib or vehicle alone twice weekly for two weeks. Tumour burden was assessed by bioluminescence imaging and flow cytometric detection of GFP-positive cells in the bone marrow. To establish the BIPN model, C57BL/6 mice were treated twice weekly with high-dose or low-dose bortezomib, or vehicle alone, for two weeks and underwent end-point assessment of spontaneous behaviour (behavioural spectrometry), mechanical sensitivity (von Frey filament) and motor function (rotarod). Neurotoxicity was assessed by histopathological analysis of toluidine blue-stained sciatic nerves and qPCR analysis of pro-

inflammatory cytokines in DRGs. To determine the effects of LCRF-0006 on BIPN, C57BL/6 mice were treated with high and low-dose bortezomib, LCRF-0006 and low-dose bortezomib, LCRF-0006 alone or vehicle twice-weekly for two weeks.

Results

High- and low-dose bortezomib reduced tumour burden 100- and 19-fold respectively ($P<0.05$) at the study end-point. Notably, pre-treatment with LCRF-0006 increased the anti-tumour effect of lose-dose bortezomib, with a 37-fold reduction in tumour burden compared with vehicle alone ($P<0.05$). Unlike low-dose bortezomib, high-dose bortezomib-treated mice displayed reduced locomotory and rearing behaviour compared with control mice and increased fine grooming activity, specifically, of paws ($P<0.001$). Moreover, high-dose, but not low-dose, bortezomib-treated mice displayed reduced sensitivity to mechanical stimulus ($P<0.0001$) and motor dysfunction ($P<0.01$). DRGs from high-dose bortezomib-treated mice showed elevated expression of pro-inflammatory cytokines compared with vehicle treatment ($P<0.05$) and histopathological analysis suggests high-dose bortezomib decreases sciatic nerve fibre diameter. Neurotoxicity was not evident with low-dose bortezomib. Preliminary behavioural spectrometry analyses suggest that the combination of LCRF-0006 and low-dose bortezomib treatment does not induce changes in spontaneous behaviour of mice compared with low-dose bortezomib alone, including track length and time engaged in grooming, rearing and locomotor activities.

Conclusion

We have developed a mouse model of BIPN that encompasses key features of the condition seen in patients with myeloma. Our studies suggest that LCRF-0006 increases the anti-tumour effectiveness of low-dose bortezomib without exacerbating bortezomib toxicity. In-depth studies are currently being undertaken to specifically examine the effect of LCRF-0006 on BIPN induction. Importantly, this work has the potential to meaningfully improve quality of life and survivorship for people with myeloma.

Supervisors: Dr Kate Vandyke, Professor Andrew Zannettino, Dr Krzysztof Mrozik

Nutrition and Metabolic Health

Poster Number	Abstract Details
95	**You Jin Chang** *Comparing Daily Caloric Restriction with Early and Delayed Time-Restricted Eating plus Caloric Restriction on Glycaemic Markers in Overweight and Obese Adults: Protocol of a Randomised Controlled Trial* Adelaide Medical School
98	**Elaheh Heshmati** *The role of NOX-dependent ROS in leptin modulation of gastric vagal afferent satiety signals* School of Biomedicine
101	**Yixuan Sun** *Relative contributions of fasting vs. postprandial hyperglycaemia to overall glycaemic control in newly-diagnosed type 2 diabetes before and following 3 months' treatment* Adelaide Medical School

Nutrition and Metabolic Health

Poster Number: 95

Comparing Daily Caloric Restriction with Early and Delayed Time-Restricted Eating plus Caloric Restriction on Glycaemic Markers in Overweight and Obese Adults: Protocol of a Randomised Controlled Trial

You Jin Chang

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Background and Aims

Time-restricted eating (TRE) is a dietary approach that limits feeding to a specific window within the day. Feeding time serves as one of the primary zeitgebers that synchronises the central circadian clock in the suprachiasmatic nucleus with peripheral clocks distributed throughout the body. Aligning meal timing with the circadian rhythm optimises physiological and biological processes, such as glucose metabolism, thereby enhancing glycaemic control. Despite its potential benefits, there is a scarcity of evidence supporting optimal meal timing. This study aims to fill this gap by conducting the first trial to compare daily caloric restriction (CR) to early (eCR) and delayed time-restricted eating plus calorie restriction (dCR) on glycaemic markers.

Methodology

This parallel, single-blinded, 3-arm randomised controlled trial will randomize 114 participants by sex and fasting blood glucose (>5.6 mmol/L) into CR, eCR or dCR (1:1:1) for 6 months. Study participants will be aged 35 to 75 years, have a BMI >25.1 but < 45kg/m2, elevated waist circumference and fasting blood glucose (>5.6 mmol/L), and score 12 or greater on the AUSDRISK questionnaire. All participants will attend the sleep research unit for a 26-h stay at baseline and week 8, followed by a 4-month follow-up phase. During these stays, blood and urine samples will be collected, and participants will have a 24-hour ambulatory blood pressure monitor (AMBP) fitted on their arm.

Outcomes

The primary outcome is the change in postprandial glucose AUC at week 8. Secondary outcomes include changes in 24h blood glucose, insulin and gut peptides AUCs and iAUCs, insulin sensitivity, fasting glucose, C-reactive protein, body weight, body composition, physical activity, sleep quality and adherence by smartphone application a 4-month follow-up

phase. The exploratory outcomes are the changes in 24h blood pressure and blood pressure markers (i.e. renin, potassium, and aldosterone).

Conclusion

This randomised controlled trial will be the first to comprehensively investigate whether early CR, late CR or CR improve cardiometabolic measures. The outcomes of this study will significantly contribute to guiding the optimal timing of meals to improve health outcomes and reduce the risk of type 2 diabetes and cardiometabolic diseases among at-risk populations.

Supervisors: Dr Amy Hutchison, Professor Leonie Heilbronn, Professor Morag Young

Nutrition and Metabolic Health

Poster Number: 98

The role of NOX-dependent ROS in leptin modulation of gastric vagal afferent satiety signals

Elaheh Heshmati

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Background and Aim

Gastric vagal afferents (GVAs) convey meal-related signals from the stomach to the central nervous system. Leptin, a satiety hormone, is released from the gastric mucosa as well as adipose tissue. Leptin effects on GVA satiety signals are dynamic, in lean-fed mice leptin increases mucosal GVA responses to mechanical stimuli but in fasted or high-fat diet-fed mice leptin decreases tension-sensitive GVA mechanosensitivity. The molecular mechanisms underpinning these dynamic effects remain to be determined. Centrally, there is a positive correlation between leptin and ROS raising the possibility that ROS is mediating leptin effects. We aimed to determine whether ROS is mediating leptin effects on GVA mechanosensitivity.

Methodology

Eight-week-old male C57BL/6 mice were either fed ad libitum or fasted for 14 hours. We used an in vitro gastric vagal afferent prepatation to determine the effect of the ROS H2O2 (10 - 100 µM) on mucosal and tension-sensitive GVA mechanosensitivity. Further, we determined the effect of inhibiting ROS production, by inhibiting the enzyme NADPH oxidase with apocynin, on leptin effects on GVA mechanosensitivity. In addition, the modulatory effects of either leptin (1nM), apocynin (1mM), or both on GVA mechanosensitivity were also determined. Quantitative RT–PCR was used to determine leptin receptors and NOX isoform mRNA expression in the stomach, whole nodose, and specific gastric mucosal and tension-sensitive vagal afferent cell bodies.

Results

H2O2 potentiated mucosal and tension-sensitive GVA mechanosensitivity in a dose-dependent manner in fed mice. In fed mice, leptin increased mucosal GVA mechanosensitivity but had no effect on tension-sensitive GVAs. In fasted mice, leptin reduced tension-sensitive and mucosal GVA mechanosensitivity. In fed mice, apocynin alone decreased mucosal and tension-sensitive GVA mechanosensitivity. However, in fasted

mice, apocynin only decreased tension-sensitive GVA mechanosensitivity. In the presence of apocynin and leptin, mucosal GVA mechanosensitivity displayed an increase in fed but not fasted mice. In contrast, tension-sensitive GVA mechanosensitivity was decreased in the presence of apocynin and leptin in fed and fasted mice. Leptin receptor, DUOX1-2, and NOX1-4 mRNA were detected in the whole nodose ganglia. Only 29% of mucosal GVAs expressed leptin receptors, of which 20%, 10% and 10% expressed NOX4, NOX3, and NOX2 respectively. 53% of tension-sensitive GVAs were leptin receptor-positive, of which 38%, 8%, and 8% expressed NOX4, NOX2, and DUOX1 respectively. DUOX1-2, NOX1-4, and leptin receptors were expressed in the antrum and corpus with NOX2, DUOX2, and leptin receptors expressed at the highest levels.

Conclusion

The reactive oxygen species H2O2 has an excitatory effect on GVA mechanosensitivity, with the blockade of endogenous NOX-dependent ROS production reducing GVA mechanosensitivity. Apocycnin did not impact leptin effects on GVA mechanosensitivity suggesting these effects are not mediated via NOX-dependent ROS production. Despite leptin effects on GVAs not all afferents express the receptor suggesting that effects may be secondary to effects on the gastric mucosa.

Supervisors: Professor Amanda Page, Dr Hui Li

Nutrition and Metabolic Health

Poster Number: 101

Relative contributions of fasting vs. postprandial hyperglycaemia to overall glycaemic control in newly-diagnosed type 2 diabetes before and following 3 months' treatment

Yixuan Sun

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Background and Aims

Achieving optimal glycaemic control (as assessed by HbA1c <7%) is key to minimising the macrovascular complications of type 2 diabetes (T2D) and requires effective management of both fasting (FG) and postprandial glycaemia (PPG). Cross-sectional studies indicate that FG predominates over PPG in determining overall glycaemic control when HbA1c is >8.5%, whereas PPG is the major contributor when HbA1c <7.5%. However, dynamic changes in the contributions of FG and PPG in individuals with T2D over time have not been adequately examined. We therefore evaluated the relative contributions of FG and PPG to overall glycaemic control in people with newly-diagnosed T2D before and after 3 months of glucose-lowering therapy.

Methodology

22 newly-diagnosed, treatment-naïve Han Chinese with T2D (11M/11F; age 51.2 ± 2.1 years; BMI 25.5 ± 0.7 kg/m2; HbA1c 10.0 ± 0.4%) consumed standardised breakfast, lunch and dinner with 24 hour continuous glucose monitoring (CGM), before and after 3 months of glucose-lowering therapy (involving initial insulin pump therapy for a week, followed by other pharmacotherapy: n=12 with metformin alone, n=2 with metformin + DPP-4 inhibitor, n=4 with metformin + SGLT-2 inhibitor, and n=4 with metformin + GLP-1 receptor agonist). The area under the glucose curve above 6.1 mmol/L was calculated to reflect hyperglycaemia over 24 hours (AUC Total). The AUC above premeal levels for 4 hours after meals (AUC Postprandial) was calculated to reflect the contribution of PPG to hyperglycaemia. The relative contributions of FG and PPG to hyperglycaemia were calculated as ((AUC Total - AUC Postprandial)/ AUC Total)*100% and (AUC Postprandial/AUC Total)*100%, respectively. Data are means ± SEM.

Results

HbA1c decreased from 10.0 ± 0.4% to 6.7 ± 0.3% (P = 0.003) after 3 months therapy. AUC Total decreased by 76.7% (baseline vs. post-treatment: 2232.0 ± 117.5 vs. 521.0 ± 65.9, P < 0.0001), while AUC Postprandial decreased by 58.9% (682.4 ± 59.0 vs. 280.3 ± 35.6, P = 0.0003). The relative contribution of FG was 69.2 ± 2.5 % at baseline, and decreased to 48.7 ± 4.0 % after treatment (P = 0.0002). The relative contribution of PPG was 30.8 ± 2.5 % at baseline, and increased to 51.3 ± 4.0 % after treatment (P = 0.0002).

