RESEARCH@ RANDWICK

TOW RESEARCH AWARDS

ABSTRACTS 2024

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RANDWICK HEALTH & INNOVATION PRECINCT
The future of lifelong health

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About Tow Research Awards

The Tow Research Day and Awards were initiated due to the vision of Dr Wally Tow, a visitor from Singapore in the early 1970s, who passed away in 2019.

The Tow Research Day provides a common forum on the Randwick Health & Innovation Precinct called the Tow Research Day for junior investigators to present their basic and clinical research. This fosters collaborations between clinical investigators and research scientists who are located at the many research institutes and hospitals around the Randwick Precinct.

The Coast Medical Association Tow Research Committee was created and registered as a charitable entity in 1973 in recognition of the origin of the Tow Research Awards, which was part of the annual meeting of the Coast Medical Association.

The purpose of the Committee is to foster the conduct of research at the Randwick Health & Innovation Precinct.

Welcome
Message

Today marks the 50th Anniversary of the Tow Research Awards, and we are delighted to celebrate the remarkable achievements and groundbreaking research of our distinguished awardees. We extend our heartfelt congratulations to all the nominees and finalists, whose work inspires us and sets a high standard for the research community. We honour the dedication, innovation, and excellence that drive the advancement of knowledge and contribute to improved health outcomes and a brighter future. We also acknowledge the late Dr. Wally Tow, the visionary behind these awards, which provide a unique forum for junior investigators to present their research and foster collaborations between clinical investigators and research scientists.

We welcome Professor Carolyn Sue, today's keynote speaker, who will share insights from her career, the importance of nurturing early and mid-career researchers, and the need for a multidisciplinary approach in translational research. We express our gratitude to our judges for their expertise and time in selecting the winners. We encourage the audience to vote for the People's Choice Award for each division, with QR codes displayed on screen and in the foyer for poster voting.

Tow Research Awards Committee

Awards Day
Program

0900	Basic Science Division.
1015	Morning Tea & Poster Viewing.
1045	Clinical Division.
1145	Keynote Speaker: Professor Carolyn Sue.
1200	Lunch, Poster Viewing, & Poster Judging.
1300	Independent Learning Project & Honours Division.
1430	Allied Health, Nursing, & Midwifery Division.
1530	Afternoon Tea
1545	Case Presentations Division.
1645	Awards Ceremony.

Division:

Allied Health Nursing & Midwifery

Applicant: Nisha Aravind
Supervisor: A/Prof Leanne Hassett

Implementing exercises using digital devices to improve mobility and physical activity in people receiving inpatient rehabilitation: Phase II of a feasibility hybrid type II randomised controlled trial. (Activity and Mobility UsiNg Technology Implement trial - AMOUNT_Implement).

Nisha Aravind (BPT; 1, 2), Daniel Treacy (PhD; 1, 3), Sakina Chagpar (MScPT; 3,), Lisa A. Harvey (PhD; 4), Joanne V. Glinsky (PhD; 5), Catherine Sherrington (PhD; 3), Leanne M. Hassett (PhD; 3).

1. Physiotherapy Department, Prince of Wales Hospital, SESLHD.
2. Sydney School of Health Sciences, Faculty of Medicine & Health, USyd.
3. Institute for Musculoskeletal Health, USyd & SLHD.
4. John Walsh Centre for Rehabilitation Research, Faculty of Medicine & Health, USyd.
5. Sydney School of Public Health, Faculty of Medicine & Health, USyd.

Background: Clinical trials have demonstrated digital devices can be used to increase dose of physiotherapy practice in rehabilitation and lead to improved mobility for adults undertaking rehabilitation. However, it is unknown if this evidence-based intervention can be implemented effectively in clinical practice.

Methods: A feasibility hybrid type II implementation-effectiveness trial was undertaken in two phases[1]. In Phase I physiotherapists were supported to use digital devices to provide exercises to improve mobility (reported separately). In Phase II patients were randomised into control or intervention groups. Both groups received usual care and the intervention group received additional exercises using digital devices. The additional exercises using digital devices in the intervention group were provided by physiotherapists trained in Phase I. Primary feasibility outcomes were: documentation of exercise dosage, rate of recruitment, and physiotherapist's ability to provide ≥30 mins exercise sessions using digital devices.

Results: Twenty-two participants were randomised; 11 in each group. Exercise dosage was documented 100% of the time, recruitment rate was 0.2 participants per week, and 36% of intervention participants received average ≥30 mins digital device sessions.

Conclusion: Exercises using digital devices can be delivered within usual rehabilitation staffing, but at a lower than intended dosage. Intervention and organisational implementation challenges were identified. Several sites would be needed for a future larger trial.

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1. Aravind N, Treacy D, Chagpar S, Harvey LA, Glinsky JV, Sherrington C, Hassett LM: Implementing digital devices to increase mobility training for people receiving inpatient rehabilitation: protocol for a feasibility hybrid type II randomized controlled trial. Pilot and Feasibility Studies 2023, 9(1):69.

Applicant: Michael Breeze
Supervisor: A/Prof Suzanne Sheppard-Law

The Wound sandwich: evaluating an educational web-based resource.

M.Breeze
Department of Surgery, Prince of Wales Hospital.

Globally, an increased prevalence of wound ulcers has been reported largely associated with an aging population and increased comorbidities such as diabetes (Sallustro & Florio, 2022). The presence of an ulcerated wound represents a considerable burden to health care and to the patient and their family's quality of life (Lommi et al., 2023; Sallustro & Florio, 2022; Welsh, 2018). The management and nursing care of ulcerated wounds involves a comprehensive individualized approach to promote healing, prevent complications, adequately support the patient, and deliver education. Conversely inadequate wound care or access to appropriate wound care may result in prolonged hospitalization, infection and possible loss of a limb (Lommi et al., 2023; Sallustro & Florio, 2022; Welsh, 2018).

Several studies suggest that nurses' knowledge and /or confidence of effective wound care is lacking (Gillespie et al., 2014; Lommi et al., 2023; Welsh, 2018). A systematic review of nurses' knowledge of wound care reported variable knowledge, a lack of competency and a lack of educational opportunities to acquire knowledge within undergraduate and post graduate nursing programs (Welsh, 2018). A cross sectional survey of Australian nurses (n=120) working in the acute setting were found to have poor practical skills and lacked an ability to make evidence based decisions in the selection of dressings despite having adequate theoretical wound care knowledge (Gillespie et al., 2014).

A web-based education resource has been developed by Primary Investigator Michael Breeze to complement and /or extend current training with a particular focus on out-of-hour access to information.

References:

1. Gillespie, B. M., Chaboyer, W., Allen, P., Morely, N., & Nieuwenhoven, P. (2014). Wound care practices: a survey of acute care nurses. Journal of clinical nursing, 23(17-18), 26182626. https://doi.org/https://dx.doi.org/10.1111/jocn.12479
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4. Welsh, L. (2018). Wound care evidence, knowledge and education amongst nurses: a semisystematic literature review. International wound journal, 15(1), 53-61. https://doi.org/https://dx.doi.org/10.1111/iwj.12822

ORAL

Applicant: Lyndall Cook
Supervisor: Prof Lynne Bilston

Evaluating Specialty Harnesses for Safe Transportation of Children with Disabilities.

L. Cook (1, 2), T.Whyte (1), and L.Bilston (1, 2).

1. NeuRA.
2. Graduate School of Biomedical Engineering, UNSW Sydney.

When travelling in motor vehicles, children with disabilities often require support that standard child restraint systems (CRS) cannot provide. Specialty harnesses designed to address postural and positioning needs of children with physical impairments, or to prevent unsafe behaviours in the vehicle, are frequently prescribed by allied health professionals [1, 2]. While these harnesses can offer support to the child, there is no research on how these harnesses affect the safety of the child during a crash. It is hypothesised the use of speciality harnesses alters crash forces exerted on a child during a crash, increasing injury risk compared to a child using an age-appropriate child restraint with a standard lap-sash seat belt.

This study investigated the performance of six commonly used specialty harnesses. Frontal crash tests at 49km/h were completed with or without the harness, on a booster seat (for a 6 year old child) or on the vehicle seat alone (for a 12 year old).

Harnesses that convert the lap-sash belt to lap belt only and those that repositioned the seat belt induced 'submarining', which is likely to increase risk of serious abdominal and spinal injuries. On booster seats, abdominal injury risk was mitigated by use of an anti-submarining clip on the restraint. Several harnesses tested showed comparable safety performance compared to baseline.

Findings highlight some harnesses currently in use increase the risk of serious injury to children. Allied health professionals must weigh benefits and risks of using harnesses during vehicle travel, ensuring selection of safest options.

References:

1. Black, M.H., Hayden-Evans, M., McGarry, S., Lindner, H., Clarkson, E., Vale, L., Picen, T., Kuzminski, R., Falkmer, T. (2023). Safe transport of children with disabilities and medical conditions: caregiver experiences. Scand J Occup Ther. 30(8), 1383-1393.
2. Cook, L., Bilston, L.E., Whyte, T. (2024). Modifications to child restraints for children with disabilities – Experiences of Australian caregivers and health professionals. J Road Safety. 35(1), 1-14.

Applicant: Michael Doumit
Supervisor: Prof Adam Jaffe

Understanding the acceptability of the increased use of telehealth in cystic fibrosis care.

Michael Doumit (1,2), Verity Pacey (2), Adam Jaffe (1, 3), Kelly Gray (2).

1. Department of Respiratory Medicine, SCH.
2. Department of Health Sciences, Macquarie University.
3. School of Clinical Medicine, UNSW Sydney.

Background: Highly effective modulator therapies and the COVID pandemic have contributed to a hybrid model of cystic fibrosis (CF) outpatient care, which incorporates telehealth and in-person reviews.

Objective: To explore the acceptability of the hybrid model of care in people with CF (PWCF) and parents of children with CF.

Methods: Semi-structured interviews were undertaken with PWCF and parents of children with CF from eight Australian CF centres. Maximum variation sampling yielded participants from different geographical and socioeconomic profiles. The interview guide and thematic analysis utilised the Theoretical Framework of Acceptability (TFA) to explore the multiple domains of acceptability.

Results: Ten PWCF and 16 parents of children with CF were interviewed. The major emergent themes from the interviews aligned with the domains within the TFA. The major themes were: (1) life is easier with a hybrid model of care, (2) hybrid care is easy and effective but not comprehensive, (3) hybrid care needs to suit individual needs, (4) confidence in hybrid care is determined by internal and external factors, (5) accepting hybrid care involves compromising certain valued aspects of in-person care, (6) hybrid care keeps reduces infection and helps normalise life.

Conclusion: PWCF and parents of children with CF determine the acceptability of the hybrid model based on the aspects of in-person care they are willing to compromise on to obtain the convenience, safety and normality that receiving part of their care through telehealth allows. Therefore, the model of care should be determined in consultation with the individual with CF.

POSTER

Applicant: Jarrad Fisher
Supervisor: Dr Xiaoying Chen

FULMA: A Novel System for Objective Upper Limb Assessment Post-Stroke.

Jarrad Fisher (1, 2), Christopher Bunn (3), Molly Barnhart (2), Wanqing Li (3), Ross Black (1), Alexandra Hurden (2), Craig Anderson (2) and Xiaoying Chen (2).

1. Occupational Therapy Department, POWH.
2. Brain Health Program, TGI.
3. School of Computing and Information Technology, UOW.

Background: Upper limb (UL) impairments post-stroke significantly affect quality of life, necessitating accurate assessment tools for effective rehabilitation. Current methods are often subjective and inconsistent. The Fisher's Upper Limb Movement Assessment (FULMA) system integrates machine learning (ML) models to enhance UL assessment accuracy and reliability.

Objectives: This study aimed to develop a laptop-based, optical motion capture system, integrating ML models to capture and analyse motion for UL assessment and rehabilitation in stroke patients.

Methods: Data for ML model development were collected from 39 stroke patients and 21 age-sex matched healthy volunteers performing 9 differing functional UL tasks, using common household items (M1 to M9). Support Vector Machine (SVM), Multilayer Perceptron (MLP), and Ensemble models were developed and tested for assessment of the Action Research Arm Test scoring criteria, compared with grading made by two experienced occupational therapists.

Results: The SVM model consistently achieved high accuracy, exceeding 94% across all movements, peaking at 100% for movement M3 (lift and lateral transport of cup), with F1 scores ranging from 0.95 to 1.0, indicating excellent precision and recall. The MLP model showed accuracy between 84.8% and 98.0%, with the highest F1 score of 0.98 for movement M3. The Ensemble model varied in accuracy from 81.6% to 90.4%, with movement M6 (reach, grasp and lift of plate) achieving the highest F1 score of 0.90.

Conclusion: The FULMA system shows strong potential as an innovative tool for assessing UL impairments post-stroke, with the high accuracy of the ML models supporting further development and clinical validation.

POSTER

Applicant: Dr Lauren Ha
Supervisor: Dr Christina Signorelli

Making Moves: a type 1 hybrid effectiveness-implementation trial of an online physical activity program for childhood cancer survivors.

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Behavioural Sciences Unit, School of Clinical Medicine, UNSW Sydney.
Kids Cancer Centre, Sydney Children's Hospital.

Childhood cancer survivors are at increased risk of developing late effects such as obesity. Despite the benefits of physical activity in reducing the risk of late effects, 86% of survivors do not meet physical activity guidelines[1]. 'Making Moves' is an online educational physical activity intervention that has shown good feasibility and acceptability[2], and has subsequently undergone consumer development[3]. Yet, the effectiveness of Making Moves and the context for implementation is unknown. The aim of our study was to (i) evaluate the effectiveness of Making Moves on survivors' physical activity self-efficacy (i.e., their confidence in their ability to be physically active), and simultaneously (ii) explore the barriers and facilitators of implementation to inform future adaptations and implementation strategies. To date, 22 survivors opted in (33% response rate). Currently, seven survivors (mean age 12.0 SD 3.0 years) have completed the study, with no adverse events reported. Survivors' mean physical activity self-efficacy scores increased, though was not significant (+5.28 mean change, p=.092). All survivors reported the program helped them in some way. For the implementation aim, 17 representatives across five potential implementors completed interviews. Key barriers to implementation included limited trained staff to deliver the intervention, limited capacity to maintain the online platform, and financial barriers to hiring an exercise physiologist into the team. Facilitators included support for implementing an online physical activity program, and compatibility to the organisation's missions and goals. Making Moves demonstrates preliminary efficacy, with further consideration needed of factors impacting its implementation in the community.

References:

1. Ha, L., et al., Patterns of physical activity and sedentary behavior in child and adolescent cancer survivors assessed using wrist accelerometry: A cluster analysis approach. 2023. 29(4): p. 14604582231212525.
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3. Ha, L., et al., Exploring childhood cancer survivor, parent, healthcare and community professionals' experiences of, and priorities for, using digital health to engage in physical activity: a mixed methods study. 2024: p. 1-16.

POSTER

Applicant: Maria Lohan
Supervisor: Dr Victoria Walton

A Hospital Quality Improvement Project to Optimise Oral Iron Treatment for Pregnant Women with Iron Deficiency Anaemia and Iron Deficiency.

Lohan M (1), Maitra A (1), Byun L (1), McLellan L (1), Kidson-Gerber G (1,3, 4, 5), Shand AW (1,2).

1. RHW.
2. USyd.
3. POWH.
4. NSW Health Pathology.
5. UNSW Sydney.

Background: Oral iron is recommended first-line treatment for iron deficiency (ID) and ID anaemia. Suboptimal dosing, adherence and response to oral iron may lead to treatment failure, necessitating intravenous (IV) iron. We aimed to determine if women receiving IV iron had received appropriate oral iron treatment for ID and IDA as part of a Royal Hospital for Women quality improvement project to improve treatment of ID and IDA.

Methods: Education targeting pregnant women, and maternity care providers was provided from November 2022 to August 2023. New educational resources were developed. Pregnant women treated with IV iron, October 2022 to October 2023 were included. Data was collected from medical records on number of women receiving IV iron, number of women receiving IV iron who had "appropriate oral iron" (dose, frequency, preparation) and number of women receiving IV iron who had Ferritin and Haemoglobin results reviewed within 4 weeks of commencing oral iron. Women were surveyed to assess their understanding of oral iron.

Results: Overall 217 women received IV iron, range 11-23 per month, with no change over time. The number of women who received appropriate oral iron increased from 25% to 87%, and 4-weekly review of blood results increased from 40% to 88%. 66 women completed the survey and results reflected inconsistent advice from providers.

Conclusion: Follow-up blood tests after oral iron treatment improved significantly after the quality improvement project commenced. In addition, appropriate oral iron treatment improved. Despite improvements in treatment and follow up, IV iron use didn't change.

Applicant: Dr Suzanne Nevin
Supervisor: Dr Lauren Kelada

Childhood Dementia Insight: Unravelling the psychosocial, quality of life and mental health impacts of childhood dementia on caregivers and bereaved caregivers.

Suzanne M. Nevin (1, 2), Lauren Kelada (1, 2), Claire E Wakefield (1, 2), Gail Hilton (3), Megan Maack (3), Jason V. Djafar (1), Kristina L. Elvidge (3), Michelle Farrar (1).

1. School of Clinical Medicine, UNSW Sydney.
2. Behavioural Sciences Unit, SCH.
3. Childhood Dementia Initiative.

Background / Aims: Childhood dementia is a devastating group of life-threatening and life-limiting disorders, defined by progressive decline of neurocognitive function and enduring loss of previously acquired developmental skills. With over 100 genetic loci identified, genetic testing has become standard care. Children and their families experience substantial bio-psychosocial impacts associated with the complex and idiosyncratic nature of this child's individually rare genetic condition1. Less than five percent of childhood dementias have disease-modifying therapies and family-centered psychosocial resources following diagnosis are lacking. Taking a collective approach, this research involves an in-depth mixed-methods, multi-perspective study to investigate and address the shared psychosocial impacts of genetic childhood dementia conditions on Australian families.

Methods: Parents of children with clinically confirmed or suspected genetic childhood dementia will complete a series of validated and purpose-designed measures to quantify the psychosocial, psychological and economic impacts of their child's diagnosis. Additionally, parents will be invited to complete an individual in-depth, semi-structured interview to elucidate their unique perspectives, experiences undergoing genetic testing and to identify parents' unmet needs. A convergent, mixed-methods approach, combining the results from the quantitative and qualitative measures will be adopted to enhance interpretation of parents' experiences.

Results: This research will quantify and qualify important themes reflecting the collective impacts of childhood dementia on Australian parents and bereaved parents.

Conclusion: Co-designed and evidence-based resources are crucially needed to provide integrated, multidisciplinary support for parents and bereaved parents of children with dementia. Our findings will inform future best-practice genetic healthcare services and psychosocial supports for children and affected families.

References:

1. Nevin SM, McGill BC, Kelada L, et al. The psychosocial impact of childhood dementia on children and their parents: a systematic review. Orphanet Journal of Rare Diseases. 2023;18(1):277.

ORAL

Applicant: Dr Annie Palermo
Supervisor: Dr Claire Boswell-Ruys

The TCT and FIST-SCI are appropriate clinical assessments of functional sitting balance in spinal cord injury rehabilitation

Anne E Palermo, Sophie Denis, Edward Gorgon, Rachel Spillane, Fernanda Di Natal, Claire Boswell-Ruys.

Functional sitting balance (FSB), the maintenance of trunk stability during functional tasks while seated, is a priority for independence and quality of life1,2 after a spinal cord injury (SCI) but there is currently no gold standard to quantify or measure FSB.3-5 The lack of a gold standard limits the ability to measure the effect of FSB interventions. The aim of this study was to investigate the reliability, validity, and responsiveness of the Trunk Control Test (TCT)6 and the Function in Sitting Test in people with SCI (FIST-SCI)7 in people with recent SCI.

Physiotherapists assessed 30 individuals receiving their initial SCI rehabilitation with the TCT and FIST-SCI 4 times within 2 weeks, and then once 6 weeks later, to investigate inter- and intra-rater reliability, via ICC analysis, and responsiveness. Validity measures included correlations with the Berg Balance Scale (BBS),8 Spinal Cord Independence Measure (SCIM-III),9 and SCI-Falls Concern Scale (SCI-FCS).10

The average time since injury was 84 days 95%CI: [64, 105]. The TCT and FIST-SCI had excellent inter- and intra-rater reliability (ICC>0.9). The TCT and FIST-SCI were able to distinguish individuals who were independent and those who required assistance to transfer ($p<.05$), establishing known-groups validity. Both assessments were related to ($p<.05$) the SCIM-IIItotal (ρTCT:0.477, ρFIST-SCI:0.555), SCIM-IIIMobility-subscore (ρTCT:0.639, ρFIST-SCI:0.552) and the BBS (ρTCT:0.627, ρFIST-SCI:0.785). After 6-weeks, the median change [range] in the TCT and FIST-SCI scores were 2 [0,6] and 2 [-4, 9], respectively. This is the first study to identify two reliable, valid, responsive and clinically translatable FSB assessments for sub-acute SCI-rehabilitation.

Applicant: Dr Annie Palermo
Supervisor: Dr Claire Boswell-Ruys

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Applicant: Janie Provencher
Supervisor: Dr Martin Heroux

Optimal Transcutaneous Spinal Stimulation: The Comparative Effectiveness of Stimulation Waveforms

Provencher J (1, 3), Finn HT (1, 2), Gandevia SC (1, 3), Butler JE (1, 2), Héroux ME (1, 2).

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3. School of Clinical Medicine, UNSW Sydney.

Transcutaneous spinal stimulation (TSS) is a promising non-invasive intervention to improve sensorimotor function in people with spinal cord injury(1–3). However, variability exists among studies that select TSS parameters without clear justification(4–6). Here, we evaluate the ability of various TSS waveforms to elicit spinally evoked motor responses (sEMR).

In 12 neurologically intact participants, ten TSS waveforms were tested: monophasic and biphasic, with high-frequency burst (HF) (2kHz, 5kHz, 10kHz; 1ms duration) and without (400µs, 1000µs phase duration). The cathode (5x10cm) was placed over L1, and the anode (10x5cm) below the umbilicus; sEMRs were recorded from soleus with surface electrodes. Waveform effectiveness was assessed by the threshold intensity to elicit an sEMR and the peak slope of the recruitment curve fitted with a log-logistic function. Outcomes were compared using mean [95%CI] differences.

Given the different phase duration, the 400µs biphasic waveform had a higher threshold (67.1mA[53.07, 81.10]) and lower peak slope (0.12mV/mA[0.08, 0.17]) than the 1000µs biphasic waveform (mean differences: threshold -19mA[-23.6, -14.4]; peak slope 0.09mV/mA[0.01, 0.16]). Compared to the 400µs biphasic waveform with equivalent total phase duration, sEMR thresholds were higher with the 2kHz (20.6 mA[15.6, 25.6]); 5kHz (83.6mA[61.6, 105.5]) and 10kHz (168.5mA[135.0, 202.0]) HF waveforms. Peak slopes were generally lower for the 2kHz (-0.02mV/mA[-0.04, 0]), 5kHz (-0.07mV/mA[-0.09, -0.05), and 10kHz (-0.10 mV/mA[-0.14, -0.06] HF waveforms. Results were similar between biphasic and monophasic variants.

Clinically available stimulators use biphasic waveforms without HF burst modulation, and our results indicate that these TSS waveforms are more effective at eliciting soleus muscle sEMR.

Applicant: Janie Provencher
Supervisor: Dr Martin Heroux

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Applicant: Praveena Rajeswaran
Supervisor: A/Prof Jane Kohlhoff

Looking Back, Moving Forward: A pilot intervention trial for parents experiencing early psychosocial and/or parenting challenges using EMDR.

P. Rajeswaran (1), V. Eapen (1), C. Lee (2), & J. Kohlhoff (1).

1. School of Clinical Medicine, Discipline of Psychiatry and Mental Health, Faculty of Medicine and Health, UNSW Sydney.
2. UWA Medical School, University of Western Australia.

