HealtheX 2021

Celebrating Student Research

CONFERENCE PROGRAMME BOOKLET
10TH SEPTEMBER

THE UNIVERSITY OF AUCKLAND
Te Whare Wānanga o Tāmaki Makaurau
NEW ZEALAND

MEDICAL AND HEALTH SCIENCES

THE UNIVERSITY OF AUCKLAND
Te Whare Wānanga o Tāmaki Makaurau
NEW ZEALAND

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F M H S POSTDOCTORAL SOCIETY

Message from the Dean

Dear Colleagues,

"Research is to see what everybody else has seen, and to think what nobody else has thought."
Albert Szent-Gyorgyi (1893-1986), a Hungarian-born biochemist and the first person to isolate vitamin C

On behalf of the Faculty of Medical and Health Sciences, it is my pleasure to welcome participants and visitors to HealtheX 2021, the fifteenth of our Faculty's celebrations of student health research and an opportunity for our students to showcase a lot of what nobody else has thought.

HealtheX is an opportunity to present in one day many of the research initiatives and themes that have helped our Faculty to be rated among the top one percent of biomedical and health faculties around the world. The event highlights the depth of talent and dedication of our students, and reiterates the importance of a strong, well supported research culture in improving health outcomes for New Zealanders in the short, medium and long terms.

HealtheX has been hugely successful in meeting the goals we as a Faculty set for it from the outset - to encourage and develop professionalism in the distillation and communication of our health research. The research projects on display at HealtheX in 2021 span a wide range of topics and activities, from the better understanding of the fundamentals of disease processes at the cellular level, through to the application of population based interventions.

I would like to acknowledge and thank the students and staff who collectively have ensured that HealtheX once again takes pride of place in the Faculty. Their efforts have ensured the event will again be a success and will again reflect well the tremendous quality of medical and health research being carried out across the Faculty of Medical and Health Sciences.

It is very appropriate to also recognise the support for HealtheX that is freely and generously provided by the Auckland Medical Research Foundation and the Maurice and Phyllis Paykel Trust. Without this support and encouragement, HealtheX would not have the impact and appeal it enjoys.
In closing, I hope each and every participant will enjoy the celebration of health research excellence by our students that is HealtheX 2021.

Professor John Fraser

Dean

Faculty of Medical and Health Sciences

On Behalf of the 2021 HealtheX Organising Committee

Dear Colleagues,

On behalf of the 2021 HealtheX organising committee, we are genuinely honoured to welcome you to the 15th anniversary of the Faculty of Medical and Health Sciences (FMHS) HealtheX conference, the Health Exposition celebrating student research.

Our long term goal has been to evolve HealtheX into a modern and reputable conference, comparable to many international conferences. Building on the progress and strengths of HealtheX 2020, we maintained a 'smart' and digitally secure abstract submission, access, judging, and administration portal. All of these avenues were built on and improved this year through the dedicated application of the extensive expertise of our beloved faculty staff member, and FMHS Staff Special Achievement award winner, Ian Sayer. His help aids in elevating HealtheX to the level of modern international conferences, providing a fertile and exciting platform for scientific networking, communication, and collaboration.

With HealtheX, we hope to provide students with ample opportunity for networking with each other and staff across the Faculty, creating an environment for research to be freely discussed, new ideas to flourish, and lasting collaborations to be forged. HealtheX therefore promotes and inspires research excellence, and has now become an annual celebration that is keenly anticipated and deeply embedded within the traditions of the Faculty. Our aim this year is to raise the standard and increase the exposure of HealtheX as a scientific conference. To do so, HealtheX 2021 has embraced the Zoom video conferencing platform in order to allow presenters, judges, and attendees to attend, participate, and compete despite COVID-19. In doing so, we hope to invite and encourage the wider community to attend the event and learn of the breakthrough scientific research being done by students at the University of Auckland. This year, we are also extremely proud to continue the success of previous HealtheX conferences, with an incredible number of presenters from both doctoral and non-doctoral research positions in biomedical, clinical, and public health fields. Through avenues of oral, poster, and 3-Minute Elevator Pitch communication categories, HealtheX imparts a colourful appreciation for the varied approaches taken by scientists to work towards the common goal of improving global health, and demonstrates the true scope and calibre of the ability of students.

HealtheX is a conference organised by the students for the students. The success of HealtheX 2021 is thanks, in no small part, to the commitment and hard work of the students and staff whose contribution continues to take HealtheX to greater heights. We thank our dedicated organising committee whose rigorous devotion over the past months has made this enjoyable and informative day possible. We are thankful for the supportive faculty academic and administrative staff for their invaluable mentorship and guidance. Last, but certainly not the least, the entire team of HealtheX 2021 is grateful for the trusted, continuous and generous support of the Auckland Medical Research Foundation, the Maurice and Phyllis Paykel Trust, FMHS Postdoc Society, FMHS Postgraduate Student Association, and the Liggins Institute. HealtheX is also grateful to the new collaboration with, and sponsorship by New Zealand Clinical Research.

We thank you all for your support, and we wish the participants the best for your presentation and future research aspirations.

Adelie Tan and Kyrah Thumbadoo

Co-Chairs

HealtheX 2021

Overall Schedule

Date: Friday 10th September
Time: 8:55 am - 6:00 pm
Location: Zoom

<table>
<tr><th>Time</th><th colspan="5">Programme</th></tr>
<tr><td rowspan="2">8:55 am - 10:15 am</td><td colspan="5">Oral Presentation Session 1</td></tr>
<tr><td>Room A
A1 - A5</td><td>Room B
B1 - B5</td><td>Room C
C1 - C5</td><td>Room D
D1 - D5</td><td>Room E
E1 - E5</td></tr>
<tr><td colspan="6">Break</td></tr>
<tr><td rowspan="2">10:40 am - 12:00 pm</td><td colspan="5">Oral Presentation Session 2</td></tr>
<tr><td>Room A
A6 - A10</td><td>Room B
B6 - B10</td><td>Room C
C6 - C10</td><td>Room D
D6 - D10</td><td>Room E
E6 - E10</td></tr>
<tr><td>12:15 pm - 1:15pm</td><td colspan="5">Poster Viewing Session</td></tr>
<tr><td rowspan="2">1:25 pm - 3:00 pm</td><td colspan="5">Oral Presentation Session 3</td></tr>
<tr><td>Room A
A11 - A16</td><td>Room B
B11 - B16</td><td>Room C
C11 - C16</td><td>Room D
D11 - D16</td><td>Room E
E11 - E16</td></tr>
<tr><td colspan="6">Break</td></tr>
<tr><td rowspan="2">3:30 pm - 6:00 pm</td><td colspan="5">3-Minute Elevator Pitch Competition</td></tr>
<tr><td colspan="5">Prize-Giving Ceremony</td></tr>
<tr><td colspan="6">Event Closes</td></tr>
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2021 HealtheX

Celebrating Student Research

Zoom Links

Oral Presentation Room A
https://auckland.zoom.us/j/99098732635?pwd=YnEwL2k3dlBGdC8yKzZza1J1bERHUT09
Meeting ID: 990 9873 2635
Passcode: 845381

Oral Presentation Room B
https://auckland.zoom.us/j/91774419092?pwd=SVpyNTd1Y0pvc2o3em5yVlExYSt3dz09
Meeting ID: 917 7441 9092
Passcode: 928448

Oral Presentation Room C
https://auckland.zoom.us/j/98487288341?pwd=R3FNWnRyZm9LWmpTZjBoZ3AxejdVZz09
Meeting ID: 984 8728 8341
Passcode: 299275

Oral Presentation Room D
https://auckland.zoom.us/j/92278760308?pwd=RzRrbjBzTjRJanlqL3lLT3djcWkzZz09
Meeting ID: 922 7876 0308
Passcode: 239193

Oral Presentation Room E
https://auckland.zoom.us/j/98801346442?pwd=bFRCeWRVUmVaajNXajR5VElxeGRnQT09
Meeting ID: 988 0134 6442
Passcode: 733228

Poster Viewing Session
https://auckland.zoom.us/j/99961065610?pwd=Y2xVUUg0cUhyUW9URVJrWXZkNUE5Zz09
Meeting ID: 999 6106 5610
Passcode: 146760

3-Minute Elevator Pitch and Prize Giving
https://auckland.zoom.us/j/95682816131?pwd=SXBKSHpxbkhkeFplZm1RaVArK1MzQT09
Meeting ID: 956 8281 6131
Passcode: 033552

Guide to Zoom

Set Up

If you haven't, download the zoom client on your device at:
https://zoom.us/download

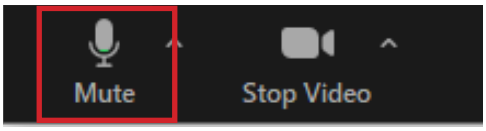
Or log in to the UoA Zoom client at:
https://auckland.zoom.us/

Once installed and logged in, just click on the linkson the previous page.

Oral Presentations

To ensure that the session flows smoothly, please read the housekeeping rules below.

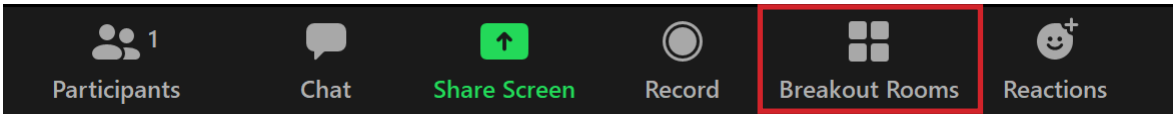
Once in the session, **please make sure that your microphone is muted** by checking the 'microphone' icon in the toolbar pictured below, in order to prevent any interruptions.



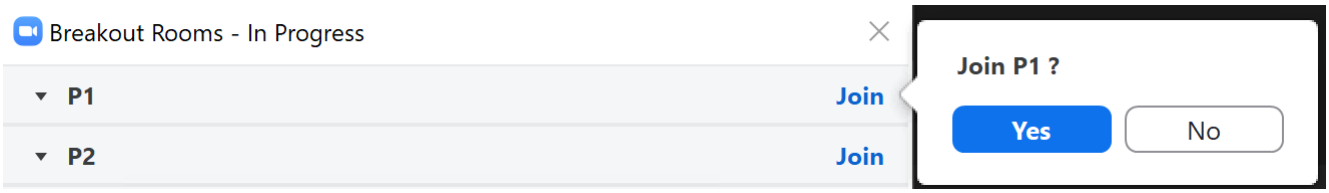
If you would like to ask a question to a presenter, open the 'chat' using the button pictured below during the question time and type your question into the chat. The room's chairperson will then call on you to ask your question at an appropriate time. Remember to un-mute yourself before speaking.

Poster Presentations

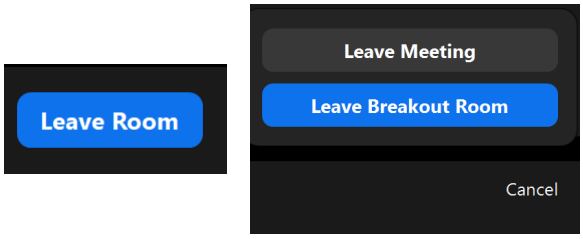
The Poster Viewing Session will be held using the Zoom Breakout Rooms. Once in the session, you can begin 'browsing' through the posters through the 'Breakout Rooms' icon in the toolbar pictured below.



Clicking on this button will pull up the list of Breakout Rooms assigned to each poster. Clicking the 'Join' button next to the poster you would like to go to will allow you to enter the Breakout Room.



To visit a different poster, repeat the previous steps. To leave this Breakout Room, click the 'Leave Room' button in the bottom left, if you wish to return to the Main Room, click 'Leave Breakout Room' and if you wish to leave the Poster Viewing Session altogether, click 'Leave Meeting'.



Time	Oral Presentations Room A
8:55 am	Introduction by Chairperson
9:00 am	**A1 - Conor Nelson** Supervisor: Associate Professor Deborah Young Characterisation of a novel transcription regulation system: optimising gene therapy in the central nervous system
9:15 am	**A2 - Caitlin Jardim** Supervisor: Dr Raewyn Poulsen Osteoarthritis: Uncovering gene expression differences between the sexes
9:30 am	**A3 - William Cook** Supervisor: Associate Professor Deborah Young Using a rapid adeno-associated virus vector screening method for optimising gene therapy for neurological disease
9:45 am	**A4 - Sophie Farrow** Supervisor: Professor Justin O'Sullivan Establishing gene regulatory networks from Parkinson's disease risk loci
10:00 am	**A5 - Alex Chan** Supervisor: Dr Troy Merry Identifying novel mitochondrial derived peptides by utilising natural variations in mtDNA
10:15 am	**Break**
10:40 am	Introduction by Chairperson
10:45 am	**A6 - Jos Smith** Supervisor: Associate Professor Johanna Montgomery Atrial fibrillation and synaptic plasticity in the intra-cardiac nervous system
11:00 am	**A7 - Anna Krstic** Supervisor: Dr Marie-Louise Ward Alterations in mitochondrial and cytosolic calcium fluxes in non-failing hypertrophic cardiomyocytes
11:15 am	**A8 - Samuel James** Supervisor: Dr Kim Mellor Molecular mechanisms of the cardiac glycogen response to physiological metabolic stress.
11:30 am	**A9 - Sachira Kuruppu** Supervisor: Dr Nira Paskaranandavadivel Electrophysiological and Contractile Nature of Mesenteric Ischemia Defined Through High-Resolution Electrical and Video Mapping.
11:45 am	**A10 - Sophie Piesse** Supervisor: Dr Sandy Lau Estrogenic influences on histological changes occurring in heart failure
12:15 pm	**Break and Poster Viewing Session**
1:25 pm	Introduction by Chairperson
1:30 pm	**A11 - Maize Cao** Supervisor: Dr Emma Scotter Identifying TDP-43 loss-of-function markers in amyotrophic lateral sclerosis with human derived brain pericytes
1:45 pm	**A12 - Dilani Senthuran** Supervisor: Professor Justin O'Sullivan Regulation of Autophagy by the Genetic Variants Associated With Huntingtin Gene
2:00 pm	**A13 - Molly Abraham** Supervisor: Dr Justin Dean Knockdown of specific hyaluronan synthases inhibits neurite development in hippocampal neurons in vitro
2:15 pm	**A14 - Serene Kim** Supervisor: Dr Molly Swanson Cell type-specific TDP-43 Nuclear Clearing and pTDP-43 Cytoplasmic Aggregation in Amyotrophic Lateral Sclerosis
2:30 pm	**A15 - Ieuan Sargent** Supervisor: Dr Malvindar Singh-Bains Blood-brain barrier pathology in the Huntington's disease human brain
2:45 pm	**A16 - Ernest Cheah** Supervisor: Associate Professor Darren Svirskis The development of electrically stimulated release of neurotrophic growth factors
3:00 pm	**Break**
3:30 pm	3-Minute Elevator Pitch Competition Prize Giving Ceremony
6:00 pm	**Event Closes**