Conclusion

In individuals with newly -diagnosed T2D, the relative contributions of FG vs. PPG to overall glycaemic control can shift substantially, so that postprandial glycaemic excursions become more important with glucose-lowering therapy. These data suggest that therapy should be re-evaluated when initial treatment is successful and that a greater focus on limiting postprandial glucose excursions is warranted.

Supervisors: Associate Professor Tongzhi Wu, Professor Christopher Rayner, Dr Cong Xie

Session 3

Poster presentations are held in the Panorama Ballroom, Upper Level of the Adelaide Convention Centre.

Students will be allowed **5 minutes** presentation time, with an additional **3 minutes** allocated for question-and-answer time with the assessors.

Poster presentations will be assessed according to the criteria below. Each assessor will provide a score out of 10 for each category.

- Quality and clarity of presentation and poster
- Scientific merit
- Quality of data/results/significance
- General understanding and ability to answer questions
- Overall poster rating

To encourage networking, collaboration, and the opportunity to meet with some of our major stakeholders and industry partners, all students are encouraged to attend both poster sessions.

Research Areas

Ageing, Frailty and Mobility

Cardiac, Respiratory and Vascular Health

Child and Adolescent Health

Fertility and Conception

Musculoskeletal Health

Pregnancy and Birth

Translational Health Outcomes

Ageing, Frailty and Mobility

Poster Number	Abstract Details
3	**Kimberly Charlton** *Manual wheelchair training programs: a scoping review of educational approaches and intended learning outcomes* School of Allied Health Science and Practice
6	**James Smyth** *Perspectives on frailty screening among emergency physicians* Adelaide Medical School

Ageing, Frailty and Mobility

Poster Number: 3

Manual wheelchair training programs: a scoping review of educational approaches and intended learning outcomes

Kimberly Charlton

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Background and Aims

Training programs grounded in educational theory offer a systematic framework to facilitate learning and outcomes. This scoping review aims to map the learning approaches and instructional design for manual wheelchair training and to record the intended learning outcomes and any relationships between educational approaches and outcomes.

Methods

Eight databases; Cochrane's Library, EMBASE, CINAHL, PubMed, Scopus, EmCare, Medline, ProQuest Nursing and Allied Health Database and grey literature were searched in September 2023, with citation chaining for relevant papers. Included papers related to manual wheelchair training programs/protocols describing intended wheelchair training outcomes for adults and/or caregivers. Data extracted included study characteristics, type of intervention, explicit learning theories, instructional design principles and intended learning outcomes. The International Classification of Functioning and Kirkpatrick's evaluation framework were used to organise intended outcomes.

Results

Of the forty-four articles included in this review, only fourteen explicitly used a learning theory in the instructional design of training. Training outcomes most commonly related to changes in knowledge/skills of manual wheelchair users (Level 2b of Kirkpatrick's evaluation (n= 43), with less emphasis on participatory outcomes. Training designs incorporating Social Cognitive Theory (n=8) were more likely to explore long term training outcomes, compared with other training designs.

Conclusion

Wheelchair training programs that are designed using educational approaches are more likely to produce learning outcomes that are retained and meaningfully applied. Such longer terms outcomes could have systemic cost and efficiency implications, such as reduction in wheelchair falls and readmissions to hospital. Deliberate integration of educational theory into manual wheelchair training design is recommended to support broad outcomes and long-term learning. This design could synergise different learning theories.

Supervisors: Associate Professor Stacie Attrill, Dr Carolyn Murray, Dr Natasha Layton

Ageing, Frailty and Mobility

Poster Number: 6

Perspectives on frailty screening among emergency physicians

James Smyth

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Background and Aims

Frailty is a syndrome of decreased physiological reserve associated with vulnerability to stressors and an increased risk of adverse outcomes. Frailty is prevalent in the older population. Frailty detection, by screening as an initial check followed by assessment, can provide insights into an older person's health status, and aid decision making on investigation and treatment for an emergency or acute illness. Frailty screening is not routinely performed in emergency departments (EDs). The aim of this qualitative study therefore is to investigate the perspectives of emergency physicians (EPs) on frailty screening.

Methodology

In this exploratory qualitative descriptive study, sixteen EPs working in one health network were interviewed about their perspectives relating to frailty screening in the ED, including their feelings about the intervention, its feasibility, and its role in ED clinical practice. The interview audio-recordings were transcribed and analysed, leading to the inductive development of themes.

Results

Three themes were developed:

Theme 1: EPs had mixed opinions about the benefits and contributions of frailty screening in the ED.
No EPs referred to screening formally for frailty in their practice.

Theme 2: EPs expected that frailty screening would guide frailty detection and further relevant action addressing frailty.

Theme 3: EPs recommended frailty screening mainly for older patients in the ED, as well as necessary features and resources needs being met to facilitate implementation. Recommended necessary features included brevity, simplicity, and accuracy. Accessing the frailty screening tool online in the ED, and the availability of multi-disciplinary care for the follow up of frail patients in the community and nursing homes after attending the ED were referred to as resource needs.

Conclusion

Most of the EP participants expressed favourable and balanced views on frailty screening for its potential roles and value in the ED, including collaborations between the ED and inpatient units, the community, as well as nursing homes.

Supervisors: Professor R Visvanathan, Adjunct Professor Hugh Grantham

Cardiac, Respiratory and Vascular Health

Poster Number	Abstract Details
12	**Olivia Girolamo** *Combined large vessel and microvascular acetylcholine-induced spasm – a new coronary vasomotor dysfunction endotype.* Adelaide Medical School
15	**Sarah Madigan** *Physiological changes measured by cardiopulmonary exercise testing in systemic sclerosis.* Adelaide Medical School
17	**Alex Minopoulos** *Effect of Vericiguat pre-treatment on phenylephrine constrictor responses in isolated human internal mammary artery segments with/without intact endothelium.* Adelaide Medical School
20	**Getandale Negera** *A model of subacute diabetic heart failure in rats: importance of microvascular permeabilization: impact on heart rate: contractility relationship* Adelaide Medical School
26	**Mitchell Nicmanis** *The psychological, social, and quality of life outcomes of people with a cardiac implantable electronic device: An umbrella review* School of Psychology
29	**Anastasia Zacharia** *α1A Adrenergic Receptor Phosphorylation is associated with heterogenous vasoconstriction and tachyphylaxis.* School of Biomedicine

Cardiac, Respiratory and Vascular Health

Poster Number: 12

Combined large vessel and microvascular acetylcholine-induced spasm – a new coronary vasomotor dysfunction endotype.

Olivia Girolamo

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Background and Aims

Acetylcholine (ACh) provocative spasm testing is the benchmark investigation to diagnose large vessel spasm (LVS). When ACh provocation produces chest pain and ischaemic ECG changes in the absence of LVS, microvascular spasm is diagnosed. Although large vessel and microvascular spasm may co-exist, routine ACh testing does not allow the presence of both. Using a novel resistance model, this project aims to assess the prevalence of elevated microvascular resistance in patients with ACh-induced left anterior descending (LAD) artery spasm.

Methodology

20 patients undergoing functional coronary angiography with a dual-sensor-tipped pressure-doppler flow wire and who had ACh-induced LAD spasm (≥90% constriction) were included. A fluid mechanic-based analytical resistance model was developed ( ), where Pm = mean arterial pressure, Pv= venous pressure, and Qm = mean LAD blood flow (calculated from average peak velocity and mean diameter, D) were used to calculate microvascular resistance (Rmv) and LAD resistance, Rfriction,), where = blood viscosity and = LAD length. These parameters were assessed at baseline and post-ACh spasm dose, with blinding to clinical diagnosis.

Results

In the 20 patients with ACh-induced LAD spasm, LAD resistance was elevated consistent with the clinical diagnosis. Amongst these patients, 5 (20%) also had an increased microvascular resistance, indicating the presence of both ACh-induced large artery and microvascular spasm.

Conclusion

A subset of patients with LVS have associated increased microvascular resistance. This may represent a novel coronary vasomotor dysfunction endotype.

Supervisors: Professor John Beltrame, Associate Professor Rosanna Tavella, Associate Professor Chris Zeitz

Cardiac, Respiratory and Vascular Health

Poster Number: 15

Physiological changes measured by cardiopulmonary exercise testing in systemic sclerosis.

Sarah Madigan

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Introduction/Aim

Systemic sclerosis (SSc, scleroderma) patients are screened annually for pulmonary arterial hypertension (PAH) using tools such as pulmonary function testing and biomarkers. These measurements are made while the patient is resting, but early stages of PAH may only be apparent during exercise. This study aims to assess changes in physiological parameters obtained during exercise such as VE/VCO2 slope, oxygen uptake and oxygen pulse for changes suggestive of PAH. A second aim was to assess what changes occur in CPET results over time in SSc patients.

Method

Patients with SSc according to the ACR/EULAR 2013 classification criteria completed a cardiopulmonary exercise test (CPET) contemporaneously with two consecutive annual screens for PAH (CPET1 and CPET2). Both CPETs were incremental tests, aiming for patients to cycle under load for between 8-12 minutes. Differences in physiological parameters of interest between tests were assessed using linear mixed effects models.

Results

63 patients (51 (81%) female) of mean age 57.3 (SD 11.5) with limited (50 (79%)) or diffuse (13 (21%)) SSc completed CPET1 and 38 completed CPET2. The average interval between CPETs was 12.0 (SD 2.7) months. Between CPETs, there was an overall decline in the adjusted mean maximum load achieved (-3.83 (IQR -6.37, -1.30), $p < 0.01$) and peak VO2 (mL/min) (-38.82 (IQR -71.75, -5.89), $p = 0.02$). There was no significant change in the VE/VCO2 slope (0.54 (IQR-0.81,1.90), $p = 0.43$), oxygen pulse -0.29 (IQR -1.02,0.45), $p = 0.45$), end-tidal CO2 (0.45 (-0.56,1.46), $p = 0.38$) or anaerobic threshold (-1.88 (-6.02,2.26), $p = 0.37$). Other parameters of interest for a diagnosis of PAH remain unchanged.

Conclusion

No patients in the study have been diagnosed with PAH to date. The decline in load and peak VO2 indicate a decline in physical fitness over the 12 months.

Key Words

Cardiopulmonary exercise test, systemic sclerosis, pulmonary arterial hypertension.

Supervisors: Professor Robert Adams, Dr Susanna Proudman, Dr Huw Davies

Cardiac, Respiratory and Vascular Health

Poster Number: 17

Effect of Vericiguat pre-treatment on phenylephrine constrictor responses in isolated human internal mammary artery segments with/without intact endothelium.

Alex Minopoulos

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Background

Vericiguat is a novel, direct soluble guanylate cyclase (sGC) stimulator thereby producing vasodilation independent of nitric oxide (NO) synthesis. This study investigated the effect of vericiguat-pre-treatment on phenylephrine-induced contraction in isolated human internal mammary artery segments with intact- or impaired-endothelial vasorelaxation responses.

Methods

Remnant internal mammary artery (IMA) segments from patients (N=15) undergoing coronary artery bypass grafting were suspended in a vascular myograph. Endothelial function was assessed using bradykinin (0-30μM), with IMA segments defined as intact- (>50% vasorelaxation) or impaired-endothelial response (<50% vasorelaxation). Phenylephrine (0-300μM) concentration-response curves were performed following pre-treatment with either Vericiguat 1μM or vehicle control (dimethyl sulfoxide).

Results

Phenylephrine concentration-response curve response data in vericiguat pre-treated endothelial-intact or endothelial-impaired IMA segments compared to vehicle control. Compared to control, vericiguat pre-treatment inhibited phenylephrine constrictor maximal responses in IMA segments with impaired endothelial function (Emax: 140.1±27 vs 66.2±18.2, $p < 0.05$). There was no significant difference on half maximal effective concentration (EC50: -5.80±0.19 vs -5.36±0.16, $p > 0.05$). In intact-endothelium, there was no significant difference on phenylephrine constrictor maximal responses (Emax: 103.4±22 vs 70.2±19, $p > 0.05$) or half maximal effective concentration (EC50: -6.14±0.04 vs -5.79±0.2, $p > 0.05$).