Parenting involves an interplay of intra- and interpsychic processes, rooted in one's personal history and emotional functioning. To support children's healthy development, focusing on parents' psychic processes may prevent the intergenerational transmission of trauma. Eye Movement Desensitisation and Reprocessing (EMDR[1]) is a psychotherapy that integratively targets traumatic memories. Preliminary evidence has highlighted potential of EMDR to improve parenting capacity and child outcomes[2,3,4]. However, extant evidence has either supplemented EMDR with other interventions[4,5,6], or is based on case studies[4,7], indicating a need for further research.

This study aims to evaluate the effect of EMDR on mothers' attachment state-of-mind, caregiving sensitivity, reflective functioning, and affective information processing. A ten-session EMDR protocol is being administered to 15-20 parents at Karitane Parenting Centres. Participants complete standardized measures before and after the protocol, including the Adult Attachment Interview with Reflective Functioning Scale (AAI + RFS), Attachment Style Questionnaire (ASQ), Infant Crying Questionnaire (ICQ), NICHD-SECCYD Sensitivity Scales, and Composite Caregiving Questionnaire (CCQ). A linear mixed-model repeated measures design will analyze the impact of EMDR on these variables. Participants also complete qualitative interviews, with transcripts undergoing thematic analysis. Six-month follow-up of the AAI will examine the sustained effects of EMDR on attachment state-of-mind and reflective functioning. Results are pending.

EMDR presents as a promising intervention for targeting maladaptive parenting-related schemas and behaviours. The current study utilises EMDR in the early stages of parenting, which may help break the cycle of intergenerational trauma and provide meaningful evidence that contributes to the field of child and family research.

Applicant: Praveena Rajeswaran
Supervisor: A/Prof Jane Kohlhoff

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ORAL

Applicant: Hannah Rawlins
Supervisor: Dr Claire Boswell-Ruys

Swallowing and lung function in individuals with motor and sensory – complete cervical spinal cord injuries.

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Objective: This study aimed to investigate the association between swallowing difficulties and lung function in individuals with both motor and sensory complete cervical spinal cord injuries (SCI). Additionally, it sought to compare these aspects with age-matched normative data from individuals without SCI.

Methods: A cross-sectional study was conducted on 16 participants with motor and sensory complete cervical SCI. Participants completed health history questionnaires and underwent lung function testing. Following safety screening, they were assessed with the Timed Water Swallow Test (TWST) and the Test of Mastication and Swallowing Solids (TOMASS) to evaluate swallowing of liquids and solids, respectively (1,2).

Results: The study found a significant association between poorer lung function and swallowing difficulties, particularly with liquids. Strong correlations were observed between lung function measures—FEV1 ($p=0.003$), FVC ($p=0.03$), PEFR ($p=0.022$), and MEP ($p=0.005$)—and the TWST performance, including both time taken and volume per time ratio. Participants with cervical SCI demonstrated significantly lower lung function compared to individuals without SCI, with marked differences in FEV1 ($p=0.001$), FVC ($p=0.001$), PEFR ($p<0.001$), MEP ($p<0.001$), and tongue strength ($p=0.001$).

Conclusion: The study identifies a significant relationship between swallowing function and lung performance in individuals with cervical SCI. Future research should utilise video fluoroscopy to better understand the dynamics between swallowing liquids and lung function. The observed differences between cervical SCI patients and normative data underscore the impact of the inhibitory reflex and suggest that targeted interventions, such as respiratory muscle training, could enhance patient outcomes and reduce mortality.

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ORAL

Applicant: Dr Ursula Sansom-Daly
Supervisor: Prof Claire Wakefield

When, and how, should we talk about palliative care concepts with adolescents and young adults with cancer? Results from an international Delphi study.

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Background: According to standard of care, adolescents and young adults (AYAs) should be introduced to palliative care concepts regardless of disease status.[1] This does not consistently occur, [2] with health-professionals reporting barriers to doing so.[3]

ORAL

Applicant: Dr Ursula Sansom-Daly
Supervisor: Prof Claire Wakefield

Objective: To explore health-professionals' practices, and perspectives, regarding introduction of palliative care concepts with AYAs with cancer.

Method: Study 1 examined palliative care communication among AYA oncology health-professionals in Australia, New Zealand and the UK. Study 2 used a modified two-round global Delphi survey to establish when health-professionals felt palliative care concepts were appropriate to introduce according to (i) patient prognosis, and (ii) treatment time-points.

Results: Study 1 (148 health-professionals from Australia/NZ/UK) found palliative care concepts were introduced regardless of disease status 'usually' or 'always' in 55% of the Australian, 20% New Zealand, and 48% UK health-professionals. Study 2 (248 health-professionals across 8 countries) reached consensus that some palliative care concepts (e.g., emotional and existential issues) were appropriate at all prognoses and treatment/disease timepoints. End-of-life-related medical care topics were only considered appropriate for patients with prognoses <50%, or from a patient's second relapse onwards. Prognosis and goals of care, and quality of life topics were considered appropriate for most patients (<75% prognosis, most of the treatment trajectory).

Conclusions: Some palliative care topics are considered appropriate for most AYAs, across most of the treatment trajectory. Our data indicate that health-professionals' opinions differ regarding introducing palliative care concepts to AYAs during cancer treatment, including at their first relapse. Supports for health-professionals will ensure best-practice team-based AYA oncology care.

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POSTER

Applicant: Ruth Smoother
Supervisor: A/Prof Suzanne Sheppard-Law

Establishing and maintaining a person-centred culture in a newly established hospital unit

A positive workplace and organisational culture has a direct impact on safe person centred practice [1]. A Quality Safety Culture Framework (QS&C) founded on the Person-Centred Practice Framework [6] was developed and implemented at the Prince of Wales Hospital in 2019 with a reformat and relaunch in 2023. The implementation encompasses a process of engaging teams in a common vision before engaging them with a unique quality cycle to improve person-centred culture.

This study aimed to evaluate how the QS&C framework influenced registered nurses' perception of ward culture and person-centred practice in a new nursing team on a newly opened ward.

A descriptive qualitative study using in-depth semi-structured interviews were conducted in April-May 2024. Eligible registered nurses consented to complete a short questionnaire and to attend an audio-recorded in-depth semi-structured interview. Audio-recordings were transcribed verbatim. Braun and Clarke's six steps of analysis were utilised to explore participant narratives.

Eight female registered nurses reporting a mean age of 35 years participated in the study. Three dominant themes with some sub-themes were identified. The themes were: Setting the foundations for a positive culture 2. Embedding a culture of safety and 3. The aesthetics of the care environment.

This qualitative study highlights how implementing a Quality Safety Culture Framework and associated activities lays the foundations for a positive ward culture by nursing leadership influence enabling a values-driven and safety orientated approach to care. The dynamic nature of a changing hospital wards disrupt this culture, so to sustain a positive culture regular evaluation is required.

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Division:

Basic Science

Applicant: Tanzina Akter
Supervisor: Prof Mark Wilcox

Comparative Study of Virulence Factors and Antibiotic Resistance between exoU and exoS Pseudomonas aeruginosa Isolated from Corneal Infections

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Background: The cytotoxic Pseudomonas aeruginosa strain carrying the exoU gene is linked to more severe corneal infections (keratitis) compared to the invasive exoS strains (1-3). This difference may be due to the expression of specific virulence factors and higher antibiotic resistance in exoU isolates.

Aims: This study aimed to investigate the differences in virulence genes and antibiotic resistance between exoU and exoS in P. aeruginosa keratitis isolates.

Methods: A total of 187 ocular P. aeruginosa strains isolated from corneal scrapes were analyzed for the presence of exoU and exoS genes, initially identified by whole genome sequencing (WGS) in 39 isolates and confirmed by PCR in 148 isolates. Minimum inhibitory concentration assays were conducted using ciprofloxacin, levofloxacin, gentamicin, and tobramycin. WGS data from 39 strains were screened for acquired resistance genes using ResFinder and for virulence genes using the Virulence Factors Database, with confirmation by PCR.

Results: Significant differences in virulence genes were observed between exoU and exoS isolates, with pldA (83.6% vs. 31.8%, $p<0.01$) and flaG (78.2% vs. 56.1%, $p<0.01$) more common in exoU strains. Antibiotic resistance was significantly higher in exoU isolates ($p<0.05$) than exoS, with resistance rates of 38.2% vs. 20.5% for ciprofloxacin, 29.1% vs. 12.1% for levofloxacin, 40% vs. 23.5% for gentamicin, and 29.1% vs. 14.4% for tobramycin. exoU strains more frequently carried aph(6)-Id and aph(3")-Ib genes conferring resistance to gentamicin and tobramycin.

Conclusion: Higher antibiotic resistance and distinct virulence factors genes (pldA and flaG) expression may contribute to the severity of exoU-associated keratitis.

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ORAL

Applicant: Asena Bingul
Supervisor: Dr Teri Furlong

Lesions of the lateral hypothalamus-nigral projection result in motor deficits in rats: implications for Parkinson's disease.

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The lateral hypothalamus (LH) is emerging as a brain region of interest in Parkinson's disease (PD). Specifically, the LH neuron populations have been shown to degenerate in PD (1), thus undergoing neuron loss like the substantia nigra (SN) which is a defining feature of PD. Interestingly, the LH has strong anatomical projections to the SN (2), but the behavioural functions associated with this projection have not been determined. Thus, in this study we sought to determine whether the lateral hypothalamus-nigral projection is involved motor control, thereby implicated in parkinsonian like motor symptoms in rats. To do so, we used a functional disconnection procedure to prevent communication between the LH and SN by infusing a short-hairpin RNA virus and 6-hydroxydopamine toxin, respectively. Rats were then assessed on their motor abilities on a range of tasks typically used to model PD motor deficits. The results showed that disconnection of LH and SN does not disrupt motor coordination on the balance beam and rotarod, nor habit learning a form of automated behaviour. However, it significantly impacted locomotor activity in the open field test, and forelimb paw use in the cylinder test. Our findings suggest that the LH and SN work together to regulate motor behaviour in rats and suggest that the LH may be engaging with the basal ganglia circuitry via the SN. Furthermore, it adds to our understanding of theneurocircuitry that may contribute to the motor symptoms of Parkinson's disease and thus possible novel targets for treatments, such as LH neuropeptides.

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Applicant: Afraah Cassim
Supervisor: Dr Fatima Valdes Mora

Molecular and cellular characterization of the ezhip-expressing diffuse midline glioma subtype.

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Diffuse midline glioma (DMG) is a terminal pediatric brain cancer, primarily caused by the epigenetic histone mutation, H3K27M. In 2020, a novel DMG subtype was discovered for cases lacking H3K27M, which instead aberrantly expressed the Enhancer of zeste inhibitory protein (EZHIP) (1). Interestingly, EZHIP is a 'mimic' of H3K27M due to sequence similarity (2). We hypothesize that molecular similarities may concur with a common epigenetic therapy for DMG subtypes. We aim to establish the epigenetic profile of EZHIP-DMG in comparison to other DMG subtypes, and explore the EZHIP-specific effects to provide intuition on the best therapeutic strategy.

To compare epigenetic profiles of DMG subtypes, patient-derived DMG cell lines expressing EZHIP or H3K27M, H3-wildtype (without EZHIP) and normal controls were used. ATAC-sequencing (n=7) and ChIP sequencing (n=7) for 5 histone marks were performed. Next, we ectopically expressed EZHIP in 3 DMG cell lines lacking EZHIP/H3K27M, to evaluate the pro-oncogenic role of EZHIP.

Epigenetically, EZHIP-DMG is comparable to H3K27M-DMG, but with unique enhancers enriched for a distinct cell oligodendrocyte cell fate for EZHIP-DMG. In EZHIP-induced cell lines, reduced H3K27me3 levels compared to non-induced controls were detected, similar to the H3K27M onco-histone effect. Further, 2/3 EZHIP-induced cell lines decreased cellular metabolism and colony formation compared to controls.

This study suggests that EZHIP epigenetically mimics H3K27M but may not be necessary to maintain oncogenesis. Rather, EZHIP could be critical only during tumor initiation, suggesting that a therapeutic approach to target the epigenetic vulnerabilities would be better than targeting EZHIP directly.

Applicant: Afraah Cassim
Supervisor: Dr Fatima Valdes Mora

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Applicant: Jennifer Chen
Supervisor: Dr Chansavath Phetsouphanh

Harnessing immunopeptidomics to characterise cd8+ t cell mediated hiv-1 control

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Combination antiretroviral therapy (cART) is effective at suppressing human immunodeficiency virus (HIV) replication, but it is non-curative. Some individuals, termed controllers, can suppress HIV replication without cART (1). One parameter that is predictive of the course of disease progression is human leukocyte antigen (HLA) class I haplotypes which present antigen peptides to T cell receptors (TCR) on CD8+ T cells (2). No study has defined the HIV peptidome during treatment interruption, or characterised post-translational modifications on HIV peptides, shown to increase antigen binding affinity (3).

Our study uses mass spectrometry-based immunopeptidomics to identify shared HIV antigen peptides in post-treatment controllers and non-controllers from a primary HIV infection cohort (PULSE). Post-treatment controllers can maintain HIV RNA levels <5000 copies/mL after cART interruption for >6 months. Peptide-HLA complexes were eluted from HLA-matched peripheral blood mononuclear cells (PBMCs) and J-Lat 10.6 cells, and analysed by mass spectrometry. We also assessed the effect of cell stimulation on HLA class I expression. Two HIV peptides mapping to the Gag protein were identified from stimulated J-Lat 10.6 cells. No HIV peptides were identified from PBMCs. Anti-CD3/CD28 stimulation increased HLA class I expression, and downregulated CD4 expression in HIV+ PBMCs without increased p24 Gag expression. Our results suggest anti-CD3/CD28 stimulation can activate latent HIVand may increase HLA surface presentation of HIV peptides.

Future studies will compare stimulated and non-stimulated HIV+ PBMCs to assess whether cell stimulation alters the immunopeptidome. Identifying shared HIV antigen peptides across patients will allow the development of TCR-based therapies targeting HIV infected cells.

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Applicant: Dr Priscilla Costa
Supervisor: Dr Tertia Purves-Tyson

Impact of maternal care behaviour on anxiety-like behaviour during adolescence of prenatal immune-exposed male and female rat offspring.

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Maternal immune activation (MIA) is a preclinical model of dopamine dysregulation relevant to neurodevelopmental disorders such as schizophrenia. Prenatal immune challenge impacts brain development causing behavioural alterations in male and female offspring. It is unknown if MIA alters postnatal maternal care or how anxiety-like behaviours change across the adolescent neurodevelopmental period of male and female offspring. This study aims to investigate differences in maternal care behaviour of dams that received a viral mimic and those that did not in mid-late gestation, and to investigate the time course of presentation of anxiety-like measures in adolescent male and female MIA offspring.

Wistar rat dams received a tail vein injection of 4 mg/kg high molecular weight-poly(I:C) or saline on gestation day 15 or 19. Maternal care behaviour was recorded on 6 postnatal days (PND) prior to weaning on PND21. Offspring performed the elevated plus maze (EPM) test at pre-adolescence (PND34) and late-adolescence (PND54) and open field test on PND43.

Preliminary data suggests decreased active nursing and licking-grooming of pups and increased passive nursing by poly(I:C)-exposed dams. On PND34, male and female MIA offspring spent less time in the open arm compared to controls, whereas on PND54 MIA female offspring only increased open arm entries. PND43 open field test showed a decrease of centre entries by MIA male offspring compared to controls.

This suggests that maternal care of MIA offspring was reduced. There data suggests increased anxiety-like behaviour at pre-adolescence in male and female MIA offspring that persists in males.

Applicant: Dr Arlene D'Silva
Supervisor: Prof Michelle Farrar

Developing a biomarker platform for childhood onset motor neuron disease: the role of neurofilament in spinal muscular atrophy.

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Purpose: The introduction of disease modifying treatments, has transformed spinal muscular atrophy (SMA) from a lethal to a survivable condition. However, therapeutic decision making and measuring treatment effects remain clinically challenging due to the heterogenous presentation within the SMA phenotypic spectrum. The currently available prognostic marker survival motor neuron 2 (SMN2), has limitations in defining disease severity. This study evaluated the utility of NfL a biomarker of neuroaxonal damage, to define disease onset, prognosis and define treatment response in children with SMA.

Methods: A prospective cross-sectional and longitudinal cohort study, conducted between 1st December 2018 and 30th July 2024 studied children with SMA, from Sydney Children's Hospital Network. Cerebrospinal fluid and sera specimens were serially collected and NfL levels were measured using an immunoassay kit.

Results: Pretreatment NfL levels were elevated in 20 infants with ≤ 2 SMN2 copies (median 8057.5, SD 9949.5) compared to those with > 2 SMN2 copies (median 180.8, SD 291.9) (p=0.003). Significantly higher NfL levels were associated with longer disease duration and in symptomatic children. Antisense oligonucleotide therapy was associated with a 50% reduction in NfL levels over the first 60 days. Children with a large magnitude of NfL suppression with treatment were predicted to have higher motor function at 2y of age.

Conclusions: NfL can fill the clinical data gap to be used as an accessible biomarker of disease activity and progression. Pivotally, it has predictive value, which can be used to inform shared decision making and set therapeutic expectations for affected children.

Applicant: Sophie Debs
Supervisor: Dr Tertia Purves-Tyson

Sex-specific alterations in inflammatory-related transcripts in midbrain following maternal immune activation and estrogen receptor modulation.

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Objective: Maternal immune activation (MIA) results in dopamine dysregulation, produces behavioural abnormalities and midbrain neuroinflammatory changes in adult offspring, similar to schizophrenia [1-4]. The selective estrogen receptor modulator, raloxifene, can benefit those with schizophrenia possibly through modulating neuroinflammation [5-10]. We investigated how raloxifene alters microglia- and complement-related gene expression in the substantia nigra (SN) in female and male adult offspring of Poly(I:C) exposed dams.

Method: MIA was induced in Wistar dams (GD19) with high molecular weight Poly(I:C) [4mg/kg, tail vein, saline/poly(I:C) n=11/10]. Raloxifene (5mg/kg) was administered to offspring daily (cookie dough) between PND58-84 with four groups/sex: vehicle/placebo, vehicle/raloxifene, MIA/placebo, MIA/raloxifene (n=23-30/group/sex; half underwent behavioural tests). Offspring were euthanised (PND83-85), SN was dissected and cDNA was prepared. Microglia- (Iba1, Tmem119, Cd11b, Cd11c, Trem2, Fcrl2) and complement-related (C1qtnf6, C2, C3, C4a, C5) mRNAs were measured (RT-qPCR).

Key findings: Cd11c, Trem2 and C3 mRNAs were reduced in female MIA offspring, whereas C1qtnf6 mRNA was reduced in male MIA offspring. C5 mRNA was increased in female MIA offspring only. Raloxifene-treated male MIA offspring displayed increased Cd11c and decreased C4a and Tmem119 mRNAs. Fcrl2 mRNA was reduced in raloxifene-treated female MIA offspring only.

Conclusion: MIA reduces multiple microglial markers in adult female midbrain and induced complement pathway changes in one specific factor in each sex. Raloxifene induced transcriptional changes that were dependent on earlier exposure to MIA and targeted distinct microglia markers in males and females, being more apparent in male MIA offspring. Further work will determine how these findings relate to behavioural abnormalities and microglia morphology.

Applicant: Sophie Debs
Supervisor: Dr Tertia Purves-Tyson

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POSTER

Applicant: Derya Dik
Supervisor: Dr Claire Shepherd

Regional changes in the cerebrovasculature underlie disease progression in Parkinson's disease.

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Parkinson's disease (PD) is characterised by α-synuclein deposition in the form of Lewy pathology in the substantia nigra (SN). Cerebral hypoperfusion of the occipital cortex (OC) has been reported in PD and associates with visual hallucinations, although the cellular mechanism/s are not known. We investigated regional changes in the cerebrovasculature in PD cases. Specifically, we assessed the presence of string vessels (remnants of dysfunctional capillaries) and changes in pericytes in relation to disease progression.

We performed immunohistochemistry using an antibody against collagen IV to identify capillaries and string vessels on tissue sections from the SN, OC and hippocampus of PD cases (n=18) compared to controls (n=7). Pericytes were identified on the same section using a haemotoxylin and eosin counterstain and the percentage of string vessels and pericytes were quantified using ImageJ.

There was no difference in age at death or post-mortem delay between the groups ($p>0.05$). Increased string vessel proportions and decreased pericyte counts were observed in the PD cases compared to the controls ($p=<0.0001$). Pericytes on functional capillaries were also decreased in PD ($p=<0.0001$). Regional analysis showed the pericyte changes were localized to the SN and OC ($p=<0.0001$). String vessel formation was additionally correlated with disease duration in the OC ($p=<0.05$), confirming the vulnerability of this region in the disease process.

Our data demonstrates that regional changes in the cerebrovasculature are prominent in the SN and OC in PD. The relative sparing of the hippocampus, and the association between cerebrovascular changes and the disease duration suggest they may play a significant role in disease progression.

Applicant: Sumyukta Garikapati
Supervisor: Prof Caroline Ford

The development of organoids as accurate pre-clinical models of endometrial and ovarian cancers.

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Introduction: In Australia, endometrial and ovarian cancer are the most common and deadliest gynaecological cancers respectively1,2. Novel therapies are urgently needed for both cancers, however the lack of accurate pre-clinical models reflecting the molecular subtypes identified in endometrial cancer and the HRD (homologous recombination deficiency) status in ovarian cancer has hindered drug discovery and development.

Methods: Endometrial and ovarian cancer tissue and ascites samples are currently being collected from patients at the Royal Hospital for Women and Prince of Wales Private Hospital. Tumour cells are isolated from tissue and ascites, embedded in 70% Matrigel and cultured in defined medium to form organoids. Molecular subtyping of endometrial organoids (POLE ultra-mutated, microsatellite instability, copy number low and copy number high) and matched parental tissue will be performed via mismatch repair and p53 immunohistochemistry, and sequencing of POLE exonuclease domain mutations. HRD status of ovarian cancer patient tissue will be determined through BRCA mutation status and Illumina TSO500-HRD assays.

Results: Organoids from endometrial cancer tissue (n=8) and ovarian cancer tissue (n=6) and ascites (n=3) have successfully been established and passaged. Frozen tissue samples from -80oC storage have also been successfully recovered for organoid establishment. Validation of models is ongoing, along with testing of various hydrogels and media to optimise growth and conditions for drug testing.

Conclusion: Molecularly defined organoids represent a promising preclinical resource for drug screening in gynaecological cancers. This PhD looks into developing and optimising organoids for endometrial and ovarian cancers and evaluating a range of novel and repurposed pharmacological therapies.

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ORAL

Applicant: Andleeb Hanif
Supervisor: Dr Chantelle Ahlenstiel

siRNA-Ago1 Complex Mediated Nuclear Dynamics and Epigenetic Silencing of HIV in Human Cells.

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Background: RNA interference (RNAi) is integral to gene silencing, with transcriptional gene silencing (TGS) involving Argonaute 1 (Ago1) and promoter-targeted siRNA. Despite identification of nuclear Ago1-siRNA complexes in human cells, their trafficking dynamics, key Ago1 domains, and the impact on gene expression are not fully understood.

Methods: Leica 3D Thunder live-cell imaging was used to track AlexaFluor647-tagged siRNAs and Ago1-GFP in HIV-1NL4.3-infected HeLa T4 cells. RNA sequencing (RNA-seq) identified differentially expressed genes (DEGs) under Mock, PromA, and Ago1-PromA conditions, with GO enrichment analysis. Pearson correlation evaluated gene expression profiles, and Ago1 truncation mutants assessed the role of specific domains in TGS.