Time	Oral Presentations Room B
8:55 am	Introduction by Chairperson
9:00 am	**B1 - Pang Yuk Cheung** Supervisor: Professor Alan Davidson Optimisation of oral cysteamine dosing in Ctns knockout rats
9:15 am	**B2 - Joseph Chen** Supervisor: Dr Suresh Muthukumaraswamy Scopolamine: a potential new pharmacotherapy for depression?
9:30 am	**B3 - Alice McDouall** Supervisor: Dr Joanne Davidson Tonabersat for treatment of hypoxic ischaemic brain injury in neonatal rats
9:45 am	**B4 - John Ho** Supervisor: Professor Mark McKeage Ergothioneine-mediated cytoprotective effects against oxaliplatin-mediated cytotoxicity in rat (Organic Cation Transporter) OCTN1 over-expressing HEK293 cells
10:00 am	**B5 - Benjamin Lear** Supervisor: Professor Laura Bennet Delayed tumor necrosis factor blockade after hypoxia-ischemia in fetal sheep ameliorates tertiary white matter injury
10:15 am	**Break**
10:40 am	Introduction by Chairperson
10:45 am	**B6 - Rebecca Hartley** Supervisor: Associate Professor Deborah Young Therapeutic effects of GluN1 antibodies
11:00 am	**B7 - Subhajit Konar** Supervisor: Dr David Musson Effect of fatty acid in tendinopathy
11:15 am	**B8 - Hossein Jahedi** Supervisor: Professor Cristin Print A hypothesis-generating tool to discover hyaluronic acid's biology in pancreatic cancer
11:30 am	**B9 - Sarah Fong** Supervisor: Dr Jichao Zhao Ryanodine Receptor is a Key Contributor to Enhanced Spontaneous Calcium Release Events in Metabolic Syndrome
11:45 am	**B10 - Wenxuan Chen** Supervisor: Dr Jonathan Astin IGF signalling mediates lymphatic vessel growth in zebrafish
12:15 pm	**Break and Poster Viewing Session**
1:25 pm	Introduction by Chairperson
1:30 pm	**B11 - Nishanth Francis** Supervisor: Dr Rosica Petrova Verification of the Expression of a Fourth Water Channel AQP3 In The Lens
1:45 pm	**B12 - Emily MacFarlane** Supervisor: Dr Gus Grey Presbyopia and Water Regulation in the Human Lens: the Relationship Between Syneresis and Protein Structure.
2:00 pm	**B13 - Anmol Sandhu** Supervisor: Professor Trevor Sherwin Optimising umbilical cord stem cells for the treatment of corneal endothelial disorders
2:15 pm	**B14 - Luis Knight** Supervisor: Dr Julie Lim Changes in mitochondrial function precede early retinal deposit formation in the cystine/ glutamate antiporter knockout mouse
2:30 pm	**B15 - Vicky Wen** Supervisor: Professor Trevor Sherwin Optimising the Isolation of Umbilical Cord Mesenchymal Stem Cells for the Treatment of Keratoconus
2:45 pm	**B16 - Ali Zahraei** Supervisor: Dr Gus Grey Mapping glucose uptake, transport and metabolism in the bovine lens
3:00 pm	**Break**
3:30 pm	3-Minute Elevator Pitch Competition Prize Giving Ceremony
6:00 pm	**Event Closes**

Time	Oral Presentations Room C
8:55 am	Introduction by Chairperson
9:00 am	**C1 - Jaime Lara** Supervisor: Dr Nira Paskaranandavadivel High-density electromyographic recordings for classification of hand gestures
9:15 am	**C2 - Petra White** Supervisor: Dr Justin Dean Assessment of cortical development using neurite orientation dispersion and density imaging in the neonatal rat
9:30 am	**C3 - Withdrawn**
9:45 am	**C4 - Brittany Manning** Supervisor: Dr Ali Mirjalili Freehand 3D-ultrasonography measurement of the volume of the triceps surae in premature infants in vivo
10:00 am	**C5 - Robyn May** Supervisor: Dr Soroush Safaei A computational model to identify cardiovascular remodelling related to prematurity and predict later cardiovascular risk
10:15 am	**Break**
10:40 am	Introduction by Chairperson
10:45 am	**C6 - Pippa McKelvie Sebileau** Supervisor: Dr Sarah Gerritsen He wairua tō te kai: Community views on regional food security and wellbeing in children
11:00 am	**C7 - Withdrawn**
11:15 am	**C8 - Magda Rosin** Supervisor: Professor Cliona Ni Mhurchu Supporting the implementation of the National Healthy Food and Drink Policy in New Zealand
11:30 am	**C9 - Bruce Kidd** Supervisor: Dr Sally Mackay The cost and greenhouse gas emissions of current, healthy, flexitarian and vegan diets in Aotearoa
11:45 am	**C10 - Litto Tharakan** Supervisor: Professor Caroline Crowther The impact of time of diagnosis of gestational diabetes on maternal and infant health outcome
12:15 pm	**Break and Poster Viewing Session**
1:25 pm	Introduction by Chairperson
1:30 pm	**C11 - Luisa Montoya Quesada** Supervisor: Associate Professor Bridget Kool Distribution of total prehospital time to first hospital for major trauma cases
1:45 pm	**C12 - Doris Zhang** Supervisor: Dr Gary Cheung The Impact of COVID19 Lockdown on Chinese Care Homes in New Zealand
2:00 pm	**C13 - Sara Mustafa** Supervisor: Professor Caroline Crowther Association of Dietary Adherence and Sociodemographic Factors Among Women with Gestational Diabetes: A Cohort Study
2:15 pm	**C14 - E Lyn Lee** Supervisor: Associate Professor Jo Barnes A scoping review of traditional, complementary and alternative medicine use in New Zealand
2:30 pm	**C15 - Sameer Bhat** Supervisor: Dr Marianne Lill Equity of colonoscopy provision and quality in Māori and New Zealand Europeans: a comparative study
2:45 pm	**C16 - Vida Bojovic** Supervisor: Dr Rhys Ponton An exploration of web-based guides used to prepare microdoses of psychedelic drugs
3:00 pm	**Break**
3:30 pm	3-Minute Elevator Pitch Competition Prize Giving Ceremony
6:00 pm	**Event Closes**

Time	Oral Presentations Room D
8:55 am	Introduction by Chairperson
9:00 am	**D1 - Charlotte Chen** Supervisor: Dr James Fisher Muscle metaboreflex sensitivity in Interstitial Lung Disease
9:15 am	**D2 - Conor O'Hanlon** Supervisor: Professor Brian Anderson An ex vivo study measuring cefazolin adsorption to cardiopulmonary bypass circuitry
9:30 am	**D3 - Oriana Munevar Aquite** Supervisor: Jay Gong The risk of bleeding with oral anticoagulants in patients with liver cirrhosis
9:45 am	**D4 - Kai Saw** Supervisor: Professor Ian Bissett Faecal immunochemical test as a triaging tool for patients with symptoms concerning for colorectal cancer
10:00 am	**D5 - Thomas Chang** Supervisor: Associate Professor Richard Roxburgh How good is the visually enhanced vestibulo-ocular reflex
10:15 am	**Break**
10:40 am	Introduction by Chairperson
10:45 am	**D6 - Kelly Zhou** Supervisor: Dr Joanne Davidson Persisting neuroinflammation and white matter injury and EEG power recovery after hypothermia
11:00 am	**D7 - Michael Beacom** Supervisor: Professor Laura Bennet Embracing the chaos of fetal heart variability: a biomarker for evolving fetal hypoxic-ischaemic brain injury
11:15 am	**D8 - Victoria King** Supervisor: Professor Laura Bennet Small and squishy: growth restriction in the chronically instrumented fetal sheep
11:30 am	**D9 - Yourong Feng** Supervisor: Professor Larry Chamley Do placental extracellular vesicles (EVs) have lasting effects on the maternal cardiovascular system?
11:45 am	**D10 - Darren Dai** Supervisor: Professor Dame Jane Harding Executive function and behaviour problems in school-age children after neonatal hypoglycaemia
12:15 pm	**Break and Poster Viewing Session**
1:25 pm	Introduction by Chairperson
1:30 pm	**D11 - Elizabeth Oliphant** Supervisor: Dr Jane Alsweiler Caffeine for the reduction of intermittent hypoxaemia in late preterm infants: the Latte Dosage Trial
1:45 pm	**D12 - Divya Mathews** Supervisor: Professor Paul Hofman Thyroid safety of hysterosalpingogram using oil soluble contrast medium for the woman and her offspring
2:00 pm	**D13 - Jennifer Barrowclough** Supervisor: Associate Professor Bridget Kool Maternal and infant outcomes of fetal malposition. A retrospective cohort study.
2:15 pm	**D14 - Samson Nivins** Supervisor: Professor Dame Jane Harding Smaller deep grey-matter volumes at nine years in children born at risk of neonatal hypoglycaemia
2:30 pm	**D15 - Devanshi Jani** Supervisor: Professor Peter Stone Effects of Maternal Position on Feto-Placental Blood Flow and Oxygenation in Fetal Growth Restriction.
2:45 pm	**D16 - Luam Ghebreab** Supervisor: Associate Professor Bridget Kool Antenatal and perinatal risk factors for unintentional injury among young children
3:00 pm	**Break**
3:30 pm	3-Minute Elevator Pitch Competition Prize Giving Ceremony
6:00 pm	**Event Closes**

Time	Oral Presentations Room E
8:55 am	Introduction by Chairperson
9:00 am	**E1 - Talia Allan** Supervisor: Dr Jonathan Astin The genetics of lymphatic vessel growth and guidance
9:15 am	**E2 - Sher Wei How** Supervisor: Professor Thomas Proft Characterization of a Novel Group A Streptococcus Virulence Factor: Spy0433
9:30 am	**E3 - Claudia Hall** Supervisor: Dr Barbara Lipert Discovering determinants of sensitivity and resistance to duocarmycin analogues using functional genomic CRISPR-Cas9 screening
9:45 am	**E4 - Withdrawn**
10:00 am	**E5 - Risa Takahashi** Supervisor: Dr Catherine Tsai Understanding the Innate Immune Response to Group A Streptococcus Pili
10:15 am	**Break**
10:40 am	Introduction by Chairperson
10:45 am	**E6 - Sita Clark** Supervisor: Professor Richard Douglas The pathogenesis of tonsillar hyperplasia in children
11:00 am	**E7 - Agrani Ratnayake Kumar** Supervisor: Dr Andrew Wood Ethnicity, deprivation and access to endoscopic sinus surgery
11:15 am	**E8 - Satya Amirapu** Supervisor: Professor Richard Douglas Sinonasal tissue remodelling during chronic rhinosinusitis
11:30 am	**E9 - Jackson Teh** Supervisor: Professor Richard Douglas Qualitative and quantitative analysis of bacterial microcolonies in the tonsils of patients with \tonsillar hyperplasia
11:45 am	**E10 - Tary Yin** Supervisor: Professor Richard Douglas The chronic rhinosinusitis microbiota: a one year longitudinal observational study
12:15 pm	**Break and Poster Viewing Session**
1:25 pm	Introduction by Chairperson
1:30 pm	**E11 - Chen Liu** Supervisor: Professor Ian Bissett Stoma-Output Reinfusion Device for Ileostomy Patients: A Feasibility Study
1:45 pm	**E12 - Samuel Robertson** Supervisor: Professor Greg O'Grady The impact of sleeve gastrectomy for weight loss on the gastric conduction system
2:00 pm	**E13 - Maria Sale** Supervisor: Dr Marco Schneider Smart surgical planning for anatomical ACL reconstruction
2:15 pm	**E14 - Faseeh Zaidi** Supervisor: Associate Professor Paul Monk Remote Patient Monitoring with Wearable Sensors following Knee Arthroplasty
2:30 pm	**E15 - Mei Lin Tay** Supervisor: Dr Simon Young Investigating mechanisms of failure for unicompartmental knee arthroplasty.
2:45 pm	**E16 - Cameron Wells** Supervisor: Professor Greg O'Grady Novel mechanisms of postoperative ileus and acute colonic pseudo-obstruction revealed by high resolution manometry
3:00 pm	**Break**
3:30 pm	3-Minute Elevator Pitch Competition Prize Giving Ceremony
6:00 pm	**Event Closes**

Poster Session	
P1 - Andrea Gu	Supervisor: Dr Stephen Jamieson
Analyses of whole-genome CRISPR/Cas9 screens identify genetic dependencies in NRAS-mutant melanoma	
P2 - Bhavya Chawdhary	Supervisor: Dr Andrea Kwakowsky
Tonabersat Rescues Inflammation in an Experimental Mouse Model of Multiple Sclerosis through Connexin-43 Hemichannel Blockade	
P3 - Chiara Gasteiger	Supervisor: Professor Keith Petrie
The delivery and content of communication strategies in biosimilar transitions: A systematic review with meta-analysis	
P4 - Delshad Kalantary	Supervisor: Dr Andrea Kwakowsky
In vivo fibre photometry in freely behaving mice: A technique to measure hippocampal neuronal activity	
P5 - Divya Mathews	Supervisor: Professor Paul Hofman
Hysterosalpingogram with oil soluble contrast medium causes iodine excess and improve pregnancy rates	
P6 - Dylan Pen	Supervisor: Professor Julian Paton
Differential expression of ectonucleotidase enzymes in carotid bodies of Spontaneously Hypertensive versus Wistar rats	
P7 - Edward Ferdian	Supervisor: Professor Alistair Young
Aortic wall shear stress estimation using deep learning on 4D Flow MRI	
P8 - Ethan Chen	Supervisor: Dr Victor Dieriks
Distinct α-synuclein conformations in Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy	
P9 - Florence Layburn	Supervisor: Dr Malvindar Singh-Bains
Immunohistochemical mapping of huntingtin protein distribution using human brain tissue microarrays	
P10 - Gabrielle Sebaratnam	Supervisor: Dr Elizabeth Broadbent
Can psychological factors and colonic motility predict postoperative complications? An observational pilot study	
P11 - Gemma Hughes-Waldon	Supervisor: Dr Caroline Walker
The role of genetic variation and childhood adversity on telomere attrition and psychosocial wellbeing	
P12 - Hanting Yong	Supervisor: Dr Tet Woo Lee
Unravelling the contribution of individual genes to tumour microenvironment stress tolerance in an unbiased fashion	
P13 - Henry Liu	Supervisor: Dr Amy Smith
Characterisation of microglia and astrocyte phenotypes in the Alzheimer's disease human brain	
P14 - Janelle Chong	Supervisor: Dr Guy Warman
The effects of general anaesthesia on the circadian clock	
P15 - John Ho	Supervisor: Professor Mark McKeage
Development and validation of a high-performance liquid chromatography-ultraviolet method for the quantification of ergothioneine	
P16 - Julia Newland	Supervisor: Dr Andrea Kwakowsky
KCC2 expression in the human Alzheimer's disease medial temporal lobe	
P17 - Judith Glasson	Supervisor: Dr Laura Domigan
Seeing is Believing in Ocular Biomaterials	
P18 - Julia Plank	Supervisor: Dr Joanne Lin
Validity of magnetic resonance spectroscopy combined with echo-planar spectroscopic imaging for measurement of neuroinflammation	
P19 - Julie Winter-Smith	Supervisor: Dr Vanessa Selak
Should Pacific people be homogenised when considering their need for CVD health services?	
P20 - Kim Rodan Burgos	Supervisor: Dr Andrea Kwakowsky
Understanding the Role of the GABA Signaling System in the Human Cerebral Vasculature	

Poster Session	
P21 - Kreesan Reddy	Supervisor: Dr Victor Dieriks
A strain-specific approach: Identification of novel therapeutic targets associated with distinct alpha Synuclein polymorphs	
P22 - Withdrawn	
P23 - Michele Zuppi	Supervisor: Dr Tommi Vatanen
The role of phages in Fecal Microbiota Transplant	
P24 - Molly Ferguson	Supervisor: Dr Andrea Kwakowsky
Mutant Huntingtin Aggregates and Neuroinflammation in the Huntington's disease Midcingulate Cortex	
P25 - Pang Ying Cheung	Supervisor: Dr Juliette Cheyne
Best method of delivering transgene for imaging widespread brain activity in live mice	
P26 - Phoebe Burns	Supervisor: Dr Dean Singleton
Investigating the influence of hypoxia on cGAS-STING signalling in macrophages	
P27 - Prakansha Kumar	Supervisor: Professor Peter Thorne
Effects of P2X Agonists and Antagonists in an In-vitro Rat Model of Cochlear Synaptopathy	
P28 - Withdrawn	
P29 - Rishi Pattabhiraman	Supervisor: Dr Bruce Harland
Assembly of a bioelectronic implant ("Backpack") for recording and stimulating the rat spinal cord.	
P30 - Samson Nivins	Supervisor: Professor Dame Jane Harding
Association between birth-size and brain volumes at nine years in children born late-preterm and at-term	
P31 - Withdrawn	
P32 - Shalinda Fernando	Supervisor: Professor Peter Shepherd
Investigating effects of RXFP4 and INSL5 gene variants found in Polynesian populations	
P33 - Shree Vijayaswathi Senthil Kumar	Supervisor: Dr Kathleen Mountjoy
Melanocortin-4 receptor activated calcium signalling is a potential new platform for screening anti-obesity therapeutics	
P34 - Soo Kim	Supervisor: Dr Andrea Kwakowsky
Optogenetic modulation of GABAergic system improves Aβ-induced memory deficits	
P35 - Svenja Meissner	Supervisor: Dr Brad Raos
The development of a hydrogel-based ultrasound-triggered delivery system for neurotrophic growth factors	
P36 - Taehoon Kim	Supervisor: Dr Nicholas Lightfoot
Association Between Quality of Recovery and Postoperative Opioid Use Following Elective Total Knee Arthroplasty	
P37 - Thalia Babbage	Supervisor: Dr James Fisher
Exercise training and chemoreflex sensitivity: endurance trained athletes versus untrained individuals	
P38 - Thulani Palpagama	Supervisor: Dr Andrea Kwakowsky
Neuroinflammation in the Human Cingulate Cortex in Huntington's disease	
P39 - Yasaman Emad	Supervisor: Professor Keith Petrie
Why do gout patients not take allopurinol?	
P40 - Yu Gao	Supervisor: Associate Professor Zimei Wu
Bufalin-doxorubicin combination therapy to target trastuzumab-resistant HER2 positive breast cancer	