Conclusion

Vericiguat pre-treatment inhibits constrictor response in human vessels with endothelial dysfunction and thus may be of benefit in ischaemic heart disease therapy.

Supervisors: Professor John Beltrame, Associate Professor Rosanna Tavella, Professor Betty Sallustio, Dr David Wilson

Cardiac, Respiratory and Vascular Health

Poster Number: 20

A model of subacute diabetic heart failure in rats: importance of microvascular permeabilization: impact on heart rate: contractility relationship

Getandale Negera

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Background and Aims

There is ongoing debate about mechanisms whereby acute and subacute heart failure (HF) occur frequently in the presence of hyperglycaemia with substantial associated mortality. A number of early reports have suggested that microvascular permeabilization may play a part, while more recent investigations have revealed oxidative stress, inflammatory damage to microcirculatory function, and a clinical presentation of HF with preserved ejection fraction (HFPEF) in most cases. We therefore developed a rat model of subacute diabetic/hyperglycaemic HF (DHF) to delineate relevant mechanisms.

Methodology

Diabetes with severe hyperglycaemia was induced in Wistar rats (with matched controls) by diet plus streptozotocin injection. After 8 weeks, echocardiography was followed by humane sacrifice, Langendorff perfusion of hearts, and quantitation of inflammatory markers. Plasma concentrations of markers of damage to the endothelial glycocalyx (EG), which controls microvascular permeability, were also measured.

Results

Induction of DHF was associated with reductions in LV ejection fraction and E/A ratio with severe attenuation of heart rate: EF relationship in DHF. Langendorff-perfused diabetic hearts lacked significant tachycardia-induced coronary vasodilatation and tended ($p=0.06$) to have impaired force-frequency relationships. Plasma concentrations of markers of glycocalyx damage were elevated, as was myocardial expression of thioredoxin-interacting protein (TXNIP), an inflammasome activator.

Conclusions

DHF is associated with (1) evidence of redox-stress-induced damage to the microvascular glycocalyx (2) inflammatory activation within the myocardium (3) incremental systolic dysfunction during tachycardia, presumably resulting from energetic impairment. All of these present potentially novel approaches to therapy of DHF.

Supervisors: Dr Cher-Rin Chong, Dr Yuliy Chirkov, Emeritus Professor John D Horowitz

Cardiac, Respiratory and Vascular Health

Poster Number: 26

The psychological, social, and quality of life outcomes of people with a cardiac implantable electronic device: An umbrella review

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Background and Aim

Cardiac implantable electronic devices such as pacemakers, implantable cardioverter-defibrillators, and cardiac resynchronisation therapy devices represent effective interventions for arrhythmias, heart failure, and the prevention of sudden cardiac death. While the impacts of these devices on cardiac function and mortality have been extensively documented, only a small body of research has considered the non-cardiac outcomes of people living with these devices. This umbrella review aimed to synthesize the psychological, social, and quality of life outcomes of people with a cardiac implantable electronic device.

Methodology

An umbrella review of systematic reviews that reported the psychological, social, or quality of life outcomes of adults with a cardiac implantable electronic device was conducted. This umbrella review was pre-registered with PROSPERO (CRD42023437078) and adhered to JBI and PRISMA guidelines. Seven databases (CINAHL, Cochrane Library, Embase, EmCare, PsycINFO, PubMed, and the Web of Science) were searched alongside supplementary methods including citation and bibliographic searches. Methodological quality was assessed using the JBI Checklist of Systematic Reviews and Research Syntheses. Due to the heterogeneity of the included reviews, the findings were reported narratively.

Results

A total of 14 systematic reviews met the inclusion criteria; 11 considered quality of life outcomes, and 3 considered psychological outcomes. No reviews considered social outcomes. Little difference in quality of life was found between people with an implantable cardioverter-defibrillator and controls; however, a high prevalence of psychological disorders was present. Cardiac resynchronization therapy devices demonstrated improvements in quality of life compared with control groups, alongside possible cognitive benefits. Quality of life did not differ between subcutaneous and transvenous implantable cardioverter-defibrillators. Pacemakers were associated with improved post-implantation quality of life.

Conclusion

Research on the psychosocial and quality of life outcomes of people with a cardiac implantable electronic device is limited and inconsistent. Given the heterogeneity of the current research, conclusions are uncertain. Nevertheless, some recipients may experience adverse psychosocial complications. Further research employing rigorous methodologies is needed, and healthcare practitioners should provide care that acknowledges the potential for adverse psychosocial experiences.

Supervisors: Professor Anna Chur-Hansen, Associate Professor Melissa Oxlad

Cardiac, Respiratory and Vascular Health

Poster Number: 29

α1A Adrenergic Receptor Phosphorylation is associated with heterogenous vasoconstriction and tachyphylaxis.

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Background

Patient variability is a confounder for many clinicians managing patient therapy and treatment outcomes. Extrinsic sources of variability include diet, exercise and disease state are often touted as the primary culprit whereas intrinsic sources of variability are harder to integrate into therapeutic approach. Despite this, the heterogeneity in patient response can generally be encapsulated within a normal distribution and further stratification may inform therapeutic approach and improve outcome.

Approximately 24% of patients experience debilitating Angina with No Obstructive Coronary Atheroma (ANOCA). The clinical and individual burden of this disorder is immense as effective treatment options are limited leaving patients undermanaged. The clinical guidelines have recently been amended to include provocative spasm testing to identify patients prone to vasospasm induced coronary ischaemia (those with ANOCA). This approach enables targeted prophylactic individualised therapy to improve patient outcomes. Current therapies for ANOCA include renin-angiotensin system inhibitors, statins, nitric oxide donors and calcium channel blockers. Surprisingly, the mechanism governing ANOCA based vasospasm currently remains unknown. Although these therapies provide benefit to some patients, they have limited efficacy long-term.

Curiously, a subset of coronary patients are hyper responsive to provocative spasm testing with α1-adernergic agonists yet another population of surgical and septic shock patients are hyporesponsive or tachyphylactic; a rapid decrease in sensitivity to a drug over time. It is common to consider extrinsic factors like circulating hormones contributing to the heterogeneity of vasoconstrictor response, however, heritable intrinsic variability in vascular responsiveness has recently been identified in a genetically diverse outbred Sprague-Dawley rats. Dogma suggests receptor internalisation is the cause of tachyphylaxis. This is well documented in β2 receptors, but has not been characterised with α1 receptors in functional arteries. An alternative hypothesis is variable phosphorylation of the α1A adrenergic receptor reduces its ligand sensitivity and contributes to the heterogenous contractile responses and tachyphylaxis. Again, well documented with β2 receptors but not α1 receptors.

Understanding these intrinsic mechanisms contributing to vasopressor sensitivity and vasospasm could improve care for ANOCA and septic shock patients.

Aims

To investigate the causes of heterogeneity in vascular responsiveness to an α1A-adrenenrgic agonist, and whether receptor phosphorylation is involved.

Methodology

Wire myography was used to investigate vascular responses to the α1-adrenenrgic agonist Phenylephrine (10μM) in an outbred male Sprague-Dawley rats (8-week-old, n=28). Phos-tag™ SDS-PAGE and Western Blotting was used to identify differences in receptor phosphorylation.

Results

Eleven phosphorylation sites were identified on the α1A-adrenenrgic receptor. Tachyphylaxis is associated with increasing degrees of phosphorylation and was highest when five to nine sites were concurrently phosphorylated. Sustained vascular contractility was associated with reduced phosphorylation at the fourth site, though this could then be restored by increased phosphorylation of the nineth site.

Conclusions

Phosphorylation of the α1A-adrenoreceptor is associated with the heterogeneity in vascular contractile responses. Phosphorylation of five to nine sites on the α1A-adrenoreceptor was associated with tachyphylaxis, providing new mechanistic insight into the cause of differential vasopressor sensitivity. Blocking kinases responsible for receptor phosphorylation may present tachyphylaxis in patients requiring therapeutic vasopressor support.

Supervisors: Dr David P Wilson, Professor John Beltrame

Child and Adolescent Health

Poster Number	Abstract Details
33	**Lucy Farrar** *The language of Developmental Language Disorder (DLD): A (critical) scoping review of discourses on adolescents diagnosed with DLD* School of Allied Health Science and Practice
36	**Angela Osborn** *Social support and hope predict child internalising symptoms and adaptive behaviour* School of Psychology
39	**Zahra Ali Padhani** *Preconception Health Interventions for Adolescents and Young Adults to Prevent Adverse Maternal, Perinatal, and Child Health Outcomes: an Evidence Gap Map* School of Public Health
42	**Meredith Smith** *Adapting assessment tools for children and young people with cerebral palsy and chronic pain* School of Allied Health Science and Practice

Child and Adolescent Health

Poster Number: 33

The language of Developmental Language Disorder (DLD): A (critical) scoping review of discourses on adolescents diagnosed with DLD

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Background and Aims

Globally, increasing attention is being paid to Developmental Language Disorder (DLD); the diagnosis of a neurodevelopmental condition for people who have difficulties understanding and using language despite normal cognitive abilities. It is estimated that approximately 7-10% of school-aged children meet the diagnostic criteria of DLD, with difficulties often persisting into adolescence and adulthood (Bishop, Snowling, Thompson, & Greenhalgh, 2016). Despite the prevalence of DLD, there remains limited understanding of the subjective experiences of individuals diagnosed with the condition. Research on DLD has traditionally focused on identifying the underlying impairments and developing interventions to support language development. However, there is a growing recognition of the need to understand the social and relational context in which DLD is experienced. Where adolescents diagnosed with DLD have been found to experience a range of adverse social, economic and mental health outcomes, the need to understand this group's unique challenges and experiences is vital.

The aim of this research is to describe the current literature in this important area, focusing on how adolescents diagnosed with DLD have been described and 'constructed' in academic literature. Using Critical Discourse Analysis as a guide, particular attention is paid to the language used as well as the underlaying discourses which produce and enable such constructions. It asks the question: What discourses have been used in academic literature to inform understandings related to adolescents diagnosed with DLD, and what conclusions has this permitted or denied?

Methodology

A search of the ERIC, MEDLINE, EMBASE, CINAHL, SCOPUS, PsycINFO, and LLBA was conducted to identify studies relating to adolescents diagnosed with DLD.

Results

The database and hand-searches identified 1060 articles; of these, 210 articles met inclusion criteria and underwent full review. Discursive analysis identified inter-related themes. We found that studies related to adolescents diagnosed with DLD are largely situated within biomedical discourse, with few studies investigating this needs and experiences of this population from a social or relational position. Even fewer studies have investigated DLD from a discursive or critical viewpoint . We also note that the literature generally focuses on DLD as an individual impairment with assessment and intervention practises focused on individual attributes, and gives little attention to relational approaches or explanations of DLD.

Conclusion

The findings highlight that the majority of academic literature has either implicitly or explicitly drawn upon biomedical discourse in understanding adolescents diagnosed with DLD and in forming conclusion and recommendations. In doing so, the majority of studies position DLD as a problem ‘within the individual’, with interventions and assessments typically focused on individual language capabilities. This finding is important, because in doing so, this deflects or denies space for alternative considerations and explanations, including examination of the discursive or relational context in which adolescents diagnosed with DLD exist. The findings also illuminates the possible impacts and implications of discourse in shaping evidence practises and experiences for adolescents diagnosed with DLD, and suggests the need for higher awareness of the language and discourse used when talking about this population.

Supervisors: Associate Professor Stacie Attrill, Associate Professor Suze Leitao, Dr Charles Marley

Child and Adolescent Health

Poster Number: 36

Social support and hope predict child internalising symptoms and adaptive behaviour

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Background and Aims

Mental health problems are becoming increasingly prevalent in Australian children. Some preventative efforts endeavour to build resilience in children to reduce the occurrence and severity of psychological distress. However, to create and appropriately target effective resilience building interventions, a thorough understanding is needed of the unique factors which prevent internalising problems in children – such as depression and anxiety – and promote adaptive behaviours.