Results: Live-cell imaging revealed significant trafficking of Ago1-siPromA complexes to the perinuclear region (528.9 vesicles, $p<0.0001$), inner nuclear membrane (265 vesicles, $p<0.0001$), and nuclear cavity (264 vesicles, $p<0.0001$), compared to controls. A strong colocalization was observed between Ago1-GFP and siPromA-AF647 (mean PCC=0.2285, $p<0.0001$), unlike with scrambled siRNA (mean PCC=0.1625, $p<0.0001$). RNA-seq identified 1,349 DEGs ($p<0.05$, log2FC cutoffs), with significant upregulation of PPP1R15A, HMOX1, and SNAPC2, and downregulation of CHRM2 and HIST1H3G. GO analysis indicated downregulation of chromosomal segregation pathways and upregulation of RNA processing pathways in Ago1-siPromA cells. Additionally, HIV-1 gag transcripts were reduced by 70% ($p<0.0001$). Epigenetic analysis showed increased H3K9me3 (5-fold, $p<0.001$), H3K27me3 (2-fold, $p<0.001$), and Ago1 (6-fold, $p<0.0001$) in siPromA-treated cells. Mutants lacking Ago1's L1, PIWI, PAZ, and MID-terminal regions showed significant increases in Gag mRNA ($p<0.0001$), and decreased methylation marks in siPromA induced truncated Ago1 domains confirming their role in TGS.

Conclusion: The study demonstrates that specific Ago1 domains are essential for siRNA-induced epigenetic silencing of HIV. Significant alterations in gene expression and repressive epigenetic modifications underscore the potential of the Ago1-siPromA complex in the 'Block and Lock' strategy for achieving a functional HIV cure.

Applicant: Hannah Ellie Hartley
Supervisor: Dr Emmy Dolman

Targeting the interplay between replication stress (RS) induced DNA damage response (DDR) and epigenetics in children with high-risk neuroblastoma and sarcoma.

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Introduction: Disrupting pediatric cancer cell dependency on the replication stress (RS) response (1,2) by ATR inhibition (ATRi) is a promising strategy towards improving survival outcomes of children with neuroblastoma and sarcoma by inducing lethal DNA damage (3). However, combination therapies are needed to overcome monotherapy resistance. Epigenetic mechanisms are essential for DNA repair; therefore, combined ATRi and epigenetic targeting will exacerbate RS and DNA damage in RS-response dependent neuroblastoma and sarcoma.

Aim: Exploit the interplay between the DNA damage response (DDR) and epigenetics by combining ATR and epigenetic targeting as a personalized approach for children with high-risk neuroblastoma and sarcoma.

Methods: Gene Set Enrichment Analysis of transcriptomic (RNA-seq) data from patients enrolled onto the Australian ZERO Childhood Cancer program (4) was undertaken to uncover the DDR and epigenetic landscapes of neuroblastoma and sarcomas. ATRi or epigenetic targeted drugs were tested alone or in combination to establish ex vivo effects on cell viability using ZERO neuroblastoma and sarcoma samples and classical cell lines.

Results: Neuroblastoma and sarcoma subgroups are differentially enriched in genes associated with DDR and epigenetic pathways. Single-agent ATRi demonstrated highest efficacy in MYCN-amplified neuroblastoma and fusion positive sarcomas, whilst epigenetic targeting showed differential effects across all subtypes. Strong synergy was observed in neuroblastoma cell lines using combined ATRi and epigenetic targeted drugs which promote chromatin closing. For drugs promoting chromatin opening, additive effects were observed.

Conclusion: Combined ATRi with epigenetic drugs which promote chromatin closing is strongly synergistic in neuroblastoma cell lines. Further functional studies will determine effective combinations for validation in vivo using ZERO patient-derived models.

Applicant: Hannah Ellie Hartley
Supervisor: Dr Emmy Dolman

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Applicant: Sean Hood
Supervisor: Dr Saree Alnaghy

The first linac-mounted photon counting detector for image guided radiotherapy: planar image quality characterisation.

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Image guided radiotherapy (IGRT) with cone-beam computed tomography (CBCT) is limited by the sub-optimal soft-tissue contrast and spatial resolution of flat panel detectors (FPDs). Spectral CT with high resolution photon-counting detectors (PCDs) could improve tumour delineation by enhancing the soft-tissue contrast with energy weighting.

This study compares the planar image quality of the first linac-mounted PCD to the conventional energy-integrating FPD. A Medipix3RX PCD was integrated with kV imaging system on an Elekta linac. A fluoroscopy phantom was imaged to compare the limiting line pair resolution of both the PCD and FPD. Inserts containing different concentrations of calcium and iodine were imaged with both detectors and were optimally energy weighted using the PCD to compare the contrast in projections.

The limiting resolution observed on the fluoroscopy phantom was 2 lp/mm for the FPD and 5 lp/mm for the PCD. Energy weighted PCD images increased contrast in the projection of a 60 mg/cc calcium insert by a factor of 1.52 at 120 kV compared to the FPD, however contrast improvements for other concentrations and tube voltages were minimal. A dynamic imaging technique was implemented to address variations in the PCD response during acquisitions.

The initial planar image quality characterisation of the first linac-mounted PCD indicated improvements in the spatial resolution and energy-weighted contrast compared to the FPD, however variations in the PCD sensor response during acquisitions must be addressed to realize the full potential of linac-mounted spectral CBCT.

ORAL

Applicant: Dr Aaminah Khan
Supervisor: Dr Maria Tsoli

IInhibition of the Polyamine Pathway: A Novel Therapeutic Approach to Treat Aggressive Paediatric Medulloblastoma.

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Medulloblastoma is a highly malignant paediatric brain tumour comprising over 20% of CNS neoplasms (1). Polyamines regulate key cellular processes and are controlled by the MYC oncogene, which drives a large proportion of medulloblastoma (2,3). We previously demonstrated that the polyamine pathway is a rational therapeutic target in paediatric high-grade gliomas (4). This study aimed to assess the efficacy of dual polyamine pathway inhibition in MYC-driven medulloblastoma and its potential to enhance chemotherapy.

Gene expression of key polyamine regulators was increased in paediatric medulloblastoma samples from the ZERO platform compared with normal foetal brain. Dual targeting of the polyamine pathway - inhibiting polyamine synthesis and transport - resulted in potent, synergistic inhibition of medulloblastoma cell proliferation and clonogenicity. RNA-sequencing revealed significant downregulation of DNA-repair pathways following polyamine inhibition, sensitising combination-treated medulloblastoma cells to DNA-damaging chemotherapeutic SN-38. This led to complete eradication of medulloblastoma cells in cytotoxicity and clonogenic assays, with the most pronounced effect in MYC-amplified medulloblastoma. Flow cytometric analysis of Annexin V-stained cells revealed that combination treatment induced apoptosis, further significantly upregulated with SN-38. In an aggressive orthotopic model of MYC-amplified medulloblastoma, dual polyamine inhibition with chemotherapy significantly extended survival (****$p<0.0001$) compared to vehicle (median survival: 18 days) and single-agent treatments (median survival: 20-25 days), with median survival in the combination cohort not yet defined.

Our findings underscore the potential of polyamine pathway inhibition as a promising, clinically translatable strategy for sensitising aggressive paediatric medulloblastoma tumours to chemotherapy. This dual therapy is currently in a Phase 1B/2A clinical trial for solid tumours.

ORAL

Applicant: Dr Aaminah Khan
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ORAL

Applicant: Dr Amy Logan
Supervisor: Prof Maria Kavallaris

GD2 targeting of siRNA lipid nanoparticles improves efficacy in neuroblastoma

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High-risk neuroblastoma is an aggressive paediatric cancer with less than 50% 5-year survival, highlighting an urgent need for more effective therapies. Polo-like kinase 1 (PLK1) overexpression correlates with poor disease survival and is a promising target for gene silencing therapies using short-interfering RNA (siRNA). However efficient siRNA delivery to neuroblastoma is a clinical challenge. Targeting siRNA-lipid nanoparticle (siRNA-LNP) delivery vehicles to tumour specific antigens, such as disialoganglioside GD2, is a promising strategy to increase delivery of PLK1 siRNA (siPLK1) to neuroblastoma. Indeed, immunotherapy using GD2 monoclonal antibodies is used in high-risk neuroblastoma treatment, highlighting the clinical potential of GD2-targeted therapies. Herein, we investigated whether a bispecific antibody (BsAb) that recognises and binds to both GD2 and siRNA-LNP can enhance siRNA efficacy in neuroblastoma.

Formulated siPLK1-LNPs were complexed with GD2 BsAbs to create αGD2-siPLK1-LNPs as we previously described (1). GD2-expressing CHP-134 neuroblastoma cells were treated with αGD2-siPLK1-LNPs for 48 hours, and PLK1 mRNA expression measured by RT-PCR. PLK1 expression was reduced by 87% ($p=0.001$) compared to non-functional control siRNA (siCTRL)-LNP treatment. Next, we examined αGD2-siPLK1-LNP efficacy in 3D-bioprinted CHP-134 tumouroids (2,3), following 6 days of incubation with αGD2-siPLK1-LNPs, tumouroid viability was reduced by 50% ($p=0.0002$) compared to siCTRL-LNPs (AlamarBlue™ cytotoxicity assay). Finally, αGD2-siPLK1-LNP treatment was shown to decrease CHP-134 tumour growth by 36% ($p<0.05$) in a xenograft mouse model following 4 weeks of biweekly treatment compared to PBS control. Collectively, GD2 tumour targeting is a promising strategy to enhance PLK1 siRNA efficacy and offers a new treatment approach for neuroblastoma.

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POSTER

Applicant: Aqsa Mazhar
Supervisor: A/Prof Belamy Cheung

Identification and development of inhibitors to target ALYREF oncogenic protein in MYCN-driven neuroblastoma.

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Introduction: Neuroblastoma (NB) is a paediatric cancer responsible for approximately 15% of all childhood cancer deaths. MYCN amplification is a major driver of high-risk neuroblastoma. Previously, we identified an oncogenic protein, ALYREF binds to MYCN directly and drives neuroblastoma tumorigenesis through effects on USP3 and MYCN stability1 .Currently, no ALYREF inhibitors are available for clinical use. We have now identified candidates ALYREF inhibitor by screening NIH drug/compound libraries.

Objective: To identify ALREF specific inhibitor and develop effective combination therapy of ALYREF inhibitors with currently used chemotherapy drugs for the treatment of high-risk NB patients.

Methods and Results: Using Dox- inducible ALYREF knockdown in SK-N-BE(2)-C cell line, we performed screening of 4 sets of NIH drug/compound libraries, including approved oncology drugs (147 drugs), Mechanistic Set (811 compounds), Diversity Set (1584 compounds) and natural products set (390).. We have selected 98 small molecules heterocyclic compounds depending upon their cell viability difference, structural analysis and drug-like properties, that targets ALYREF oncogenic signals. Two of the compounds, designated as ALY2 and ALY9 has IC50 concentration 8.1μM and 1.5 μM respectively in SK-N-BE(2)-C cell line. ALY2 have shown good therapeutic window. Importantly, we showed that these two compounds decreased ALYREF, MYCN and USP3 protein expression, suggesting that they are potential inhibitors for ALYREF/MYCN/USP3 axis. The short-listed candidates will be further studied for their molecular mechanism, protein-drug binding and their efficacy in NB cell lines and animal models.

Conclusion: Our discovery of small molecule compounds, will lead to the development of the first-in-class novel ALYREF inhibitors for the treatment of MYCN-driven NB.

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Applicant: Gerado Mendez Victoriano
Supervisor: Prof Cynthia Shannon Weickert

Evidence for Diminished Dopamine Neurons in the Midbrains of Schizophrenia and Bipolar Disorder.

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Introduction: Neuroinflammation [1, 2], dopamine imbalance [3-6], and reduced brain volume [7-9] are core pathologies of schizophrenia and bipolar disorder (BD). We and others have found increased inflammatory cytokines [10-12] and reduced transcripts related to dopamine function in people with schizophrenia and BD [13-16], suggesting that a loss of dopaminergic cells/function is occurring.

Aim & Methods: With a new cohort (n=35/group), we used RT-qPCR and stereological quantification of tyrosine hydroxylase (TH)+ neurons to determine the levels of dopamine-related transcripts [(NURR1, TH, dopamine transporter (DAT), and dopamine receptor 2/isoforms (DRD2)], the volume of the substantia nigra (SN), and the number of dopamine neurons in people with schizophrenia and BD compared to controls.

Results: Compared to controls, we found that the mRNA levels of 5/6 dopamine-related transcripts were decreased in high-inflammation schizophrenia (all $p<0.05$); whereas only TH was decreased in high-inflammation BD ($p= 0.008$). SN area was reduced in high-inflammation BD compared to controls, and in high-inflammation schizophrenia compared to low-inflammation schizophrenia (all $p<0.05$). The high-inflammation schizophrenia group had increased TH+ cell densities compared to controls ($p<0.01$) and high-inflammation BD had decreased SN length/volume and TH+ cell counts as compared to controls and low-inflammation schizophrenia (all $p<0.05$).

Conclusions: Our results show the potential for diminished dopamine neuron function in chronic schizophrenia which is in contrast to previous notions of increased dopamine neurotransmission in schizophrenia. Furthermore, the loss of both substantia nigra volume and dopamine neuron number in BD means there may be a loss of dopamine neurons not previously documented in this population.

Applicant: Gerado Mendez Victoriano
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Applicant: Layla Neuhaus
Supervisor: Dr Adam Walker

NF-κB pathway gene expression is elevated in the midbrain of people with high-inflammation schizophrenia.

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Approximately 40% of people with schizophrenia exhibit neuroinflammation, but the underlying molecular causes remain unclear. Neuroinflammation in schizophrenia is characterised by pro-inflammatory cytokines, whose expression is regulated by the NF-κB pathway. However, no changes in this pathway have been reported in the schizophrenia midbrain. Since midbrain dopaminergic neurons are dysfunctional in schizophrenia and sensitive to inflammation (1, 2), it is crucial to determine how it is altered in high- vs. low-inflammation schizophrenia compared to controls.

Age-matched midbrain tissue from two post-mortem cohorts including healthy controls (n = 62) and people with schizophrenia (n = 62) was analysed using high-throughput qPCR for 17 major transcripts in the NF-κB pathway. Each case was previously classified as low- or high-inflammation based on cytokine and SERPINA3 mRNA levels (3, 4). mRNA expression was analysed by both diagnosis and inflammatory subtype.

By diagnosis, we found significantly increased mRNA expression levels in schizophrenia midbrain for four activating receptors, one inducing kinase, three NF-κB subunits, one pathway inhibitor. High-inflammation schizophrenia cases showed significant upregulation for these transcripts as well as for an additional activating receptor. Compared to low-inflammation controls, only one cytokine receptor was increased in the low-inflammation schizophrenia group.

These results suggest NF-κB activity is upregulated in high-inflammation schizophrenia, which may drive midbrain inflammation and thus contribute to dopaminergic dysfunction. Elevated IL1R1 levels in low-inflammation schizophrenia may indicate heightened susceptibility to inflammatory stimuli, with a potential inability to regulate inflammation effectively. This highlights NF-κB as an important regulatory pathway in inflammatory schizophrenia.

Applicant: Layla Neuhaus
Supervisor: Dr Adam Walker

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Applicant: John Paul Ong
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Using Small Molecule Chemical Probes to Target Novel Childhood Cancer Dependencies.

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Background: Despite advances in cancer treatment, children with cancer are still treated with drugs developed for adults, leading to suboptimal efficacy and increased adverse effects. Addressing the need for effective, safer treatments for children requires overcoming two major challenges: the lack of druggable targets in childhood cancer proteomes, and the scarcity of drugs developed for these targets.

Methods: This study integrates functional genomics [1] (which explores gene function through tools like RNA interference) with chemoproteomics [2] (which explores how small molecules interact with amino acid residues) to uncover cancer-relevant targets specific to childhood malignancies and identify promising small molecule chemical probes targeting these dependencies. This cancer-agnostic pipeline "ChemProTarget" is made accessible via a user-friendly RShiny application. The feasibility of this method is validated through proof-of-concept studies in neuroblastoma (NB), medulloblastoma (MB), and Ewing sarcoma (EWS).

Results: The "ChemProTarget" pipeline identifies 65, 70, and 100 cancer-specific targets in NB, MB, and EWS, respectively, along with selective chemical probes that bind to these proteins. Computational predictions indicate that these chemical probes possess characteristics desirable for drug development and clinical application. Initial cytotoxicity assays reveal promising IC50 values across NB, MB, and EWS cell lines. The anti-cancer and selective features of these chemical probes are further confirmed in biological validation experiments, demonstrating the pipeline's potential to effectively target cancer dependencies.

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Applicant: Dr Nasir Shah
Supervisor: Dr Jonathan Erlich

PRINTcision Medicine: a Re-useable, 3D-printed, Patient-Specific In Vitro Model of Arteriovenous Fistulas for Endothelial Cell Studies.

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3. School of Mechanical & Manufacturing Engineering, Faculty of Engineering, UNSW Sydney.
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Approximately 850 million people worldwide have CKD. For those with end stage kidney disease on haemodialysis, vascular access is best achieved using a native AVF. Though the molecular mechanisms underpinning AVF maturation are not well-established, endothelial cells appear to play a critical role in AVF maturation. Standard cell culture provides valuable insight into endothelial cell function, but the flat surface neglects the complex physiology of disturbed blood flow through intricate vessel geometries. We have developed and refined a macrofluidic model of AVFs using true patient geometries. Patient AVFs were imaged using a modified ultrasound machine, digitally segmented to generate AVF geometries, and 3D-printed using a water-soluble filament. Prints were cast in silicone and dissolved leaving an AVF-shaped cavity. Human dermal microvascular endothelial cells (HMEC-1) were cultured on the internal surface of these models. Custom components were fabricated to create a flow circuit using autoclave-sterilisable materials. Patient-specific AVF doppler recordings were used to program a peristaltic pump. Immunofluorescence with DAPI and Phalloidin confirmed the presence of a HMEC-1 monolayer on the luminal surface of the patent-specific AVF models. Using autoclave sterilised components, the flow circuit ran for 10 days without bacterial contamination. Pulsatile flow was successfully achieved using the programmable peristaltic pump. Our macrofluidic device overcomes many of the limitations of current cell culture techniques and animal models. By using patient-specific geometries, physiologic pulsatile flow, and running flow experiments over biologically relevant timelines, this novel in vitro model will facilitate investigation of endothelial cell biology under patient-relevant conditions.

Applicant: Dr Caitlin Ung
Supervisor: Dr Maria Tsoli

Breaking Through Barriers: Innovative Approaches to Enhance Drug Delivery in Diffuse Intrinsic Pontine Glioma (DIPG).

Caitlin Ung (1), Dannielle H. Upton (1, 2), Pooja Venkat (1), Ruby Pandher (1), Chelsea Mayoh (1), David S. Ziegler (1, 3), Maria Tsoli (1, 2).

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DIPG remains incurable largely because of the failure of active therapies to penetrate the intact blood-brain barrier (BBB). Our research indicates that DIPG cells tighten the BBB, thus further reducing permeability in the brainstem. We aimed to develop BBB modulators that can enhance drug permeability and efficacy. We utilised immunofluorescence imaging to examine structural differences and fluorescent-dye penetration in the BBB in vivo and found a significant decrease in dye infiltration between DIPG-engrafted and control mice; however, no structural differences were observed. We used single-cell RNA sequencing (scRNAseq) to examine the effect of DIPG cells on brain-endothelial pathways that regulate BBB integrity. ScRNAseq unveiled distinct transcriptomic changes in brainstem endothelial cells, including significant downregulation of inflammatory and apoptotic pathways, with upregulation of targetable drivers such as MCL-1. To overcome the tightened BBB, we tested MCL-1 inhibitors and SNGR-TNFα (tumour necrosis factor-targeting CD13) as potential modulators. These agents reduced transendothelial resistance and increased permeability in an in vitro BBB/DIPG model, and improved dextran permeability in vivo. An efficacy study with SNGR-TNFα and temsirolimus, resulted in extended mouse survival of 169 days post orthotopic injection, compared to vehicle and SNGR-TNFα alone (median survival 77 and 69 days, respectively), with 65% reduction in proliferative cells. Overall, this study revealed the direct impact of DIPG on endothelial cells at the transcriptional level, tightening the BBB and diminishing treatment efficacy. MCL-1 inhibitors and SNGR-TNFα show promise for BBB modulation, unlocking the potential to expand the range of therapies, and enhancing efficacy of currently available treatments.

Applicant: Mst Umme Laila Urmi
Supervisor: Prof Mark Wilcox

Antimicrobial peptides and their mimics can synergise to reduce the infection of enveloped viruses in cell culture.

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The ongoing fight against viral pandemics remains a pressing concern, underscoring the need for effective antiviral agents capable of tackling a broad spectrum of viruses. This study aimed to explore the synergistic potential of various antimicrobial peptides (AMPs) and their mimics against surrogate coronavirus (MHV-1) (1), HSV-1 (2), and H1N1 (3) through the checkerboard assay. The synergy between compounds was evaluated using the fractional inhibitory concentration index (FICI), where a FICI ≤ 0.5 indicates synergy, >0.5 to ≤1.0 denotes an additive effect, >1.0 to ≤4.0 signifies indifference, and >4 suggests antagonism (4). The peptides Melimine, Mel4, and mimics 610 and 758 were tested both individually and in combination. Mimic 610 displayed IC50 values of 2.18 µM against MHV-1, 35 µM against HSV-1, and 2.35 µM against H1N1, while mimic 758 showed IC50 values of 23.7 µM, 25 µM, and 12.34 µM, respectively. However, neither peptide was effective at concentrations up to 500 µM when tested alone. Notably, the combination of mimics 610 and 758 demonstrated strong synergy against MHV-1 (FICI 0.14) and H1N1 (FICI 0.5), while Mel4 combined with 610 showed synergy against HSV-1 (FICI 0.18). Additive effects were observed in other combinations, with significant reductions in IC50 values, suggesting that these peptide and mimic combinations hold promise as potential antiviral therapies. Further research is needed to elucidate their mechanisms and enhance their efficacy against viral infections.

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POSTER

Applicant: Elena Venuti
Supervisor: Dr Dominik Fröehlich

A mild HBSL disease model that facilitating AAV-mediated in-utero gene therapy.

Elena Venuti (1), Elizabeth Kalotay (1), Gary Housley (1), Matthias Klugmann (1), and Dominik Fröhlich (1).

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Hypomyelination with Brainstem and Spinal Cord Involvement and Leg Spasticity (HBSL) is a rare disease of the white brain matter caused by biallelic mutations in the DARS1 gene.

Symptoms typically appear between 3-36 months, leading to a progressive and potentially fatal disease. Due to its monogenic nature, gene therapy holds promise as a precision treatment option. We have developed AAV.PHPeB.hDARS1 vectors to deliver a codon-optimized, CpG-free version of the human DARS1 gene to the CNS, and these vectors have shown efficacy in acute HBSL mouse models.

Here, we introduce a novel HBSL mouse model carrying two DARS1 variants (Dars1A274V/D367Y, referred to as 'Massi'), first identified in the HBSL index patient, and investigate the potential of in-utero gene therapy in this model.

Massi mice display mild HBSL symptoms but have a high perinatal mortality rate, with only 40% surviving beyond weaning. This makes the model ideal for studying in-utero gene therapy.
We tested an UltraSound-guided, PerCutaneous, Foetal IntraPeritoneal (USPCFIP) injections as a minimally invasive delivery approach. Unexpectedly, delivery of our vector, AAV.PHP.eB-eGFP, resulted in a postnatal death rate of 75%, compared to 25% in saline controls. Vector copies were found only in 2/15 newborn brains, with eGFP mRNA expression in one.

In summary, Massi mice model moderate HBSL forms, enabling testing of disease-modifying therapies, including AAV-mediated in-utero gene delivery to address high perinatal mortality. While CNS transduction in foetuses can be achieved by USPCFIP delivery, challenges with target accuracy and potential eGFP toxicity highlight the need for refinement of this method.