Elevator Pitch
EP1 - Alice Little Supervisor: Dr Samantha Holdsworth Magnetic Resonance Imaging (MRI) of brain motion for non-invasive assessment of abnormal intracranial pressure
EP2 - Daiana Yedgey Supervisor: Professor Maurice Curtis Pathological load of phosphorylated α-synuclein and phosphorylated tau in the human olfactory mucosa
EP3 - Greta Holland Supervisor: Dr Vaughan Feisst Incorporating sweat gland organoids into a human 3D printed skin matrix
EP4 - Hadassah Patchigalla Supervisor: Dr Cherie Blenkiron A Multidisciplinary Approach to Understanding the Pathophysiology of Endometriosis
EP5 - Jenna Keepa Supervisor: Dr Cynthia Wensley Atrial Fibrillation after cardiac surgery; An analysis of New Zealand Cardiac Surgery Registry data
EP6 - Withdrawn
EP7 - Lucy Hinton Supervisor: Dr Ali Mirjalili Investigating the functional anatomy of the terminal thoracic duct and lymphovenous junction using ultrasonography
EP8 - Marvin Liu Supervisor: Associate Professor Jingyuan Wen Visualisation of PEGylated Nanocarrier for Thymopentin in Immunodepression Modulation
EP9 - Michael Brown Supervisor: Dr Moana Tercel What Makes a Good Sulfatase Substrate? Application in the Design of Antibody-Drug Conjugate Linkers.
EP10 - Michael Pudjihartono Supervisor: Professor Justin O'Sullivan Functional interpretation of enhancer mutations driving the onset and progression of melanoma
EP11 - Natasha Lust Supervisor: Dr Justin Dean THE ROLE OF CD44 IN NEURODEVELOPMENT: INTERACTIONS WITH HYALURONAN DURING RAT HIPPOCAMPAL NEURITE OUTGROWTH
EP12 - Nicholas Pudjihartono Supervisor: Professor Justin O'Sullivan Machine learning to identify the functional targets of genetic contributions to diseases with different heritability
EP13 - Oliver Wood Supervisor: Dr Andrea Kwakowsky EAAT2 expression in the Alzheimer's disease hippocampus, subiculum, entorhinal cortex and superior temporal gyrus.
EP14 - Serena Young Supervisor: Dr Petr Tomek Arylformamidase: a prospective drug target for potentiating cancer immunotherapy
EP15 - Taehoon Kim Supervisor: Dr Nicholas Lightfoot Effect of Perioperative Slow-Release Opioid Use on Long-Term Opioid Dispensing Following Total Knee Arthroplasty
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Pania Bridge-Comer, 2019 HealtheX winner says:
"After the global Covid-19 pandemic cancelled my original conference mid-travel, I'll now attend an alternate in virtual format. Even in the face of global crisis we can still bring together scientists and clinicians with extensive knowledge in my area of interest and provide a platform to not only disseminate my research, but to gain essential knowledge and connect with top researchers globally. I am extremely grateful for the opportunity AMRF's award grants me and wish to express my thanks to AMRF for their flexibility during these uncertain times."

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The FMHS and HealtheX greatly appreciate the assistance of the Liggins Institute, New Zealand Clinical Research, FMHS Postdoctoral Society, and FMHS Postgraduate Student Association in the funding and staging of HealtheX 2021.

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ABSTRACTS

Oral Presentations: Room A

A1

Characterisation of a novel transcription regulation system: optimising gene therapy in the central nervous system

Nelson C[1], Wu A[1], Mouravlev A[1], Fong D[1], Young D[1]
[1]Pharmacology & Clinical Pharmacology & Centre for Brain Research

Background: Gene therapy has the potential to change the way we treat neurological disease. A significant barrier to widespread clinical application of this technology in the central nervous system is transgene regulation. To fill this niche, our lab has developed a novel regulatory cassette that offers homeostatic control over therapeutic transgene transcription via proteolytic cleavage of a nuclear export signal from auxin response factor 5 (ARF5) in response to pathological stimuli. **Objectives:** Our primary objective was to characterise the capacity of the regulatory cassette to modify transgene expression in response to drug-stressors. We also tested the hypothesis that the quantity of reporter transgene (eGFP) generated scales with an increase in nuclear ARF5. Subsequent investigation questioned whether ARF5 gene truncation modifies the functionality of our regulatory system. **Methods:** Drug-stressor mediated calpain protease activation was induced within transformed *in vitro* systems, and changes in transgene expression with insult severity were assessed through immunocytochemistry and high content screening techniques. **Results:** It was observed that ARF5 localisation was modified in response to drug-stressors, and the production of the eGFP reporter scaled with the amount of nuclear ARF5. Notably, there was a significant difference in the ability of proteins generated by full-length and truncated ARF5 genes to drive eGFP production. **Discussion:** These findings have implications for the potential utility of these ARF5 genes in future cassettes. Following optimisation, this system may be able to effectively regulate transgene expression in neurological disorders associated with proteolytic induction.

Primary Supervisor: Associate Professor Deborah Young

A2

Osteoarthritis: Uncovering gene expression differences between the sexes

Jardim C[1], Jain L[2], Poulsen R[2]
[1]Department of Pharmacology, FMHS, UoA, [2]Department of Pharmacology

Background: Osteoarthritis (OA) is a degenerative disease affecting older adults (50+) with a female bias and is characterised by loss of articular cartilage resulting in joint damage physiologically and functionally, causing disabling symptoms & extensive burden of disease. Currently there are no clinical biomarkers or disease-modifying treatments for OA, and end-stage treatment involves total joint replacement. **Objectives:** To identify differential expression of disease-relevant phenotype markers, between males & females, in chondrocytes from patients with OA, and the effect of 17β estradiol on the markers. **Methods:** Chondrocytes were isolated from damaged OA & adjacent macroscopically normal cartilage from a total of 10 donors (5 male, 5 female) following total knee replacement surgery and cultured with/without 10nM 17β-estradiol for 24 hours. Real-time PCR was performed to measure differential gene expression between groups. **Results:** Multiple genes were significantly differentially expressed between males and females in osteoarthritic chondrocytes which included decreased *SOX9* ($p=0.001$) and *IL11* ($p=0.03$) in females. *SOX9* is a master transcription factor for chondrocyte lineage determination, and *IL11* is a pleiotropic cytokine typically anti-inflammatory in OA. There was no significant difference in gene relevant phenotype markers with 17β-estradiol treatment compared to control. **Discussion:** These results show sex differences in gene expression in OA-affected joints which may play a role in the female bias seen in OA. The lack of significant effect of 17β-estradiol treatment on gene expression explains the lack of efficacy of hormone replacement therapy as a treatment option for osteoarthritis.

Primary Supervisor: Dr Raewyn Poulsen

A3

Using a rapid adeno-associated virus vector screening method for optimising gene therapy for neurological disease

Cook W[1, 2], Wu A[1, 2], Cooper E[1, 2], Mouravlev A[1, 2], Fong D[1, 2], Correia J[3], Mee E[2], Schweder P[4], Park T I-H[1, 2], Dragunow M[1, 2], Young D[1, 2]

[1]Department of Pharmacology and Clinical Pharmacology, [2]Centre for Brain Research, [3]Department of Neurosurgery, Auckland City Hospital, [4]Department of Neurosurgery, Auckland City Hospital

Background: Adeno-associated virus vectors (AAVs) are the delivery vehicle of choice for gene therapy of the central nervous system (CNS). Successful clinical translation relies on the selection of efficient vectors for human use, and although multiple AAV serotypes and promoters exist, few have been directly compared. We have developed a rapid AAV screening method to aid the selection of optimal AAVs for the delivery of transgenes to specific target cells. **Objectives:** To determine the optimum AAV serotype and promoter combinations for transduction of specific CNS cell types. **Methods:** In proof-of-concept studies, primary mouse hippocampal neurons or patient-derived glioblastoma (GBM) cells cultured from biopsy tissue were treated with a panel of AAV serotypes expressing a green fluorescent protein (GFP). Cells were fixed at specific time points and high-content imaging was performed. **Results:** AAV serotypes varied in their ability to transduce these cell types. AAVs under the control of human synapsin promoter mediated strong GFP expression in mouse neurons. AAV serotypes 1 and 1/2 demonstrated the highest tropism for mouse neurons, 80% and 90%, respectively. While AAV2 and 6.2 appeared to be the strongest transducers of patient-derived GBM cells, transducing 50% of cells, these efficiencies were not significantly higher than other serotypes tested. **Discussion:** These results demonstrate probable advantages to using specific AAV serotypes for transducing mouse hippocampal neurons and patient-derived GBM cells. Our data suggest the utility of this approach as a tool to select AAV vector serotypes that are most efficient at delivering a transgene to a cell of interest.

Primary Supervisor: Associate Professor Deborah Young

A4

Establishing gene regulatory networks from Parkinson's disease risk loci

Farrow SL[1], Schierding W[1], Fadason T[1], Gokuladhas S[1], Golovina E[2], Cooper A[3], O'Sullivan JM[4]

[1]Liggins Institute, The Maurice Wilkins Centre, [2]Liggins Institute, [3]Australian Parkinson's Mission - Garvan Institute of Medical Research, St Vincent's Clinical School, UNSW Sydney, [4]Liggins Institute, The Maurice Wilkins Centre, Australian Parkinson's Mission - Garvan Institute of Medical Research, Brain Research NZ, MRC Lifecourse Epidemiology Unit - University of Southampton

Background: Parkinson's disease (PD) is a complex neurodegenerative illness. The latest meta-analysis of genome-wide association studies (GWAS) identified 90 independent variants across 78 genomic regions associated with PD. However, the majority of these variants are non-coding, and thus elucidating underlying functional mechanisms and identifying interactions remains a challenge. **Objectives:** We aimed to analyse the 90 variants within a regulatory network, as opposed to in isolation, to gain a global understanding of how they contribute to PD. **Methods:** To establish the functional gene regulatory networks associated with these 90 variants, we utilised an approach combining spatial (chromosomal conformation capture) and functional eQTL data. We then used Louvain clustering methods to identify significantly connected clusters within the gene regulatory network. **Results:** We identified 518 genes subject to regulation by 76 of the 90 variants across 49 tissues (36 peripheral and 13 CNS). Notably, one-third of these genes, including a known PARK gene – SYNJ1, were regulated via trans-acting mechanisms (>1Mb). Through utilising Louvain clustering we extracted nine significant and highly intra-connected clusters within the entire gene regulatory network. The nine clusters are enriched for specific biological pathways, some of which have only recently been considered in association with PD, such as DNA replication and repair. **Discussion:** Together, our results contribute to an overall understanding of the mechanisms and impact of specific combinations of PD GWAS variants.

Primary Supervisor: Professor Justin O'Sullivan

A5

Identifying novel mitochondrial derived peptides by utilising natural variations in mtDNA

Chan A[1], Hedges C[1], Merry T[1], Gosling A[2], Miller B[3], Kim SJ[3], Yen K[3], Kumagai H[3], Cohen P[3], Merriman T[4]

[1]Department of Nutrition, UoA, [2]Department of Anatomy, UoO, [3]Leonard Davis School of Gerontology, USC, [4]Department of Biochemistry, UoO

Background: The mitochondrial DNA (mtDNA) encodes more than 700 short open reading frames (sORFs) and to date, eight sORFs have been found to encode bioactive mitochondrial-derived peptides (MDPs) that regulate metabolic health. **Objectives:** To identify novel MDPs by associations between metabolic diseases and single nucleotide polymorphisms (SNPs) in sORFs that lead to amino acid changes in putative MDPs. **Methods:** Analysis on mtDNA sequences from 931 participants with Polynesian ancestry revealed the SNP A6905G was associated with gout (n=456; OR=4.39, p=0.02156) and diabetes (n=309; OR=1.91, p=0.002829). A6905G alters the sequences of putative MDPs 34A, 29B, and 59C. To directly test whether the native forms of these MDPs could improve metabolic function, we fed mice a high-fat diet for 10 weeks and treated them daily (i.p, 5mg/kg) with 34A, 29B, or 59C and assessed changes in body composition, glucose homeostasis, and energy metabolism. **Results:** High-fat diet treatment resulted in an increase in fat mass, impairs glucose tolerance, insulin resistance, and both fed and fasted hyperglycaemia. However, there was no effect of MDP treatment on these metabolic phenotypes. Resting energy expenditure, activity levels, and food intake were similar between control and all MDP treated groups. **Discussion:** We identified an association between diabetes prevalence with a mtDNA SNP, potentially encoding three MDPs. Individually treating each native MDP in mice on a high-fat diet did not change their metabolic phenotype. Whilst the current study did not show a protective effect of the MDPs, further research will help elucidate their biological relevance on metabolic health.

Primary Supervisor: Dr Troy Merry

A6

Atrial fibrillation and synaptic plasticity in the intra-cardiac nervous system

Smith J E G[1], Montgomery J M[1]

[1]Department of Physiology

Background: Atrial Fibrillation (AF) is the most common type of arrhythmia and has severe clinical outcomes. Interconnected groups of neurons termed ganglionated plexi (GP) are found within the hearts epicardial fat. These GP represent the final site of integration of neuronal signals that control heart function and have been implicated in the induction and maintenance of AF. **Objectives:** To determine whether changes in GP neuron excitability (synaptic plasticity) underlie AF. We have pioneered the use of Cal520, a Calcium indicator dye, to visualise calcium changes in ex-vivo GP slice preparations. We assessed the calcium response of neurons to acetylcholine, the major neurotransmitter in the GP, in Spontaneously Hypertensive Rats (SHRs) (an established model for AF) and Wistar Kyoto (WKY) controls. **Results:** The amplitude (SHR 0.0713±0.00645 vs. WKY 0.0530±0.00456 dF/F_0, p=0.0428) and width (SHR 8.78±0.469 vs. WKY 5.71±2.96 p<0.0001) of calcium transients with acetylthiocholine application was greater in SHRs than in WKYs. This response was partially blocked in both groups by Hexamethonium, a nicotinic acetylcholine receptor inhibitor. These findings were validated with whole-cell patch clamp electrophysiology to record the electrical responses of individual GP neurons to acetylthiocholine stimulation. **Discussion:** Together, these data show that while nicotinic acetylcholine receptors have a major role at GP synapses, other receptor subtypes may also be involved. Furthermore, the exaggerated response of SHR GP neurons to cholinergic stimulation suggests that these neurons are more excitable in the disease state, consistent with our hypothesis that the GP neuron plasticity is aberrant in AF.