Methodology

Our study modelled a range of factors that contribute to overall wellbeing in children. This involved a large-scale factor analysis and subsequent structural equation modelling in a sample of 24,262 children in grades 3 to 6 at Australian primary schools. Children completed self-report surveys, providing responses to a range of demographic, social and wellbeing items.

Results

Factor analysis provided six factors relevant to the study aims: Family support, Friendship, Adaptive behaviours, School engagement and support, Internalising symptoms, and Hope. Family, friendship and school factors were significantly predictive of both internalising symptoms and adaptive behaviour, with the exception that family support did not directly predict adaptive behaviour. Family support was the strongest predictor of internalising symptoms, whereas school engagement and support was the strongest predictor of adaptive behaviour.

Greater hope positively predicted adaptive behaviours and negatively predicted internalising symptoms. Hope either partially or fully mediated the relationship between family, friendship and school factors on internalising symptoms and adaptive behaviour. The overall pattern of relationships remained similar for different levels of socioeconomic status, and between genders.

Conclusion

Combined, these results suggest that a child's external social environment plays a major role in wellbeing outcomes, with the family context being of particular importance for internalising problems, and the school context for the development of adaptive behaviours. Instilling a sense of hope, or personal agency, appears to be a critical path by which these external environments operate on wellbeing. These findings make a valuable contribution to resilience theory by demonstrating the complex relationships between factors at multiple levels that underlie resilience processes.

Supervisors: Dr Mark Kohler, Dr Scott Coussens

Child and Adolescent Health

Poster Number: 39

Preconception Health Interventions for Adolescents and Young Adults to Prevent Adverse Maternal, Perinatal, and Child Health Outcomes: an Evidence Gap Map

Zahra Ali Padhani

Preconception Health Interventions to Prevent Adverse Maternal, Perinatal, and Child Health Outcomes

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Background and Aims

Preconception is the period before a young woman or woman conceives, which draws attention to understanding how her health condition and certain risk factors affect her and her baby's health once she becomes pregnant. Adolescence and youth represent a life-course continuum between childhood and adulthood, in which the pre-pregnancy phase lacks sufficient research. Therefore we aimed to identify, map, and describe existing empirical evidence on preconception interventions that enhance health outcomes for adolescents, young adults, and their offspring.

Methodology

We conducted an evidence gap map (EGM) activity following the Campbell guidelines by populating searches identified from online databases such as Medline, Embase, Cochrane Library, etc. We included interventional studies and reviews of interventional studies that report on the impact of preconception interventions for adolescents and young adults (aged 10 to 25 years) on adverse maternal, perinatal, and child health outcomes. All studies underwent title/abstract and full-text screening on Covidence software. All the included studies were coded using the EPPI-Reviewer software. Cochrane Risk of Bias tool 2.0 and AMSTAR-2 was used to assess the quality of the included trials and reviews. A 2D graphical EGM eas developed using the EPPI-Mapper software.

Results

Through the electronic search, we identified 131,031 publications after de-duplication. After the screening process 18 studies (124 papers) were included in the review. The majority of the included studies were from upper-middle- and higher-income countries, with limited evidence from low and middle-income countries. More than half focused on females with very limited evidence on men. The impact of human papillomavirus (HPV) vaccination was found to be the most well-evidenced area, with very little evidence on herpes simplex virus (HSV) 'candidate' vaccine for genital infections, human immunodeficiency virus prevention, sexual reproductive health and substance use. Perinatal outcomes were the most frequently reported outcomes followed by maternal and child health outcomes. Healthcare facilities were the most commonly utilised delivery platforms, with limited or no evidence on school, community, and digital platforms. The overall quality of the systematic reviews was moderate while most of the trials had some concerns.

Conclusion

The study findings highlight a well-evidenced area in HPV vaccination with significant gaps in research on other key health interventions, particularly in non-healthcare settings such as schools, communities, or digital platforms. EGM suggests that future research should evaluate the effectiveness of a broad range of preconception interventions, among adolescents and youth for improving long-term maternal perinatal and child health outcome

Supervisors: Associate Professor Zohra Lassi, Associate Professor Gizachew Tessema, Dr Jodie Avery

Child and Adolescent Health

Poster Number: 42

Adapting assessment tools for children and young people with cerebral palsy and chronic pain

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Background and Aims

Children and young people with cerebral palsy (CP) experience chronic pain more frequently than other paediatric populations, with prevalence rates up to 76%. Despite this, chronic pain in CP remains poorly understood, identified and managed. This may be due to under utilisation of pain assessment tools and/or a lack of suitable available tools. The assessment of the impact of pain on emotional wellbeing in children with CP is considered an essential aspect of care, however few pain assessment tools are valid for use in CP. Tools that are available lack suitability across the spectrum of cognitive, communication and motor abilities seen in CP. The aim of this study was to identify ways to improve the relevance, comprehensiveness, comprehensibility and feasibility of key tools for assessing the impact of chronic pain on emotional wellbeing for children and young people with CP.

Methodology

Ethics was obtained through the Women's and Children's Health Network Human Research Ethics Committee (2022/HRE00154). A qualitative descriptive study, guided by the Consensus-based Standards for Measurement INstruments (COSMIN) and informed by a consumer advisory group, was conducted. Eligible participants were: consumers (individuals with CP older than 8 years and parents of children with CP), and clinicians with at least 5 years' experience in CP. Participants were recruited from Novita, Women's and Children's Hospital, South Australian CP register and the Australasian Academy of Cerebral Palsy and Developmental Medicine. Focus groups and semi-structured interviews were conducted online and explored the relevance, comprehensiveness, comprehensibility, feasibility and potential modifications to two tools: the Fear of Pain Questionnaire for Children – Short Form (FOPQ-C-SF) and the Modified Brief Pain Inventory (mBPI). The FOPQ-C-SF and mBPI have potential for use in people with CP to assess impact of pain on emotional wellbeing. Data were analysed through inductive content analysis. Coding was completed in two

rounds: firstly, identifying big picture meaning units and secondly, identifying subcategories within the bigger units.

Results

Data from focus groups and interviews (n=30), including 58 unique modification suggestions, were coded to six main categories: 1; accessibility of the assessment for people with cognitive and communication impairment, 2; comprehensibility of wording and response options, 3; feasibility of the tools for clinicians and consumers, 4; relevance to children and young people with CP, 5; visual presentation of the tool/response options and 6; comprehensiveness of the construct. Consumer feedback largely focused on relevance and comprehensibility of the tools, whereas clinicians focused on visual presentation. Recommended changes included ways to enhance visibility and simplify wording, administration aspects to enhance feasibility, examples and phrasing relevant to young people with CP and ensuring accessibility for augmentative and alternative communication users.

Conclusion

Potential modifications have been identified to improve the FOPQ-C-SF and mBPI for children and young people with CP. Future research should implement and pilot test these modifications in young people with CP and varying communication/cognitive abilities. These assessment tools can then be used in clinical practice to increase access to best practice multidisciplinary pain interventions for this vulnerable group

Supervisors: Professor Rachel Gibson, Associate Professor Adrienne Harvey, Associate Professor Ray Russo

Fertility and Conception

Poster Number	Abstract Details
45	**Minnu Jayapal** *Unravelling the role of phosphodiesterases in ovulation* School of Biomedicine
47	**Kimberly Lush** *Expert Insights and Public Perceptions: Evaluating the Quality of Online Fertility Nutrition Claims in Australia* Adelaide Medical School
50	**Cathryn Tully** *Assessing the influence of preconception diet on male fertility: a systematic scoping review* Adelaide Medical School

Fertility and Conception

Poster Number: 45

Unravelling the role of phosphodiesterases in ovulation

Minnu Jayapal

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Introduction/Aim

Contraception is one of the key aspects of female reproductive health which is aimed at preventing unwanted pregnancies and also to control population explosion. Importantly it provides women full power of control of their reproductive choices. However, current contraceptive pills currently available for females are hormonal, and these interfere with the pituitary-gonadotrophin hormonal axis causing numerous side effects. Thus, there is an urgent need to develop non-hormonal contraceptive options and one possible approach for it, is by targeting to block ovulation.

Ovulation is the timely release of a functional oocyte from the ovary. It is controlled by a network of signalling pathways, one of which is the cAMP (Cyclic Adenosine Mono Phosphate)/PKA (Protein Kinase A) signalling pathway that is involved in the ovulatory process. Briefly, following the LH (Luteinizing Hormone)-surge LH binds to the LHR, which activates Adenyl Cyclase (AC), which converts ATP to cAMP, subsequently activating Protein Kinase-A(PKA), upon translocation of the regulatory unit into the nucleus, it phosphorylates CREB (p-CREB), triggering ovulatory gene expression. Phosphodiesterase (PDEs) are an integral component of this cyclic nucleotide signalling pathway, which hydrolyses cAMP to 5'AMP, thereby maintaining balanced cAMP levels within the cell.

The objective of our study is to identify these ovary-specific phosphodiesterase subfamily isoforms, elucidate their roles and explore their potential as a potential contraceptive target. Firstly, we hypothesised that the distribution and profile of the Pde4d subfamily isoforms are unique to the ovarian compartments and Pde4d inhibitors will have a distinct effect on cAMP signalling within the ovary, thus affecting the ovarian functions.

Methods

Granulosa and cumulus oocyte complex (COCs) were collected from the CBAF1 mice treated with PMSG (Pregnant Mare Serum Gonadotrophin) for 44hours, followed by hCG(human chorionic gonadotrophin). The cells were ten collected at various time points over a period of 16 hours. RT-qPCR using custom Taqman assays was used to measure the gene expression. Pde4d isoform expression and localization was performed using immunohistochemistry. The effect of Pde4 selective inhibitors on the adhesion of the COCs was also assessed using an xCELLigence assay. Granulosa cells extracted from CBAF1

mice, cultured on chamber slides were treated with selective PDE4 inhibitors and examined for p-CREB phosphorylation using immunofluorescence.

Results

Preliminary data from the RT-qPCR gene expression studies indicate that the shorter isoforms of both the Pde4d and Pde4b (Pde4d1 and Pde4b2) respectively are elevated within 2 hours of hCG treatment, followed by a downward trend. Out of all long, short, and super-short isoforms, the short isoform expression is significantly higher at 2 hours post hCG compared to other isoforms/. This is like the the trend that is observed in Sertoli cells as well as a few other hormone-responsive cells, after hormonal stimulation. In the immunohistochemistry analysis, the expression of the Pde4d(pan) was expressed in follicles of all stages, from small pre-ovulatory follicles to large antral follicles. Immunofluorescence experiments using Selective Pde4d inhibitors have shown to have increased levels of pCREB. Additionally, our xCELLigence adhesion experiments show that using the specific-PDE4D selective inhibitor blocks the adhesion of COCs.

Our preliminary findings support our hypothesis that PDE4D is a potential key player in regulating ovulatory mechanisms. Further investigations are necessary to elucidate distinct mechanisms mediated by the shorter isoforms and to comprehensively understand the functional significance of these shorter isoforms in regulating ovulation-related processes. Future experiments will contribute to establishing phosphodiesterase as a potent and promising contraceptive target.

Supervisors: Professor Darryl Russell, Dr Tasman Daish

Fertility and Conception

Poster Number: 47

Expert Insights and Public Perceptions: Evaluating the Quality of Online Fertility Nutrition Claims in Australia

Kimberly Lush

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Background and Aims

Women frequently utilise the internet when searching for information prior to a pregnancy, and often perceive this information to be reliable and useful. It remains unclear whether fertility-related nutrition and lifestyle information found online is consistent with preconception guidelines. The aims of this project are to 1) explore and analyse current online preconception health claims from Google, YouTube, Open AI, Instagram and TikTok and assess against a selection of current preconception guidelines and 2) to understand the perceived accuracy of a sample of identified claims among reproductive aged men and women.