Applicant: Yashna Walia
Supervisor: Dr Charles de Bock

Epigenetic determinants conferring glucocorticoid-resistance in paediatric acute lymphoblastic leukaemia.

Yashna Walia (1, 2), Dominik Beck (3), Duohui Jing (3, 4), Richard Lock (1, 2), Yizhou Huang (1, 2)* and Charles de Bock (1, 2)*.

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Glucocorticoid(GC)-based chemotherapy achieves >90% survival for paediatric acute lymphoblastic leukaemia (ALL). However, GC resistance remains a clinical challenge and barrier to cure. Here we sought to identify genomic regions differentially bound and regulated by the glucocorticoid receptor (GR) upon GC treatment in resistant vs. sensitive ALL. Candidate regulatory regions were identified using the following filtering criteria: (i) open chromatin regions in lymphocytes, (ii) presence of GR binding in GC-treated sensitive ALL, and (iii) active chromatin marked by histone modifications in GC-treated sensitive ALL. Through this pipeline, we identified 320 regions and selected the top 100 regions for in vivo functional validation in clinically relevant GC-sensitive ALL patient-derived xenografts (PDXs) using a customized dual gRNA library (n=4 gRNA pairs per region). Using an improved lentiviral transduction method, PDX cells were infected ex vivo with the CRISPR/gRNA library and then injected into immune-compromised NSG mice. Mice were treated with vehicle control or dexamethasone for 4 weeks using the standard preclinical dosing schedule. At pre-defined endpoint, relapse/resistant clones were isolated, DNA amplified and sequenced to identify the enriched gRNA. A novel intragenic region within the JAK1 gene, which encodes a tyrosine kinase involved in haematopoiesis, was among the top hits, implicating involvement of JAK/STAT signalling in GC response. This finding will be validated independently in additional PDX models. In summary, this is the first study using in vivo CRISPR/Cas9-mediated deletion to identify critical regulatory regions responsible for GC-resistance, providing valuable insights that will inform the development of novel therapeutic strategies to enhance GC-sensitivity.

POSTER

Applicant: Dr Gregory Walker
Supervisor: Prof William Rawlinson

Characterising the surge of RSV detections in Sydney following relaxation of COVID-19-related public health measures.

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Introduction: In 2022, a surge of RSV cases were detected globally, including in Sydney. To characterize factors underlying this epidemic, we performed clinical, genomic, and immunological analysis of RSV-infected infants presenting to Sydney Children's Hospital Randwick.

Methods: Whole genome sequences of RSV were generated from 264 RSV-infected infants and linked to case-matched clinical data from the 2022 Southern Hemisphere RSV season. We then performed immunological analysis of baseline RSV-specific humoral immunity in women of childbearing age before and throughout the COVID-19 pandemic.

Results: Clinical analysis found a high burden of disease across patients of all health backgrounds. Over half of RSV-related healthcare visits by infants resulted in hospitalization, and one quarter required high-flow respiratory support or a higher level of care. Viral phylogenetic analyses found the Sydney epidemic was driven by pre-existing viral lineages circulating globally since 2017, including those detected in recent USA outbreaks. There was no difference in baseline RSV-neutralizing antibody titres between 2020 and 2022.

Conclusion: Collectively, these findings suggest that neither the emergence of a novel RSV genotype or hypothesized immune debt was associated with the surge of RSV cases and hospitalisations in 2022. Further, epidemiological evidence has since suggested that surging RSV detections from 2022-onwards are tied to dramatic increases in testing rates locally, and overseas. Continued genomic and immunological surveillance is required to understand factors driving outbreaks of RSV globally, and to inform guidelines for the rollout and ongoing use of recently developed immunotherapeutics and vaccines.

POSTER

Applicant: Benjamin Wu
Supervisor: Prof Robert Gilchrist

Re-aggregation of young somatic cumulus cells with young nude oocytes partly restores soma-germline communication.

Benjamin Wu (1, 2), Kaushiki Kadam (2), Irene E. Sucquart (2), Lindsay E. Wu (1, 2), Robert B. Gilchrist (2).

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Age-related female infertility is associated with a decline in oocyte quality. Oocytes in the ovary are surrounded by somatic cumulus cells (CCs), forming the cumulus-oocyte complex (COC), which supports oocyte development by transporting important factors via CC transzonal projections (TZPs) to oocytes1. Whether the ageing of CCs influences oocyte ageing to drive declining oocyte quality and fertility with age is poorly understood. We aim to develop an age-mismatched "heterochronic COC" experimental paradigm using young CCs and old oocytes. As proof of concept, we used age-matched young oocytes and young CCs taken from hyperstimulated 5-8 week old Swisstac mice. These cells were subjected to a reaggregation protocol including culture for 24 hrs in vitro. Immunocytochemical assessments for TZP counts were performed to evaluate re-establishment of CC-oocyte communication. After re-aggregation, CCs create new TZPs to previously denuded oocytes that lack CCs, partly restoring TZP numbers vs denuded ($p=0.0354$) and nude ($p<0.0001$) oocytes, though TZP numbers do not reach that of intact COC controls ($p=0.0005$). Oocyte survival after 48hrs in vitro culture was greater in re-aggregated COCs compared to nude oocytes ($p=0.0134$), and similar to young COC controls. The ability of re-aggregated COCs to prevent precocious maturation to meiosis II, important for oocyte development within 'pre-in vitro maturation' culture systems, was similar to intact COCs and significantly greater than denuded oocytes ($p<0.0006$). Overall, re-aggregation improved multiple aspects of denuded oocyte function. This pilot study with young age-matched cells provides proof of concept for subsequent investigations into heterochronic re-aggregation.

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Applicant: Joshua Zhu
Supervisor: Dr Jean Bertoldo

Targeted drug discovery in paediatric diffuse midline glioma using chemoproteomics.

J. Zhu, M. Tsoli, D.S. Ziegler, J. Bertoldo.

Chemical Biology and Target-Based Drug Design/Brain Tumours, CCI.

This project focuses on developing cysteine-targeting covalent drugs for paediatric diffuse midline gliomas (DMGs), an incurable cancer with a median survival of < 1 year (1). We aim to discover novel drug targets and targeted covalent compounds using chemoproteomics; validate potential therapeutic targets and drug candidates; and conduct preclinical evaluations of the most promising drug candidates.

Preliminary target engagement assays, activity-based protein profiling (ABPP) assays, and molecular docking simulations identified JNSY1, a cysteine-reactive compound, as a potential modulator of histone H3.1. The H3K27M mutation in histone H3.1 or H3.3 drives over 80% of diffuse midline gliomas (DMGs) (2), but until now has been considered 'undruggable'. In CellTiter-Glo cell viability assays and IncuCyte spheroid proliferation assays, JNSY1 potently inhibited cell proliferation in a range of aggressive DMG cell cultures, particularly in H3.1K27M cell lines compared to wild-type and H3.3K27M cell lines. Western blotting revealed increased γH2AX and cleaved PARP-1, indicating DNA damage and apoptosis. LC-MS proteomic analysis showed JNSY1 downregulated histone-binding partners, chromatin remodelers, E2F targets, including TIMELESS and PRIM2, and DNA repair proteins such as BRAT1 and POLD1, with enrichment of pathways managing reactive oxygen species and UV damage response, suggesting a DNA damage-related mechanism of action.

These findings suggest that JNSY1 is a first-in-class molecule that targets the Achilles' heel of DMG – the H3K27M mutation. JNSY1 disrupts histone H3.1 function, induces DNA damage, and triggers apoptosis. The mechanisms potentially include epigenetic reprogramming, cell cycle inhibition, and DNA repair repression. Further ABPP experiments are in progress to confirm additional JNSY1 targets.

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Division:

Case Presentations

ORAL

Applicant: Dr Michael Connors
Supervisor: Dr Adith Mohan

Conversations with a Dead Man: Cotard Syndrome and its Underpinnings.

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Cotard syndrome is a very rare condition that involves the delusional belief that one is dead. The condition can be highly distressing and debilitating. It also poses fundamental questions for neuropsychiatry in terms of how such beliefs can arise and persist despite incontrovertible contradictory evidence. A wide range of theories have been offered over the last century. These include proposals that dissociation, deficits in autonomic responsiveness, or impaired facial processing may explain the content of the belief. Another influential theory holds that a second, additional factor – a bias against disconfirmatory evidence – is needed to explain why the belief is not rejected. Empirical data to test these accounts, however, has been lacking. We report the case of an individual with Cotard syndrome. The patient was able to describe their experiences in detail and completed a comprehensive neuropsychiatric assessment and neuropsychological battery, which assessed factors postulated in different theories. The patient also had neuroimaging completed, with previous scans available for comparison. Notably, while the patient reported dissociation and had specific cognitive deficits in memory and executive function, there was no evidence of impaired face processing or a bias against disconfirmatory evidence. The case thus challenges existing theories and suggests specific neuropsychological deficits responsible. The case constitutes the most detailed examination of Cotard syndrome so far and highlights greater complexity than previously assumed, with broader implications for understanding delusions and other nonpathological beliefs.

Applicant: Dr Maria Lean
Supervisor: Prof Jeffrey Post

Always Wash Your Greens: A case of Eosinophilic Meningoencephalitis Caused by Angiostrongylus cantonensis in Sydney.

Angiostrongylus cantonensis (rat lungworm) is a parasite that is increasingly affecting Australian native wildlife populations through the ingestion of infected slugs and snails.1 Humans can also become incidental hosts, often by consuming poorly washed green vegetables contaminated with the slime of infected slugs or snails.2

This case involves a 70-year-old Sydney woman who developed eosinophilic meningoencephalitis secondary to Angiostrongylus cantonensis. The otherwise well woman presented to the emergency department with an acute and severe onset of abdominal and lower limb pain. Despite low inflammatory markers, she was admitted under the surgical team for further investigation; these investigations did not identify a surgical cause for her pain. The patient was subsequently discharged but returned to the hospital the next day with symptoms of meningoencephalitis, including severe headaches and altered cognition. The patient was managed with empiric antimicrobials. Initial investigations, including a lumbar puncture and brain MRI, did not reveal the cause of the meningoencephalitis. A repeat lumbar puncture identified significant cerebrospinal fluid (CSF) eosinophilia. Further history-taking revealed the patient's long-term consumption of homegrown lettuce, providing a critical epidemiological clue for a parasitic infection caused by Angiostrongylus cantonensis. The diagnosis was confirmed with serological and PCR tests. The patient was treated with a short course of prednisone, resulting in a favourable clinical outcome. The case highlights the need for increased awareness of angiostrongyliasis and the caution when preparing green vegetables grown in the Sydney region for consumption.

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Applicant: Dr Caroline Lee
Supervisor: Dr Kristen Overton

Travel or transplant? A case of malaria in a renal transplant recipient.

Caroline Lee, Department of Infectious Diseases, POWH.
Kristen Overton, Department of Infectious Diseases, POWH.
Grant Luxton, Department of Nephrology, POWH.

Malaria is a globally important infection with changing patterns due to travel, migration, and globalisation. Malaria is a recognised cause of post transplantation infection. It can occur due to de novo infection, reactivation of dormant or asymptomatic infection, or as donor derived transmission through allografts or blood products (ref needed). Transplant transmitted malaria (TTM), caused by allograft infection from donor to recipient, is a rare entity with a handful of published cases in the literature, including in kidney, liver and heart transplant recipients (1, 2). TTM post renal transplantation can present with fevers, cytopenias, and is a cause of acute kidney injury (AKI). Diagnosis is often delayed by days to weeks. We describe a case of successfully treated TTM with Plasmodium ovale in a renal transplant recipient and discuss review previous literature of TTM amongst renal transplant recipients.

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Applicant: Dr Christian Pappas
Supervisor: Dr Parth Shah

From vitreous to ventricles: serial imaging of intracranial silicone oil migration.

C. Pappas, A. Waldie and P. Shah.
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Intravitreal silicone oil endotamponade is indispensable to modern vitreoretinal practice, having been used to manage complex retinal detachment for over 60 years. While long-term placement of silicone oil is associated with several recognised intraocular complications, intracranial migration is exceedingly rare and thought to be associated with suboptimal post-operative intraocular pressure control and anatomical optic disc abnormalities, producing variable symptomatology. We present a 52-year-old male with advanced right eye proliferative diabetic retinopathy managed by ipsilateral placement of 1000 mPa.s viscosity Oxane ® 1300 Silicone Oil (Bausch & Lomb Inc.), presenting with sudden loss of consciousness 31 months post-operatively. Serial neuroimaging over 53 post-operative months demonstrated intracranial silicone oil migration with unilateral optic nerve, optic chiasm, and bilateral mobile intraventricular deposits with progressive parenchymal atrophy. We analyse features on serial computed tomography and magnetic resonance neuroimaging, review possible migration pathways between the cerebrospinal fluid-filled spaces of the optic nerve and brain, and reiterate the necessity for vigilance towards potentially significant neurological sequelae.

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Division:
Clinical

Applicant: Dr Lakshmi Balaji
Supervisor: Prof Michelle Farrar

Low or no developmental risk and protective factors in emerging spinal muscular atrophy phenotypes in era of new diagnostic and treatment capabilities: a cross sectional real-world biopsychosocial study.

Lakshmi Balaji, Didu Kariyawasam, Michelle Farrar
On behalf of SMA study group

Background: New clinical diagnostic and treatment pathways have provided the opportunity for children with spinal muscular atrophy (SMA) to access novel, life-saving treatments. While these children are surviving and thriving, new phenotypes are emerging. Feedback from people living with SMA recommends adopting a strengths-based approach to assessing and supporting neurodevelopment.

Aims: To determine the proportion of children with SMA at no, or low developmental risk and identify associated protective factors within a biopsychosocial framework.

Methods: In this quaternary paediatric hospital cross-sectional study, parents/caregivers of children with SMA aged 1-66 months completed questionnaires. Parent-reported development of children was assessed using the Ages and Stages Questionnaires® Third Edition (ASQ-3™). Risk of autism spectrum disorder, parental distress, sociodemographics and clinical characteristics were assessed using M-CHAT-R, Kessler-10, and custom-designed questionnaires. Reflecting community values, binomial regression was used to identify factors associated with development on track (ASQ>-2SD).

Results: Thirty-nine children with SMA participated (response-rate 92%, 53% girls). Across the five ASQ domains, 41% had scores >2SD, associated with SMN≥3, 13 (81%) of which were diagnosed through newborn screening and treated within the first month of birth. No/low risk of autism was identified in 37/39 (91.6%) children. Parental affluence and employment were positively associated with better developmental outcomes, as were metropolitan residence, parental affluence and employment. Detailed statistical analyses will be presented.

Conclusions: There is variation in developmental outcomes in children with SMA, associated with biological and psychosocial factors. We recommend routine assessment of developmental progress. Consolidation of protective factors and early intervention can enhance developmental outcomes through tailored support.

POSTER

Applicant: Ana Rita Barreiros
Supervisor: Prof Colleen Loo

Understanding the effects of demographic, clinical and treatment factors on recovery of orientation after ECT: A CARE Network Study

Barreiros, A. R. (1, 2, 3, 4), Tuneu, C. N. (1, 2), Waite, S. (5), Sarma, S. (6, 7), Branjerdporn, G. (6, 7, 8), Zeng, C. (1, 2), Dong, V. (1, 2), Loo, C. (1, 2), Martin, D.M. (1, 2).

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Background: Electroconvulsive therapy (ECT) is an effective treatment for various psychiatric disorders, but it can lead to cognitive adverse effects, including transient disorientation and retrograde amnesia (1). Longer recovery of orientation after ECT has been associated with greater retrograde amnesia at post treatment (2). Clinical monitoring of orientation recovery during the acute treatment course is therefore important, so that treatment can potentially be modified if needed. This study investigated the impact of age and other potential clinical and treatment factors on the recovery of orientation after ECT.

Methods: Data from 555 ECT patients were analysed from two different clinical sites from the CARE Network. The main outcome variable in this study was recovery of orientation on the 10-Item Orientation Questionnaire (3) assessed after every ECT treatment. A linear mixed-effects repeated measures model was used to predict the recovery of orientation across the ECT course based on multiple demographic, clinical and treatment factors.

Results: The type of ECT demonstrated a significant effect, with individuals on right unilateral (RUL) ECT exhibiting lower orientation scores compared to those receiving RUL ultrabrief or bifrontal ECT. Furthermore, baseline cognitive impairment, age and gender significantly influenced orientation scores, with individuals with moderate cognitive impairment, older age groups and female patients exhibiting the lowest scores.

Conclusions: This large-scale retrospective study found that recovery of orientation after ECT was affected by multiple demographic and treatment factors. These findings have relevance for improving clinical monitoring of orientation recovery after ECT and patient outcomes from treatment.

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Applicant: Lizel-Antoinette Bertie
Supervisor: Prof Jennifer Hudson

Predicting remission following CBT for childhood anxiety disorders: A machine learning approach.

Lizel-Antoinette Bertie, (1, 2), Juan C Quiroz (3, 4), Shlomo Berkovsky (4), Kristian Arendt (5), Susan Bögels (6), Jonathan R.I. Coleman (7), Peter Cooper (8) , Cathy Creswell (8, 9), Thalia C. Eley (7), Catharina Hartman (10), Krister Fjermestadt (11), Tina In-Albon (12), Kristen Lavallee (13), Kathryn J. Lester (14), Heidi J. Lyneham (17), Carla E. Marin15, Anna McKinnon (17), Lauren F. McLellan (17), Richard Meiser-Stedman (16), Maaike Nauta (10), Ronald M. Rapee (17), Silvia Schneider (18), Carolyn Schniering (17), Wendy K. Silverman (15), Mikael Thastum (5), Kerstin Thirlwall (8), Polly Waite (8, 9), Gro Janne Wergeland (19), Viviana Wuthrich (17), Jennifer L Hudson (1, 2).

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Applicant: Lizel-Antoinette Bertie
Supervisor: Prof Jennifer Hudson

Predicting remission following CBT for childhood anxiety disorders: A machine learning approach.

Background: The identification of predictors of treatment response is crucial for improving treatment outcome for children with anxiety disorders. Machine learning methods provide opportunities to identify combinations of factors that contribute to risk prediction models.

Methods: A machine learning approach was applied to predict anxiety disorder remission in a large sample of 2114 anxious youth (5-18 years). Potential predictors included demographic, clinical, parental and treatment variables with data obtained pre-treatment, post-treatment, and at least one follow-up.

Results: All machine learning models performed similarly for remission outcomes, with AUC between 0.67-0.69. There was significant alignment between the factors that contributed to the models predicting two target outcomes: remission of all anxiety disorders and the primary anxiety disorder. Children who were older, had multiple anxiety disorders, comorbid depression, comorbid externalising disorders, received group treatment and therapy delivered by a more experienced therapist, and who had a parent with higher anxiety and depression symptoms, were more likely than other children to still meet criteria for anxiety disorders at the completion of therapy. In both models, the absence of a social anxiety disorder and being treated by a therapist with less experience contributed to the model predicting a higher likelihood of remission.

Conclusions: These findings underscore the utility of prediction models that may indicate which children are more likely to remit or are more at risk of non-remission following CBT for childhood anxiety.

POSTER

Applicant: Dr Hilary Cahill
Supervisor: A/Prof Adam Nelson

A single institute experience of secondary malignancies in survivors of childhood cancer: a retrospective review.

Background: Over the past 60 years, treatment and supportive care of children with cancer has improved, increasing the number of survivors living to adulthood. Treatment regimens have been modified to improve outcomes and reduce long-term sequelae. Secondary malignancies (SMs) contribute to high morbidity and mortality and the estimated 25-year cumulative incidence in one study of nearly 50,000 survivors was 5.4% (1).

Objectives: We describe characteristics of patients known to a single institution's long-term follow up (LTFU) service since 1968 who have known SMs following treatment for childhood cancer.

Method: We performed a retrospective review of a database of patients treated by our institution and followed up in the LTFU clinic. Further information regarding treatment and type of SM was collected from LTFU service health summaries, where patients had self-reported SMs. Patients treated by the service with chemotherapy or radiation with a non-malignant diagnosis were also included.

Findings/ Results: There were 95 patients with reported SMs (59% female, 41% male). The majority were diagnosed between 1-4years of age, with 28% of patients diagnosed with acute lymphoblastic leukaemia. 81% were diagnosed before the year 2000. The most common reported SM was thyroid cancer (18%), followed by sarcoma (11%) and meningioma (10%). 31/95 (33%) patients have reported a third malignancy. 64/95 (67%) of patients had received radiation, with 37 having received TBI or craniospinal irradiation.

Conclusion: SMs contribute to significant health burden in survivors of childhood cancer. In our population thyroid cancer is the most common SM, which is known to be associated with radiation exposure before 18years. Analysis of data is ongoing.

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Applicant: Dr Michael Connors
Supervisor: Prof Henry Brodaty

Distinguishing Apathy and Depression in Dementia: A Longitudinal Study

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Objectives: Apathy is a common symptom in dementia, though can be difficult to distinguish from depression due to shared features and frequent co-occurrence. As such, a significant limitation of much previous research on apathy is the failure to control for depression. The current study sought to address this by examining the trajectory and clinical correlates of apathy after controlling for depression.

Methods: Seven-hundred-and-seventy-nine patients with dementia were recruited from nine memory clinics around Australia. Measures of dementia severity, cognition, functional ability, neuropsychiatric symptoms, caregiver burden, and medication use were completed at baseline and at regular intervals over a three year period. Driving and institutionalisation data were obtained throughout the study. Mortality data were obtained from state registries eight years after baseline.

Results: Of 662 patients with completed measures of neuropsychiatric symptoms, 342 (51.7%) had apathy and 332 (50.2%) had depression at baseline, while 212 (32.0%) had both. Whereas apathy increased over time, depression remained relatively stable. Apathy, but not depression, was associated with greater dementia severity, poorer cognition and function, driving cessation, and mortality. Both apathy and depression were associated with greater neuropsychiatric symptoms, psychosis, caregiver burden, and institutionalisation.

Conclusions: Apathy increases over the course of dementia and is associated with worse clinical outcomes independent of depression. Distinguishing apathy and depression appears important given their different implications for prognosis and management.

ORAL

Applicant: Dr Roshan Dhanapalaratnam
Supervisor: Prof Arun Krishnan

Novel Diagnostic Markers and Therapeutic Strategies for Diabetic Peripheral Neuropathy

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Randwick Clinical Campus, UNSW Medicine.

Type 2 diabetes mellitus (T2DM) affects over half a billion people worldwide, and diabetic peripheral neuropathy (DPN) is a disabling condition, affecting approximately 60% of those with T2DM, causing a limb to be amputated worldwide every 30 seconds. DPN is currently considered to be irreversible and progressive, with no definitive treatment.

For the first time a validation study confirmed peripheral nerve ultrasound as a structural biomarker in DPN in 156 participants with type 2 diabetes with progressively increasing tibial nerve cross-sectional area corresponding with an increasing grade of neuropathy severity (1). Axonal excitability studies undertaken in 178 participants then provided novel insight into DPN pathogenesis with node of Ranvier Na+ channel dysfunction implicated in early DPN, followed by progressive upregulation of juxtaparanodal Kv1.1 channels characterising more advanced DPN severity (2).

In a metformin intervention study, superior DPN measures were observed in metformin-treated participants with clinical, morphological and neurophysiological measures (3). Mechanistic studies with axonal excitability suggested that metformin directly improved nodal Na+ and K+ ion channel function in peripheral nerves. A prospective glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy study was the first worldwide to demonstrate reversal of DPN with clinical neuropathy scores, nerve conduction studies and peripheral nerve ultrasound (4). Axonal excitability studies then demonstrated that GLP1-RA improved DPN outcomes by reversing Na+/K+−ATPase pump dysfunction, and mathematical modelling supported this as a likely explanation for the observed improvements in neuropathy outcomes.

These are the first intervention studies to demonstrate reversal of nerve dysfunction in T2DM with novel diagnostic biomarkers.