Primary Supervisor: Associate Professor Johanna Montgomery

A7

Alterations in mitochondrial and cytosolic calcium fluxes in non-failing hypertrophic cardiomyocytes

Krstic A[1], Ward ML[1]
[1]Department of Physiology

Background: Mitochondrial calcium flux is a key regulator of ATP production in the heart. Pathological ventricular hypertrophy has been associated with alterations in Ca^{2+} handling and mitochondrial function. Previous findings from a rat model of right ventricular (RV) hypertrophy showed both asynchronized Ca^{2+} handling and reduced mitochondrial ATP supply. **Objectives:** Our aim was to investigate mitochondrial and cytosolic calcium fluxes in isolated, hypertrophic cardiomyocytes prior to the onset of heart failure. **Methods:** A protocol for obtaining beat-to-beat mitochondrial calcium signals using di-hydroRhod-2AM was optimized using isolated ventricular myocytes. Subsequently, Male Wistar rats were injected with 60mgkg^{-1} monocrotaline (MCT, n=7) or saline (CON, n=8). Four weeks post injection, hearts were isolated and enzymatically digested to yield rod-shaped, quiescent cardiomyocytes. RV myocytes were collected and measurements of mitochondrial Ca^{2+}, intracellular Ca^{2+} (fura-2AM) and Ca^{2+} sparks (Fluo-4AM) were made. **Results:** Beat-to-beat mitochondrial calcium transients ($[Ca^{2+}]_m$) were smaller in amplitude and had a slower time to peak ($P<0.001$) relative to cytosolic Ca^{2+} transients. Hypertrophic MCT myocytes showed larger beat-to-beat changes in $[Ca^{2+}]_m$ relative to CON myocytes at 0.1Hz and 0.5Hz ($P<0.001$). Furthermore, MCT myocytes also had larger intracellular Ca^{2+} transients and Ca^{2+} spark amplitudes relative to CON myocytes. **Discussion:** Our results show $[Ca^{2+}]_m$ transients occur on a beat-to-beat basis, and for the first time, we have shown that these transients are larger in hypertrophic myocytes relative to healthy, control myocytes. This could potentially indicate a need for increased mitochondrial ATP production in order to match energy supply to the higher demands of hypertrophic myocytes.

Primary Supervisor: Dr Marie-Louise Ward

A8

Molecular mechanisms of the cardiac glycogen response to physiological metabolic stress.

James S[1], Koutsifeli P[1], Mellor K[1], Merry T[2], Delbridge L[3]
[1]Department of Physiology, [2]Department of Nutrition, [3]University of Melbourne

Background: Cardiac glycogen accumulation can be observed in response to cardiac metabolic stress, in both pathophysiological and physiological settings. Understanding the regulatory mechanisms underlying the glycogen response to exercise may highlight differences from pathological mechanisms in disease states. **Objectives:** The aim of this study was to track the time-course of the cardiac glycogen response to physiological metabolic stress (exercise) and examine glycogen regulatory mechanisms. **Methods:** Cardiac tissues were collected from mice following either 8 weeks voluntary running-wheel, 1hr high intensity interval (treadmill; 0, 2, 4 and 16hrs post-exercise) or exhaustive exercise (treadmill; 0, 2, 4 and 16hrs post-exercise). Glycogen was measured by amyloglucosidase assay and protein expression evaluated by immunoblot. **Results:** Cardiac glycogen content was positively correlated with running distance over 8 weeks. Following high intensity interval exercise, delayed cardiac glycogen accumulation was evident at 16hrs (1.8-fold). Following exhaustive exercise, cardiac glycogen elevation peaked at 2hrs (3.7-fold) and remained elevated at 16hrs (1.6-fold). In this model, initial glycogen synthase activation was evident, followed by inactivation at 2 and 4hrs post-exercise. Glycogen recovery towards basal levels was not associated with upregulation of the cytosolic glycogen degradation enzyme, phosphorylase, and may be mediated by autophagic-lysosomal breakdown. Upregulation of the glycophagosome protein, GABARAPL1, was observed at 16hrs post-exercise. **Discussion:** This study provides evidence that glycogen synthase drives the initial cardiac glycogen response to physiological metabolic stress, but phosphorylase-mediated glycogen degradation appears not to be involved in glycogen recovery. Evidence suggests a role for autophagic-lysosomal degradation of glycogen post-exercise and further research is warranted.

Primary Supervisor: Dr Kim Mellor

A9

Electrophysiological and Contractile Nature of Mesenteric Ischemia Defined Through High-Resolution Electrical and Video Mapping.

Kuruppu S[1], Cheng LK[1], Angeli-Gordon TR[1], Avci R[1], Paskaranandavadivel N[1]
[1]Auckland Bioengineering Institute

Background: Intestinal motility is governed, in part, by bioelectrical 'slow-waves' and 'spike-bursts'. Electrophysiological changes during mesenteric ischemia due to restricted blood flow, are not well-understood. **Objectives:** To map the bioelectrical signals and intestinal deformations due to ischemia and reperfusion. **Methods:** Experiments were performed on (n=5) anesthetised pigs. A segment of the small intestine jejunum was exteriorised, and placed on a high-resolution electrode array (16×8 configuration; inter-electrode spacing: 4mm) to record slow-waves and spike-bursts, from which their frequencies were quantified. Contractions were simultaneously captured using a machine vision camera, and the intestinal diameter was measured. The section of mesentery supplying blood to the intestinal segment was clamped to cause ischemia (duration=18.2±9.0min), and later unclamped for reperfusion (duration=3.5±1.0min). Repeated measures ANOVA and Tukey post-hoc test were used to test for statistical significance. **Results:** Slow-wave entrainment within the ischemic region diminished, resulting in sporadic slow-wave activations, and a reduction in the baseline frequency from 12.4±3.0 cycles-per-minute (cpm) to 2.5±2.7cpm ($p<0.001$). After reperfusion, slow-waves regained the normal periodic nature and increased to 11.5±2.9cpm ($p=0.002$). Spike-bursts increased from baseline to ischemia (1.1±1.5cpm vs. 7.1±2.6cpm, $p=0.001$), and decreased to 2.7±1.4cpm after reperfusion ($p=0.01$). The intestine underwent tonal contraction during ischemia. The diameter decreased from baseline to ischemia (29.3±2.6mm vs. 21.2±6.2mm, $p=0.002$), and increased to 27.3±3.9mm during reperfusion ($p=0.041$). Baseline and reperfusion measurements were statistically similar ($p>0.05$). **Discussion:** Decrease in slow-waves, increase in spike-bursts, and presence of tonal contraction can objectively identify ischemic segments in the intestine, and could verify successful revascularisation in bowel resection surgery.
Primary Supervisor: Dr Nira Paskaranandavadivel

A10

Estrogenic influences on histological changes occurring in heart failure

Piesse S[1], Loftus M[1], Barrett C[1], Lau S[2]
[1]Department of Physiology, [2]Department of Obstetrics and Gynaecology

Background: Globally, 1-2% of people present with heart failure (HF), with men and women at equal risk of developing the disease. Aetiology, clinical presentation and outcome of HF are sexually dimorphic. Heart failure tends to develop when women are post-menopausal, suggesting an association between sex hormones and development of HF in women. **Objectives:** The objective of this work is to compare cardiac remodelling following myocardial infarction (MI) between pre- and post-menopausal states. **Methods:** Ovariectomized rats modelled the post-menopausal state. MIs were modelled by ligation of the left anterior descending coronary artery. Four groups were studied: ovariectomy + MI (n=9), ovariectomy + sham MI (n=6), sham ovariectomy + MI (n=7) or sham ovariectomy + sham MI (n=10). Eight weeks post-MI, hearts were sectioned and stained with Masson's trichrome to quantify heart dimensions, infarct size and fibrosis. Myocyte size and t-tubule density will be quantified after staining with phalloidin and wheat germ agglutinin. Immunohistochemistry of tyrosine hydroxylase will quantify sympathetic innervation to the heart. **Results:** At eight weeks post-MI, female rat hearts were not significantly heavier than Sham-MI hearts. Ejection fraction was reduced in the ovariectomy + MI group, but not the sham ovariectomy + MI group. Analysis is ongoing to establish the histological differences between pre- and post-menopausal women during HF. **Discussion:** The cessation of ovarian estrogen production may alter myocardial remodelling processes explaining the age and sex-related differences in HF presentation. Understanding this relationship could lead to changes in the clinical management of women with HF, improving health outcomes.
Primary Supervisor: Dr Sandy Lau

A11

Identifying TDP-43 loss-of-function markers in amyotrophic lateral sclerosis with human derived brain pericytes

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Background: Amyotrophic lateral sclerosis (ALS) is a neurological movement disorder that is fatal within 2-5 years after diagnosis. ALS lacks reliable diagnostics and effective treatment, likely due to the heterogeneity of disease. However, a common pathological signature exists in 97% of ALS cases; the aggregation of TAR-DNA binding protein (TDP-43) in motor neurons. TDP-43 normally resides in the nucleus and interacts with DNA and RNA, therefore it has a critical role in regulating gene expression. **Objectives:** We aim to identify mRNA and protein targets of TDP-43 loss-of-function to assess the mechanistic role of TDP-43 in ALS. **Methods:** We generated a TDP-43 loss-of-function model by depleting TDP-43 using siRNA in primary human brain pericytes. The resulting gene expression and splicing changes were determined by RNA sequencing. Quantitative RT-PCR and immunoassays were then performed to validate these changes. **Results:** Differentially expressed genes (padj <0.05, fold change >2) included *RANBP1*, *PFKP* and *KIAA1324*. Additionally, TDP-43 knockdown led to the inclusion of 'cryptic exons' in the transcripts of several genes. These appeared in *EXD3*, *NYNRIN* and ALS-associated gene *UNC13A*. These changes were all confirmed by quantitative RT-PCR. To extend these findings, we aim to evaluate whether these TDP-43 loss-of-function mRNA markers and their cognate proteins can be detected in ALS brain tissue. **Discussion:** Understanding whether TDP-43 loss-of-function is pathomechanistic in ALS, and in what cell types it occurs, will inform the development of therapeutic strategies to restore TDP-43 function.
Primary Supervisor: Dr Emma Scotter

A12

Regulation of Autophagy by the Genetic Variants Associated With Huntingtin Gene

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Background: Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded trinucleotide repeat (CAG) in the first exon of the huntingtin gene (*HTT*). Expanded trinucleotide repeats are associated with severity of the neurodegenerative process, with greater than 40 repeats considered pathological. Normal *HTT* is ubiquitously expressed and regulates many processes, including autophagy (delivery of aggregated proteins to the lysosome for degradation). Pathological trinucleotide expansion leads to protein aggregation and a breakdown of the autosomal pathway. Genome-wide, there are genetic variants associated with *HTT*/HD as well as changes in gene expression across 9 neural tissues in the GTEx database. **Objectives:** To determine the biological impact of common genetic variants within *HTT* and their potential for modulating the penetrance of HD. **Methods:** CoDeS3D identified expression quantitative trait loci (eQTLs) which modify *HTT* expression in brain tissues, as well as which genes these variants co-regulate. CoDeS3D identified eQTLs present in the *HTT* locus which regulate other HD-related genes in brain tissues. All associated genes were searched for associations with *HTT* or HD by literature review. **Results:** Two eQTLs regulate *HTT* in the amygdala and co-regulate two other genes in nerve-tibial tissues. 37 eQTLs present in the *HTT* locus regulate four genes in four brain tissues. Collectively, these 39 genetic variants regulate a set of genes that are associated with autophagy. **Discussion:** Autophagy is important for cell survival in neurodegenerative disorders. Variants which impact *HTT* and its co-regulated genes regulate autophagy. Thus, the associated eQTLs could impact HD by inhibiting autophagy.
Primary Supervisor: Professor Justin O'Sullivan

A13

Knockdown of specific hyaluronan synthases inhibits neurite development in hippocampal neurons in vitro

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[1]Department of Physiology

Background: The brain's extracellular matrix (ECM) provides key structural and functional support to neurons and glial cells. Hyaluronan is a major component of the developing brain's ECM and is synthesised by the family of hyaluronan synthases (HAS1–3). Our lab previously demonstrated that developing neurons express functional HAS2 and HAS3 enzymes *in vitro*. However, the role of HAS enzymes and hyaluronan in neurodevelopment remains unclear. This study aimed to examine the effects of HAS2 or HAS3 knockdown on the morphological development of immature hippocampal neurons *in vitro*. **Methods:** HAS 2-3 Knockdown was achieved using short hairpin loop RNA (shRNA)-based interference of protein translation. Primary hippocampal neuron cultures were established from E18 rat embryos. Neurons were transfected at days *in vitro* 0 (DIV0; 2 hr) using Lipofectamine 3000 with shHAS2, shHAS3, and scrambled controls. To quantify changes in HAS protein and hyaluronan expression, cells were fixed at DIV7 for immunocytochemistry with HAS2–3 antibodies and hyaluronic acid binding protein. For morphological analyses, transfected cells were live-imaged at DIV7 and traced with Neurolucida software. **Results:** Selective knockdown of HAS2 and HAS3 reduced relevant HAS protein and hyaluronan expression on transfected knockdown neurons compared to adjacent untransfected cells and scrambled controls. Preliminary morphological analyses suggest that HAS2 or HAS3 knockdown reduced developing neurite length and complexity. Further, HAS2 knockdown also reduced putative axonal length at DIV7 compared to scrambled controls. **Discussion:** Overall, these findings suggest that hyaluronan synthesis by developing hippocampal neurons is important for control of neurite extension.

Primary Supervisor: Dr Justin Mark Dean

A14

Cell type-specific TDP-43 Nuclear Clearing and pTDP-43 Cytoplasmic Aggregation in Amyotrophic Lateral Sclerosis

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Background: Tar DNA-binding protein 43 (TDP-43) is a key protein in the pathogenesis of Amyotrophic Lateral Sclerosis (ALS), with 97% of ALS cases exhibiting cytoplasmic phosphorylated TDP-43 (pTDP-43) aggregates. pTDP-43 aggregation is thought to cause both a toxic gain of function and loss of wildtype TDP-43 function. The loss of function is thought to be driven by the sequestration of TDP-43 into aggregates, leading to 'clearing' of TDP-43 from the nucleus. To date, research has focused on TDP-43 nuclear clearing and aggregation in motor neurons, but TDP-43 localisation and function in other neuronal subtypes and in non-neuronal cells in ALS are poorly understood. **Objectives:** We aim to determine which neuronal subtypes and non-neuronal cells undergo TDP-43 nuclear clearing and/or pTDP-43 cytoplasmic aggregation in the ALS brain. **Methods:** We will utilise post-mortem human motor cortex from 10 ALS and 5 normal cases. We will use multiplex immunohistochemistry to co-label TDP-43, pTDP-43, and specific markers for neurons, oligodendrocytes, astrocytes, endothelia, and microglia. Single-cell image analysis will be conducted for cell identification and quantification of nuclear TDP-43 and cytoplasmic pTDP-43. **Results:** In the ALS motor cortex, we expect to see pTDP-43 aggregates in neurons, oligodendrocytes, and in some microglia. It is yet unclear whether astrocytes and endothelia will harbour aggregates. Furthermore, we expect to see nuclear clearing in ALS motor neurons, but it is unclear whether we will see clearing in other neuronal subtypes. **Discussion:** A robust characterisation of TDP-43 dysfunction in ALS may reveal useful biomarkers or potential cell-type-specific therapeutic targets.