Methodology

Five online media platforms were searched using fertility nutrition-related search terms. A content analysis of identified claims was conducted (n=191) using NVivo 12 Plus to group recurring topics into themes and categories. All claims were assessed by an expert panel against nine Australian and International preconception guidelines. A sample of 80 reproductive aged men and women ranked a random sample of 40 claims, using a Likert scale from “Not at all likely (1)” to “Highly likely (5)”. A claim was considered ‘likely to be true’ by the public if over 75% of respondents rated the claim as greater than 4 on the Likert scale. Likewise, a claim was considered unlikely to be true if over 75% of respondents rated the claim as less than 2 on the Likert scale.

Results

Content analysis generated two themes; nutrition claims and lifestyle claims. The nutrition theme (dietary patterns, whole foods and their components, and supplements) contained 159 total claims, while the lifestyle theme (sleep and stress, exercise, and personal characteristics) contained 32 total claims. Five percent (10/191) of claims were present in preconception guidelines, and 54% (103/191) of claims had no evidence for the health claim. TikTok and Instagram contained a higher proportion of non-evidence-based claims (75% (21/28) and 73% (22/30) respectively), whereas Google (35%), YouTube (57%), and Chat

GPT (38%) had less. The surveyed public considered 3/40 claims likely to be true, two of which were deemed to have ‘insufficient evidence’ by the expert panel, and one was considered to have ‘no evidence’ for the health claim made. Additionally, the surveyed public considered 3/40 claims unlikely to be true, where one was identified to have ‘insufficient evidence’ by the expert panel, and two contained ‘no evidence’ for the health claim. Two claims available in preconception guidelines were presented to the public, however neither was considered ‘likely to be true’.

Conclusion

There is a large volume of misinformation online regarding fertility nutrition and lifestyle claims, and it is evident the public struggle to identify evidence-based claims. Targeted social media public health campaigns to disseminate high level evidence for nutrition and lifestyle strategies in the preconception period are necessary to improve awareness in men and women accessing this information online. Engaging with consumers to better understand their internet use behaviours when accessing fertility related information would facilitate the creation of effective strategies to target misinformation online.

Supervisors: Dr Jessica Grieger, Dr Amy Hutchison, Dr Leanne Pacella-Ince

Fertility and Conception

Poster Number: 50

Assessing the influence of preconception diet on male fertility: a systematic scoping review

Cathryn Tully

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Background and Aims

The last decade has seen increased research on the relationship between diet and male fertility, but there are no clearly defined nutritional recommendations for men in the preconception period to support clinical fertility outcomes.

The purpose of this scoping review was to examine the extent and range of research undertaken to evaluate the effect(s) of diet in the preconception period on male clinical fertility and reproductive outcomes.

Methodology

Four electronic databases were searched from inception to July 2023 for randomized controlled trials and observational studies. Primary outcomes included the effect(s) of male preconception diet on clinical outcomes such as conception, pregnancy rates and live birth rates. Secondary outcomes included time to conception and sperm parameters.

Results

A total of 37 studies were eligible, including one RCT and 36 observational studies. The RCT found that tomato juice may benefit sperm motility. In observational studies, some evidence suggested that increasing fish or reducing sugar-sweetened beverages, processed meat or total fat may improve fecundability. Evidence for other clinical outcomes, such as pregnancy

rates or live birth rates, showed no relationship with cereals, soy and dairy, and inconsistent relationships with consuming red meat or a ‘healthy diet’ pattern. For improved sperm parameters, limited evidence supported increasing fish, fats/fatty acids, carbohydrates and dairy, and reducing processed meat, while the evidence for fruits, vegetables, cereals, legumes, eggs, red meat and protein was inconsistent. Healthy diet patterns in general were shown to improve sperm health.

Conclusions

Specific dietary recommendations for improving male fertility are precluded by the lack of reporting on clinical pregnancy outcomes, heterogeneity of the available literature and the paucity of RCTs to determine causation or to rule out reverse causation. There may be some benefit from increasing fish, adopting a healthy dietary pattern, and reducing consumption of sugar-sweetened beverages and processed meat, but it is unclear whether these benefits extend beyond sperm parameters to improve clinical fertility. More studies exploring whole diets rather than singular foods or nutritional components in the context of male fertility are encouraged, particularly by means of RCTs where feasible. Further assessment of core fertility outcomes is warranted and requires careful planning in high-quality prospective studies and RCTs. These studies can lay the groundwork for targeted dietary guidelines and enhance the prospects of successful fertility outcomes for men in the preconception period. Systematic search of preconception diet suggests that increasing fish and reducing sugary drinks, processed meats and total fat may improve male fertility, while consuming healthy diets, fish, fats/fatty acids, carbohydrates and dairy and reducing processed meat can improve sperm health.

Supervisors: Dr Jessica Grieger, Dr Leanne Pacella-Ince, Dr Nicole McPherson

Musculoskeletal Health

Poster Number	Abstract Details
53	**Kexun Kenneth Chen** *High intensity exercise may worsen temporal summation in chronic neck pain: a randomised crossover trial.* School of Allied Health Science and Practice
56	**Cameron Dickson** *Physiotherapist-related barriers to the implementation of high-value physiotherapy for chronic pain: a systematic review and qualitative meta-synthesis of 44 studies* School of Allied Health Science and Practice
59	**Oscar Russell** *The impact of socioeconomic status on disease outcomes in an Australian early arthritis clinic cohort* Adelaide Medical School

Musculoskeletal Health

Poster Number: 53

High intensity exercise may worsen temporal summation in chronic neck pain: a randomised crossover trial.

Kexun Kenneth Chen

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Physical exercise is the first treatment of choice for chronic neck pain (CNP), yet the mechanisms of effect of different exercise intensities are poorly understood. The presence of central sensitisation (CS) possibly mediates the effects of exercise on patient-reported outcomes. We conducted a randomised crossover trial, investigating the effects of high- and low-intensity exercise on measures of CS in people with CNP. In the study, participants performed high-intensity and low-intensity aerobic exercise session in randomised order, one week apart. CS measures included conditioned pain modulation (CPM) a measure of descending pain inhibition, and temporal summation (TS), a measure of facilitatory pathways. CPM was assessed in series, using a cold pressor test as conditioning stimulus and pressure pain threshold as test stimulus, TS was assessed using PinPrick over the cervical region. After high-intensity exercise, there was a significant increase in TS. No differences were found after low-intensity exercise.. No changes in CPM were found after both exercises. High-intensity aerobic exercise had a detrimental effect on pain facilitatory pathways, whereas low-intensity exercise did not worsen outcomes. To avoid exacerbation of central sensitisation outcomes, these results suggests that low-intensity exercise might be a better option than high-intensity exercise. These findings may assist in the development of personalised approaches to exercise therapy.

Introduction

Physical exercise is the first treatment of choice for chronic neck pain (CNP), yet the mechanisms of effect of different exercise intensities are poorly understood. The presence of central sensitisation (CS) possibly mediates the effects of exercise on patient-reported outcomes.

Aims

To investigate the effects of high- and low-intensity exercise on measures of CS in people with CNP.

Methods

This was a randomised crossover trial (n=35 people with CNP, 63.2% female, age= 36.5±14.1 years). Participants performed a high-intensity (INVHIGH) and a low-intensity (INVLOW) aerobic exercise session in randomised order, one week apart. CS measures included conditioned pain modulation (CPM) a measure of descending pain inhibition, and temporal summation (TS), a measure of facilitatory pathways. CPM was assessed in series, using a cold pressor test as conditioning stimulus and pressure pain threshold as test stimulus, TS was assessed using PinPrick over the cervical region.

Results

After INVHIGH, there was a significant increase in CS (mean difference=0.51±1.24, p=0.02). No differences were found after INVLOW (mean difference=-0.06±1.37 p=0.80). No changes in CPM were found after INVLOW and INVHIGH.

Conclusions

High-intensity aerobic exercise had a detrimental effect on pain facilitatory pathways, whereas low-intensity exercise did not worsen outcomes. To avoid exacerbation of central sensitisation outcomes, these results suggests that low-intensity exercise might be a better option than high-intensity exercise. These findings may assist in the development of personalised approaches to exercise therapy.

Supervisors: Dr Rutger de Zoete, Professor Mark Hutchinson, Professor Paul Rolan

Musculoskeletal Health

Poster Number: 56

Physiotherapist-related barriers to the implementation of high-value physiotherapy for chronic pain: a systematic review and qualitative meta-synthesis of 44 studies

Cameron Dickson

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Background and Aims

Evidence supports high-value physiotherapy (HVP) management of commonly encountered chronic musculoskeletal pain conditions. Examples of such physiotherapy treatments include exercise-based rehabilitation and pain education. However, traditional treatments (e.g. manual therapies) which have only demonstrated modest effects remain widely implemented. This review aimed to identify, and synthesize patient-related barriers to, and interventions to enhance, the implementation of high-value physiotherapy for chronic pain.

Methodology

We systematically searched APA PsycInfo, Embase, CINAHL, Medline, Scopus, and PEDro databases for peer-reviewed studies (published in English) investigating barriers and enablers to, and/or interventions to enhance, HVP management of adults with chronic musculoskeletal pain. Qualitative barrier and enabler themes have been synthesized using the Theoretical Domains Framework of Behaviour Change; interventions have also been qualitatively synthesized.

Results

Our search yielded 1381 studies for title and abstract screening, from which 44 studies (21 barrier and enabler studies, 24 intervention studies, 1 both) met criteria for inclusion. This review is ongoing, and provisional results derived from 23 studies relating to chronic low

back pain are available for reporting. Barriers to the implementation of six HVP elements were described in 12 of these these studies, and included: outcome measures, stratified care approaches, clinical practice guidelines, psychosocial screening tools, biopsychosocial care, and interdisciplinary care. Physiotherapists reported barriers to all but one of these clinical elements which aligned with the knowledge; and environmental context and resources domains of the Theoretical Domains Framework. Individual themes relating to environmental context and resources domain included: time constraints, organizational financial constraints, lack of administrative resources, physician-related barriers, and cost to the patient; and for the knowledge domain: knowledge and lack of training. Ten of the 11 studies relating to interventions sought to enhance knowledge or skills of physiotherapists through education and training, whilst one study assessed implementation of an alternate model of care.

Conclusion

Provisional findings from studies relating to chronic low back pain indicate that physiotherapists encounter barriers to delivering HVP including knowledge and lack of training, which have been a frequent focus of interventions reported in the literature. However, the success of education and training endeavours may be thwarted by concurrent barriers relating to environmental context and resources, such as lack of time and organizational financial constraints.

Supervisors: Associate Professor Paul Rothmore, Dr Rutger de Zoete, Dr Carolyn Berryman, Professor Philip Weinstein

Musculoskeletal Health

Poster Number: 59

The impact of socioeconomic status on disease outcomes in an Australian early arthritis clinic cohort

Oscar Russell

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Background and Aims

Rheumatoid arthritis (RA) is a chronic autoimmune disease which, if untreated, may lead to joint deformities, disability and poorer quality of life. Despite the increasing availability of efficacious targeted treatments in recent years, poorer disease outcomes have been observed in RA patients with lower socioeconomic status (SES). The reason for this observation is not understood. The Royal Adelaide Hospital Early Arthritis Clinic (EAC) manages patients with newly onset RA using a ‘treat-to-target’ strategy, which applies stepwise treatment escalation according to patients’ RA disease activity. We aimed to determine the effect of SES on disease outcomes of early RA patients within an EAC.