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POSTER

Applicant: Dr Eric Fong
Supervisor: A/Prof Stephen Thompson

Long term radiotherapy outcomes of early-stage primary gastric diffuse large B-cell lymphoma: a multi-centre retrospective study.

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Purpose: In primary gastric diffuse large B cell lymphoma (PG-DLBCL), the role of radiotherapy (RT) is not well established, and outcome data is lacking (1). We assessed the long-term outcomes of patients who received RT as part of curative-intent treatment in early-stage PG-DLBCL.

Methods: A retrospective, multi-centre study of patients with PG-DLBCL who had radiotherapy between 01/03/1999 and 29/05/2020 was performed. Eligible patients were ≥18 years old, received radiation as part of combined modality therapy, and had early-stage (Lugano stage I-II) disease. Time-to-event outcomes were calculated from day one of treatment. Toxicities were extracted from medical charts per CTCAE v4.0.

Results: Fourteen eligible patients met criteria. Median age was 75 years (range 48–84). Ten (71%) had stage I and four (29%) stage II disease. IPI at diagnosis was zero in 14%, one in 57% and two in 29%. All were treated with chemotherapy prior to RT, with most (79%) treated with R-CHOP. Five (33.3%) were H pylori positive and received eradication prior to treatment. Median prescribed RT dose was 30 Gy in 17 fractions. At a median 56 months follow-up (IQR 29-70), estimated five-year local relapse free survival, distant relapse free survival, and progression free survival were 100%, 93%, and 93% respectively. Five-year overall survival was 93%. There were no acute grade 3-5 radiotherapy toxicities. There was one grade 3 late toxicity. No treatment-related deaths occurred.

Conclusion: Combined modality treatment with radiotherapy for early-stage PG-DLBCL has excellent local control and survival outcomes. Treatment was well tolerated with low toxicity.

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Applicant: Dr Deanna Francis
Supervisor: Prof Jennifer Hudson

Reading worriers: An evaluation of the first digital anxiety program for children with reading difficulties.

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Background: One in three children with reading difficulties experience elevated anxiety. While several literacy interventions exist to support students reading skills, there are no evidence-based anxiety interventions to support children struggling with reading and anxiety. This is an alarming clinical gap in the field that our research team is addressing. Available anxiety interventions also place high demands on reading skills for children and their parents. As a result, children with anxiety and reading difficulties miss out on effective treatment. To address this gap, we have co-designed a digital cognitive behavioural therapy program for children with reading difficulties.

Methods: This program is currently under evaluation in a randomized controlled trial (N = 86). Participants include children aged 7 to 12 years of age with reading difficulties and elevated anxiety. Children are randomly assigned to receive the 12-week program immediately or after a 12-week delay. Primary outcome includes remission of primary anxiety disorder, with secondary outcomes including remission of additional anxiety disorders, anxiety symptoms, and reading accuracy and fluency.

Results: The trial is currently underway (N = 57). This presentation will provide an overview of our co-designed anxiety program for children with reading difficulties (e.g., co-design process and program materials), as well as preliminary results on the efficacy of the program to reduce anxiety and improve reading outcomes.

Conclusion: Evidence-based programs are urgently needed to support children with reading difficulties and anxiety. Our program and evaluation provide the first step to address the burgeoning rates of anxiety for children with reading difficulties.

Applicant: Harrison Hansford
Supervisor: Dr Matthew Jones

Decompression surgery with or without fusion in subgroups with degenerative lumbar spondylolisthesis: a target trial emulation.

Harrison Hansford (1, 2), Margreth Grotle (3, 4), Bjørnar Berg (3), Tore Solberg (5, 6), Christian Hellum (7), Ivar Austevoll (8), Tor Ingebrigtsen (9, 10), Issa Dahabreh (11, 12, 13), Hopin Lee (2, 14, 15), Matthew Jones (1, 2), James McAuley (1, 2), Aidan Cashin (1, 2).

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Applicant: Harrison Hansford
Supervisor: Dr Matthew Jones

Decompression surgery with or without fusion in subgroups with degenerative lumbar spondylolisthesis: a target trial emulation.

Lumbar spinal surgery is indicated for patients with degenerative spondylolisthesis (DS) who have minimal improvement from non-surgical care. Adding fusion to decompression has been shown to have no benefit beyond decompression in two randomised trials but comes with increased costs and complications.[1,2] However, it is suggested some subgroups benefit from fusion.[3][4] Using observational data from the Norwegian Spine Surgery Register (NORSpine) we emulated the NORDSTEN trial[2] to compare decompression to fusion surgery. We included patients aged 18-80 with a diagnosis of DS and back or leg pain for ≥3months. We estimated the between-group mean difference on the Oswestry Disability Index and reoperation rate at 1-year post surgery, and risk of peri-operative complications. Subgroups investigated were back pain intensity, BMI, sex, age, ASA score and smoking status. We adjusted for confounding using inverse probability of treatment weighting. From 2007-2021, we included 1409 patients who received decompression and 770 who received fusion surgery. Our primary outcome had estimate agreement with the index trial[2] (trial=0.7/100 95%CI -2.8-4.3; emulation=1.8/100, 0.1-3.5), favouring fusion surgery. There was no additional risk of reoperation (RR=1.2, 0.89-1.84) and lower risk of complications (RR=0.62, 0.41-0.95) from decompression. The subgroup with back pain >6/10 had a 3.2/100 (0.6-6) greater treatment effect from fusion than those with lower pain. All other subgroups were not significantly different. There may be a small benefit of adding fusion to decompression, with this effect larger in people with higher back pain intensity. However, fusion comes with increased risk of adverse events and benefits are small.

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Applicant: Seng Hansun
Supervisor: Prof Guy Marks

Two-tier ensemble transfer learning method for pulmonary tuberculosis detection based on chest radiograph.

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Deep Learning (DL) is now extensively used to create Artificial Intelligence (AI) tools for interpreting image data from chest radiographs (CXR). Transfer Learning (TL) is a promising approach to address the substantial data volume demands inherent in DL (1). This methodology leverages the knowledge acquired by a model that has been pre-trained (PTM) on a comprehensive general-purpose dataset and applies it to a new domain with a smaller, domain-specific task dataset. In this context, we introduce a two-tier ensemble TL method tailored for the detection of pulmonary tuberculosis (PTB) using CXR. In the first tier of our proposed method, we conducted experiments with an ensemble of classifiers trained on features extracted from various intermediate layers of a PTM (2). Subsequently, models built from each intermediate layer were amalgamated to obtain the final classification outcome in the second tier. We assessed the accuracy of our approach using two publicly accessible TB radiology datasets: the Montgomery County (MC, n=138) and Shenzhen (SZ, n=662). We used four variants of EfficientNets (B0, B1, B2, and B3) as classifiers. To gauge the performance, we measured accuracy using 5-fold cross-validation. Compared to the conventional direct usage of a PTM with various EfficientNets' architectures, our proposed two-tier ensemble TL method consistently demonstrates superior accuracy results across both the MC (B0: 92.03%, B1: 92.80%, B2: 92.83%, B3: 93.54%) and SZ (B0: 91.39%, B1: 91.39%, B2: 91.54%, B3: 92.45%). This novel two-tier ensemble TL method improves the accuracy of AI interpretation of CXRs for the detection of PTB.

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Applicant: Fleur Harrison
Supervisor: Prof Henry Brodaty

Apathy and fatigue, but not depression, associated with inflammatory biomarkers in older adults.

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Major depressive disorder is highly heterogeneous. Deconstructing depression into individual symptoms or clusters may provide insight into its biological dysregulation, including systemic inflammation (1). Symptoms of apathy and fatigue, in particular, may have strong links with inflammation (2). However, this has received little attention. This research evaluates the hypothesis that inflammatory biomarkers will be differentially associated with apathy, depression and fatigue in older adults. Data from a population-based cohort of 1,037 older adults included apathy and depression measures from the Geriatric Depression Scale, and fatigue from Assessment of Quality of Life-6D. Biomarkers from peripheral blood collection included C-reactive protein (CRP) and interleukin-6. Logistic regressions investigated levels of biomarkers as predictors of apathy, depression and fatigue separately. Analyses were unadjusted, then adjusted for demographics, cognition, health conditions, medications and BMI.

Interleukin-6 was associated with apathy, depression and fatigue in unadjusted models. Apathy remained significantly associated after covariate adjustment (OR 1.45, 95% CI 1.02-2.06, p=.035), but associations for depression and fatigue were attenuated. CRP was associated with apathy and fatigue when unadjusted, however only the latter remained significant after covariate adjustment (OR 1.35, 95% CI 1.09-1.67, p=.005). In conclusion, apathy and fatigue were differentially linked with inflammatory biomarkers in older persons, whereas previous associations with depression were not replicated. Findings are consistent with sickness behaviour theory (3), confirm the relevance of fatigue, and provide novel insight into apathy, as symptoms which map to inflammation at population level. This may help inform the development of novel treatments to target these prevalent and debilitating symptoms (4).

Applicant: Fleur Harrison
Supervisor: Prof Henry Brodaty

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POSTER

Applicant: Cameron Hicks
Supervisor: Prof Stephen Lord

Two simple modifications to the World Falls Guidelines Algorithm improves its ability to stratify older people into low, intermediate and high fall risk groups

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We conducted a secondary analysis of a cohort study to examine the World Falls Guidelines algorithm's (1) ability to stratify older people into sizable fall risk groups or whether minor modifications were necessary to achieve this.

Six hundred and ninety three community living people aged 70 – 90 years (52.4% women) were stratified into low, intermediate, and high fall risk groups using the original algorithm and a modified algorithm applying broader Timed Up and Go test screening with a >10s cut point (originally >15s). Prospective fall rates and physical and neuropsychological performance among the three groups were compared.

The original algorithm was not able to identify three sizable groups, i.e. only five participants (0.7%) were classified as intermediate-risk. The modified algorithm classified 349 participants (50.3%) as low-risk, 127 participants (18.3%) as intermediate-risk and 217 participants (31.3%) as high-risk. The sizable intermediate-risk group had physical and neuropsychological characteristics similar to the high-risk group, but a fall rate similar to the low-risk group. The high-risk group had a significantly higher rate of falls than both the low (IRR = 2.52, 95% CI =1.99-3.20) and intermediate-risk groups (IRR = 2.19, 95% CI = 1.58-3.03).

A modified algorithm stratified older people into three sizable fall risk groups including an intermediate group who may be at risk of transitioning to high fall rates in the medium to long term. These simple modifications may assist in better triaging older people to appropriate and tailored fall prevention interventions.

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POSTER

Applicant: Dr Niall Johnston
Supervisor: Dr Phoebe Williams

Increase in the frequency, morbidity and mortality of invasive streptococcus pyogenes infections following relaxation of non-pharmaceutical interventions directed against COVID-19

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Introduction: The epidemiology of paediatric invasive Group A Streptococcus infection (iGAS) caused by Streptococcus pyogenes has changed following the relaxation of COVID-19 non-pharmaceutical interventions [1]. While increases in iGAS incidence and severity have been documented in Europe [2] and several Australian states [3], minimal clinical data are available on paediatric iGAS infections in New South Wales (NSW).

Methods: We conducted a retrospective cohort study to evaluate iGAS infections among children (0-16 years) admitted to Sydney Children's Hospital, Randwick. We compared epidemiological and clinical characteristics of iGAS infections over a pre-pandemic period (August 2018-July 2019) and post-pandemic period (August 2022-July 2023).

Results: In the post-pandemic period, iGAS infections increased fourfold (32 versus 8 cases). The seasonality of iGAS also shifted. The incidence of viral co-infections remained consistent (50% versus 54%), with influenza comprising one-third of the viral co-infection burden. Post-pandemic cases were more severe, with higher ICU admissions (59% versus 17%) and rates of toxic shock syndrome (45% vs. 0%). One death was recorded post-pandemic. Common symptoms included cough (46%) and limb pain (25%). Rash was infrequent (7%). Household chemoprophylaxis was offered in 61% of cases.

Conclusion: Our granular analysis of iGAS cases in a NSW centre reveals the evolving epidemiology and increasing severity of disease in children, emphasizing the need for heightened clinical vigilance and timely treatment. The high burden of viral co-infection underscores the importance of increasing vaccination coverage against preventable diseases like influenza. Our findings reveal the significant iGAS morbidity and mortality, supporting the prioritisation of vaccine development.

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Applicant: Meenakshi Kumar
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Spatial Topography Of Choroidal Angioarchitecture In Intermediate Age-Related Macular Degeneration(iAMD) Indicates A Superior Bias.

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Purpose: Retinal vasculature and thickness alterations have specific pattern of loss in intermediate Age related macular degeneration(iAMD) which provide insight of it's origin1.Choroid is also known to undergo changes2 but spatial patterns are unclear.This gap will be addressed by this study by analyzing the Choroidal vascularity Index(CVI).

Methods: Eyes of healthy individuals and those with iAMD matched for age, gender and ethnicity were included(n=30). OCT(Optical Coherence Tomography) volume scans were acquired and individual B scans were marked with 8 segment similar to Spectralis software and individually assessed for luminal area (LA), total choroidal area (TCA) and CVI (LA: TCA) using CVIgrid(www.ocularimaging.net/home). These segmented values were averaged to synthesize 8x8 grid adjusting for fellow eye status, visual acuity, presence of reticular pseudo drusen, pigmentary abnormality and drusen load within 5mm dia(mm2). The mean difference was then plotted as topographical map and analysed for spatial differences.

Results: Loss in TCA and LA was observed in iAMD showing greater loss superiorly (TCA: Superior: -8.78 ± 3.56%, Inferior: -3.87 ± 2.28%, $p<0.0001$, LA: Superior: -6.86 ± 3.64%, inferior: -4.54 ± 2.67% $p<0.001$). The CVI map displays mixed spatial changes with increase in iAMD vs normal eyes superiorly (Superior: 1.77 ± 1.55%, Inferior: 1.09 ± 1.19%, $p<0.05$) and reduction nasally (-1.867 ± 0.96%, temporally:0.98 ± 0.98%, $p<0.01$).

Conclusion: Loss of LA and TCA displayed a superior bias. CVI showed a superior bias as well as nasal differences. These results suggest a disproportional loss of LA to TCA and need for spatial considerations when assessing choroidal parameters in iAMD.

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Applicant: Mifetika Lukitasari
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Visit-to-Visit Blood Pressure Variability as a Risk Factor of Premature Cardiovascular Disease.

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Background and Aims: Understanding risk factors for premature cardiovascular disease (CVD) is essential for effective public health interventions and reducing the CVD burden. This study examines visit-to-visit blood pressure variability (BPV) in young adults, comparing those who develop CVD before age 55 with those who do not.

Methods: Data from 2,747 patients, each with at least five blood pressure measurements between ages 18 and 35, were analyzed using the 2019 electronic Practice-Based Research Network (ePBRN) linked dataset. Patients developing CVD within 12 months following their fifth measurement were excluded. BPV was assessed using standard deviation (SD), coefficient of variation (CV), and variability independent of mean (VIM) from the first five measurements, taken over a median period of 2.69 years. CVD outcomes were sourced from hospital records.

Results: Among the included patients, 66 developed CVD before age 55, while 1,771 did not. BPV —measured by SD, CV, and VIM—was slightly higher in those who developed CVD (SD: 9.62 ± 6.04, CV: 0.08 ± 0.06, VIM: 0.06 ± 0.02) compared to those who did not (SD: 8.84 ± 4.55, CV: 0.07 ± 0.04, VIM: 0.05 ± 0.02).

Conclusions: Young adults who developed CVD before age 55 exhibited slightly higher BPV between ages 18 and 35. Future research will explore the association between BPV and CVD using time-to-event analysis.

Applicant: Mifetika Lukitasari
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Applicant: Dr Anandit Mathew
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Effect of a single session of acute intermittent hypoxia or acute intermittent hypercapnia on voluntary activation the upper limb in able bodied humans.

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Acute intermittent hypercapnic hypoxia (AIHH) may improve motor outcomes over acute intermittent hypoxia (AIH) alone. However, the effect of acute intermittent hypercapnia (AIC) alone is poorly understood. This study examined the effect of AIH and AIC on motor function in humans. Twelve able-bodied adults (4 males) breathed three 30-minute conditions on separate days: AIH (alternate 1-min 9% FiO2 and 1-min 21% FiO2), AIC (alternate 1-min 7% FiCO2 and 1-min 21% FiO2), and SHAM (30-min 21% FiO2), in a randomized crossover design. At baseline and up to 80-mins post-intervention, maximal voluntary contraction (MVC) force, voluntary activation (VA), and motor evoked potentials evoked by transcranial magnetic stimulation (TMS) were measured for adductor pollicis (AP). Generalised linear mixed models were used to compare motor and breathing parameters between the conditions (AIH, AIC, SHAM). VA was higher after both AIH ($p = 0.044$), and AIC ($p = 0.044$) compared to SHAM, but AIH was not different from AIC ($p= 0.956$). MVC force decreased after all conditions ($p < 0.001$). There was no difference between AIH and SHAM ($p = 0.118$) but MVC reduced less after AIC than SHAM ($p < 0.001$). There was no difference in MEP size for AP between the conditions ($p > 0.25$). The functional improvements after AIH and AIC although significant were small. Absence of MEP increases provided no evidence of corticospinal facilitation after AIH or AIC. More studies are needed to explore the mechanisms for functional facilitation in response to these novel interventions before they can become treatment options.

Applicant: Nur Amalina Md Isa
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The impact of ocular lubrication on migraine severity in individuals with dry eye disease and migraine: A randomized crossover trial.

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Migraine disorder and dry eye disease (DED) share prevalent comorbidity, often have similar risks (1), clinical presentations, and potential physiological similarities that are linked to the trigemino-vascular system (2). These suggest a reciprocal relationship between both conditions. Therefore, we investigated the impact on migraine severity by treating DED in migraine patients using ocular lubricants.

A randomized, double-blind, crossover trial was conducted on 24 participants with both migraine and DED. They received either Systane® Hydration UD (SH) or saline eyedrops, 4 times/day for 4 weeks each, with a 2-week washout period between treatments. Migraine severity was assessed using the Headache Impact Test-6 (HIT-6) and Migraine Disability Assessment (MIDAS) questionnaires. DED was evaluated using the Ocular Surface Disease Index (OSDI) questionnaire, Dry Eye Questionnaire-5 (DEQ-5), tear break-up time, tear osmolarity and corneal surface integrity (corneal staining). All outcomes were assessed at baseline, and after using the first, and then second eyedrops.

Ocular lubrication significantly reduced migraine severity and DED. The HIT-6 score was reduced from baseline when using SH (mean change, Δ= -3.0, P= 0.013) and saline (Δ= -3.9, P= 0.002). DED symptoms and corneal staining were reduced when using SH (OSDI Δ= -8.3, P= 0.004; DEQ-5 Δ= -2.1, P= 0.004; corneal staining Δ= -2.2, P= 0.001) and saline (OSDI Δ= -6.4, P= 0.026; DEQ-5 Δ= -1.5, P= 0.032; corneal staining Δ= -1.5, P= 0.005).

The results indicated that when migraine and DED co-exist, successfully treating DED reduces the severity of migraine, at least as measured by HIT-6.

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Applicant: Dr Meg Musarra
Supervisor: Dr Neevika Manoharan

A Single Centre Experience of Peripheral Blood Stem Cell Mobilisation and Collection Practices in Paediatric Patients with Solid Tumours

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Background: High dose chemotherapy followed by autologous haematopoietic stem cell transplant is integral in the treatment of paediatric solid tumours. Mobilisation practices vary widely, with a paucity of literature comparing effectiveness of differing approaches. Successful collection also relies on adequate venous access and the likelihood of successful collection via double lumen Hickman lines (DLHLs) and factors predicting their failure are currently unknown. Objective: To evaluate effectiveness of different mobilisation approaches in paediatric patients with solid tumours. To explore the adequacy of DLHLs for peripheral stem cell collection and identify factors predicting their failure.

Method: We conducted a single institution retrospective review of patients aged 0-18 years with cranial or extracranial solid tumours, undergoing peripheral blood stem cell mobilisation and collection between January 2013 and December 2023.

Results: 109 patients, predominantly with diagnoses of neuroblastoma (44%) or medulloblastoma (33%) underwent 120 peripheral stem cell mobilisation procedures, with a median of 1 apheresis sessions per mobilisation (range 1-4). Mobilisation strategies were predominantly steady-state GCSF mobilisation (57%), and mobilisation following planned chemotherapy (43%). 14 patients required the addition of plerixafor which was highly efficacious as only 2 patients failed peripheral mobilisation. Of 88 patients with pre-existing DLHLs, only 15.9% required insertion of alternate vascular access to facilitate successful collection.

Conclusion: Most paediatric solid tumour patients experience successful peripheral stem cell mobilisation and collection, especially with the addition of plerixafor in poor mobilisers. DLHLs are adequate for collection in the majority of patients and further analysis is required to determine predictors of their failure.

Applicant: Dr Nashwa Najib
Supervisor: Dr Ashish Diwan

The MYelopathy NAtural History (MYNAH) Registry: 6-month and 12-month analysis of outcomes for Degenerative Cervical Myelopathy (DCM) patients in an Australian setting.

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Hypothesis: Operated Degenerative Cervical Myelopathy(DCM) patients have favourable outcomes as compared to non-operated DCM patients in Australia.

Methods: The MYelopathy NAtural History(MYNAH) Registry(ACSQHC-ARCR-258) is Australia's first observational registry recruiting operative and non-operative DCM patients conducting 6-monthly follow-ups. Patients are recruited via an opt-in approach and must be diagnosed by a spine/neurosurgeon. Outcome variables are modified Japanese Orthopaedic Association(mJOA) score, Nurick Grade, Neck Disability Index(NDI), EQ-5D-5L and EQ-VAS. Ethics approved by UNSW HREC(iRECS3634). All statistical analysis was performed using Rv4.2.2.

Results: Participant recruitment is ongoing from eleven approved study sites across Australia. Fifty participants have been recruited; six-month follow-up has been completed for 34(68%) and twelve-month follow-up for 18(36%). Male participants are 31(62%) and females are 19(38%) with a mean age of 63 years(SD 13.6). At baseline, 18 participants had a previous cervical spine surgery. No change in mJOA score at 6 and 12-months was observed within the operated and non-operated groups(p=NS). At 6-months, NDI among the non-operated was 25% less than compared to the operated(p=NS) which did not change at 12-months(p=NS). In the operated, Nurick grade improved by 53% and 55% at 6 and 12-months respectively compared to the non-operated(p=NS). In the operated, EQ5D5L was 14% and 18% lower compared to the non-operated(p=NS) at 6 and 12-months, respectively. At 6-months, EQ-VAS was 3.5% lower in the operated but improved at 12-months and was 5.8% higher than the non-operated(p=NS).

Principal conclusions: The ongoing prospective follow-ups will inform the natural history of DCM which has remained elusive to the spinal community.

Applicant: Monireh Nazari
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Engaging adolescent and young adult cancer survivors in research: A scoping review of recruitment and retention methods.

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Background: Recruiting and retaining an adequate number of participants into research with AYA (adolescents and young adult) cancer survivors is challenging for many researchers. Inadequate recruitment/retention can compromise study validity, increase costs, and lead to delays or premature termination. Effective strategies for recruitment and retention are crucial to address these challenges.

Objective: This research aimed to evaluate recruitment and retention methods commonly used in psychosocial research with AYA survivors. Objectives included assessing the effectiveness of different recruitment strategies, identifying retention methods, and exploring associated costs for optimized implementation.

Methods: Following PRISMA-ScR guidelines, we developed a keyword-based search strategy and searched the PubMed database. Papers were screened based on inclusion/exclusion criteria, focusing on English-language, peer-reviewed articles from 2000 to 14 September 2023 involving AYA cancer survivor populations. Data extraction included key information on methods, rates, incentives, costs, and participant burden.