Primary Supervisor: Dr Molly Swanson

A15

Blood-brain barrier pathology in the Huntington's disease human brain

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Background: Although there are no current disease-modifying treatments for Huntington's disease (HD), clinical trials have targeted the brain through intrathecal injections of huntingtin protein—lowering therapies. Whilst this is one approach to deliver potential therapeutics to the brain, other delivery pathways exist. In healthy individuals, the blood-brain-barrier (BBB) serves as a highly selective barrier, protecting the brain from foreign matter while serving as a potential gateway for therapeutics. During disease, the BBB may become dysfunctional and problematic for drug delivery. In HD, evidence surrounding BBB dysfunction is emerging and has been linked to disease pathogenesis. However, the defined role of BBB cell types in the HD human brain is yet to be fully elucidated. **Objectives:** This study investigates the role of the BBB in human HD through immunohistochemical screens on human brain tissue microarrays (HBTMAs). **Methods:** 3,3'-diaminobenzidine (DAB) and fluorescence immunohistochemistry was carried out using antibodies specific for human brain BBB cells on paraffin embedded HBTMAs, containing up to 55 cortical samples from both control and HD brains. Images of immunoreactivity were acquired using a Vslide microscope and analysed with Metamorph software. **Results:** Preliminary results demonstrate successful immunoreactivity with 2 pericyte markers, 2 endothelial cell markers, vascular smooth muscle cells and basement-membrane associated extracellular matrix molecules within the BBB. Further investigation will reveal any significant differences for each marker between control and HD human brain tissue within the HBTMAs. **Discussion:** Deducing the role of the BBB and its various cellular components in HD will unveil new targets for treatment strategies.
Primary Supervisor: Dr Malvindar Singh-Bains

A16

The development of electrically stimulated release of neurotrophic growth factors

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Background: Spinal cord injury is a debilitating and devastating condition that often affects healthy individuals worldwide. Injuries to the spinal cord cause axonal connection disruptions so the reestablishment of these networks are required for functional recovery. Neurotrophic growth factors are a family of polypeptides that have been shown to positively influence neuronal regrowth but its clinical use is limited due to difficulties in appropriate delivery to the injury site. **Objectives:** To develop a electrically stimulated drug delivery system capable of delivering neurotrophic growth factors in a tuneable manner. **Methods:** A conducting polymer hydrogel (CPH) was developed utilising a network of gelatin methacrylate and poly(3,4-ethylenedioxythiophene) doped with para-toluene sulfonate. The CPH was loaded with bovine serum albumin as a model protein. Passive release was compared to electrically stimulated release over 4 hours. **Results:** Electrical stimulation was found to modulate protein release from the CPH. A negative constant potential (-0.6 V) stimulation increased the rate of release by 73.5% ($p = 0.0049$), while a positive constant potential (0.6 V) stimulation reduced the rate of release by 33.7% ($p = 0.0316$) when compared to passive diffusion over 4 hours. **Discussion:** Performance of the CPH shows a promising drug delivery system that can control the release of proteins using electrical stimulation. Optimisation of electrical stimulation parameters can further precisely tune the release profile. Furthermore, the delivery system can be patterned onto a multi-electrode array for *in vitro* cell culture to assess biocompatibility and to study the effects of growth factors on neuronal cell populations.
Primary Supervisor: Associate Professor Darren Svirskis

Oral Presentations: Room B

B1

Optimisation of oral cysteamine dosing in Ctns knockout rats

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Background: Nephropathic cystinosis is a rare lysosomal storage disorder caused by mutations in the cystine transporter cystinosin (*CTNS*), resulting in cystine accumulation in all cells of the body. The kidney is the first organ affected and without treatment results in renal failure in early life. We have shown previously that a combination treatment of cystine-depleting drug, cysteamine and the mTOR inhibitor, everolimus, can rescue the cystinotic phenotype in induced pluripotent stem cells. To evaluate the therapeutic potential of this therapy *in vivo,* we will perform pre-clinical testing in our rodent model of cystinosis which faithfully recapitulates the human condition. **Objectives:** To determine any synergistic effect of everolimus we will first identify the optimal dose of cysteamine that results in a 50% reduction of cystine levels in *Ctns* knockout (KO) rats. **Methods:** To overcome the distastefulness of cysteamine we delivered the drug in raspberry flavoured jelly pills to 3-month old *Ctns* KO rats twice daily for 10 days. Following treatment, blood and kidney tissue were harvested and cystine levels measured using HPLC-MS/MS. **Results:** *Ctns* KO rats tolerated cysteamine in a dose dependant manner. At 30 mg/kg, cystine levels in blood were decreased by 79% and 55% 2 hours after treatment while kidney cystine levels were reduced by 19% and 32% in females and males respectively. **Discussion:** Although there was not a 50% reduction, cystine levels in the blood and kidneys were reduced following 10 days of treatment in a sex-dependant manner. Further optimisation is required.
Primary Supervisor: Professor Alan Davidson

B2

Scopolamine: a potential new pharmacotherapy for depression?

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Background: Depressive disorders are leading causes of disability, but current pharmacotherapies and psychotherapies typically take several weeks before achieving efficacy. Comparatively, prior studies involving intravenous scopolamine infusions reduced depressive symptomologies compared to saline placebo infusions within days. However, several parameters of scopolamine's antidepressant effect remain unknown, such as the dose-response profile and washout period. Glycopyrronium was chosen as the active placebo as it has antimuscarinic properties similar to scopolamine but is unable to cross the blood-brain barrier. **Objectives:** To determine whether scopolamine exhibits rapid acting antidepressant effects. **Methods:** The present clinical trial recruited depressed individuals and randomises participants to receive single intravenous doses of either scopolamine hydrobromide (4-6µg/kg) or glycopyrronium bromide (4µg/kg). The primary mood outcome measure for detecting depression severity was the Montgomery–Åsberg Depression Rating Scale, which was administered from pre-infusion and 1, 3, 7, 14, 28, 42 days post-infusion. **Results:** Both scopolamine and glycopyrronium reduce depressive symptomologies within a day of drug administration and maintain such antidepressant effect until 1 week post-drug administration. No significant mood difference was detected between the two drugs. **Discussion:** The results show scopolamine has no more antidepressant effects than the active placebo glycopyrronium. This raises questions about the magnitude of the placebo response and the central and peripheral antimuscarinic contributions to depression.
Primary Supervisor: Dr Suresh Muthukumaraswamy

B3

Tonabersat for treatment of hypoxic ischaemic brain injury in neonatal rats

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[1]Department of Physiology

Background: A lack of oxygen around birth can lead to hypoxic-ischaemic encephalopathy (HIE). Currently there is no approved treatment for infants with mild HIE despite the fact they have increased risk of brain damage, disability and poor developmental outcomes. Connexin hemichannels (half a gap junction) contribute to the evolution of injury after hypoxia-ischaemia (HI) and therefore blocking these channels may be neuroprotective. **Objectives:** To determine whether blocking connexin hemichannels with tonabersat is neuroprotective after HI in the term-equivalent neonatal rat. **Methods:** HI was induced by right carotid artery ligation of P10 Sprague Dawley rats followed by 80 minutes of hypoxia in 8% oxygen. Pups were randomised to receive tonabersat (2 mg/kg; n=30), vehicle (n=29) or saline injections (n=29) 60 minutes, 24 and 48 hours after hypoxia. Brains were fixed in paraformaldehyde on day 7 for immunohistochemical analysis. **Results:** HI resulted in the development of brain infarcts and a significant reduction in hemisphere volume compared to sham control, which was significantly attenuated with tonabersat ($P<0.05$). HI was associated with decreased hippocampal volume and reduced neuronal number in the CA1 and CA3 regions, which was significantly attenuated with tonabersat ($P<0.05$). HI resulted in a significant loss of white matter volume, which was significantly attenuated by tonabersat ($P<0.05$). Tonabersat also significantly reduced the loss of oligodendrocytes in the white matter after HI ($P<0.05$). **Discussion:** Blockade of connexin hemichannels after HI had a significant neuroprotective effect. These data suggest that tonabersat may be a useful neuroprotective treatment for infants that have suffered HI.

Primary Supervisor: Dr Joanne Davidson

B4

Ergothioneine-mediated cytoprotective effects against oxaliplatin-mediated cytotoxicity in rat (Organic Cation Transporter) OCTN1 over-expressing HEK293 cells

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[1]Department of Pharmacology

Background: Oxaliplatin is a third-generation platinum drug whose effectiveness in the treatment of metastatic colorectal cancer is limited by peripheral neuropathy. Ergothioneine is a sulphur-containing dietary amino acid with metal chelation properties. Oxaliplatin and ergothioneine are both substrates of the Carnitine/Organic Cation Transporter (OCTN1). **Objectives:** The study was to investigate the involvement of the OCTN1 transporter in mediating oxaliplatin-cytotoxicity as well as the inhibition of OCTN1 mediated oxaliplatin accumulation and cytotoxicity by ergothioneine. **Methods:** HEK293 cells previously transfected to stably overexpress rat *Octn1* (HEK-rOCTN1) were treated with oxaliplatin in the presence or absence of ergothioneine. Cell viability was assessed via MTT assays. Cellular platinum accumulation and ergothioneine was analysed via inductively coupled plasma mass spectrometry (ICP-MS) and high-performance liquid chromatography-ultraviolet (HPLC-UV) respectively and normalised to cellular protein levels. HEK293 cells stably expressing empty vector (HEK-MOCK) were used as a control. **Results:** HEK-rOCTN1 cells demonstrated ergothioneine uptake while the control HEK293-MOCK cells did not. HEK-rOCTN1 cells were 1.83-fold more sensitive to oxaliplatin-mediated cytotoxicity and accumulated 1.37-fold higher levels of platinum compared to HEK293-MOCK cells. Concurrent ergothioneine exposure with oxaliplatin concentration-dependently reduced the accumulation of platinum and provided cytoprotective effects to both cell lines. The ergothioneine-mediated cytoprotective effect was 4.18-fold greater in the HEK293-rOCTN1 line. **Discussion:** The current study demonstrated the involvement of the OCTN1 transporter in ergothioneine uptake, oxaliplatin-mediated growth inhibition and platinum accumulation as well as ergothioneine-mediated cytoprotective effects. These findings may provide insight into the potential cytoprotective effects of ergothioneine on oxaliplatin-induced neurotoxicity.

Primary Supervisor: Professor Mark McKeage

B5

Delayed tumor necrosis factor blockade after hypoxia-ischemia in fetal sheep ameliorates tertiary white matter injury

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[1]Department of Physiology

Background: Preterm infants have high rates of neurodevelopmental disability including cerebral palsy. This is associated with hypoxia-ischemia (HI) before birth and with cystic white matter injury (WMI). Our research suggests cystic WMI develop late after HI in association with marked neuroinflammation, meaning delayed anti-inflammatories may be a possible therapeutic avenue. **Objectives:** To investigate delayed Etanercept treatment as a potential therapeutic for HI brain injury in preterm fetal sheep. **Methods:** Chronically instrumented fetal sheep (0.7 gestation) were randomly selected into either sham-HI (n=10), HI (n=9) or HI plus delayed Etanercept treatment (n=9) groups. HI was induced by 25 minutes of umbilical cord occlusion. 1.0 mg of Etanercept was administered via intercerebroventricular infusion to the right hemisphere over 4 hours at 3, 8 and 13 days post-HI. Fetal brains were processed for histology at day 21 post-HI. **Results:** HI was associated with white matter atrophy in 4/9 fetuses and bilateral cystic lesions in 3/9 fetuses. Etanercept attenuated cystic WMI with 4/9 fetuses developing unilateral cystic lesions within the untreated hemisphere and 2/9 fetuses developing white matter atrophy. Etanercept reduced numbers of microglia ($p<0.05$), and astrocytes ($p<0.05$) compared to the HI-group and restored the levels of myelin and mature oligodendrocytes to sham levels. **Discussion:** Delayed Etanercept treatment markedly attenuated both macroscopic and microscopic WMI, supporting a role of delayed excessive neuroinflammation in the pathogenesis of cystic WMI after HI. Importantly, this study demonstrates that late rescue therapies targeting inflammation may ameliorate WMI and improve neurodevelopmental outcomes for babies at risk of cerebral palsy.
Primary Supervisor: Professor Laura Bennet

B6

Therapeutic effects of GluN1 antibodies

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Background: N-Methyl-D-aspartate receptor (NMDAR) activation has been linked to various functions, including mediating neurotoxicity, increased blood-brain barrier permeability and exacerbating glioblastoma cell growth. Previous research from our lab has demonstrated that rodents vaccinated with recombinant protein (recGluN1), derived from the obligatory GluN1 NMDAR subunit, generate antibodies that improve cognition and memory by modulating NMDAR activity. **Objectives:** To generate polyclonal recGluN1 IgG in rats via protein immunisation and investigate their potential therapeutic effects in *in vitro* models of blood-brain barrier dysfunction and glioblastoma cell proliferation. **Methods:** recGluN1 antibodies were generated by immunising rats with recGluN1 protein and harvesting the serum at 12 weeks. Western blot analysis will monitor the development of recGluN1 reactive antibodies over the 12-weeks. recGluN1 IgG antibodies will be characterised by epitope mapping and screening of GluN1-transfected HEK293 cells. GluN1 expression in brain microvascular endothelial cell lines hCMEC/D3 and hCMVEC and patient-derived glioblastoma cell lines will be characterised by Western blot analysis of cell lysates. **Results:** Western blot analysis of serum samples from immunised rats demonstrated high titres of recGluN1 antibodies by 10 weeks post-immunisation. Contrary to previous reports, GluN1 subunit expression has not been detected by Western blots of hCMEC/D3 cells and hCMVEC cell lysates under basal conditions. **Discussion:** The lack of GluN1 expression in the endothelial cell lines limits their utility as cell models for assessing the therapeutic application of recGluN1 antibodies. We expect inflammatory activation of endothelial cells to increase GluN1 expression, therefore, creating a suitable model to study the therapeutic effects of recGluN1.
Primary Supervisor: Associate Professor Deborah Young

B7

Effect of fatty acid in tendinopathy

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Background: Tendons are connective tissues fundamental to our ability to move. Several studies have demonstrated an association between obesity and poor tendon health. However, the mechanisms driving this are largely un-explored. We hypothesized that increased exposure to fatty acids (FA), which are elevated in obesity, contribute to poor tendon health. **Objectives:** To investigate the effect that FAs have on tenocyte (tendon cell) behaviour, and determine whether blocking mitochondrial fatty acid metabolism inhibits their effects. **Methods:** Rat tenocytes were treated with oleic acid (OA), palmitic acid (PA) and stearic acid (SA) (0-10µg/ml), with cell viability (alamar blue) and gene expression analysis (RT-PCR) assessed at 24hrs and 48hrs, and collagen deposition (sirius red staining) measured at 72hrs. Tenocytes were further pre-treated with a CPT-1 inhibitor (etomoxir) prior to PA treatment to determine whether effects were dependent on mitochondrial fatty acid metabolism, with cell viability and gene expression analysis determined. All experiments n=3. **Results:** PA and SA (10µg/ml) significantly decreased tenocyte viability ($p<0.0001$), while PA also significantly decreased the expression of the tendon markers scleraxis ($p=0.0039$) and tenomodulin ($p=0.0054$), and significantly increased Matrix metalloproteinase-3 (MMP-3) ($p=0.0358$), MMP-13 ($p=0.0059$) and cyclooxygenase-2 ($p=0.0075$) expression; all hallmarks of tendon disease. PA also significantly decreased collagen deposition ($p=0.0311$). Blocking the FA metabolic pathway with etomoxir recovered the negative effects of PA. **Discussion:** The saturated FAs, PA and SA, have detrimental effects on tenocytes, which appear to be dependent on mitochondrial fatty acid metabolism. These negative effects likely contribute to the association between obesity and poor tendon health.
Primary Supervisor: Dr David Musson

B8

A hypothesis-generating tool to discover hyaluronic acid's biology in pancreatic cancer

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a deadly malignancy with overall survival of <5%. Hyaluronic acid (HA) is a glycosaminoglycan that is overexpressed in PDAC compared to normal pancreas and other malignancies. In cancer, HA leads to vascular collapse and low drug perfusion. Additionally, HA interacts with receptors (e.g. CD44) and activates signaling pathways associated with tumour growth and metastases. Several proteins that interact with HA have been identified; however, in PDAC, there is ambiguity about which one(s) play a major role. Here we describe the development of a hypothesis-generating tool that allows us to gain a better understanding of HA's biology. To develop a hypothesis-generating tool using available genomics data to better understand HA's biology in PDAC. **Methods:** Using a literature search and multi-omic platforms (e.g. the Ingenuity Pathway Analysis), 50 genes coding for proteins that interact with HA were identified. Gene expression data for these genes was extracted from public datasets on PDAC. A web tool was developed in R that utilized these expression data and performed differential expression and survival analyses to identify important genes. **Results:** A number of genes (such as HMMR and TNFSF10) were identified that were significantly overexpressed in PDAC compared to normal pancreas, and were associated with survival of patients. **Discussion:** Our tool assists with hypothesis generation in a systematic manner, especially in complex scenarios where little is known about a process, and multiple genes are involved. This enables researchers to ask more informed questions to be tested in the lab.
Primary Supervisor: Professor Cristin Print