Methodology

Participants who had commenced treatment since 1st June 2003, had at least one year of clinic follow up, and were residents of South Australia when residential address was recorded were included. South Australian population area-level SES was assigned as quintiles of Index of Relative Social Advantage and Disadvantage (IRSAD) according to SA1 geographical regions. Outcome measures were RA disease activity (Disease Activity Score in 28 joints using C-reactive protein [DAS28-CRP]) and disability (modified Health Assessment Questionnaire [mHAQ]). Analysis was performed using longitudinal random effects models, with restricted cubic splines (RCS) to model non-linear changes over time. Baseline was defined as the time of treatment commencement. All analyses were performed in StataMP v18.0.

Results

At baseline, there were 286 participants with median age 56 years (IQR 45, 66), and 66% were female. Fewer ‘never smokers’ and university graduates were observed amongst participants in the lowest SES quintile (Q1), without significant differences in rheumatoid factor and anti-cyclic citrullinated peptide antibody positivity.

At baseline, predicted DAS28-CRP was significantly higher for Q1 participants (4.9, 95% confidence interval [CI] 4.6, 5.2) compared to higher SES quintiles (Q2-5) (4.3, 95% CI 4.1, 4.4; difference between groups [∆] 0.6, 95% CI 0.3, 1.0). The RCS model term for the interaction with years of follow-up was statistically significant (β -0.1, 95% CI -0.2, -0.1, $p < 0.001$), with significantly higher disease activity predicted in Q1 at 1 year (∆ 0.5, 95% CI 0.2, 0.8) and 2 years (∆ 0.4, 95% CI 0.0, 0.7) compared with Q2-5 participants, though this difference was no longer statistically significant at 3 years (∆ 0.2, 95% CI -0.1, 0.6).

Similarly, predicted mHAQ was higher at baseline for Q1 participants (0.7, 95% CI 0.6, 0.8) compared with Q2-5 participants (0.5, 95% CI 0.5, 0.6; ∆ 0.2 95% CI 0.1, 0.3); and this difference similarly persisted until 2 years’ follow up.

Conclusion

Low area-level SES was associated with greater RA disease activity and disability at baseline and during initial follow-up, though these differences equalised after approximately 2 years’ treatment. This could reflect the success of a protocolised, treat-to-target treatment paradigm. Further investigation into differences in medications used by SES quintile will be valuable in interpreting this result.

Supervisors: Professor Catherine Hill, Dr Rachel Black

Pregnancy and Birth

Poster Number	Abstract Details
63	**Elaheh Ghaemi Mahdavi** *A Scoping Review of Reproductive Coercion and Abuse During Pregnancy* School of Psychology
66	**Farina Gul** *The Process of Integrating Family Planning Services with Other Reproductive Health Services in Low and Middle-Income Countries: A Scoping Review* School of Public Health
69	**Evangeline Lovell** *Maternal regulatory T cells are an early pregnancy determinant of cardiometabolic health in adult mouse offspring.* School of Biomedicine
72	**Aasiya Mohebi** *Prevalence of metabolic syndrome among pregnant women* Adelaide Medical School
75	**Maedeh Moradi** *Associations between intrapartum antibiotic prophylaxis and childhood autoimmune diseases and obesity: A systematic review and meta-analysis of observational studies* Adelaide Medical School

Pregnancy and Birth

Poster Number: 63

A Scoping Review of Reproductive Coercion and Abuse During Pregnancy

Elaheh Ghaemi Mahdavi

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Background

Research on Reproductive Coercion and Abuse (RCA) has for the most part been focused on behaviors which lead to pregnancy. However, little attention has been paid to RCA towards discontinuation of pregnancy (abortion) and behaviors that attempt to coerce the continuation of an unwanted or unviable pregnancy.

Aims

This scoping review aims to find the extent of the existing evidence on RCA during pregnancy. Methods: Four databases were searched for quantitative or qualitative data on RCA during pregnancy, resulting in 3710 studies. Title and abstract screening was conducted by two independent reviewers. Full text screening will be conducted by one reviewer. All resulting studies will be included in the data synthesis.

Results

Quantitative data will be charted and reported. Qualitative data will undergo descriptive content analysis and basic coding.

Conclusion

Areas where more research is required will be identified, and recommendations will be made for future research.

Supervisors: Associate Professor Clemence Due, Dr Amanda Taylor, Dr Leah Sharman

Pregnancy and Birth

Poster Number: 66

The Process of Integrating Family Planning Services with Other Reproductive Health Services in Low and Middle-Income Countries: A Scoping Review

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Background and Aims

In low-resource settings, the provision of family planning services is often fragmented, leading to high unmet needs for contraception and unintended pregnancies. Women who miss out on family planning services during their visit to the clinic for other maternal and reproductive health services may have a high risk of unintended pregnancies and unmet needs. Integrating family planning services with existing reproductive health services would improve accessibility. This scoping review aims to map the process of integrating family planning services with other reproductive health services in low and middle-income countries.

Methodology

We used five bibliographic databases for peer-reviewed literature and Google Scholar for grey literature. The JBI and Arksey & O'Malley's frameworks were followed to guide the review. The data charting involves recoding basic characteristics of studies and specific information related to the integration process and relevant factors. Results are reported following the PRISMA-ScR guidelines.

Results

The final review considered 37 studies on the integration process of managing and organising FP, reproductive, and other services at clinical and professional levels. Integration was delineated differently across studies, but only five studies provided a clear definition. The studies emphasised the importance of aligning family planning methods with existing services and promoting dual FP methods with HIV/AIDS services, long-acting reversible contraceptive methods with postpartum and post-abortion care, and screening for pregnancy risk assessment in the clinics where immunisation services are provided. The review identified that peer educators and counsellors from HIV/AIDS care were trained for counselling; vaccinators from immunisation services were trained for screening and assessing pregnancy risks among mothers; and doctors and nurses from post-abortion or postpartum care were trained for insertion of intrauterine devices or implants. The referral mechanism mainly consisted of co-location, where the service is provided in a different unit

at the same facility and location in the same unit. The studies used novel approaches to identify ways to strengthen the integration, such as the Happy Client Model and establishing private counselling units for postpartum women. The facilitating factors consist of improving providers' ability and confidence and strengthening communication among providers. The hindering factors were related to increased provider workload, insufficient training, and contraception stock-out.

Conclusion

To integrate effectively, it is crucial to design the integration process by defining it and considering facilitating and hindering factors. Research is necessary to develop a framework for integrating family planning services with other reproductive health services in low-income areas.

Supervisors: Dr M. Afzal Mahmood, Associate Professor Zohra S. Lassi, Associate Professor Gizachew A. Tessema

Pregnancy and Birth

Poster Number: 69

Maternal regulatory T cells are an early pregnancy determinant of cardiometabolic health in adult mouse offspring.

Evangeline Lovell

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Background

Offspring from preeclamptic pregnancies have an increased risk of cardiometabolic disease, neurodevelopmental delay, and immune dysfunction. Preeclampsia and related pregnancy complications are associated with a deficit in maternal regulatory T (Treg) cells, a subset of anti-inflammatory immune cells, in maternal blood. We have previously shown that Treg cell deficiency in early pregnancy in mice (Foxp3DTR) causes uteroplacental dysfunction and fetal growth restriction, but the impact on cardiometabolic health in adult offspring is unknown. Therefore, we evaluated whether Treg cell deficiency induced in early pregnancy impaired offspring cardiometabolic health.

Methodology

Transgenic Foxp3DTR mice have FOXP3 promoter-driven expression of the human diphtheria toxin (DT) receptor, which allows specific deletion of FOXP3+ (Treg) cells upon DT administration. Foxp3DTR females were mated to wild-type allogeneic BALB/c males and injected with DT (37.5 ng/g body weight) on gestational day (GD)3.5 and GD5.5 to deplete Treg cells in early pregnancy, or with vehicle for controls. Cardiometabolic health of adult offspring was assessed at 16-18 weeks of age by intraperitoneal glucose tolerance test and vascular function (wire myography, aorta). N=7-16 dams/group; 1-2 offspring/sex/dam.

Results

There was no difference in litter size or sex ratio between offspring of control and DT-treated dams. At birth, both male and female offspring from DT-treated dams were 15% smaller compared to controls ($P<0.001$) and remained smaller through to adulthood (4-16% lower body weight; $P<0.05$). Adult male, but not female, offspring from DT-treated dams had impaired glucose tolerance compared to same-sex controls (16.3% increase in area under the curve [AUC]; $P=0.05$). Aortae from female offspring of DT-treated dams had lower maximal constriction to phenylephrine compared to female offspring from control dams ($P<0.01$). In contrast, aortic constriction to phenylephrine was comparable between male

offspring groups. However, preincubation with the pan nitric oxide (NO) synthase inhibitor L-NAME increased the AUC in male offspring from DT-treated dams to a lesser extent (P=0.16) than in male offspring from control dams (P=0.002), indicating a lower NO contribution to modulation of vasoconstriction.

Conclusion

Maternal Treg cell deficiency in early pregnancy affects the cardiometabolic health of adult offspring in a sex-specific manner. As many pregnancy complications can affect maternal Treg cells, it is important to define the consequences for offspring cardiovascular health.

Supervisors: Dr Alison Care, Professor Sarah Robertson, Professor Laura Parry

Pregnancy and Birth

Poster Number: 72

Prevalence of metabolic syndrome among pregnant women

Aasiya Mohebi

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Prevalence of Metabolic Syndrome among pregnant women: a systematic review and meta-analysis

Background

Metabolic syndrome (MetS) is a cluster of risk factors which increases risk of cardiometabolic diseases. We aimed to identify the prevalence of MetS and its components among pregnant women.

Methods

PubMed, EMBASE, CINAHL, Web of Science and Scopus databases were searched. The review protocol is registered in PROSPERO (CRD42023460729). Quality assessment was done using the JBI critical appraisal checklist. The study selection, data extraction and data analyses were performed in accordance with MOOSE guidelines.

Results

16 studies provided data on 18411 pregnant women. Prevalence of MetS was 17.6% (n=1703) among pregnant women. Prevalence of MetS components were: low HDL 13% (n=1088), high fasting glucose 16.6% (n=2283), high triglycerides 50.4% (n=2785), high blood pressure 34.1% (n=1076)). When stratified according to the definition used to diagnose MetS, the prevalence of MetS was 17.4%, 13.1% and 19.3% for World Health Organization, International Diabetes Federation and National Cholesterol Education Program Adult Treatment Panel III definitions respectively. When stratified based on gestational age at assessment, the prevalence of MetS was 9.9% and 24.7% for assessments performed prior to 16 weeks' and after 20 weeks' gestation respectively.

Conclusion

Prevalence of MetS varies based on the definition used to diagnose it. A higher prevalence is seen in later pregnancy when compared with early pregnancy. Physiological changes of pregnancy may underlie the higher prevalence detected during later pregnancy.

Key words: Metabolic Syndrome, prevalence, pregnant women, low HDL, high triglycerides, high fasting glucose, high blood pressure

Supervisors: Dr Prabha Andraweera, Associate Professor Margaret Arstall

Pregnancy and Birth

Poster Number: 75

Associations between intrapartum antibiotic prophylaxis and childhood autoimmune diseases and obesity: A systematic review and meta-analysis of observational studies

Maedeh Moradi

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Background and Aims

Intrapartum antibiotic prophylaxis (IAP) is administered to the majority of pregnant women who test positive for Group B Streptococcus (GBS) to prevent early-onset GBS infections (EOGBS). The worldwide incidence of EOGBS infections is 0.041% but accompanied by an average fatality rate of 8.4%. The impact of IAP on the infant gut microbiome and subsequent impact on immune system development and potential for obesity remain a critical concern. The objective of this systematic review and meta-analysis is to synthesise the available evidence of IAP exposure on autoimmune diseases and obesity prevalence in childhood. As an exploratory aim, we also examine the influence of IAP on microbial diversity in babies.