Results: Initial search found 171 articles; after exclusions, 18 were assessed. Recruitment methods were Classic or Digital, averaging 59.63% recruitment rate. Retention methods included offering participants Monetary Incentives (MI) and Participant Involvement and Support (PIS) strategies. The average overall retention rate was 77.76%, with PIS demonstrating efficacy at rates from 61% to 95%. Cost analysis showed varied recruitment costs, with direct mailings the most cost-effective at $35 per person.

Conclusions: This evaluation of 18 studies underscores the role of combining digital and classic approaches, emphasizing the importance of participant involvement for enhanced retention rates. Challenges in digital methods, such as data integrity concerns, warrant development of innovative solutions. By tailoring strategies to the specific needs and preferences of AYAs, researchers enhance engagement and improve the overall success of research studies in this demographic.

ORAL

Applicant: Dr Suzanne Nevin
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Psychosocial experiences of clinicians providing care for children with severe neurological impairment.

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Background/Objectives: Severe neurogenetic conditions of childhood present with heterogenous aetiologies. Clinicians exert strenuous effort undertaking complex prognostication and management, in the face of an unprecedented explosion of genetic diagnoses with limited natural history data and high-quality management guidelines regarding newly-described conditions. Despite this burgeoning scale and density of neurogenetic clinical care, supports for clinicians navigating ongoing uncertainties and balancing families realistic hopes are lacking. This can impart unabating professional and intrapersonal stress on clinicians over substantial stages of their career.

The primary aim of this study was to investigate paediatric clinicians' psychosocial and psychological experiences navigating care for children with severe neurogenetic conditions. The secondary aim was to identify clinician preferences for tailored and codesigned supports.

Methods: We conducted a qualitative descriptive study with interdisciplinary clinicians using a purposeful sampling recruitment strategy. Twenty-four participants with expertise caring for children with severe neurogenetic conditions completed in-depth, semi-structured interviews. Interviews were transcribed, deidentified and an inductive thematic analysis was performed.

Results: Thematic analysis elicited interrelated themes. Clinicians experienced immense professional barriers providing patient-centred care across fragmented healthcare contexts. Physical, emotional, and psychological impacts were attributed to inadequate reflective practice training and a paucity of integrated resources. Multi-pronged strategies incorporating psychoeducation, interdisciplinary peer mentorship opportunities, and psychological resources to build clinician reflective practice skills providing complex care in an advancing era of medicine, were prioritised.

Conclusion: This study provides novel and in-depth insight into clinicians' experiences navigating care for children with severe neurogenetic conditions. Results will be used to inform the co-development of multipronged resources tailored for interdisciplinary clinicians.

ORAL

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The members of the ClinEquip advisory group who contributed to this project as part of a group authorship are as follows: Anna van Beek, Carola Wittekind, Carolyn Shalhoub, Christine Yuen-Yan Lau, Christopher Elliot, David Rogers, Devika Wijetilaka, Elizabeth Argent, Elizabeth Cotterell, Erica Elizabeth Jacobson, Hugh McCarthy, Hugo Sampaio, Jacqui Dalby-Payne, Joanne Ging, Katrina Doyle, Kaustuv Bhattacharya, Kylie Stark, Michelle Lorentzos, Rob Slade, Ruth Evans, Sekhar Pillai, Shekeeb Mohammad, Susie Piper, Vanessa Sarkozy.

Applicant: Dr Anita Nitchingham
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Long-Acting Intranasal Insulin as a Novel Treatment for Delirium: Findings from a Randomised Controlled Trial.

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Delirium affects up to 25% of older hospitalised patients; however, there are no established treatments. We have previously shown altered glucose metabolism during delirium (1, 2). Intranasal insulin (INI) enhances cognitive function and cerebral metabolism, representing a tangible therapeutic option (3). This study examined the feasibility, safety and efficacy of intranasal insulin for delirium treatment.

We conducted a single-site, randomised, double-blind, placebo-controlled trial on two geriatric wards at the Prince of Wales Hospital. One hundred participants with delirium received either 20IU of insulin or placebo intranasally twice daily. The primary outcome was duration of delirium measured by the Confusion Assessment Method. Secondary outcomes included length of stay (LOS), delirium severity, antipsychotic use, hospital complications and mortality.

The intention-to-treat analysis included 97 patients (intervention N=48, control N=49; mean[SD] age, 87.5[7.0] years; 51% female). Median delirium duration was 4.8 days for INI and 6.8 days for placebo (P=0.23). No significant differences were observed in secondary outcomes. Median acute LOS was 7.93 days for INI and 12.9 days for placebo (P=0.06). INI demonstrated favourable tolerability. Prespecified subgroup analysis revealed an age-related response, with patients aged ≤88 years showing faster delirium resolution with INI (N=46; median days 3.9 INI vs 7.0 placebo; P=0.02), while no difference was observed in patients aged >88 years (N=51; INI 5.4 vs placebo 4.9; P=0.69).

This was the first study of INI for delirium treatment. The magnitude of difference in length of stay and the observed age-related effects warrant further investigation into the clinical potential of INI in delirium management.

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Applicant: Dr Christian Pappas
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Herpes simplex keratitis: an evaluation of local treatment guidelines 2020 - 2022.

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Purpose: To evaluate clinician adherence to evidence-based treatment guidelines for Herpes Simplex Keratitis (HSK) in Sydney, Australia between 2020 and 2022, and to compare results with previous studies conducted in 2017, and from 2018 to 2019.

Methods: A retrospective review was conducted of all cases of HSK aged 18 years and over at Sydney Eye Hospital between January 1, 2020, and December 31, 2022. Patients were identified from hospital coding data (International Classification of Diseases 10), viral swab results and pharmacy records. Medical history, antiviral and topical steroid therapy and outcomes were collected.

Results: 189 eyes from 187 patients with HSK were included. The median age was 71 years, with 56% being male. The most common antiviral regimes included oral valaciclovir 500-1000mg, once to three times daily and topical aciclovir five times daily. Antivirals were prescribed for therapeutic and prophylactic indications in 141 (75%) and 46 patients (25%) respectively. Evidence-based guidelines were adhered to in 13/23 (56%) eyes with epithelial keratitis, 25/50 (50%) with stromal keratitis, 8/8 (100%) with endothelial keratitis, and 44/60 (73%) with herpes simplex keratouveitis. Prophylactic antiviral dosage was appropriate in 33/46 (72%). Collectively, 123 patients (66%) received evidence-based antiviral treatment. This result is similar to adherence rates of 69% in 2018 to 2019 ($p=0.456$), and lower than 75% in 2017 ($p=0.116$).

Conclusion: While clinician adherence to evidence-based guidelines 5 years post-implementation appears to be decreasing, this result was not statistically significant. Regular educational activities are required to sustain knowledge of and adherence to guidelines.

Applicant: Dr Katherine Petrie
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Interventions to reduce symptoms of common mental disorders and suicidal ideation in physicians: an updated systematic review and meta-analysis.

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This updated systematic review and meta-analysis presents the latest evidence regarding effectiveness of controlled trials of interventions aimed at reducing or preventing symptoms of common mental disorders (CMD) and suicidality among doctors. This study updates and extends a previous review (1). Four databases were searched and screened independently by two reviewers. Randomised and non-randomised controlled trials of interventions to reduce or prevent depression, anxiety, general psychological disorder, or suicidality among doctors, published after March 2018, were included. The primary outcome was differences in symptoms of CMD following intervention. Random-effects modelling and planned subgroup and sensitivity analyses were conducted (PROSPERO registration: CRD42018091646). 5,212 articles were identified for screening. 16 articles (n=1,681 doctors) were included in the review and 13 were included in the meta-analysis. A small and significant effect in favour of interventions directed at the individual doctor for reduction in symptoms of CMD was found at both post-intervention and follow-up. Large to small effects in favour of a combined group of other intervention approaches (stress management, peer support and Cognitive Behavioural Therapy) and mindfulness/mind and body-based interventions were identified for symptoms of CMD at post-intervention, with a moderate-sized positive effect for mindfulness/mind and body-based approaches maintained at follow-up. Considerable heterogeneity was present, however no significant publication bias was identified. High-quality evidence available to date indicates that individual-level interventions, specifically mindfulness/mind and body-based approaches and other types of interventions, and interventions delivered face-to-face, are effective in addressing CMD among doctors in the immediate and longer-term.

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ORAL

Applicant: Chiettha Prajnadewie
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Simultaneous application of the abdominal binder and abdominal functional electrical stimulation prevents signs of orthostatic hypotension during postural change in people with subacute spinal cord injury

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Orthostatic hypotension after a spinal cord injury (SCI) limits active participation in therapies and daily activities, impacting rehabilitation progress and adaptation post-injury. Non-pharmaceutical management is limited to abdominal binders, which show mixed efficacy. Abdominal functional electrical stimulation (AFES) may improve blood pressure (BP) management in SCI but is largely unexplored. Here, we compared the effects of three interventions: the abdominal binder, AFES, both combined, and no intervention control, over four days, on BP during a passive sit-up test in 11 males (21-78 years) with subacute (<1 year) C1-T5 SCI and at least one sign, or symptom, of orthostatic hypotension. We recorded non-invasive beat-to-beat BP during 4 assessment periods: a 10-minute supine baseline, 5-minute supine; the intervention/control applied 5 minutes into baseline and during transition to sitting for up to 15 minutes; transition to supine for 10 minutes recovery, without intervention. Average mean arterial pressure (MAP) during the supine with intervention/control, seated, and supine recovery periods was normalised to supine baseline without intervention and compared using a mixed linear model. There was an interaction effect between condition and postural change across the 3 periods ($p=0.01$), an overall effect of condition ($p<0.001$) and postural change across the periods ($p<0.001$). When seated, the application of AFES and binder combined increased MAP (mean [95%CI]) compared to control (4.8mmHg [1.7,7.9]), the binder (7.2mmHg [4.2,10.3]) and AFES (7.6mmHg [4.4,10.8]). AFES and the binder have an additive effect on BP that prevents signs of orthostatic hypotension in subacute SCI when applied simultaneously, but not when applied alone.

Applicant: Mahar Safdar Ali Qasim
Supervisor: A/Prof Nicole Carnt

Improving the detection of limbal stem cell deficiency in contact lens wearers
To establish parameters to diagnose limbal stem cell deficiency using AS-OCT readings, including total and epithelial thickness of the cornea and limbus

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There are more than 140 million contact lens wearers worldwide [1], including over 3.4 million Australians [2], and the incidence of contact lens related LSCD is growing. Currently, it is estimated that 2.4 to 5% of contact lens wearers have limbal stem cell deficiency (LSCD) [3]. The early stages of LSCD present with no symptoms, and patients remain untreated until it becomes severe [4]. However, early-stage diagnosis is important in managing LSCD in contact lens users as it allows timely management and improves the prognosis of the condition. The hallmark of LSCD is conjunctival vascularisation, neovascularisation, and chronic inflammation [5]. Diagnosis is based on history and examination with in-vivo confocal microscopy (IVCM), which has shown a reduction in basal cell density of 6.6% (27.09±4.945 cells/mm^2) and palisades in LSCD [6, 7]. However, IVCM is a contact-based technique which requires specific operator skills and typically used in research rather than in clinical settings.

Anterior segment optical coherence tomography (AS-OCT) has been recently used in the investigation of LSCD, showing reduction in corneal and limbal epithelial thickness. In LSCD patients, corneal and limbal epithelial thickness reduced by 22.2% and 32.12% compared to normal corneas, with average values of 41.33µm and 43.188µm [8]. AS-OCT presents as a viable alternative technique to diagnose LSCD as it provides accurate and repeatable measures of the corneal and limbal epithelial thickness. Other advantages include that the device is non-invasive, non-contact, requires minimal operator skill, is user-friendly, and more widely available in clinical practices compared to IVCM. The proposed study aims to establish parameters to diagnose LSCD using AS-OCT readings, including total and epithelial thickness of the cornea and limbus.

The study aims to identify early signs of LSCD in contact lens wearers using AS-OCT an accurate, repeatable and non-invasive technique. Being readily available, by establishing AS-OCT parameters to detect LSCD, it will allow clinicians to diagnose the condition promptly, facilitating timely management that may improve prognosis of the condition. The number of contact lens wearers are expected to rise, and particularly in children [9]. Therefore, proper investigations of limbal stem cell function and early detection of LSCD are critical in the management of contact lens wearers. The outcomes of this study will also provide insight into safe duration and type of materials for contact lens use.

Applicant: Dr Rodrigo Rizzo
Supervisor: Prof James McAuley

Non-pharmacological and non-surgical treatments for low back pain in adults: an overview of Cochrane Reviews

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Clinical practice guidelines recommend non-pharmacological and non-surgical interventions for managing pain and improving function in people with non-specific low back pain (LBP). The effects of these treatments have been reported in multiple systematic reviews, sometimes reductant, incomplete, or with poor methodological quality, making it confusing for clinicians, researchers, and policymakers about the current evidence. We conducted an overview of Cochrane systematic reviews to summarise the efficacy, effectiveness, and safety of non-pharmacological and non-surgical interventions for adults with non-specific LBP. We searched the Cochrane Database of Systematic Reviews (from inception to 15 April 2023). Two authors independently assessed eligibility, extracted data and assessed the quality of the reviews using AMSTAR-2 and the certainty of the evidence using GRADE. We included 31 Cochrane reviews of 644 trials that randomised 97,183 adults with LBP. We found no high-certainty evidence that any investigated non-pharmacological or non-surgical intervention reduced pain intensity or improved function in adults with non-specific LBP compared to sham/placebo or no treatment/usual care. For acute LBP, spinal manipulation probably does not provide a reduction in pain intensity at one-week follow-up compared to placebo, and multidisciplinary therapies probably provide benefits in the long term compared to no treatment/usual care. For chronic LBP, traction probably does not reduce pain intensity in the short term compared to sham traction, but acupuncture, exercise, multidisciplinary therapies, and psychological therapies probably provide benefits in short-intermediate or long-term follow-ups compared to no treatment/usual care.

This Overview is under review in the Cochrane Database of Systematic Reviews and will be cited as follows:
Rizzo RRN, Cashin AG, Wand BM, Ferraro MC, Sharma S, Lee H, O'Hagan E, Maher CG, Furlan AD, van Tulder MW, McAuley JH. Non-pharmacological and non-surgical treatments for low back pain in adults: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews TBD, Issue TBD. Art. No.: CD014691. DOI: 10.1002/14651858.CD014691.

Applicant: Dr Eden Robertson
Supervisor: Dr Kate Hetherington

What matters most? Identifying consumer research priorities for inherited retinal diseases in Australia.

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Applicant: Dr Eden Robertson
Supervisor: Dr Kate Hetherington

What matters most? Identifying consumer research priorities for inherited retinal diseases in Australia.

Objective: Involving consumers as early as possible is considered good research practice. However, there is often a mismatch between what is researched and what consumers want researched.1,2 We sought to identify the research priorities for inherited retinal diseases (IRDs) in Australia, from the perspective of individuals with an IRD, caregivers, and health professionals (i.e., stakeholders).

Methods: We conducted a James Lind Alliance Priority Setting Partnership.3 This involved identifying any uncertainties that stakeholders had about IRDs, a literature review to verify the uncertainties, an interim prioritisation exercise with stakeholders to shortlist verified uncertainties, and workshops with stakeholders to decide on the top 10 research priorities.

Results: The top 10 priorities highlighted the value of an integrated model of care. Priorities included a mix of research focussed on treatment/cure (e.g., treatment to prevent, slow down or stop vision loss), psychosocial impacts (e.g., psychological impact of having an IRD), symptoms (e.g., impact of environmental and lifestyle factors on symptoms), early detection, and health professional training.

Conclusions: We will share our findings with funding bodies, government and researchers with the aim of maximising research impact and utilisation of health dollars. We acknowledge that funds for research and to expand the healthcare system are limited. Until further funding is available, the sector must cooperate to ensure that all research priorities are addressed. For now, efforts to educate patients/caregivers about how IRDs occur, how to access genetic testing, and available clinical trials and support services are critical to enhance health literacy as IRD research rapidly advances.

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Applicant: Dr Aidan Tan
Supervisor: Dr Lene Seidler

Data sharing policies across health research globally: cross-sectional meta-research study

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Data sharing improves the value, synthesis and integrity of research, but rates are low. Data sharing might be improved if data sharing policies were prominent and actionable at every stage of research. We aimed to systematically describe the epidemiology of data sharing policies across the health research lifecycle. This was a cross-sectional analysis of the data sharing policies of the largest health research funders, all national ethics committees, all clinical trial registries, the highest-impact medical journals, and all medical research data repositories. Stakeholders' official websites, online reports and other records were reviewed up to May 2022. The strength and characteristics of their data sharing policies were assessed, including their policies on data sharing intention statements (a.k.a. data accessibility statements) and on data sharing specifically for COVID-19 studies. Data were manually extracted in duplicate, and policies were descriptively analysed by their stakeholder and characteristics. 935 eligible stakeholders were identified: 110 funders, 124 ethics committees, 18 trial registries, 273 journals and 410 data repositories. Data sharing was required by 41% (45/110) of funders, no ethics committees or trial registries, 19% (52/273) of journals and 6% (24/410) of data repositories. Among funder types, a higher proportion of private (63%, 35/55) and philanthropic (67%, 4/6) funders required data sharing than public funders (12%, 6/49). Data sharing requirements, and even recommendations, were insufficient across health research. Where data sharing was required or recommended, there was limited guidance on implementation. Public funders and ethics committees are two stakeholders with particularly important untapped opportunities.

Applicant: Josie van Dorst
Supervisor: A/Prof Keith Ooi

Integrative multi-omics analysis of intestinal dysbiosis and inflammation in children with Cystic Fibrosis.

Josie van Dorst (1), Michael J Coffey (1, 2), B.L.D. Uthpala Pushpakumara (1), Jessica Halim (1), Dovile Anderson (3), Darren Creek (3), Chee Y Ooi (1, 2), on behalf of PEARL-CF.

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Background: Early alterations to the gastrointestinal microenvironment in cystic fibrosis (CF) contribute to gastrointestinal inflammation and microbial dysbiosis that persists into adulthood. This disruption is linked to poor growth and pulmonary health outcomes yet the underlying causes and mechanisms of inflammation and dysbiosis remain poorly elucidated.

Methods: The PEARL-CF study is a multicentre, probiotic RCT in young children (0-6 years old) with CF (ACTRN12616000797471). Stool calprotectin, microbial metagenomics, untargeted and targeted short chain fatty acid (SCFA) metabolites were extracted from stool samples at baseline (prior to commencement of probiotic/placebo intervention) and quantified utilising shotgun metagenomic sequencing and Liquid Chromatography Mass Spectrometry (LCMS).

Results: Seventy children with CF were compared to 67 healthy non-CF controls. A total of 1147 bacterial species, 1245 putative metabolites and six SCFA were identified. Individuals with CF had significantly lower faecal alpha diversity: Richness (IQR) (69.50 (37.00-74.11) vs 122.0 (62.0-118.5), $p < 0.001$), higher calprotectin concentrations (143.8 vs 63.42, $p = 0.0046$), reduced SCFA concentrations (12530 ug/mg/DW vs 15520 ug/mg/DW, $p = 0.003$) and significantly different metabolites ($F = 28.74$, $r2 = 0.09$ $p = 0.001$) compared to healthy non-CF controls. The greatest differences in microorganisms and metabolites occurred in the first 3 years of life, while differences in calprotectin increased after 3 yrs.

Conclusions: Bacterial species and metabolites are significantly altered in young children with CF, consistent with delayed microbiome maturation. Metabolite production in the first 3 years of life precede increased inflammation. These preliminary findings provide rationale for gut microbial modulation in young children with CF.

Applicant: Jessica Wang
Supervisor: Dr Gemma Sicouri

Exploring adolescent insights: enhancing digital cognitive bias modification for anxiety and low mood

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Anxiety and depressive disorders commonly emerge during adolescence. Cognitive Bias Modification of Interpretation (CBM-I) is a digital intervention that has shown promising outcomes for symptom reduction in anxiety and depression. It is accessible, low cost, and does not require therapist input. However, engagement in real-world settings is poor and adolescents report that the training is boring. This study sought to understand the needs of adolescents to enhance engagement in CBM-I for anxiety and depression. Three focus groups and two interviews were conducted, comprising 13 Australian adolescents with lived experience of worry and/or low mood. A fourth focus group comprised five psychologists with experience treating this demographic and presentation. Lived experience advisors assisted in creating the interview guide and facilitating focus groups. Preliminary thematic analysis indicates adolescents value a tailored intervention, including the ability to match the training content to their primary concerns, via an automated algorithm. They also wanted control over user interface features (e.g., music, notifications). While adolescents wanted a social element (e.g., messaging friends), they were cautious of social comparison. Most preferred short-format content that did not exceed 10 minutes of daily use. Participants reported that psychoeducation alongside training was needed to increase motivation to complete it. Digital CBM-I is an evidence-based intervention with the potential to be scaled up in a cost-effective manner. Our findings also help to inform the development of other digital mental health interventions and will ensure greater uptake when disseminated at the community level, aligning with the “stepped care model” of mental health.

Applicant: Bonnita Werner
Supervisor: Prof Caroline Ford

Cell-free DNA from ascites identifies clinically relevant variants and tumour evolution in patients with advanced ovarian cancer [1]

Bonnita Werner (1), Elyse Powell (1), Jennifer Duggan (2), Marilisa Cortesi (1, 3), Yeh Chen Lee (2, 4), Vivek Arora (4, 5), Ramanand Athavale (2, 4), Michael Dean (6), Kristina Warton (1) & Caroline E. Ford (1).

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Background: The emergence of targeted therapies and predictive biomarkers is transforming the ovarian cancer treatment paradigm. However, the demand for high quality, tumour-enriched samples for biomarker profiling can be limited by access to adequate tissue samples. The use of cell-free DNA (cfDNA) in ascites presents a potential solution to this clinical challenge.

Methods: A unique set of sequential ascites-derived cfDNA samples (26 samples from 15 human participants) were collected from people with ovarian cancer (age range 36-82 years). cfDNA was sequenced using targeted next-generation sequencing, along with matched DNA from ascites-derived tumour cells (n=5) and archived FFPE-tissue from surgery (n=5).

Results: Similar tumour purity, variant detection and reference alignment were achieved with cfDNA when compared to FFPE and ascites derived tumour cell DNA, as well as improved coverage. No artefactual single-base mutation signatures were identified in cfDNA. Combined analysis of large-scale genomic alterations, loss of heterozygosity and tumour mutation burden identified 6 cases of high genomic instability (including 4 with pathogenic variants in BRCA1 and BRCA2). Copy number profiles and subclone prevalence changed between sequential ascites samples, particularly in a case study where deletions and chromothripsis in Chr17p13.1 and Chr8q resulted in changes in clinically relevant TP53 and MYC variants over time.

Conclusions: Ascites cfDNA successfully identified clinically actionable information, concordant to tissue biopsies, enabling opportunistic molecular profiling. These findings advocate for analysis of ascites cfDNA in lieu of accessing tumour tissue via biopsy.

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Applicant: Xian Zou
Supervisor: Dr Marion Mateos

Factors That Determine Treatment Decision Making in Precision Medicine in Paediatric Cancer: a Systematic Review of Qualitative and Quantitative Studies.

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Background: Despite the benefits of precision-guided treatment recommendation found from paediatric cancer clinical trials, its adoption rate remains low. Understanding factors that influence uptake is crucial for enhancing clinical implementation. This systematic review aimed to identify factors that affect the uptake of precision-guided treatment recommendations in paediatric cancer.

Method: A systematic search of literature was conducted within EMBASE, CINAHL, PubMed, PsycINFO, and Scopus. Qualitative and quantitative studies focusing on paediatric cancer patients (0-21yrs old) involved in precision medicine were included. Title and abstract screening, full text screening, and data extractions were conducted by two reviewers.