B9

Ryanodine Receptor is a Key Contributor to Enhanced Spontaneous Calcium Release Events in Metabolic Syndrome

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Background: Metabolic syndrome (MetS) is implicated in the genesis of atrial fibrillation (AF). Studies demonstrated that increase spontaneity and asynchronicity in calcium release events (CREs) is strongly correlated to the promotion and maintenance of arrhythmia. **Objectives:** This study aims to discover the precise mechanism of calcium (Ca^{2+}) homeostasis in MetS and its risk components in the development of AF. **Methods:** Single atrial cardiomyocytes (CMs) were isolated using the novel chunk approach from a diet-induced control (Ctl) and MetS rabbit model. Live Ca^{2+} analysis was then performed on isolated CMs with a fast confocal microscopy. Key Ca^{2+}-related proteins ultrastructural properties, ryanodine receptor (RyR) and sarco/endoplasmic reticulum Ca^{2+} ATPhase (SERCA) inhibitor, were further examined with the high-resolution confocal microscopy (STED) on fixed atrial samples. **Results:** Line scan images revealed greater spontaneity and asynchronicity of CREs in quiescent MetS cells. Both Ca^{2+} frequency (MetS 4.07 ± 0.36, n =72 vs Ctl 1.30 ± 0.42 events/s/mm, n = 26) and amplitude, F/F_0 (MetS 1.75 ± 0.12, n = 70 vs Ctl 2.14 0.07, n = 8) were considerably enhanced. 10mM caffeine exposure to measure Ca^{2+} load markedly raised their frequencies (MetS 24.16 ± 4.12, n= 29 vs 37.99 ± 8.88 events/s/mm, n = 21). CREs were successfully abolished by blocking RyRs with tetracaine, but to a lesser extent with thapsigargin, SERCA inhibitor. STED showed RyR reorganization and cluster fragmentation. **Discussion:** MetS displayed higher spontaneity and asynchronicity of CREs, which is a key indicator of arrhythmia. This was contributed by RyR fragmentation and reorganization.
Primary Supervisor: Dr Jichao Zhao

B10

IGF signalling mediates lymphatic vessel growth in zebrafish

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Background: The lymphatic system is essential for body fluid homeostasis. Understanding how lymphatic vessels develop will increase our capability to cure lymphatic diseases such as lymphoedema, a condition caused by damaged or underdeveloped lymphatic vessels. Zebrafish are an important model in this field as they allow *in vivo* analysis of lymphatic development. We found that lymphatic growth in zebrafish is guided by pre-existing structures including craniofacial cartilage. A forward genetic screen uncovered a zebrafish mutant displaying abnormal craniofacial cartilage and inhibition of cartilage-guided lymphatic growth. Smarca5, an SWI/SNF chromatin remodelling factor, contains a potential causative mutation in this mutant. An RNA-seq experiment was performed to compare the transcriptional profiles between wild-type and mutant craniofacial cartilage to uncover potential mechanisms that regulate lymphatic growth. **Objectives:** To discover novel molecular mechanisms that regulate lymphatic vessel development. **Methods:** Lymphatic and cartilage phenotypes were visualised in transgenic zebrafish by confocal imaging. Gene knockout was carried out by CRISPR-Cas9 gene editing. Potential pathways involved in facial lymphatic growth were tested by drug treatment. **Results:** *smarca5* crispants phenocopied the *smarca5* mutants. Analysis of the RNA-seq data revealed that *pappa2*, a secreted metalloproteinase regulating Insulin-like Growth Factor (IGF) signalling, is downregulated in mutant cartilage. Inhibition of IGF signalling blocked lymphatic growth, phenocopying the mutant, while boosting IGF signalling by blocking endogenous IGF-inhibiting proteins rescued the facial lymphatic defect in mutants. **Discussion:** I have confirmed that mutations in *smarca5* cause the lymphatic phenotype and identified the IGF signalling pathway as a possible pathway involved in cartilage-guided lymphangiogenesis.
Primary Supervisor: Dr Jonathan Astin

B11

Verification of the Expression of a Fourth Water Channel AQP3 In The Lens

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Background: Cataract presents as cloudiness within the ocular lens, resulting in vision occlusion and potentially blindness. Lacking a blood supply, the microcirculation system of the lens, mediated by Aquaporin (AQP) water channels 0, 1, and 5, has been proposed as an experimental paradigm for the development of anti-cataract therapies. The recently localised fourth AQP (AQP3 aquaglyceroporin) enables us to define the details of the molecular operation of the microcirculation system and continue our effort to find alternative strategies to delay and prevent cataract. **Objectives:** To verify the expression of AQP3 in the mice, rat, bovine and human lens. **Methods:** Reverse transcription-polymerase chain reaction (RT-PCR) was conducted to verify AQP3 expression at the transcript level. Whole lenses or microdissected fractions from the outer cortex, inner cortex, and core were used in Western Blotting for AQP3 expression verification at the protein level. Immunomapping analysis of AQP3 subcellular localisation in axial sections was conducted by immunolabelling sections with AQP3 antibody, membrane marker Wheat germ agglutinin (WGA), and nuclei marker DAPI (a DNA-specific probe) serving as a marker of cellular differentiation. **Results:** AQP3 protein expression in mice, rat and bovine lenses, and the presence of AQP3 mRNA transcripts in mice and rat lenses, have been confirmed via Western Blot analysis and RT-PCR, respectively. **Discussion:** These results confirm AQP3 expression throughout the lens at the transcript and protein level. AQP3's roles in H2O and H2O2 transport may be critical for complementing AQP5-mediated water transport and the maintenance of normal redox balance of the lens.

Primary Supervisor: Dr Rosica Petrova

B12

Presbyopia and Water Regulation in the Human Lens: the Relationship Between Syneresis and Protein Structure.

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Background: As we age, the eye lens becomes stiff and clear near vision is lost (presbyopia), which is hypothesized to precede age-related nuclear cataract. Our current understanding of both conditions is that damage to lens proteins accumulates over time, leading to modifications to protein structure, inhibiting their ability to bind water, subsequently increasing tissue stiffness. The amount of water that proteins can bind can be measured by determining their water holding capacity (WHC). **Objectives:** Develop WHC methods to determine whether our bovine model of lens aging induces changes to lens proteins that are reflected in their ability to bind water. To measure WHC, freshly dissected bovine lenses (young) or lenses exposed to hyperbaric oxygen as a model of lens aging were microdissected into three regions. Samples were spun in microcentrifuge tubes containing filters. The weights of tissue regions before and after centrifugation was measured to determine the WHC from each lens region. **Results:** Preliminary results show most of the water is protein bound, with 18.4%, 7.2% and 3.2% being "free" water (outer, inner cortex and nucleus respectively). With this optimized method established, these values will be compared with aged lens regions. **Discussion:** The WHC measurements will show how the aged bovine lens model effects the ability of lens proteins to bind water. Mass spectrometry-based experiments can then be used to look at protein structural changes in more detail. Understanding structural changes in proteins gives better understanding of the underlying mechanism of presbyopia development, and lens stiffening in aging lenses.

Primary Supervisor: Dr Gus Grey

B13

Optimising umbilical cord stem cells for the treatment of corneal endothelial disorders

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Background: Corneal endothelial disorders, such as Fuchs endothelial corneal dystrophy (FECD), are a leading cause for corneal transplantation. Due to a limited availability of donor corneal tissue, it is essential for alternative therapeutic strategies to be developed. Current research is exploring the potential of umbilical cord (UC) stem cells. The ability to differentiate human umbilical vein endothelial cells (HUVECs) into corneal endothelial cells (CECs) will provide a pathway to generate artificial endothelial layers or cells to be directly injected into the endothelium. **Objectives:** To optimise the isolation of HUVECs with potential to differentiate into CECs. **Methods:** A successful and reproducible HUVEC isolation protocol was developed. HUVECs (n=4) were characterised at 24-hour, day-7, and day-14 timepoints, by polymerase chain reaction (PCR) and immunocytochemistry (ICC). HUVECs were differentiated into CECs (n=2) by using three differentiation protocols: (1) a defined media containing a ROCK inhibitor and a TGF-beta inhibitor, (2) a CEC-conditioned media, and (3) seeding cells onto Descemet's membrane. Differentiation was measured by changes in morphology, ICC, and PCR analysis. **Results:** Isolated HUVECs showed expression of CD31 and CD146, two common HUVEC markers. Following differentiation, a clear change in cell morphology and the upregulation of CEC markers ATP1A1 and ZO1 was observed. Conditioned media treatment gave the best results. **Discussion:** These results show that HUVECs can successfully be isolated and differentiated into CEC-like cells. Differentiated CECs show a hexagonal morphology and an upregulation of several CEC markers. As such, UC stem cells may represent a novel and innovative solution to endothelial dystrophies.
Primary Supervisor: Professor Trevor Sherwin

B14

Changes in mitochondrial function precede early retinal deposit formation in the cystine/glutamate antiporter knockout mouse

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Background: The cystine/glutamate antiporter (CGAP) mediates exchange of extracellular cystine for intracellular glutamate. Observations of the CGAP knockout (KO) mouse demonstrate accelerated development of age-related retinal deposits compared to wild-type (WT) mice. Due to its localisation to the retinal synapse and its role in glutamate export and glutathione (GSH) synthesis in other tissues, we hypothesised that CGAP knockout alters glutamate/glutamine cycling, mitochondrial physiology, and antioxidant capacity. **Objectives:** To investigate how loss of CGAP may induce the early appearance of retinal deposits by examining retinal mitochondrial metabolism. **Methods:** Retinas from C57BL/6J and CGAP-KO mice aged between 6 weeks (6W) to 9 months (9M) were collected and analysed. Glutamate, glutamine, and GSH concentrations were measured using biochemical assays, and localised and quantified using silver-intensified immunogold labelling. Mitochondrial activity and reactive oxygen species (ROS) production were measured via high-resolution respirometry using the Oroboros™ Oxygraph-2k. **Results:** KO retinas exhibited accumulation of glutamate in photoreceptors ($p<0.05$), disruption of glutamate/glutamine cycling ($p<0.05$), and depletion of GSH in photoreceptors ($p<0.05$) compared to age-matched WT retinas in both age groups. High-resolution respirometry revealed increased baseline ROS levels in 6W KO retinas compared to WT ($p<0.05$), increased respiratory complex I activity ($p<0.01$), and decreased mitochondrial ROS production ($p<0.05$) at 6W. **Discussion:** Taken together, loss of CGAP results in glutamate accumulation and GSH depletion in the photoreceptor, which induces alterations in mitochondrial function at 6W but not at 9M. These alterations are normalised by 9M, suggesting early metabolic changes due to loss of CGAP predisposes the retina to accelerated ageing.
Primary Supervisor: Dr Julie Lim

B15

Optimising the Isolation of Umbilical Cord Mesenchymal Stem Cells for the Treatment of Keratoconus

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Background: Keratoconus is a primary ectasia characterised by a cone-shaped cornea that leads to a loss in vision. Due to the unclear aetiology of this disease, approximately 21% of patients eventually need corneal transplants. To combat the chronic lack of donor tissue, stem cell therapy using umbilical cord mesenchymal stem cells (UMSCs) from the Wharton's jelly is being investigated. **Objectives:** To analyse the distribution of UMSCs along the length of the umbilical cord and define the location with the greatest differentiation potential. **Methods:** Sequential regions along umbilical cords were sectioned and stained with H&E to illustrate the longitudinal anatomical and cellular changes. Subsequently, UMSCs were identified and quantified by immunohistochemistry using CD73, CD90 and CD105 markers. **Results:** The matrix of the Wharton's jelly was denser surrounding the vessels compared to regions near the epithelium with a gradual loosening of the matrix from the placental to fetal end. Cells within Wharton's jelly were found to be more concentrated in the perivascular regions while UMSCs showed a heterogeneous expression in the matrix when single-labelled by CD70, CD90 and CD105. **Discussion:** The changes observed suggest there are differences in distribution of UMSCs cross-sectionally and along the length of the umbilical cord. The heterogeneous expression pattern of UMSC markers further suggests a variation in cell maturity or cell type. Further investigation of UMSC markers by double and triple-labelling will confirm the location of 'true' mesenchymal stem cells determined by internationally accepted criteria.

Primary Supervisor: Professor Trevor Sherwin

B16

Mapping glucose uptake, transport and metabolism in the bovine lens

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Background: As a primary nutrient, glucose is required to drive the functional processes that actively maintain lens transparency. In lieu of a blood supply, glucose is taken up from its surrounding humours, and it can be utilised in many metabolic processes. Objectives: This study aims to map glucose uptake and metabolism in cultured lenses and correlate the pattern of glucose uptake to glucose transporter distributions and abundance. **Methods:** Bovine lenses were incubated in artificial aqueous humour containing normoglycaemic stable isotopically-labelled (SIL) glucose. Following incubations, lenses were either fixed for immunohistochemical labelling and microscopy analysis or frozen for subsequent MALDI imaging mass spectrometry (IMS). The lens epithelial layer and fibre cell fractions were utilised for either IMS or proteomic analysis. Indirect immunofluorescence and confocal microscopy were utilised for protein localisation. **Results:** SIL glucose uptake was initially concentrated in the peripheral epithelium and lens equatorial region. Glucose is gradually distributed throughout the epithelium and the cortical lens fibres. SIL glucose metabolites from glycolysis, the sorbitol pathway, and the pentose phosphate pathway were also detected. Spatial proteomic analysis of the lens epithelium detected GLUT1 and GLUT3. Immunohistochemical mapping localised GLUT1 to epithelial and cortical fibre cell membranes. **Discussion:** The major uptake site of glucose in the bovine lens has been mapped to the peripheral epithelium. SIL glucose is rapidly metabolised in epithelial and fibre cells to many metabolites, which are most abundant in the metabolically more active cortical fibre cells compared to central fibres.

Primary Supervisor: Dr Gus Grey

Oral Presentations: Room C

C1

High-density electromyographic recordings for classification of hand gestures

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Background: High-density electromyography (HD-EMG) provides neuro-physiological insights into the underlying mechanisms of muscle contraction and coordination, which can be used for rehabilitation and myoelectric control applications. Existing electrode platforms for measuring hand EMG are not muscle-specific which hinders the accurate assessment of hand muscle function during manipulation tasks. **Objectives:** To address this limitation, muscle-specific HD-EMG electrode arrays were developed to capture myoelectric activity from the muscles of the hand. **Methods:** The arrays consisted of 60 individual electrodes placed on the palm and dorsal side of the hands targeting 10 intrinsic muscles. For validation, the myoelectric activity of 5 healthy volunteers with no neuromuscular disorders was recorded. The collected data was displayed as spatio-temporal maps to visualise muscle activation. Time-domain features were extracted to train support-vector machine classifiers to predict user motion based on EMG inputs. **Results:** The experimental data collected from 5 subjects showed distinct patterns of activation in the spatio-temporal maps and correlated to the muscles recruited during each motion. Muscle fibre conduction velocity (CV) for all subjects was estimated at 4.7±0.3 m/s for the thenar muscle. Hand motions were correctly classified from HD-EMG with an average accuracy of 92±2% for all subjects. **Discussion:** The muscle-specific electrode arrays reliably recorded HD-EMG signals from intrinsic hand muscles and were used to classify subject motions. The performance of the presented muscle-specific electrode arrays could be used to contribute in electrophysiological research using EMG decomposition techniques to assess motor unit activity and in applications involving the analysis of dexterous hand movements.

Primary Supervisor: Dr Nira Paskaranandavadivel

C2

Assessment of cortical development using neurite orientation dispersion and density imaging in the neonatal rat.