Methodology

The Embase, Emcare, PubMed, Scopus and Web of Science databases were searched from inception until 1 May 2024 for observational studies investigating the effect of IAP on autoimmune diseases, obesity, and gut microbiota. For autoimmune diseases, adjusted relative risk ratios (RRs) and corresponding 95% confidence intervals (CIs) from eligible studies were pooled using a random-effects model. Standardized mean difference (SMD) and corresponding CIs were performed for gut microbiome alpha diversity, child BMI and BMI z-scores. Pre-specified subgroups analyses were also performed to investigate the potential differential effect of IAP on each outcome according to type of autoimmune disease (composite outcome; atopic dermatitis; allergic rhinitis), infant age (< 3 or ≥3 months), child age (< 3 or ≥3 years), IAP type (single or mixed) and/or if studies adjusted for a range of important confounding factors such as parity, use of other prenatal antibiotics, neonatal antibiotic exposure and breastfeeding.

Results

19 studies were eligible of which 16 were included in the meta-analysis (autoimmune disease, n=5; child obesity, n=4; gut microbiome biodiversity, n=7). On meta-analysis, IAP exposure was associated with a higher mean BMI (SMD= 0.05; 95% CI: 0.03–0.06, P < 0.0001, k=2 studies) and higher BMI z-score (SMD= 0.21; 95% CI: 0.14–0.27, P < 0.0001, k=3 studies). IAP exposure was associated with increased risk of autoimmune disease (RR= 2.21; 95% CI: 1.00–4.90, P < 0.0001, k=5 studies). Following subgroup analysis for autoimmune disease, results were even stronger for atopic dermatitis outcome (RR=3.73; 95% CI: 1.13-12.27, k=2 studies), for children <3 y (RR=3.89; 95% CI: 1.87-8.08, k=3 studies) and for the unadjusted subgroup of autoimmune disease (RR= 2.84; 95% CI: 1.40–5.75, P < 0.0001, k=2 studies). IAP exposure was not associated with changes in microbiome diversity among infants aged less than 12 months of age (SMD= -0.09; 95% CI: -.20- 0.02, k=7 studies).

Conclusion

IAP exposure significantly increases the risk of autoimmune disease and is associated with higher mean BMI and BMI z-score in childhood. Given its impact on child health, it is important for GBS positive women to be fully informed of the benefit to risk with IAP before undergoing the treatment. A risk-based approach to the administration of IAP, focusing on factors like premature rupture of membranes, may be worth considering instead of universal screening.

Supervisors: Professor Leonie K Heilbronn, Dr Jessica A Grieger

Translational Health Outcomes

Poster Number	Abstract Details
77	**Madeleine Bryant** *Real-world implementation of a Patient Reported Experience Measure (PREM) in Australian rheumatology care.* Adelaide Medical School
80	**Jessica Charlton** *How is Access Problematised in NDIS policy? A Policy Analysis* School of Allied Health Science and Practice
83	**Yohannes Tefera Damtew** *Current and future burden of Enteric infections attributable to increasing temperature in Australia* School of Public Health
86	**Tahlia Grammatopoulos** *Effectiveness of vaping cessation interventions: rapid review of global evidence* Adelaide Medical School
89	**Anna Kalamkarian** *Measuring multidimensional disadvantage of children in Australia using whole-of-population linked administrative data* School of Public Health
93	**Kate Neadley** *Identifying and responding to the unmet social needs of cancer patients in Adelaide's northern suburbs: successes, challenges and lessons learnt* Adelaide Medical School
96	**Damon Phillips Chantelois** *What does substance abstinence cost? A review on the efficacy of financial incentives to treat substance use disorders* Adelaide Medical School
99	**Maryam Sajjad** *The effects of combined intragastric administration of quinine with L-leucine on gastric emptying of, and the postprandial blood glucose responses to, a mixed-nutrient drink* Adelaide Medical School
102	**Ellen Williams** *From bench to bedside: translation of transcranial magnetic stimulation into speech-language pathology practice* School of Biomedicine

Translational Health Outcomes

Poster Number: 77

Real-world implementation of a Patient Reported Experience Measure (PREM) in Australian rheumatology care.

Madeleine Bryant

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Background and Aim

To determine patient care experience in public rheumatology clinics using Commissioning for Quality in Rheumatoid Arthritis-PREM-Australian version (CQRA-PREM-AU).

Methodology

All patients attending rheumatology outpatient clinics within Central Adelaide Local Health Network (October 2022-2023), were invited to complete a survey via encrypted SMS message, or mail. Sites included Royal Adelaide Hospital, The Queen Elizabeth Hospital, and Port Pirie Rural Outreach Clinic. Survey included: CQRA-PREM-AU (22-item experience measure, 8 domains, scored 1-5), demographics, Patient Global Assessment (PtGA) and Patient Reported Disease Activity (DA) Visual Acuity Scores (VAS). Data were collected via REDCap. The survey opened for 4 weeks; with a reminder at 2 weeks. Analyses included descriptive statistics, multivariable median regression for each CQRA-PREM-AU domain, with covariate analysis by diagnosis.

Results

The response rate was 1408/4591 (31%); 97.7% completed online. 214 records were excluded due to missing data. Patient characteristics: 62% female, median age 64 years, 26% rurally located, 6% spoke language other than English at home. The PtGA median score was 50 (IQR 27, 63), and Patient-reported DA median score was 50 (IQR 26, 69). Domain 1 (Needs and Preferences) had the best overall median CQRA-PREM-AU score (4.2, IQR 3.8-5); Domain 3 (Information about care), Domain 4 (Daily living) and Domain 5 (Emotional care) had the lowest overall median score, all 3.5, IQR 3-4. Compared to RA, a poorer overall care experience was reported by those with SLE (median difference -0.25, p

0.02), fibromyalgia (median difference -0.35, $p < 0.001$), and the worst by those who did not know their diagnosis (median difference -0.8, $p<0.001$).

Conclusion

This study identifies potential targets for improving patient care experience: information transfer, understanding perceptions of disease impact, and emotional support were poorer performing domains. Differences in care experience by diagnosis were evident, particularly for participants unaware of their diagnosis.

Supervisors: Professor Catherine Hill, Dr Rachel Black

Translational Health Outcomes

Poster Number: 80

How is Access Problematised in NDIS policy? A Policy Analysis

Jessica Charlton

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Background

The NDIS was implemented in Australia following the transition from state funded to federal funded disability support, following recommendations from the Australian Productivity Commission (APC) in 2011. Gaining access to the NDIS requires high levels of skill and self-determination. There is limited research examining how NDIS policy achieves its stated aims, and how access to the NDIS is represented in policy. This policy analysis aims to identify how access is represented in the NDIS Act, and how the Act facilitates or constrains an individual's self-determination to access the Scheme.

Methods

Bacchi's What the Problem is Represented to be (WPR) approach was used to explore how access is problematised in the NDIS Act 2013. The approach identifies the problem represented in the Act, its origins, the presuppositions and assumptions of the problem, and the silences. The Act was coded and categorised into core themes using NVIVO, against the first four WPR questions. SDT was used to identify how an individual's motivation to access the NDIS was influenced, and identified the effects of standardisation and how the representations and underlying assumptions can be disrupted.

Results

Our analysis found that access was problematised in the NDIS Act 2013 as one of standardisation, which facilitates or constrains an individual's autonomy. Standardisation during access originated from the objectives, general principles, and eligibility criteria of the Act. The intersectional contextual and personal factors influenced an individual's ability to request access to the Scheme.

Conclusion

This policy analysis used the WPR framework to problematise access in the NDIS Act. We identified that the Act can either support or control an individual's self-determination to access the scheme, and exercise choice and control during the access stage. This allows us to provide recommendations for future policy reform.

Supervisors: Associate Professor Stacie Attrill, Associate Professor Emma George

Translational Health Outcomes

Poster Number: 83

Current and future burden of Enteric infections attributable to increasing temperature in Australia

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Objectives

As temperatures rise, the transmission and incidence of enteric infections such as Salmonella and Campylobacter increase. Our study aimed to estimate the current and future burden of these infections in Australia due to temperature increase.

Methods

Although Salmonella and Campylobacter infections are common in Australia, death associated with these infections is rare. Therefore, we used years lived with disability (YLDs) as our measure. We obtained data from the Australian Institute of Health and Welfare (AIHW) Burden of Disease database for the period 2003-2018. We used a meta-analysis to determine the relative risks of Salmonella and Campylobacter infection per 1°C increase in temperature at statistical area 2 (SA2), and adjusted for relevant covariates using meta-regression. We calculated exposure distributions for each Köppen-Geiger climate zone separately and compared them to the theoretical-minimum-risk exposure distribution to calculate the burden of these infections attributable to increasing temperatures during the baseline period (2003–2018) at SA2 level and later combined at Climate zone and state level. We also projected future burdens for the 2030s and 2050s under two greenhouse gas emission scenarios (Representative Concentration Pathways, RCP 4.5 and RCP 8.5), two adaptation scenarios, and population growth series.

Results

During the baseline period (2003-2018), increasing mean temperatures contributed to 35.8 DALY/100,000 (5.1%) of the observed Salmonella burden and 39.2 DALY/100,000 (5.4%) of the observed Campylobacter burden in Australia. The mean temperature-attributable burden for both infections varied across climate zones, sex, age groups, and jurisdictions. Males and older individuals had a higher burden. Under both RCP scenarios, the projected burden of enteric infections is expected to increase in the future, despite adaptation scenarios. The burden is projected to be highest in tropical climate zones and the Northern Territory. By the 2050s, without adaptation, the burden of Salmonella infection could reach 45.8 YLDs/100,000 under RCP4.5 and 51.1 YLDs/100,000 under RCP8.5. Meanwhile, the burden of Campylobacter infection could reach 54.8 YLDs/100,000 under RCP4.5 and 62.1 YLDs/100,000 under RCP8.5. Implementing a 10% adaptation strategy under RCP8.5 could reduce the burden of Salmonella and Campylobacter to 41.8 and 46.4 YLDs in 2050, respectively, but it would still be higher than the baseline period.

Conclusion

These findings provide scientific evidence to inform policy decisions and guide resource allocation for mitigating the future burden of enteric infections. The current findings emphasize the need to develop location-specific adaptation strategies for the control and prevention of climate-sensitive enteric infections.

Keywords

Salmonella; Campylobacter; Burden of disease; Climate change; Attributable burden; Adaptation

Supervisors: Professor Peng Bi, Dr Blesson Mathew Varghese, Dr Olga Anikeeva

Translational Health Outcomes

Poster Number: 86

Effectiveness of vaping cessation interventions: rapid review of global evidence

Tahlia Grammatopoulos

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Background and Aims

Electronic cigarette use (e-cigarette use/vaping) is a global crisis; Australia's prevalence has increased from 1.4% in 2018 to 8.9% in 2023. Urgent interventions are needed to aid policymakers in addressing this issue. This rapid review aims to synthesise the evidence surrounding the effectiveness of vaping cessation interventions, to inform recommendations for interim quit-vaping guidelines.

Methodology

Preferred Reporting Items for Systematic Reviews (PRISMA) and Cochrane guidance informed the methods. Eligibility criteria included vaping cessation interventions for all ages, and studies spanning the National Health and Medical Research Council (NHMRC) Evidence Hierarchy levels 1-4. Primary outcomes were biochemically validated or self-reported vaping abstinence, and meta-analyses were conducted using a random effects model in RevMan software. A quality assessment was performed using Integrated Quality Criteria for Review of Multiple Study Designs (ICROMS).

Results: Of 23 extracted records, 5 were systematic reviews, 9 randomised controlled trials (including 2 fully powered), 1 cohort study, and 8 feasibility studies. Most studies were from the United States (n=18), and sample sizes ranged from 6-2588. Common intervention elements included pharmacological aids (n=6), smartphone apps (n=7), and counselling (n=7). 9 studies reported on the primary outcome; meta-analyses were statistically significant in favour of cessation interventions, but each held 1 heavily weighted study. Preliminary assessments show predominately moderate (n=6) and low (n=8) quality of studies.

Conclusion

Though heterogeneity in sample size and quality limits conclusions about effectiveness, observed trends align with established tobacco cessation methods and warrant powered clinical trials on pharmacological and smartphone interventions. Local, at-risk populations and e-cigarette policy changes should be considered to ensure the relevance and availability of these urgently needed interventions.