Results: Seventeen included studies were all conducted in developed countries: 10 prospective and 4 retrospective studies. The cohort consisted of 3976 patients; 527 newly diagnosed high-risk cancer patients (9 studies), 1103 primary refractory/relapsed cancer patients (12 studies), 208 healthcare professionals, 189 parents, 532 general community members. Fifteen quantitative studies aimed to explore new therapies. Only two qualitative studies utilised semi-structured interviews to explore clinicians' or parents' perspectives regarding adopting treatment recommendations, while the others primarily collated factors from clinical records. Factors identified through the systematic review related to: (1) Disease/Treatment; (2) Drug availability/evidence; (3) Clinician factors; (4) Clinical Trials; (5) Patient/family; (6) Cost.

Conclusion: To our knowledge, this is the first systematic review to explore factors affecting the adoption of precision-guided treatment in paediatric oncology. Further research is needed to explore treating oncologists' perspectives as they determine whether to adopt treatment recommendations in discussion with patients and their families.

Registration: PROSPERO database (CRD42023410199)

Division:

Independent Learning Projects Honours

Applicant: Sidharth Anand
Supervisor: A/Prof Angela Chiew

Effects of Fomepizole on Paracetamol Oxidative Metabolism: A Randomized, Cross-Over Study in Human Volunteers

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Introduction: Paracetamol is a leading cause of acute liver injury due to intentional self-poisoning and accidental overdoses. Acetylcysteine is the main treatment and is effective if given within 8 hours but may fail with massive overdoses or delayed treatment. The toxic metabolite is produced by oxidative metabolism via cytochrome P450 2E1 (CYP2E1). Fomepizole is a CYP2E1 inhibitor and human volunteer studies have shown if given at the time of paracetamol ingestion inhibits oxidative metabolism(1). The aim was to assess the effect of fomepizole on paracetamol metabolism when administered 2-hours after ingestion of immediate-release or modified-release paracetamol.

Methods: Simulated supra-therapeutic paracetamol randomised cross-over study with eight healthy volunteers. Participants received 80 mg/kg of paracetamol product (immediate or modified-release) and were then randomised to receive fomepizole or placebo at 2-hours post-ingestion. Crossing over to the other arm after a 2-week washout. Urine and plasma samples were collected for 24-hours, non-toxic and oxidative metabolites (APAP-Mer, APAP-Cys) were measured. The primary outcome was the percentage of ingested paracetamol excreted as oxidative metabolites, in urine.

Results: Compared to paracetamol alone, treatment with fomepizole decreased the percentage of ingested paracetamol recovered as oxidative metabolites in 24-hour urine, in both immediate and modified-release paracetamol groups from 4.80% vs 1.66% (95%CI:1.53–4.75%, p=0.004) and 4.69% vs 1.28% (95%CI:2.40–4.40%, p=0.0002) respectively. Plasma area under the concentration curve was also decreased.

Conclusions: Fomepizole administered 2-hours after paracetamol ingestion effectively reduced oxidative metabolites following supratherapeutic doses. Fomepizole may be a useful adjunct in treating massive paracetamol poisonings with high concentrations.

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POSTER

Applicant: Aakash Annadurai
Supervisor: Dr Ki Wook Kim

Identifying viruses that contribute to the development of type 1 diabetes using comprehensive antiviral antibody profiling.

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Introduction: Molecular and epidemiological data support viral infections as prime candidate triggers for islet autoimmunity (IA) and type 1 diabetes (T1D). However, these data are largely based on targeted investigations using virus detection methods which screen for a pre-selection of specific viruses1. An unbiased investigation of all human-infecting viruses (the "virome") is yet to be deeply investigated.

Objective: To examine the human virome in both pregnant mothers and children preceding the development of IA/T1D in childhood and identify viruses that associate with IA/T1D.

Methods: This nested case-control study within the larger Environmental Determinants of Islet Autoimmunity (ENDIA) study2 includes 54 cases (IA/T1D positive) and 161 age/sex matched controls (215 individuals, 1:3 ratio). For each case and control, a single representative maternal pregnancy sample and one sample at the time of seroconversion to IA were serologically profiled using VirScan – a high-throughput phage-immunoprecipitation sequencing technique3. Virus positivity (based on presence/absence of antiviral antibody signals) and its association with IA/T1D for each virus was tested via univariate conditional logistic regression with confounder-adjustment.

Results: Infection with human mastadenovirus F in infancy (OR=5.14x10-7, 95%CI= 4.24x10-11–0.006, p=0.05) and enterovirus B during pregnancy (OR=3.16x10-7, 95%CI=4.59x10-11–0.002, p=0.02) were associated with protection against IA development, without confounder adjustment (prevented by statistical model instability).

Conclusion: Results indicate a possible protective effect against IA/T1D development of maternal enterovirus B infection and childhood human mastadenovirus F infection. Confounder adjustment, longitudinal, and multivariate analysis should be further explored.
Key Words: Islet Autoimmunity, Type 1 Diabetes, Virome, Antibody Profiling, Phage-immunoprecipitation Sequencing.

POSTER

Applicant: Aakash Annadurai
Supervisor: Dr Ki Wook Kim

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Applicant: Meher Bhagat
Supervisor: A/Prof Orazio Vittorio

Novel Erythrocyte-Derived Therapeutic Delivery System for Targeting of High Grade Gliomas

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Background: Treatment of high-grade gliomas (HGGs) is limited by the selective permeability of the blood-brain-barrier (BBB), restricting entry of molecules/particles larger than 200 nanometres. Erythrocyte derived extracellular vesicles (RBC-EVs) present a novel solution as therapeutic delivery systems (TDS) due to their endogenous origin, longer half-life, reduced immunogenicity, ability to cross the BBB and cost-effectiveness compared to current TDS. The protooncogene c-MYC which regulates critical enzymes of aerobic glycolysis, can be downregulated by siRNA, shifting HGG's reliance to mitochondrial respiration. This shift can be targeted by copper chelators like tetrathylenepentamine (TEPA), which limit mitochondrial respiration by depleting intracellular copper. Encapsulating unstable therapeutics such as anti-c-MYC siRNA in RBCs and combining them with TEPA, aims to enhance HGG treatment efficacy.

Methods: Erythrocytes were isolated, loaded with anti-c-MYC siRNA via electroporation, and underwent extrusions through nanoporous filters to convert erythrocytes into smaller vesicles. RBC-EVs were utilized to transfect HGG cells with anti-c-MYC siRNAs and transfection efficiency was compared to lipofectamine RNAiMax. Subsequently, HGG cells (wildtype and c-MYC knocked-down) were treated with various concentrations of TEPA to evaluate the impact of c-MYC downregulation on TEPA efficacy.

Results: RBC-EVs of 105-110nm average diameter were stable through two freeze-thaw cycles, with no therapeutic loss. Anti-c-MYC loaded RBC-EVs achieved a 60% downregulation of c-MYC in HGG cells through transfection, comparable to lipofectamine, and increased HGG sensitivity to TEPA.

Conclusion: RBC-EVs can effectively deliver siRNAs to HGG in-vitro, providing a promising strategy for targeting HGGs. This study establishes the foundation for preclinical evaluation of RBC-EVs-based TDS with potential applications for other cancers.

POSTER

Applicant: Richa Chaluvadi
Supervisor: Dr Dominik Fröehlich

Gene therapy proof-of-concept for spastic paraplegia 56 (SPG56)

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Hereditary spastic paraplegias (HSP) are a group of neurological disorders characterized by progressive limb weakness and spasticity; with a global prevalence of 3.6 in 1000 people. SPG56 is a subtype of HSP caused by autosomal recessive mutations of the CYP2U1 gene, which encodes CYP2U1, a cytochrome P450 hydroxylase predominantly found in cells of the central nervous system (CNS) and thymus. To date, no curative treatments exist. This study tests the efficacy of adeno-associated virus (AAV)-mediated CYP2U1 gene replacement in a Cyp2u1-/- knockout mouse model.

AAV9 was used for effective CNS transduction paired with either the CAG (AAV9.CAG.hCYP2U1) or EF1a promoter (AAV9.EF1a.hCYP2U1) for strong and moderate CYP2U1 expression, respectively. Cyp2u1-/- mice were treated via intravenous or intracerebroventricular injections. Controls included untreated Cyp2u1-/-, Cyp2u+/- (heterozygous) and Cyp2u+/+ (wild-type) mice. All mice underwent behavioural assessments and blood serum samples were collected for analysis.

The Cyp2u1-/- mouse strain was first established as an SPG56 model. Serum levels of biomarkers (CoQ9 and CoQ10) were elevated in Cyp2u1-/- mice compared to controls, consistent with human SPG56 patients. Cyp2u1-/- mice also showed sensorimotor gating deficits, indicated by reduced pre-pulse inhibition of the acoustic startle response, along with learning deficits on the y-maze and passive avoidance tests. Subsequently, AAV-mediated CYP2U1 gene replacement showed significantly lower biomarker levels and depicted trends towards normalisation of behavioural impairments.

This study provides the proof-of-concept for CYP2U1 gene replacement as an effective treatment for HSP SPG56, which paves the way for further development and clinical translation – holding promise to cure this debilitating condition.

ORAL

Applicant: Clare Ghows
Supervisor: Dr Clarissa Schilstra

Treatment related toxicities in childhood cancer and impact on quality of life

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ORAL

Applicant: Clare Ghows
Supervisor: Dr Clarissa Schilstra

Treatment related toxicities in childhood cancer and impact on quality of life.

Background: Although paediatric Acute Lymphoblastic Leukaemia (ALL) is one of the most treatable forms of paediatric cancer, increasing evidence links ALL treatment with treatment-related toxicities (TRTs) (1). However, the long-term changes in children's quality of life (QoL) due to toxic treatments are not well understood. Additionally, there is limited insight into trajectories of QoL changes during and after ALL treatment, and even less understanding of families' perceptions of the treatment impacts on their child's QoL.

Aims: To define trajectories of parent-reported QoL of children with ALL over a 5-year period from diagnosis, describe families' perspectives on children's QoL, and identify risk factors associated with parent-reported QoL.

Methods: Two studies were conducted: (1) a longitudinal prospective study, which invited parents of children diagnosed with ALL within 100 days to evaluate QoL and (2) a qualitative interview study that invited parents and children up until 18 years old to understand their experiences with cancer.

Results: 186 parents participated (representing children mean age = 74.16 months, 56.5% male). Parents reported poor QoL through ALL treatment, with procedural anxiety and cognitive dysfunction accounting for poor QoL beyond treatment. Interviews showed that pain, worry, and procedural anxiety negatively impacted their QoL. Age and time were the only significant factors affecting QoL, where older age was associated with lower QoL scores than younger children.

Conclusion: This study is the first to identify that Australian children experience poor long-term QoL due to procedural anxiety, worry, pain, nausea and cognitive dysfunction post-treatment, showing the need for psychosocial interventions.

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Applicant: Mason Ginters
Supervisor: Dr Oliver Fisher

Gemcitabine/Oxaliplatin/Lenvatinib (GEMOX-Len): a neoadjuvant therapy for refractory, relapsed or unresectable fibrolamellar carcinoma.

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Background: Fibrolamellar carcinoma (FLC) is a rare primary liver malignancy typically affecting young adults.Although surgical resection is the primary treatment, 50-80% of cases have disease recurrence and >20% have "unresectable" disease (1). Gemcitabine/Oxaliplatin/Lenvatinib (GEMOX-Len) is a systemic therapy developed by the Rush University FLC Program for refractory, relapsed or unresectable FLC.

Methods: Tumour response (using RECIST 1.1 and volume estimates), progression-free survival (PFS) and overall survival (OS) were the primary study endpoints (2). The Kaplan-Meier method was used to construct survival curves with the log-rank test applied to compare survival distributions. Ethics was approved by UNSW HREAP (2024/iRECS5847).

Results: 52 patients (25 female, median age 21.4) received a median of 9 cycles of GEMOX-Len (G:1000mg/m2, O:100mg/m2, L:8mg daily). 5/3/44 patients had AJCC stage IIIA/IVA/IVB disease with 50/52 deemed unresectable. Post-GEMOX-Len, 0/11/41 patients had complete response (CR)/partial response (PR)/stable disease (SD) per RECIST 1.1, with mean RECIST and volume responses of -18.5% and -36.9% respectively. Median OS and PFS was 31.8 months and 21.6 months. 28 patients were surgical candidates post-therapy: 18 underwent definitive surgery, with 77.8% achieving R0 resection. Achieving R0 surgery (p=0.016) or CR through post-GEMOX-Len intervention (p=0.005) were significant predictors of OS. Tumour necrosis post-GEMOX-Len (p=0.044) and AJCC stage <4 at definitive surgery (p=0.040) were predictors of PFS. 32/48 patients experienced adverse effects including peripheral neuropathy (n=25) and cytopaenias (n=5).

Conclusion: 52% of patients became surgical candidates post-GEMOX-Len. OS exceeded the typical <12 months life expectancy for unresectable FLC (1). Further controlled, prospective studies are required.

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Applicant: Farzaana Hossain
Supervisor: Dr Sandra Chuang

Exploration of care for asthma in children from priority populations - a single-centred experience.

Farzaana Hossain, Melinda Gray, Adam Jaffe, Louisa Owens, Sandra Chuang.

Discipline of Child Health, School of Clinical Medicine, UNSW Sydney.
Respiratory Department, SCH.

Background: Priority populations often experience magnified impacts of paediatric asthma. This study aimed to assess prevalence of priority populations in children attending Sydney Children's Hospital (SCH) Randwick for management of asthma, and differences in health outcomes in both acute and follow-up settings.

Methods: This is a retrospective cohort study of data from the Electronic Medical Records of patients aged 2-18 years who presented to the Emergency Department (ED) of SCH or enrolled under the SCH Respiratory Specialist Outpatient Clinic for management of asthma, over the 2023 calendar year. Primary analysis involved identification of priority populations subgroups, including Indigenous and Culturally and Linguistically Diverse (CALD) groups. Secondary and exploratory analyses were conducted using variables for health outcomes and asthma management.

Results: The study identified 2 cohorts of patients in the ED (n=863) and outpatient clinic (n=190), of which 17.3% and 26.6% satisfied the priority population criteria respectively. There was no significant relationship between priority population status and number of ED or ICU admissions in the 24 months prior to index presentation, and length of stay of the index ED presentation. Priority population patients were more likely to miss outpatient respiratory clinic appointments (IRR=4.45 $p<0.001$) and have obstructive lung defect on spirometry testing (IRR=16.16 $p=0.01$). The Indigenous subgroup had higher rates of ED presentations in the 24 months preceding index presentation (IRR=1.67 $p<0.001$).

Conclusion: Findings of poorer asthma management and clinical outcomes in priority populations demonstrate a need to address these disparities through further research and targeted support for these children.

ORAL

Applicant: Mohammed Moonaad Huda
Supervisor: Dr Sarah Ellis

Impact of Symptom Clusters on Health-Related Quality of Life of Childhood and Adolescent Cancer Survivors

Huda M., Ellis SJ., Schilstra CE., Fardell J.

Introduction: Many childhood and adolescent cancer survivors experience ongoing symptoms after treatment and into survivorship. These symptoms often co-occur in 'symptom clusters' which can significantly impact survivors' health-related quality of life (HRQoL). This multi-perspective cross-sectional study aimed to identify symptom clusters, and their impact on HRQoL in child/adolescent survivors and their parents.

Methods: Questionnaires were completed by 33 child survivors (7-12years), 19 adolescent survivors (13-17years) and 61 parents (child age: 7-17years) including 41 parent-survivor dyads. We used hierarchical cluster analysis to identify symptom clusters, Kappa tests to compare inter-rater reliability between child/adolescent survivors and their parents, and multiple regression to assess the impact of symptom clusters on depression/emotional outcomes (PROMIS-depression/Emotion Thermometers) and general health outcomes (CHU9-D/EQ-5D-5L).

Results: The most commonly reported symptoms were fatigue (53.9%), anxiety (32.5%) and problems completing schoolwork (29.0%). Average inter-rater reliability between parent-child dyads' symptom reporting was 'fair' (Mean Kappa=0.362) and 'weak' for parent-adolescent dyads (Mean Kappa=0.141). We found seven symptom clusters, of which, three were significantly associated with poor HRQoL outcomes. In children/adolescents, a sleep and function cluster (problems with sleep, daily routine, ability to complete schoolwork and ability to join activities) and a sad-annoyed cluster were significantly associated with increased depressive symptoms (p=0.003 and p=0.020 respectively). A sad-activities cluster (feeling sad and problems joining activities) was significantly associated with poorer general health outcomes (p=0.012).

Conclusion: This study found a significant association between prevalence of symptom clusters and reduced HRQoL, emphasising the need to develop appropriate interventions to improve long-term HRQoL of childhood cancer survivors.

Applicant: Yoonji Kim
Supervisor: Dr Emma Palmer

Evaluating GeneAdd: How an Undiagnosed Rare Disease Program Enhances Diagnosis and Care for Australian Children.

Rare diseases (RDs) collectively affect over 2 million Australians [1] and 450 million people globally [2]. The molecular diagnosis of these diseases is complex and often results in inconclusive findings [3–5], leaving 43-71% of patients with suspected monogenic conditions undiagnosed [6,7]. Undiagnosed disease programs (UDPs), such as GeneAdd at the Sydney Children's Hospitals Network (SCHN), aim to address this issue. However, UDPs are not yet standard in genetics care, and their value within national healthcare needs to be assessed [8].

This study has two objectives:
1)To determine the diagnostic yield in a cohort of paediatric patients with suspected undiagnosed RD through the GeneAdd research pathway,
and
2) To evaluate clinicians' perspectives on the clinical utility of GeneAdd.

Short-read whole genome sequencing (WGS) data from 4 undiagnosed families were analysed using a phenotype-centric approach and assessed using criteria from the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) [9], resulting in one likely-pathogenic variant and three variants-of-uncertain-significance which are being further evaluated with collaborative research. The clinical utility of GeneAdd was assessed using the validated C-GUIDE tool [10]. Additionally, a focus group within the SCHN genetics department examined the acceptability and impact of UDP implementation on clinician experience, using the theoretical framework of acceptability (TFA)11 and domains from the clinician experience measure (CEM) [12], and found high clinical utility and acceptability.

This study provides an evidence-based evaluation of GeneAdd's effectiveness in improving diagnostic outcomes and its potential role in supporting implementation of a UDP into Australian genetics healthcare.

Applicant: Yoonji Kim
Supervisor: Dr Emma Palmer

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Applicant: Sujit Krishnan
Supervisor: Prof Michelle Farrar

Childhood Dementia Theratyping: Evaluating Variant Suitability For Antisense Oligonucleotide Therapy Development.

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Applicant: Sujit Krishnan
Supervisor: Prof Michelle Farrar

Childhood Dementia Theratyping: Evaluating Variant Suitability For Antisense Oligonucleotide Therapy Development.

Background: Childhood dementias (CD) are a clinically and genetically heterogeneous group of neurodegenerative disorders. Less than 5% have effective treatments. Antisense oligonucleotides (ASOs) are small nucleic acid molecules that modulate the RNA-level impacts of genetic variants and hold great promise as future CD treatments. This study aimed to identify potentially ASO-targetable disease-causing variants in a well-characterised CD cohort.

Methods: Clinical, demographic and causative variant data from a cohort of children with genetically confirmed CD were analysed. Bioinformatic tools were used to predict the RNA- and protein-level impacts of all cohort member variants. Existing ASO theratyping frameworks and additional expert opinion were then leveraged to determine which variants were potentially amenable to ASO-based treatments.

Results: The CD cohort comprised 30 children with 38 disease-causing variants in 22 nuclear and three mitochondrial genes. Overall, ten children from seven families had at least one variant potentially amenable to ASO treatment. This included 1) six children with an intronic variant amenable to ASO-masking aimed at restoring full-length protein expression, and 2) four children with an exonic variant amenable to ASO-induced exon skipping aimed at feasibly producing a shorter, partially functional protein. Additionally, eight children had variants requiring more nuanced consideration of ASO treatment options.

Conclusions: We have consolidated and applied an effective ASO theratyping methodology that incorporates comprehensive in silico predictive analyses and a clinically useful decision-making framework. This approach could evaluate the ASO-targetability of other rare disease-causing variants in the context of an Australian-led ASO treatment discovery, development, and translational pipeline.

POSTER

Applicant: Jerrica Kuan
Supervisor: Prof Jane Kohlhoff

Outcomes of Circle of Security-Parenting (COS-P) at an Australian Early Parenting Centre: Investigating education, ethnicity and gender-based parent outcomes.

Kuan, J., Camberis, A-L., Johns, A., & Kohlhoff, J.

Background: The role of secure attachment relationships in positive child socioemotional development highlights the importance of early attachment-based interventions such as Circle of Security-Parenting (COS-P)1. COS-P has been widely disseminated but effectiveness studies have yielded mixed results2-6. Furthermore, little is known about the impact of demographics on intervention outcomes.

Study Aims: To examine outcomes of COS-P at an Australian early parenting centre and assess the role of parental demographics (sex, education, ethnicity) on outcomes.

Method: 144 parents attended COS-P at an Australian Early Parenting Centre and completed the Composite Caregiving Questionnaire2 (CCQ) before and after intervention. The CCQ includes 4 scales: the Tool for Parental Self-efficacy7, the Hostile Parenting scale from the Longitudinal Study of Australian Children8, the Caregiver Helplessness Questionnaire9, and Diamond's Reflective Functioning Scale10. Outcomes were analysed using a mixed models repeated measures design.

Results: Results showed significant main effects for 'time' on all CCQ domains (ps <.05). When demographic group moderators were examined (mother vs father, university vs non-university educated, Western vs Asian vs African), fathers and African parents were found to report greater improvements in parental self-efficacy post-intervention. Asian parents showed no significant improvements in parent hostility and African parents showed no significant improvements in parent mentalising.

Conclusion and Implications: COS-P is associated with positive outcomes across multiple parenting domains, however differential outcomes for some cultural groups highlights the potential for additional targeted supports.

POSTER

Applicant: Jerrica Kuan
Supervisor: Prof Jane Kohlhoff

Outcomes of Circle of Security-Parenting (COS-P) at an Australian Early Parenting Centre: Investigating education, ethnicity and gender-based parent outcomes.

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Conclusion and Implications: COS-P is associated with positive outcomes across multiple parenting domains, however differential outcomes for some cultural groups highlights the potential for additional targeted supports.

Applicant: Jung Min Lee
Supervisor: Dr Holly Evans

Australian Health-professionals' Perspectives on End-of-Life Discussions for Adolescents and Young Adults with Cancer.

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Cancer is a leading cause of death for adolescents and young adults (AYAs). Timely and appropriate end-of-life conversations with AYAs with cancer allow the exploration of patient's perspectives about ongoing treatment, life-sustaining measures and overall well-being in relation to their incurable illness1,2,3. As patients rely on health-professionals to guide these discussions2, we investigated the factors that health-professionals believed to act as barriers and facilitators to end-of-life conversations. Twenty-eight health-professionals participated in semi-structured interviews about end-of-life conversations. The data was analysed though qualitative content analysis using an inductive approach3. The results revealed four broad themes: intrapersonal factors, interpersonal factors, teams and hospital systems and cultures, and societal influences. The interplay of factors such as patients' and caregivers' emotional barriers, the patients' maturity levels, the stigma around the naming of palliative care and the social taboos of speaking about the death of young people were found to negatively impact end-of-life conversations. Good communication between members of the multidisciplinary team was identified as a facilitator, as working effectively in a team was found to mitigate some of the emotional burden and logistical constraints of conducting end-of-life conversations. The results to this study add to existing literature to provide Australian health-professionals' perspectives on factors that influence end-of-life conversations. Future work to address these identified barriers to effective end-of-life communication, and to support implementation of facilitators in practice, will ensure patients receive optimised treatment and symptom support, which will allow them to focus more on quality of life at the end-of-life stage.