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Background: Preterm birth increases the risk of brain injury, identified clinically by diffusion tensor imaging (DTI), a magnetic resonance imaging (MRI) model. Neurite orientation dispersion and density imaging (NODDI) is a MRI model developed to increase the specificity of assessment of cellular components through alterations in tissue diffusivity. However, the histological correlates of NODDI parameters, thus its ability to specifically identify preterm brain injury remains unclear. **Objectives:** To determine the histological correlates of NODDI and DTI parameters in the developing cortex of the neonatal rat. **Methods:** Brain tissues of postnatal day (PND) 1, 3, 7, 14, 21, and 35 Sprague Dawley rats (n=10, per age) were processed for Golgi-Cox staining or *ex-vivo* MRI analysis (9.4T). Data were fitted with the NODDI toolbox and spatially normalised DTI. MRI tissues were processed for immunohistochemistry and cellular process density calculated (Stereoinvestigator software). Dendritic morphology was assessed in Golgi-Cox tissue (Neurolucida software). **Results:** In both the motor and somatosensory cortices, the DTI parameter fractional anisotropy progressively decreased from PND1–PND7, while the NODDI parameter orientation dispersion index progressively increased from PND1–PND14. Both values plateaued thereafter. The NODDI parameter neurite density index decreased from PND1–PND3 and then increased from PND3–PND7. Histologically, there was a progressive increase in all dendritic complexity measures in the motor and somatosensory cortices from PND1–PND21. Dendritic density decreased at PND3 and then increased from PND3–PND7. **Discussion:** NODDI measurements specifically reflect changes in dendritic morphology and density with brain development, suggesting that NODDI may be useful for assessing cortical pathology in preterm-born infants.

Primary Supervisor: Dr Justin Dean

C3

Withdrawn

C4

Freehand 3D-ultrasonography measurement of the volume of the triceps surae in premature infants in vivo

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Background: Premature birth (gestational age <37 weeks) is a leading cause of childhood morbidity and mortality and is associated with significant motor sequalae. Compared to their term-born peers, premature infants have significantly higher rates of a range of motor impairments that impact health, development, and function. **Objectives:** To investigate the volume of the Triceps-surae muscle in 7 premature infants at 3- and 6-months corrected ages. **Methods:** Using freehand 3D ultrasound, the bilateral volumes of the medial gastrocnemius (MG), lateral gastrocnemius (LG) and soleus (SOL) were assessed at 3 and 6-months corrected ages. Scanning was performed by a single researcher, while two researchers independently digitised the images for volume calculation. **Results:** At 3-months, mean volumes were 1.74ml (1.34 – 2.23), 0.94 ml (0.82 – 1.06) and 4.15ml (3.16 – 4.88) for the MG, LG, and SOL respectively. At 6 months, mean volumes were 2.58ml (2.14 – 3.12), 1.36ml (1.23 – 1.64) and 5.14ml (4.45 – 6.03) for the MG, LG, and SOL respectively. **Discussion:** Muscle volume (MV) determines muscle strength and indicates muscle growth. Reduced growth of the Triceps-surae during infancy is associated with muscle weakness, motor delays and impairments. As the first study to measure MV in premature infants during their first 6 months of life, these results provide insight into the effects of prematurity on muscle growth and may assist in establishing a structural basis for milestone attainment, determining the aetiology of motor impairments, and facilitating detection of abnormal development.

Primary Supervisor: Dr Ali Mirjalili

C5

A computational model to identify cardiovascular remodelling related to prematurity and predict later cardiovascular risk

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Background: Preterm birth before 37 weeks' gestation and low birth-weight (<2500 g) globally affect ~30 million babies each year. These babies are at increased cardiovascular risk in adulthood; they also frequently suffer neonatal cardiovascular instability that may impact their development. We hypothesise that factors related to early growth and remodelling of the cardiovascular system predict later cardiovascular structure and function. **Objectives:** We aim to develop anatomical computational models of the cardiovascular system for newborns, expressive enough to model preterm and term scenarios. **Methods:** A 0D closed-loop model simulates blood pressure and flows in the newborn cardiovascular system using bond graph methodology. Bond graph vessel segments representing the large thoracic arteries are parameterised by geometric data (length and radius) allometrically scaled from an adult cardiovascular model. The peripheral vascular beds, venous and pulmonary components are optimised using a reduced order unscented Kalman filter. In an observational, prospective ultrasound study in term and late-preterm (34^{+0}-36^{+6} weeks' gestation) newborns, we collect anatomical data on cardiovascular geometry to personalise the model for each participant. Blood flow predictions will be validated against Doppler measurements. **Results:** Simulated haemodynamic fields are in agreement with the ranges from the literature: systemic blood pressure 78/33 mmHg (normal 73±11/45±12 mmHg) with a mean of 45 mmHg (normal 58±12 mmHg); aortic peak flow velocity 55 cm/s (normal 88±12 cm/s). **Discussion:** These models could be clinically applicable to provide haemodynamic insights for diagnosis and surgical planning. Additionally, this approach allows investigation of mechanisms of cardiovascular remodelling related to prematurity with lifelong consequences.

Primary Supervisor: Dr Soroush Safaei

C6

He wairua tō te kai: Community views on regional food security and wellbeing in children

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Background: Our current food system is failing to deliver on health, wellbeing, equity and food security and the Hawke's Bay (HB) region has one the highest levels of childhood obesity nationally. 'He wairua tō te kai' suggests there is more to food than nutrition, advancing a cultural connectedness approach to food and nourishment of tamariki (children) and rangatahi (youth). **Objectives:** This initial phase of Nourishing HB aims to determine what the community considers to be important for an initiative to improve nutrition in the region and to co-construct a shared vision for action. **Methods:** Eleven stakeholder interviews were undertaken using cognitive mapping methods to elicit participants' mental models of the factors driving unhealthy nutrition for children in the region. Subsequently, three community Group Model Building workshops with rangatahi and adults were held to co-construct a systems map of the local food environments and identify potential levers of systems change. **Results:** The community enquiry directed this initiative to focus on children's hauora in a holistic fashion to build food security; include mātauranga Māori throughout the project; work with existing initiatives, community and whānau; and to start in schools. Proposed initiatives include building a network of schools cooking lunches on site as part of the Ka Ora, Ka Ako government school lunch programme. **Discussion:** Using a strengths-based approach, including more Mātauranga Māori in the school curriculum was seen by the community as an important way of building cultural identity which would lead to kaitiakitanga and potentially to increased awareness of nutritional values.

Primary Supervisor: Dr Sarah Gerritsen

C7

Withdrawn

C8

Supporting the implementation of the National Healthy Food and Drink Policy in New Zealand

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Background: The National Healthy Food and Drink Policy was adopted in 2016 to encourage organisations such as District Health Boards (DHBs) to provide healthier food and drink options in line with the NZ dietary guidelines. However, food vendors and caterers may face barriers in providing healthy and nutritious foods, and by extension, in the implementation of the National Policy. **Objectives:** To support the National Policy adoption in NZ institutions by developing and testing resource(s) to facilitate its implementation. **Methods:** This research will systematically synthesise evidence on barriers and enablers to healthy food and drink policy implementation in public sector workplaces internationally, audit relevant existing tools and resources, identify barriers and enablers experienced by the NZ food vendors and caterers through interviews, and develop and test tool(s) and resource(s) to support the National Policy implementation. **Results:** Preliminary systematic review findings suggest that although vendors encounter challenges, there are also factors that support healthy food and drink policy implementation in public sector workplaces. The audit revealed that current tools and resources are predominantly paper-based and often many pages long, while online/digital tools are rare and tend to focus on specific elements of the policy implementation process. The next phase of the research will involve in-depth interviews with approximately 20-30 food vendors and caterers. **Discussion:** Having an understanding of barriers to and factors and resources that are beneficial for successful policy implementation will significantly benefit stakeholders interested in, or engaging in, healthy food and drink workplace policy development and implementation.

Primary Supervisor: Professor Cliona Ni Mhurchu

C9

The cost and greenhouse gas emissions of current, healthy, flexitarian and vegan diets in Aotearoa

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Background: Currently food systems are substantial contributors to environmental damage and health loss, with cost a significant determinant in affording healthier compared to unhealthy food. **Objectives:** To compare the costs and climate impact (greenhouse gas emissions) associated with *current (based on national nutrition surveys)* and *healthy (based on dietary guidelines)* diets and two healthy and environmentally friendly dietary patterns: *flexitarian* and *vegan (based on the EAT-Lancet planetary diet).* **Methods:** The DIETCOST programme (a python-based, iterative, multiple solution solver that finds diet outputs that fit constraints) was used to model the cost differential between the four diets. Climate impact measures (kg of CO2 equivalent emissions per kg of food product), food prices, and each dietary scenarios were incorporated into DIETCOST. **Results:** There were stepwise differences between diet scenarios (P<0.001) with the *current* diet having the lowest mean cost (95% CI) in New Zealand Dollars of $584 ($580-588) per fortnight for a family of four) but highest mean (95%CI) climate impact of 597 $kgCO_2e$ (590-604) followed by the *healthy* diet at $637 ($632-642) and 452 $kgCO_2e$ (446-458), the *flexitarian* diet at $728 ($723-734) and 263 $kgCO_2e$ (261-265), and the *vegan* diet, which had the highest mean cost and lowest mean climate impact at $789 ($784-794) and 203 $kgCO_2e$ (201-204). **Discussion:** Moving from current diets towards diets which are healthy and sustainable will improve health and reduce climate impacts but at a higher cost to households. Among other things, fiscal policy action is needed to reduce cost barriers for eating sustainable healthy diets.
Primary Supervisor: Dr Sally Mackay

C10

The impact of time of diagnosis of gestational diabetes on maternal and infant health outcome

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Background: Gestational diabetes mellitus (GDM) is associated with short- term and long-term adverse outcomes in the mother and her infant. The optimal time of diagnosis of GDM to prevent and reduce these complications is still not clear. **Objectives:** Our aim was to conduct a systematic review to evaluate the current evidence on time of diagnosis of GDM and to compare the health outcomes in mother and infant due to early diagnosis versus late diagnosis. **Methods:** A systematic review and meta-analysis was conducted using Cochrane research methodology, including randomised controlled trials and cohort studies comparing the standard core pregnancy outcomes in women diagnosed with GDM early (< 24 weeks' gestation) with women diagnosed later (≥ 24 weeks' gestation). **Results:** In this meta-analysis, 10 cohort studies, involving 7121 women, was eligible for inclusion. Our results indicated an increase in requirement for oral hypoglycaemic agents (relative risk (RR) 1.88 [1.08, 3.25]) and insulin (RR 1.92 [1.51, 2.44]) for glycaemic control in women diagnosed with early onset GDM compared to late onset GDM. The maternal weight gain during pregnancy was less in women diagnosed with early onset GDM (RR -2.34 [-2.80, -1.88]). Perinatal mortality was increased in infants of women diagnosed with early onset GDM (RR 6.00[2.28,15.80]) despite treatment. **Discussion:** Women with an earlier diagnosis of GDM identify a subgroup of women with severe gestational diabetes. Early diagnosis and management of GDM combined with prevention of excessive weight gain during pregnancy may reduce some of the adverse outcomes associated with GDM.
Primary Supervisor: Professor Caroline Crowther

C11

Distribution of total prehospital time to first hospital for major trauma cases

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Background: Time is an important determinant of trauma outcome. In New Zealand (NZ), patients are dying in the prehospital setting from injuries that are potentially survivable. Optimising prehospital trauma systems and care, and ensuring people get to the appropriate receiving facility are necessary to contribute to a reduction in serious injury-related mortality and morbidity. **Objectives:** To determine the distribution of total prehospital time (activation, response, on-scene and transport) to first hospital for major trauma cases attended by Emergency Medical Services (EMS) in NZ. **Methods:** In this retrospectively-designed prospective cohort study analysing routinely collected data, individuals attended by an EMS provider after suffering major trauma between 1 December 2016 and 30 November 2018 were included. Qualitative variables are shown as frequencies and percentages. Quantitative variables are described using mean, standard deviation, median, interquartile range (IQR) and/or 95% confidence intervals (CI). **Results:** 3,352 cases met the eligibility criteria. Median age was 48 years (IQR: 27-65), 69.6% were male, 57.3% were NZ European and 21.3% were Māori. From call pick up to arrival at first hospital, EMS providers spent on average 110.9 minutes (CI: 107.9-113.8). Activation time contributed 11% of total prehospital time, while response time, on-scene time and transport time contributed 26%, 31% and 32% respectively. **Discussion:** In NZ, total prehospital time is nearly double of the optimal time recommended to provide advanced-level hospital care to major trauma patients ('golden hour'). Reducing the 37% (activation and response time) in which no EMS care is provided to the patient should improve patient outcomes.
Primary Supervisor: Associate Professor Bridget Kool

C12

The Impact of COVID19 Lockdown on Chinese Care Homes in New Zealand

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Background: In response to the COVID19 pandemic, the New Zealand government implemented nationwide lockdowns throughout 2020 and 2021. Consequently, strict visiting restrictions were enforced in care homes across the country. This placed an already vulnerable population at risk of functional and cognitive decline, as well as psychological difficulties. Despite a growing international body of literature evaluating the impact of COVID19 isolation on care facilities, there is a lack of evidence exploring experiences of minority groups. The Chinese community is one of the fastest growing ethnic groups in New Zealand and face additional challenges, including language barriers, differing cultural beliefs and COVID19-related discrimination. **Objectives:** To explore the experiences of Chinese care home residents in New Zealand during the COVID19 lockdowns. **Methods:** We performed in-depth semi-structured interviews with predominantly Chinese individuals (n=18) across two Chinese-run care homes in Auckland. Participants included residents (n=6), family members (n=6) and facility staff (n=6). We conducted and transcribed interviews in either English or Mandarin Chinese. Transcripts were coded and thematically analysed to synthesise themes. **Results:** The preliminary analysis suggests a disproportionate impact on Chinese residents with dementia compared with cognitively intact peers, lockdown led to difficulties for families to fulfil the obligation of filial piety, and relationships between residents, family and staff were enhanced by the use of technology. **Discussion:** The lockdown promoted a sense of unity in residential facilities in the study. The necessary and rapid adoption of technology during lockdown was beneficial and strengthened relationships between residents, family and staff.
Primary Supervisor: Dr Gary Cheung

C13

Association of Dietary Adherence and Sociodemographic Factors Among Women with Gestational Diabetes: A Cohort Study

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Background: Gestational diabetes mellitus (GDM) is glucose intolerance first recognised in pregnancy. Initial management of GDM is via dietary intervention. Appropriate adherence to the dietary recommendations may reduce the risk of maternal and infant complications related to GDM. **Objectives:** To identify the proportion of women with GDM who adhere to the New Zealand dietary recommendations and to assess whether adherence is associated with maternal sociodemographic factors. **Methods:** The dietary intake of 313 women with GDM was compared against the New Zealand Ministry of Health dietary recommendations. Individual dietary scores were calculated to assess adherence to the guideline where zero=no adherence to the recommendations and 10=complete adherence to the recommendations. The association between adherence and maternal sociodemographic factors was assessed using ANOVA, chi square, logistic and linear regression. **Results:** On average, women scored 6.17 out of 10 for adherence to dietary recommendations, but no woman adhered to all ten recommendations. Adherence to recommendations was lowest for saturated fat intake and the wholegrain breads and cereals food groups. Most women (85%) visited a dietitian, but fewer than 30% of women gained the appropriate amount of weight during pregnancy. Lower dietary adherence scores were associated with being underweight (P=0.030), having no previous history of GDM (P=0.021), smoking (P=0.014) and primiparity (P=0.045). **Discussion:** Among women with GDM, dietary adherence to the New Zealand recommendations could be improved. Additional research should identify appropriate ways to increase dietary adherence for better management of GDM which may reduce the adverse perinatal health outcomes associated with GDM.