Supervisors: Associate Professor Kristin Carson-Chahhoud, Dr Shagufta Perveen, Professor Smita Shah

Translational Health Outcomes

Poster Number: 89

Measuring multidimensional disadvantage of children in Australia using whole-of-population linked administrative data

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Background and Aims

Quantifying the size and characteristics of populations experiencing disadvantage is a pre-requisite for informed resource allocation of scarce prevention resources. We used individual-level linked administrative data on children and their parents to describe the prevalence and distribution of multiple disadvantages that children are born and grow into from the 12 months before birth to age 5.

Methodology

De-identified linked administrative data was used from the Better Evidence Better Outcomes Linked Data (BEBOLD) platform on all children born in South Australia between 2004 and 2011 in addition to data on their parents.

Eleven domains were created to capture different forms of disadvantage: economic, education, access to services, mental health, substance misuse, smoking during pregnancy, domestic and family violence, health, child protection contact, justice system contact, and parental death.

Prevalence estimates of age-specific disadvantage were measured for each domain over the six-year period from birth to age 5. Persistent disadvantage was also measured in each of the domains by counting the total number of years that the disadvantage occurred. Co-occurrence of the 20 most prevalent disadvantage domain combinations were investigated using UpSet Plots.

Results

We present multi-dimensional disadvantage using a “dashboard approach,” where the proportion of the population experiencing disadvantage on each possible combination of domains was examined but not combined. The prevalence of disadvantage domains varied among children and across ages, and some forms of disadvantage were more likely to co-occur than others.

Conclusion

This study demonstrates the potential for administrative data collections to quantify individual-level disadvantage across domains. Given the whole-of-population linked administrative data available, this study provides an alternative to the use of area-level disadvantage measures and highlights the experience of multiple disadvantages in families before age 5 in South Australia.

Supervisors: Associate Professor Catherine Chittleborough, Dr Rhiannon Pilkington, Professor John Lynch, Associate Professor Murthy Mittinty, Associate Professor Catia Malvaso

Translational Health Outcomes

Poster Number: 93

Identifying and responding to the unmet social needs of cancer patients in Adelaide's northern suburbs: successes, challenges and lessons learnt

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Background and Aims

It is well-established that unmet social needs, e.g. homelessness, financial instability and social isolation, impact health and wellbeing. Healthcare systems are exploring interventions to address these needs to reduce hospital admissions and improve quality of life. Health Navigator (HN) interventions identify patients' needs, and provide referrals and advocacy to appropriate government and community resources. Most interventions occur in primary care, despite research suggesting disadvantaged populations struggle to access this care. Our research will explore the feasibility and acceptability of a HN intervention to address the unmet social needs of cancer patients at the Lyell McEwin Hospital. Our primary aim is to explore the feasibility and acceptability of a HN-led screening and referral intervention for unmet social needs. Our secondary aim is to explore changes to unmet social needs pre- and post-HN intervention.

Methodology

This mixed-methods feasibility study is funded by the Hospital Research Foundation and was conducted at the Northern Adelaide Cancer Centre at the Lyell McEwin Hospital. Eligible participants were 18 years or older, presenting to the Cancer Centre and with a life expectancy of more than six months. Patients with limited English proficiency were excluded, as funding was insufficient to support interpreting services. Participants who reported unmet social needs and requested assistance were referred to the HN. HNs are typically non-medical workers, who provide support and advocacy whilst navigating participants to government and community resources. HNs were led by participants to prioritise their three most urgent needs and co-developed referral plans. The HN referred participants to appropriate services and provided follow-up for a six-month period, assisting with paperwork and advocating for participants as required. Primary outcomes: Feasibility outcomes were assessed using an 80% success threshold for process measures. Intervention acceptability was explored through separate focus groups with participants, their carers and clinicians. Secondary outcomes: Prevalence and type of unmet social needs were assessed at study

baseline and repeated after the six-month intervention. As this is a feasibility study, no sample size calculation is required.

Results

Of 153 participants approached, 73 consented to take part in the study, with all 55 participants that reported unmet social needs requesting assistance from the HN. Eight participants with unmet needs were deceased prior to end of the intervention, with n=36 (75%) completing the HN intervention period. Of the 29 participants that completed both baseline and final measures, 83% (n=24) reported support as their most urgent need, followed by finances (52%, n=15) and transport (31%, n=9). The prevalence of all needs reduced following HN intervention, with the greatest reductions reported in support (↓62%), and finances and transport (↓28% each). Focus groups with participants, carers and clinicians reported the intervention to be acceptable, but cited HN workload and the availability of community resources as key factors impacting intervention success.

Conclusion

Our study is one of the first to explore the feasibility and acceptability of an HN intervention in Australia. Participants and clinicians report the intervention to be appropriate, but further research is required to determine intervention feasibility, health economics, HN role description, and the wellbeing and overall quality of life for those who have received HN services over prolonged periods of follow-up.

Supervisors: Professor Mark Boyd, Associate Professor Cheryl Shoubridge, Dr Brianna Poirier, Professor John Lynch

Translational Health Outcomes

Poster Number: 96

What does substance abstinence cost? A review on the efficacy of financial incentives to treat substance use disorders

Damon Phillips Chantelois

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Background and Aims

Approximately 1 in 20 Australians grapple with addiction or substance use disorder (SUD), costing the economy AU$80 billion per year. Financial incentive interventions are a promising tool to increase health behaviour change including substance abstinence. However, the last systematic review of financial incentives for SUD was undertaken in 2014 and didn't evaluate key characteristics that may inform optimisation for future treatment options such as individually tailored machine learning algorithms. We aim to update the literature since 2014.

Methodology

The primary outcome was substance abstinence at longest follow-up. The review was undertaken in accordance with Cochrane Systematic Review and PRISMA guidelines. Medline, PsychINFO, and EMBASE were searched with no date limitations for randomised controlled trials (RCTs) on financial incentives for SUD. Two independent reviewers screened titles, abstracts, and full texts against eligibility criteria. Substance users were offered an intervention to initiate abstinence with no diagnoses required. Financial Incentive (FI) interventions that exchanged some kind of voucher, cash, gift-card, etc for biochemically verified substance abstinence. Measurements were extracted in order of priority as continuous, point prevalence, or % days of intervention abstinence. Only biochemical verifications were extracted.

Results

A total of 4,388 studies were identified for title and abstract screening after duplicates and non-RCTs were removed. 235 were shortlisted for full-text review with data extraction completed for 37 included RCTs totalling 26,144 participants. 24 were undertaken in the USA with SUD categories spanning nicotine (n=27), alcohol (n=3), cannabis (n=3), stimulants (n=2), heroin (n=1), and polydrugs (n=2). 36 of the 37 studies reported the primary outcome producing 18 statistically significant abstinence results in favour of the intervention and overall effectiveness was significant (OR = 1.93, 95% CI 1.65-2.27).

Conclusions: Findings from this investigation suggest that financial incentives are an effective tool for increasing substance abstinence but further investigation is necessary for some substance types to make a strong claim on treating all SUD.

Supervisors: Dr Shagufta Perveen, Dr Karen Szumlinski, Associate Professor Kristen Carson-Chahhoud

Translational Health Outcomes

Poster Number: 99

The effects of combined intragastric administration of quinine with L-leucine on gastric emptying of, and the postprandial blood glucose responses to, a mixed-nutrient drink

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Background and Aims

The stimulation of glucoregulatory hormones and the rate of gastric emptying are key determinants of the rise in postprandial glucose concentrations. We have established that intraintestinal administration of different nutrients (e.g. amino acids), or the bitter compound, quinine, have potent effects to lower postprandial glucose in healthy participants, associated with stimulation of glucoregulatory hormones (i.e. insulin and GLP-1) and/or slowing of gastric emptying. For example, L-leucine, when administered intragastrically, 30 min before a mixed-nutrient drink, in a dose of 10 g, lowered postprandial glucose, while a 5-g dose had a submaximal effect. Intragastric administration of quinine, in doses of 300 and 600 mg, when given 60 min before a mixed-nutrient drink, also reduced postprandial glucose dose-dependently, with effects marked at the dose of 600 mg, and also apparent, but less potent, at the 300-mg dose. We have now investigated whether combined administration of quinine with L-leucine, each in submaximal doses, enhances their individual effects on postprandial glycaemia in healthy individuals.

Methodology

Fifteen healthy men (age 27±2yrs, BMI 23±0.5 kg/m2) received, on 4 separate occasions, intragastric administration of either i) 300 mg quinine (QHCl), ii) 5 g L-leucine (Leu), iii) 300 mg quinine+5 g L-leucine (QHCl+Leu) or iv) control in randomised, double-blind fashion. At t=-60 min, either QHCI or control was administered, and 30 min later, either Leu or control, each within 1 min. At t=-1 min, participants consumed a mixed-nutrient drink (350 mL, 500 kcal; 74 g carbohydrates), which was labelled with 100 mg sodium acetate-1-13C, for measurement of gastric emptying by 13C-acetate breath test. Plasma glucose was measured at baseline, for 60 min before the drink, and for 180 min following the drink (t=0-180 min). Breath samples were also collected at baseline and at regular intervals post-drink, for subsequent analysis of 13CO2 concentrations.

Results

Both QHCl and QHCl+Leu reduced plasma glucose before the drink, and also lowered postprandial glucose response to the drink, compared with control and Leu (all P<0.001). While a treatment*time interaction was found for the ‘early’ gastric emptying (t=0-60 min) (P<0.001), the post-hoc comparison did not reveal any significant differences between treatments. However, QHCl+Leu tended to slow gastric emptying, compared with both QHCl and Leu (P=0.094). There was a correlation between early

gastric emptying with plasma glucose concentration at t= 30 and t = 60 min, indicating that slowing of gastric emptying, may at least in part, contribute to the lowering of plasma glucose.

Conclusion

In the doses used, QHCl+Leu did not lead to a greater effect than the individual compounds to lower blood glucose. The fact that QHCl and QHCl+Leu had comparable effects suggests that either the effect of quinine, in the dose of 300 mg, could not be enhanced further or that leucine, in the dose of 5 g, was ineffective and, thus, unable to enhance the effect of quinine. Slowing of gastric emptying contributed to blood glucose lowering.

Supervisors: Professor Christine Feinle-Bisset, Professor Amanda Page

Translational Health Outcomes

Poster Number: 102

Translation of transcranial magnetic stimulation into speech-language pathology practice: a survey

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Background and Aims

Transcranial magnetic stimulation (TMS) has a range of potential applications in the rehabilitation of communication and swallowing disorders. These emerging treatments are still under development, however once they are suitable for use in clinical practice, speech-language pathologists (SLPs) will likely be responsible for their delivery. The present study aimed to identify determinants of SLP behaviour that might influence translation of TMS into practice.

Methodology

An online, international survey of 184 SLPs was conducted to collect both quantitative and qualitative data in a convergent parallel design. The refined Theoretical Domains Framework (rTDF) was used to guide survey design, analysis, interpretation, and reporting.

Results

Overall, surveyed SLPs had limited familiarity and experience with TMS. Approximately half of currently practising respondents did not believe TMS would fit within their role. Very few respondents perceived themselves capable of administering TMS at the time of the survey, however 62.5% believed they would be capable following standard training. Many respondents were optimistic about TMS, while others described potential consequences. Respondents reported environmental barriers such as cost and training requirements/availability.

Conclusion

Future research and translation efforts should not only increase TMS knowledge and skills among SLPs through traditional education and training frameworks, but should also address SLP beliefs about TMS in relation to role and identity, capabilities, optimism, and consequences. This study can be regarded as a case study for how new technologies are integrated into speech-language pathology. Further research is warranted to capture broader translation issues facing the profession.

Supervisors: Associate Professor Stacie Attrill, Dr Brenton Hordacre, Dr Mitchell Goldsworthy, Dr Nigel Rogasch