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Applicant: Yujie Li
Supervisor: Dr Chai-Ann Ng

Decoding SCN2A: a high-throughput approach to characterise variants associated with epilepsy and neurodevelopmental disorders

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Background: SCN2A encodes the neuronal sodium channel Nav1.2 [1]. Variants in SCN2A are implicated in drug-resistant epilepsies, neurodevelopmental conditions and movement disorders [2]. While >1000 SCN2A missense variants have been identified, >800 are classified as variants of uncertain significance (VUS)3. High-throughput automated patch clamp assays (APC) have proven efficacy for reclassification of ion-channel gene variants and provide critical biophysical insights for guiding treatment [4-6].

Aim: To establish and validate a robust, high-throughput APC for characterising SCN2A variants.

Methods: Using a double-Flp-In method, SCN2A, SCN1B and SCN2B subunits were stably expressed in HEK293 cells [7, 8]. We assessed assay performance on 22 benign and 20 pathogenic variants, clinically classified without functional data. Variants were analysed for current density, steady-state activation/inactivation, window current, late current and rate of recovery from inactivation.

Results: We established ranges of function compatible with normal physiology for each parameter based on analysis of the 22 SCN2A benign variants. Using a cut-off of $Z < \pm 2$ (defined by the mean and standard deviation of the benign population), the APC assay had 95% specificity and 85% sensitivity for differentiating pathogenic and benign variants. These results provide strong functional evidence for pathogenicity (PS3_strong) and moderate-strength evidence (BS3_moderate) for benignity per ClinGen Sequence Variant Interpretation and ACMG guidelines for variant classification [9, 10].

Conclusion: Our APC assay, validated against gain-of-function and loss-of-function variants, offers a reproducible and efficient approach for interpreting SCN2A VUS as well as providing insights into biophysical mechanisms of altered function . Clinical implementation of our assay could reduce the diagnostic odyssey for patients and families.

Applicant: Yujie Li
Supervisor: Dr Chai-Ann Ng

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Applicant: Denise Lin
Supervisor: Dr Bettina Mihalas

Effect of Excessive NMN Supplementation on In Vitro Pre-Implantation Embryo Development.

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The rising prevalence of infertility has led to an increased demand for in vitro fertilisation (IVF). Recently, the supplementation of nicotinamide mononucleotide (NMN), a precursor of nicotinamide adenine dinucleotide (NAD+) biosynthesis, to IVF culture media has emerged as a promising approach to enhance embryo development and quality. However, supplementing NMN at high concentrations may adversely affect embryo development. Elevated NMN levels are hypothesised to increase NAD+, nicotinamide, 1-methylnicotinamide, and nicotinamide N-methyltransferase levels, leading to the depletion of methyl donors that are essential for embryo development.

This study investigated the effects of NMN at concentrations up to 1000 µM in IVF culture media. Oocytes from 5–7-week-old SwissTacAusb mice were subjected to IVF, and embryo developmental rates were assessed. We showed that increasing NMN concentrations of up to 1000 µM in IVF culture media have no adverse effects on pre-implantation embryo development. Via liquid chromatography-mass spectrometry, we confirmed that supplementing high concentrations of NMN led to increased NAD+, nicotinamide, and 1-methylnicotinamide levels. However, this may not correlate with a depletion of methyl donors. We also demonstrated that supplementation of the methyl donor, betaine, with high NMN concentrations had no effect on pre-implantation embryo development. Furthermore, when we induced an accumulation of nicotinamide via FK866 supplementation, betaine did not impact embryo development, suggesting that elevated nicotinamide may not substantially deplete methyl donors.

These findings suggest that NMN and betaine supplementation in IVF culture media could represent a safe approach to maintain or improve embryo development and quality, providing improved infertility solutions.

Applicant: Alison Ma
Supervisor: Prof Ralph Mobbs

Comparing patient recovery following endoscopic versus open lumbar spine surgery: an objective analysis of postoperative mobility and gait patterns using wearable sensors.

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There has been a gradual shift from traditional open spine surgery to minimally invasive spine surgery, including endoscopic spine surgery, to reduce approach-related trauma, collateral damage and complications (1). While surgeons have demonstrated interest in endoscopic spine surgery to improve recovery and surgical morbidity, broader practice has been limited by the steep learning curve due to challenges including lack of depth perception and spatial orientation (2). To date, there has been no objective evidence comparing post-operative recovery of endoscopic and open spine surgery using continuous measurements. Consequently, this prospective study compares mobility and postoperative gait patterns of endoscopic and open spine surgery patients by analysing data captured by a wearable sensor. Study participants comprised of 24 patients who underwent either a single-level endoscopic lumbar decompression or open lumbar fusion. During the first 48 hours post-surgery, patients wore a wireless sensor that continuously monitored position, step count and gait metrics. This study found that endoscopic spine surgery patients experience a quicker return to mobility, with less time lying down, higher daily step counts, faster walking speed, and greater stability in the first 48 hours post-surgery, compared to open surgery patients. These findings support the use of endoscopic techniques to enhance early post-operative recovery and mobility, predicting a better long-term recovery trajectory. These integral results can guide resource allocation towards endoscopic spine surgery and training program development for surgeons to build endoscopic skills to reduce recovery times and enhance patient care.

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Applicant: Hayley Mallinder
Supervisor: A/Prof Rebecca Deans

Exploring the effect of first laparoscopy in adolescent and young adult females and its association with chronic pelvic pain: a sub-study.

H. Mallinder and R. Deans

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Chronic pelvic pain (CPP) affects 5.7%-26.6% of women globally, severely impacting quality of life (1-4). Despite its prevalence, the condition is rarely acknowledged in isolation and is often considered a symptom of other diagnoses. Although disproportionately impacted by CPP, adolescent and young adult (AYA) females are underrepresented in clinical trials (5-9). Laparoscopy, a common diagnostic tool for CPP, often yields negative findings, making its application controversial in this demographic (10). This study aimed to evaluate the effectiveness of laparoscopy in improving pain and quality of life in AYA females after 12 months.

This sub-study of a single-centre, prospective comparative trial at the Royal Hospital for Women followed 50 AYA females aged 16-25 with CPP. Participants were allocated to either surgical or non-surgical management, with some selecting their treatment path and others assigned randomly. The study's primary outcomes were changes in pain, measured by the Brief Pain Inventory (BPI) Numerical Rating Scale (NRS), at >12 months post-intervention. Secondary outcomes assessed quality of life and psychological wellbeing.

Results revealed a statistically and clinically significant reduction in average pain scores in the surgical group (24.06%, $p<0.01$), while the non-surgical group showed a borderline statistically significant reduction (17.74%, $p=0.05$). Quality of life declined in both groups, with a more pronounced drop in the non-surgical cohort. These findings offer valuable insights into CPP management in AYA females, contributing to the ongoing debate about the role of surgery in CPP. Future research should prioritise larger trials and more comprehensive evaluations of non-surgical interventions.

Applicant: Hayley Mallinder
Supervisor: A/Prof Rebecca Deans

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ORAL

Applicant: Natasha Ong
Supervisor: Prof Ju Lee Oei

Inhaled Nitric Oxide for the Preterm Infant: a population-based study of mortality and morbidity outcomes.

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Background: Inhaled nitric oxide (iNO) is used to treat term infants with hypoxia from pulmonary hypertension but is also increasingly used to rescue preterm infants with respiratory failure1-3. Despite this, its impact on death and morbidity in extremely preterm infants (EPI, <29 weeks gestation) is uncertain.

Methodology: Linked population data for live births (n=1,154,865) between 1 January 2007 and 31 December 2018 in New South Wales, Australia was used to identify EPI and infants treated with iNO (n=1,429). Causal mediation analysis was used to determine the indirect effect of iNO on the risk of death before hospital discharge, bronchopulmonary dysplasia (BPD) and severe intraventricular haemorrhage (IVH; Grades 3-4) in EPI.

Results: A total of 5,497 EPI were admitted into an NICU between 2007-2018. Compared to EPI without iNO, EPI needing iNO were more likely to die (34.8 v 15.9%;p<0.001) and develop BPD (46.6% v 24.7%;p<0.001) and severe IVH (17.5% v 4.8%;p<0.001). Treating all EPI with iNO could counterfactually reduce risk of death versus that of a full-term infant (n=1,106,749), from OR 521.01(95% Confidence Interval[CI]:405.14,749.63) to 1.02(1.01,1.03), and the risk of BPD from OR 55.86 (95%CI:37.71, 98.87) to 1.02(1.01, 1.03) and IVH from OR 3.07(95%CI:2.82, 3.49) to 1.03 (1.02,1.04), after adjusting for confounders.

Conclusion: iNO is currently used only in the sickest preterm infants and the increased risk of adverse outcomes is not surprising. Treating all EPIs with iNO, however, may reduce risk of death and other complications of prematurity. These findings require further examination in large-scale, well-designed trials.

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Applicant: Mina Rezkalla
Supervisor: Prof Nick Di Girolamo

Characterisation of partial limbal stem cell deficiency induced by alkali injury in a preclinical mouse model.

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Background: Limbal stem cell deficiency (LSCD) is a debilitating eye disease that results from damage to limbal epithelial stem cells (LESCs) often secondary to alkali burns1. Depending on the extent of LESC destruction, it may be categorised as partial LSCD (pLSCD) or total LSCD (tLSCD), with up to a third of all cases being pLSCD2. To date, no animal models have been developed to successfully recapitulate the clinicopathological features of pLSCD3.

Methodology: Male and female 6-8 week old C57BL/6J mice (n=89) received an alkali injury to their right eye via topical application of 0.15M NaOH on the cornea. Clinical (slit-lamp and anterior segment optical coherence tomography), histopathological, and immunophenotypical assessments were performed on mice from 24 hrs to 9 months post-injury. Statistical analysis was performed using GraphPad Prism 10.2.0.

Results: The model successfully reproduced the clinical hallmarks of pLSCD demonstrating evidence of inflammation and self-repair within 3-months of injury. However, later time points exhibited evidence of stem cell exhaustion, yielding features that resemble tLSCD. These corneas displayed significant opacification ($P<0.0001$), were devoid of K12+ corneal epithelial cells ($P<0.01$), and instead were populated by K15+ conjunctival epithelial cells ($P=0.0125$), goblet cells and neovascularisation.

Conclusion: This model provides new insights into the biphasic pathological progression of pLSCD into what could be considered tLSCD. It also indicates that there may be a critical window of opportunity for treatment before the cornea is severely damaged. This study also presents a viable model for testing therapies that augment the function of damaged LESCs.

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Applicant: Vania Valentina Setyawan
Supervisor: Dr XingZhong Jin

The Effect of Bariatric Surgery Prior to Lower-Extremity Total Joint Arthroplasty on Prosthetic Joint Infection and All-cause Revision – A Target Trial Emulation Study of New South Wales Hospital Surgical Data.

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Obesity is a risk factor for postoperative complications following total joint arthroplasty (TJA) for osteoarthritis (OA) (1,2). While bariatric surgery (BS) has been suggested as an effective intervention to lose weight before TJA, its impact on TJA outcomes is inconclusive. This study aims to determine whether prior BS improves TJA outcomes for patients with severe obesity and OA.

A target emulation trial was conducted utilising two Australian databases. Patients who had undergone primary total knee arthroplasty (TKA) or total hip arthroplasty (THA) for OA were identified. Patients with severe obesity who had undergone prior BS were matched 1:1 with those who had not, by age, sex, ASA category, hospital characteristics, and comorbidities. A multivariable logistic regression model was conducted to assess adjusted odd ratios for prosthetic joint infection (PJI) and all-cause revision surgery at 90 days post-TKA/THA.

2,198 TKA and 802 THA patients were identified. The incidence of 90-day PJI was higher in patients with prior BS for TKA (1.8% versus 0.9%, P = 0.08) compared to those without. There was no statistically significant difference in incidence of PJI (1.0% versus 1.5%) or all-cause revision (1.7% versus 1.2%) between patients with prior BS and those who did not within 90 days post-THA.

BS prior to TJA may not reduce early-onset PJI and 90-day all-cause revision. Future studies are required to investigate the impact of BS on long-term infection and revision rate.

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ORAL

Applicant: Teresa Sheng
Supervisor: Prof Alta Schutte

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High blood pressure (BP) is the leading risk factor for preventable death globally and 1 in 3 Australian adults have hypertension1. With only 32% of Australians with hypertension having their BP controlled, it is urgent to improve current hypertension management practices2. A key intervention area is medical education, but the knowledge of Australian medical students and perspectives of medical teaching staff delivering the education is unknown. We investigated both of these aspects in our study. From February to June 2024 we distributed two online surveys, one for final-year medical students and one for academic and clinical staff affiliated with Australian medical schools. Medical students were questioned on two case studies, assessing 13 knowledge components. Staff and students scored their opinions of medical education training in hypertension using Likert scales.Medical students from 21 out of the 22 Australian medical schools participated in the survey. We received 270 student responses, of which 221 were complete. The average student score was 8.1/13 (62%) knowledge components answered correctly and the highest score achieved was 12/13 by one student. A passing score of 7/13 was achieved by 4 out of 5 students. Staff from 11 Australian medical schools participated with a total of 27 responses. Positive self-perceptions of confidence and knowledge were reported by 60% of students and staff. Student knowledge scores did not have any association with their self-perception of knowledge. Australian final-year medical students demonstrated insufficient knowledge regarding hypertension management, despite high confidence in knowledge and education from student and staff.

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Applicant: Stephen Siu
Supervisor: Prof Kei Lui

Evaluating the Novel Application of a Physiological Assessment Criteria for Chronic Lung Disease (CLD) in Extremely Preterm Infants (EPT) in a Neonatal Network.

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Background: CLD is a major morbidity in EPT survivors with long-term health burden. Current definitions are based on categorical respiratory support need at 36-week post-menstrual age (PMA). We hypothesise SHIFT Test,a novel continuous physiological assessment scoring the rightward shift of oxyhaemoglobin dissociation curve, has significant added predictive values.

Methodology: Population-based retrospective cohort study of ANZ infants born <28 w gestation between 2016-2020, who underwent SHIFT Test between 35+0 and 36+6 weeks PMA.

Results: Total 2866 infants, mean gestation 26.2 (SD 1.5) w and birthweight 857 g, were studied. Within 1867 (65.1%) infants with CLD at 36 w PMA, 1004 (53.8%) mild, 550 (29.5%) moderate, and 313 (16.8%) severe. Infants with CLD associated with lower gestation [26.0 (1.7) w vs 26.6 (1.0) w], small-for-gestational age (11.5% vs 2.2%), and male sex (57.3% vs 50.5%). SHIFT scores ranged from 8.7-82.6. Mechanical ventilation >250 hours was associated with increasing CLD severity and SHIFT scores ($p<0.001$). Multivariate analysis including perinatal factors and CLD definition showed high SHIFT scores independently associated with prolonged respiratory support beyond 40 weeks' PMA and home oxygen. SHIFT scores >20 demonstrated highest odds (adjusted OR=14.70, 95%CI 9.10-23.73, $p<0.001$). Increasing SHIFT scores showed clear stepwise increase in respiratory support duration, and compared favourable against other CLD definitions.

Conclusion: SHIFT Test demonstrated high potential to objectively measure and enhance CLD definitions in defining short-term outcomes of prolonged respiratory support. Further research needed to relate SHIFT Test results to other respiratory and neurodevelopmental outcomes, and adopt for quality improvement monitoring and benchmarking.

Applicant: Jemilla Strode Smith
Supervisor: A/Prof Keith Ooi

Anxiety in the pediatric cystic fibrosis population: evaluation of a younger cohort.

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Introduction: Elevated rates of anxiety have been observed in adults and teenagers with cystic fibrosis (CF). The International Committee on Mental Health in CF recommends commencing mental health screening at age twelve, yet limited data reports anxiety prevalence under this age cutoff. This single-centre study aimed to assess the risk of anxiety in a young pediatric cohort with CF.

Methods: Spence Children's Anxiety Scale questionnaires were distributed to CF participants and healthy controls ('HC') at baseline and follow-up at a single CF centre. Follow-up surveys distributed from 6 months after baseline.

Results: Surveys were collected from 41 patients with CF (Female= 21(51%), median (IQR) age =6.80 (2.30-12.40) years) and 43 HC (Female =18(42%), median (IQR) age =9.00(3.80-12.85) years). There was no significant difference in age (p=0.27) or gender (p=0.51) between groups. At baseline, 1 CF (2.5%) and 3 HC (7%) participants had elevated total anxiety scores. HC showed significantly higher social phobia/anxiety (W=654, p=0.04) and obsessive compulsive anxiety scores (W=644, p=0.02), when compared to CF participants.

Follow-up survey results were obtained from 20 CF patients (Female =12(60%), median (IQR) follow-up age =7.70(4.55-10.00) years) and 7 HC (Female =1(14.29%), median (IQR) follow-up age =12.94(12.80-15.95) years). No differences in total or subscale Spence scores or t-scores were observed in the follow-up period between cohorts.

Conclusion: Anxiety symptoms did not differ between CF and HC in our young cohort. Further large-scale, longitudinal studies are required to validate our findings and investigate the need for earlier intervention or screening for anxiety in CF preadolescents.

POSTER

Applicant: Jemilla Strode Smith
Supervisor: A/Prof Keith Ooi

Disorders of gut brain interaction in a pediatric cystic fibrosis cohort.

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Introduction: Disorders of gut brain interaction (DGBI) such as irritable bowel syndrome are higher in the adult cystic fibrosis (CF) population and are associated with impaired quality of life and significant health-system costs. Little is known of the prevalence of DGBI in children with CF (cwCF). This single-centre study aimed to assess the prevalence of DGBI in cwCF, compared to healthy controls (HC).

Methods: ROME IV surveys were distributed to cwCF and HC aged 0-18 years as part of the Evaluating the Alimentary Tracts in Health and Disease programme. Follow-up surveys were collated from 6 months after baseline over a period of 18 months.

Results: 44 cwCF (female=22(50%), median (IQR) age=7.04(2.25-11.06) years) and 48 HC (female=22(45.83%), median (IQR) age=8.04(3.57-12.77) years) completed baseline surveys. Symptoms consistent with DGBI were observed more frequently in cwCF compared to HC (31.82% versus 10.42%, p=0.02). However, no significant differences in the prevalence of specific disorders were observed between cwCF and HC. 29 cwCF (female=17(58.62%), median (IQR) follow-up age=9.42(6.08-12.17) years) and 10 HC (female=3(30%), median (IQR) follow-up age=12.83(7.83-15.50) years) completed follow-up surveys. In our cohort, postprandial distress decreased with age (p=0.01). Risk of other DGBIs did not significantly change over time.

Conclusion: In our cohort, cwCF were significantly more likely to experience at least one DGBI compared to HC, yet no specific DGBI was more prevalent in cwCF. Further large-scale studies are needed to validate our findings and ascertain the role of routine screening for DGBI in pediatric CF cohorts.

POSTER

Applicant: Geraldine Yang
Supervisor: Dr Jerome Ozkan

Investigating microplastic presence in eye drops using micro-fourier transform infrared spectroscopy

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The ubiquity of microplastics (MPs) in daily life has raised significant health concerns, however knowledge on how MPs can enter the eye is limited. MPs have a multitude of direct and indirect effects on human health, with a recent mouse study demonstrating that they can cause toxic, inflammatory, and dry eye like damage to the ocular surface [1-4]. The small size of MPs may facilitate their uptake into human tissues, including the vitreous humour [5]. Given the prevalence of plastic in eye drop packaging, MPs have the potential to be present in topical ocular medications and thus be absorbed into ocular and system tissues. This project aims to assess if microplastics are present in commonly used eye drop medications.

Commercially available eye drops from 20 brands were analysed in triplicate (n=60) for MPs. Particles ≥ 50 µm were examined using micro-Fourier Transform Infrared Spectroscopy and their identities were confirmed by cross-referencing with a comprehensive polymer and chemical database. Additionally, particle size and appearance were documented.

No MPs were identified in any of the 60 samples. While 484 visible particles were detected, none were confirmed as polymers through spectroscopic analysis. This underscores the necessity of using spectroscopic techniques for accurate particle identification, rather than assuming all visible particles are MPs.

The results indicate minimal evidence for the presence of MPs ≥ 50 µm in commercial eye drops. However, further investigation using advanced techniques, such as micro-Raman spectroscopy, is required to definitively rule out the presence of MPs in these products [6].

POSTER

Applicant: Geraldine Yang
Supervisor: Dr Jerome Ozkan

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Applicant: Kristy Yeats
Supervisor: Dr Charles de Bock

Understanding the genetic determinants regulating AKR1C3 expression in acute lymphoblastic leukaemia

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* Equal contribution

Continued development of novel targeted therapies is essential for patients diagnosed with acute lymphoblastic leukemia (ALL) to increase survival rates and minimise toxicities associated with conventional chemotherapy. ACHM-025 is a new prodrug that is activated into a potent alkylating agent by the enzyme aldo-keto reductase family 1 member C3 (AKR1C3). T-cell ALL (T-ALL) has high levels of AKR1C3 expression and is sensitive to ACHM-025. However, B-cell ALL (B-ALL) that accounts for 85% of ALL cases have low AKR1C3 expression and is resistant to ACHM-025. Therefore, identifying the genetic determinants that regulate AKR1C3 expression in both B-ALL and T-ALL is crucial to expanding the therapeutic potential of ACHM-025.

Using a bioinformatic approach, we identified two enhancer regions downstream of AKR1C3 gene locus predicted to regulate AKR1C3 expression. To determine whether these enhancers are important in regulating AKR1C3 expression, we used CRISPR/Cas9 to knock out the AKR1C3 gene or delete enhancer regions in T-ALL cell lines. Immunoblots and quantitative-PCR (qPCR) analysis showed a decrease in AKR1C3 expression and concomitant ACHM-025 resistance. Complementing this approach, we used CRISPR activation (CRISPRa)/dCas9 system in B-ALL cell lines to increase AKR1C3 expression. By targeting either the enhancer regions or AKR1C3 promoter, AKR1C3 expression was increased as was sensitivity to ACHM-025. This is the first study to show that endogenous expression of AKR1C3 can be regulated by targeting the promoter and downstream enhancer regions. These findings will support efforts to increase AKR1C3 expression and extend the use of ACHM-025 to both B-ALL and T-ALL leukemia patients.

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Patterns of clinical toxicologist referrals at the New South Wales Poisons Information Centre: Management advice for massive paracetamol ingestions

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Background: Australian Poisons Information Centres (PIC) receive over 200 000 calls annually, with 2-4% of calls referred to clinical toxicologists (1-2). Despite the significant prevalence of paracetamol exposures in NSW (3-4), n-Acetylcysteine (NAC) dosing guidelines for massive ingestion with a paracetamol ratio ≥3 have not been elucidated. Assessing for variation in management advice can inform opportunities to improve clinical guidelines and advance research.

Methods: This retrospective study explored the patterns of clinical toxicologist referrals in NSW PIC calls. Demographic and clinical data were collected. The variation in management advice provided for massive immediate-release paracetamol ingestions (≥30g or paracetamol ratio ≥2) was assessed through NAC dosing regimens. Data were analysed with descriptive statistics.

Results: Among 16 004 calls referred between 2017-2022, the average referral rate per year was 2.5%. Paracetamol was the most frequently cited substance in referred exposure calls (13%, 1158/9127) excluding recalls. For massive immediate-release paracetamol ingestions (n=61), the median ingested dose was 49 grams (IQR=29.6-50.0) and the median time to NAC was 7.8 hours (IQR=5.1-14.1). In patients who had a paracetamol ratio ≥3 (n=28; time to paracetamol level between 4-24 hours), single (n=1), double (n=18), triple (n=8) and quadruple (n=1) dose NAC regimens were recommended. Furthermore, 36% (10/28) of these individuals developed hepatotoxicity (ALT >1000U/L).

Conclusions: The lack of consensus observed regarding appropriate NAC dosing regimens is evident through the variation in management advice provided. Future research in evaluating the impact of different dosing regimens in massive paracetamol ingestions is critical to optimising clinical guidelines and patient care.

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