Primary Supervisor: Professor Caroline Crowther

C14

A scoping review of traditional, complementary and alternative medicine use in New Zealand

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Background: Traditional, complementary, and alternative medicine (TCAM) is widely used and accepted globally. In New Zealand, the extent and scope of data available on TCAM use are not known. **Objectives:** This scoping review aims to map the available evidence from studies/reports exploring use of TCAM (including prevalence, expenditure, and concurrent use with conventional medicines) in New Zealand. **Methods:** The following databases were searched for studies published before June 7th, 2019: MEDLINE, EMBASE, AMED, IPA, CINAHL, PsycINFO, and Scopus. Grey literature (Google Scholar and New Zealand government and relevant organisation websites) were also searched. Studies reporting on the prevalence of use of any TCAM practices/products and/or investigation of any aspects of TCAM use in New Zealand were included. **Results:** In total, 72 studies were included. TCAM use is widespread in New Zealand, and a broad range of TCAM practices and products were used across consumers of all ages, ethnicities, and health conditions. Some consumers paid substantial out-of-pocket costs. There is some evidence of concurrent use of TCAM with conventional medicines. **Discussion:** Although many New Zealand studies/reports on TCAM use are available, studies were generally small, localised, and examined sub-populations (e.g., particular age group(s)/health condition(s)). Various TCAM definitions, data collection tools and methods, and prevalence measurements were used across these studies, restricting data comparability locally and internationally. There is a lack of comprehensive, nationally representative data on prevalence and patterns of use of TCAM products and practices, including use in relation to conventional medicine(s), in New Zealand.

Primary Supervisor: Associate Professor Jo Barnes

C15

Equity of colonoscopy provision and quality in Māori and New Zealand Europeans: a comparative study

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Background: High-quality colonoscopy is essential for investigating suspected colorectal cancer and relies on endoscopists meeting key performance indicator (KPI) targets. The rising demand for colonoscopy raises concerns that Māori populations could be under-served. **Objectives:** This study aimed to compare rates of colonoscopy provision and colonoscopy KPIs between Māori and New Zealand (NZ) European patients. **Methods:** This retrospective comparative study was conducted at Whanganui Hospital (NZ). Consecutive colonoscopies performed between September 2016-March 2020 were included. Primary outcome was the rate of colonoscopy provision for the population. Secondary outcomes were the colonoscopy completion rate (CCR), colonoscope withdrawal time (CWT), polyp detection rate (PDR), and adenoma detection rate (ADR). Subgroup analysis of ADR in index symptomatic colonoscopies was also performed. **Results:** In total, 2,962 colonoscopies were analysed (385 Māori; 2,577 NZ European). Rates of colonoscopy provision in participants aged ≥40 were significantly lower among Māori (6.1% *versus* 9.1%; $p<0.0001$). The CCR ($p=1.00$), CWT ($p=0.28$), and PDR ($p=0.24$) were similar. Whilst the ADR in the overall cohort was significantly lower in Māori (32.7% *versus* 40.0%; $p=0.028$), this was not observed when stratified by 10-year age cohorts. The ADR was similar on subgroup analysis of index symptomatic colonoscopies ($p=0.42$). **Discussion:** This study found inequities in access to colonoscopy services for Māori compared to NZ European patients. Among those that did receive colonoscopy, there were no differences in colonoscopy quality after age stratification. Improving equity will require the addition of colonoscopy provision rates to other mandatory KPIs, and reporting these by ethnicity in all endoscopy units.

Primary Supervisor: Dr Marianne Lill

C16

An exploration of web-based guides used to prepare microdoses of psychedelic drugs

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Background: Regular consumption of low doses of psychedelic drugs such as LSD and psilocybin has become a popular practice worldwide in recent years (termed 'microdosing'). It has been promoted to improve creativity and reduce anxiety and depression. Typically, LSD is sold for recreational use in doses ten times that of a microdose. Psilocybin is found in some mushroom species and the drug content may vary. These drugs are illegal in most of the world, which makes microdosing an under-studied practice with no formalised guidelines. As a result, many users utilise the internet as their primary source of information. **Objectives:** To identify and characterise information available on the internet that users use to guide their microdosing practices. **Methods:** A novel search process located resources that could be used by potential microdosers from medical databases, internet fora, and social media. Data were then collected from these, with a focus on preparation techniques and harm reduction practices. **Results:** The majority of resources discussed LSD and psilocybin microdosing, and recommended volumetric dosing, cutting dosage forms, or grinding of mushrooms as preparation methods. However, there was considerable variation in the harm reduction advice each resource offered. **Discussion:** The nascent nature of microdosing is apparent when examining the variety of preparation methods discussed on the internet. The illegality of psychedelic substances may contribute to this, and it may be at the expense of harm reduction. Further research into microdosing to evaluate the safety of these practices may reduce any potential harm to microdose consumers.

Primary Supervisor: Dr Rhys Ponton

Oral Presentations: Room D

D1

Muscle metaboreflex sensitivity in Interstitial Lung Disease

Chen C[1], Paton J[1], Fisher J[1], Kolbe J[2]
[1]Department of Physiology, [2]Department of Medicine

Background: Physiological mechanisms of exercise intolerance in fibrotic Interstitial Lung Disease (ILD) are poorly understood. In other respiratory diseases there is emerging evidence that the sensitivity of metabolically responsive skeletal muscle afferents (muscle metaboreflex) is augmented. This can contribute to exercise intolerance through dyspnoea, exaggerated sympathetic vasoconstriction and hypoperfusion of the active muscle. **Objectives:** To determine whether muscle metaboreflex sensitivity is augmented in fibrotic ILD. **Methods:** 13 fibrotic ILD patients and 15 healthy controls were recruited. In a randomized cross-over design, participants completed two min of rhythmic handgrip followed by either i) two min of post-exercise circulatory occlusion (PECO trial) to isolate muscle metaboreflex activation or ii) rested for four min (control trial). Muscle metaboreflex sensitivity was calculated as the intra-individual difference in physiological response between the PECO trial and the corresponding period in the control trial. **Results:** Exercise increased minute ventilation (V_E), mean arterial pressure (MAP) and heart rate (HR) ($p<0.05$) in all groups. V_E and MAP remained elevated during PECO ($p<0.05$) with no differences between groups. There was no difference in muscle metaboreflex sensitivity for the MAP, V_E or HR responses between the groups. In the ILD patients, PECO did not increase the mean dyspnoea rating compared to control (1.3±1.3 units vs 1.0±1.2 units, $p=0.19$). **Discussion:** These findings suggest that skeletal muscle metaboreflex sensitivity is not augmented in ILD. Metaboreflex activation did not result in increased dyspnoea. The contribution of other sensory afferents should be explored.
Primary Supervisor: Dr James Fisher

D2

An ex vivo study measuring cefazolin adsorption to cardiopulmonary bypass circuitry

O'Hanlon CJ[1], Hannam JA[1], Holford NHG[1], Anderson BJ[2], Greaves M[3]
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Background: Cefazolin is commonly used for antibiotic prophylaxis during surgery supported by cardiopulmonary bypass (CPB). Antibiotic pharmacokinetics (PK) can be altered by CPB through haemodilution, haemofiltration, hypothermia and drug adsorption to the circuitry. Adsorption can contribute to decreased antibiotic concentrations with consequent reduced prophylactic effectiveness. Highly protein bound drugs like cefazolin can have substantial adsorption to CPB machine circuitry. An *ex vivo* (benchtop) study was conducted to investigate possible cefazolin adsorption. **Objectives:** To quantify cefazolin adsorption to the CPB machine circuitry. **Methods:** Enclosed CPB machines (not connected to a patient) were primed with either whole blood or crystalloid solutions. Cefazolin was administered into the circuit and samples taken at regular intervals over 1 hour. Twelve experimental runs were conducted using different CPB device sizes (neonate to adult), priming solutions, cardioplegia volumes and temperature changes. Unbound concentrations of cefazolin were quantified using high performance liquid chromatography. Data analysis was performed using NONMEM 7.5.0. **Results:** Antibiotic concentrations in 300 samples were quantified. Cefazolin showed high affinity, but low-capacity binding to the CPB machine circuitry. CPB device size and addition of albumin were significant covariates. The maximum amount of cefazolin adsorption to the CPB machine was 157 mg for a child circuit over 1 hour. **Discussion:** Adsorption of cefazolin to the machine circuitry is not clinically relevant due to low capacity but can account for some of concentration variability seen *in vivo*. The model for cefazolin adsorption can be incorporated into a population PK model in patients supported by CPB.
Primary Supervisor: Professor Brian Anderson

D3

The risk of bleeding with oral anticoagulants in patients with liver cirrhosis

Munevar Aquite O[1], Gong J[1], Chan A[1], Beyene K[1], Hayes M[2], Wei H[3], Schauer C[2]

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Background: The safety of dabigatran, a novel oral anticoagulant, is poorly studied in cirrhotic patients due to their exclusion from primary landmark trials. Traditionally, the standard of care for thrombotic conditions in patients with cirrhosis has been warfarin. **Objectives:** To assess the rate of bleeding complications in cirrhotic patients taking dabigatran compared to those taking warfarin. **Methods:** This was a retrospective cohort study on adult patients admitted with liver disease to three district health boards in Auckland from 2008 to 2020. Patients were included if they had a confirmed liver cirrhosis diagnosis and if they received warfarin or dabigatran therapy during the study period. The primary outcome measured was the incidence of any bleeding event that resulted in hospital admission. **Results:** Initially, 4518 patients admitted with liver disease were identified; after applying our inclusion and exclusion criteria, the final cohort included 100 patients. Overall, 52 patients took warfarin, and 48 took dabigatran. Baseline characteristics for both groups were generally similar. The incidence rate of bleeds for patients taking warfarin was 14.4 per 100 person-years (95% CI 8.8-23.5) compared to 9.1 per 100 person-years (95% CI 4.5-18.1) for patients taking dabigatran, but this difference was not statistically significant, (p=0.251). **Discussion:** Our study found no statistically significant difference in the bleeding rate in cirrhotic patients treated with warfarin and those treated with dabigatran. Our results suggest dabigatran may be as safe to use as warfarin in patients with cirrhosis.

Primary Supervisor: Jay Gong

D4

Faecal immunochemical test as a triaging tool for patients with symptoms concerning for colorectal cancer

Saw KS[1], Liu C[1], Xu W[1], Varghese C[1], Bissett I[1], Parry S[2]

[1]Department of Surgery, [2]Department of Medicine

Background: There is increasing interest in the application of faecal immunochemical test (FIT) to assess patients with symptoms of possible colorectal cancer (CRC) to manage the increasing demand for colonoscopy. **Objectives:** This review evaluates the utility of quantitative FIT as a triaging tool for patients with symptoms of possible CRC, the effect of symptoms on FIT accuracy and the impact of FIT incorporated triaging on service provision. **Methods:** Five databases were searched systematically. Meta-analysis of extracted FIT sensitivities and specificities for detection of CRC at reported faecal haemoglobin (f-Hb) thresholds were performed. Secondary outcomes include sensitivity and specificity for advanced colorectal neoplasia and serious bowel disease. **Results:** Thirteen prospective cohort studies were included with 23 251 symptomatic patients. Heterogeneity was low and QUADAS-2 assessment yielded low risk of bias. At the commonly reported f-Hb positivity threshold of ≥10 µg Hb/g faeces, summary sensitivity was 88.6% (95% CI = 84.3-91.8) and specificity was 81.3% (95% CI = 75.4-86.1) for CRC. At lower limits of detection of ≥2 µg Hb/g faeces, summary sensitivity was 96.8% (95% CI = 94.3-98.2) and specificity was 68.6% (95% CI= 60.1-76.0). FIT performance at higher f-Hb thresholds cannot be adequately evaluated due to limited data. FIT sensitivity between different assay brands was comparable. FIT sensitivity may be higher in patients reporting rectal bleeding. **Discussion:** Use of a single quantitative FIT at lower f-Hb positivity thresholds can adequately exclude CRC in symptomatic patients. It provides a data-based approach to prioritisation and efficient allocation of colonoscopy resources.

Primary Supervisor: Professor Ian Bissett

D5

How good is the visually enhanced vestibulo-ocular reflex

Chang T[1], Roxburgh R[2], Taylor R[3]
[1]School of Medicine, [2]School of Medicine and Department of Neurology ADHB, [3]Department of Physiology and Centre for Brain Research

Background: Examining the visually enhanced vestibulo-ocular reflex (VVOR) can help identify combined cerebellar ataxia and vestibulo-ocular reflex dysfunction. The patient's head is rotated slowly from side-to-side while they fixate on an earth-fixed target. A reduced VVOR and/or the presence of corrective saccades indicates a positive (abnormal) result. However, the sensitivity and specificity of the test has not been determined. **Objectives:** To define video-VVOR characteristics in healthy controls and to validate use of a metronome as a method for controlling the frequency of head movement. To determine the optimal frequency of head rotation that best separates CABV from cerebellar ataxia (CA) or bilateral vestibulopathy (BV) alone. **Methods:** Four groups were studied: controls, CABV, CA and BV. Testing was conducted at five frequencies of head rotation while gain (ratio of eye to head movement) and rates of saccades were measured. **Results:** *Use of a metronome achieved good* control over the frequency of head rotation. Control group analysis showed no effect of frequency ($p=0.146$) or age ($p=0.981$) on VVOR gain or rates of corrective saccades. Compared with controls, VVOR gains in CABV were lower and rates of saccades were higher. Inter-group analysis was not conducted, although preliminary observations indicate decreasing gain with increasing frequency in BV. **Discussion:** The metronome is a valid tool for monitoring frequency. Preliminary results are consistent with the theoretical framework that considers VVOR as an additive process between vestibular and cerebellar eye movements. VVOR testing at higher frequencies may be a more sensitive, but less specific indicator of CABV.

Primary Supervisor: Associate Professor Richard Roxburgh

D6

Persisting neuroinflammation and white matter injury and EEG power recovery after hypothermia

Zhou KQ[1], Bennet L[1], Gunn AJ[1], Davidson JO[1]
[1]Department of Physiology

Background: Ischemic brain injury due to oxygen deprivation around birth is associated with death and disability. The only treatment is therapeutic hypothermia, but this is only partially effective. We have previously shown that cerebral ischemia is associated with a loss of neurons and reduced brain activity. Hypothermia partially improved the recovery of brain activity, despite completely restoring neuronal number to sham control level. **Objectives:** To investigate whether the deficit in EEG power after hypothermia is related to neuroinflammation and white matter injury. **Methods:** Fetal sheep (n=24) were randomised to sham control, ischemia-normothermia, or ischemia-hypothermia. Ischemia groups underwent 30 minutes of carotid artery occlusion. Hypothermia was induced from 3-72 hours after ischemia. Electroencephalogram (EEG) was recorded until 7 days. Brain tissue was labelled with NeuN (neurons), Iba1 (microglia) and MBP (myelin). **Results:** Ischemia was associated with suppressed EEG power, a significant loss of neurons and loss of myelin in the white matter compared to sham control ($p\leq0.05$). There was formation of lesions and significant microgliosis ($p\leq0.05$). Hypothermia significantly improved EEG recovery compared to ischemia, but remained below sham control. Hypothermia prevented lesions and improved neuronal survival ($p\leq0.05$), but only partially reduced myelin loss and microgliosis. Greater microglial number or greater myelin loss were correlated with reduced EEG power ($p\leq0.05$). **Discussion:** Hypothermia significantly improved neuronal survival and prevented lesions. However, the deficit in EEG recovery after hypothermia may relate to persistent white matter injury and long-term inflammation. Treatments targeting white matter restoration and inflammation may further improve outcomes after ischemic brain injury.

Primary Supervisor: Dr Joanne Davidson

D7

Embracing the chaos of fetal heart variability: a biomarker for evolving fetal hypoxic-ischaemic brain injury

Beacom MJ[1], King VJ[1], Gunn AJ[1], Lear CA[1], Bennet L[1]
[1]Department of Physiology

Background: Hypoxia-ischaemia (HI) during fetal life is a major cause of brain injury leading to life-long neurodevelopmental disability. Detection and treatment during pregnancy would improve neural outcomes. Fetal heart rate variability (FHRV) derived from electrocardiographic (ECG) activity can be used as a diagnostic biomarker. However, current methods don't account for the non-linear nature of fetal physiological signals. Objectives: To evaluate the diagnostic potential of non-linear HRV metric detrended fluctuation analysis (DFA) after HI. **Methods**: Pre-term fetal sheep were surgically instrumented for continuous measurement of ECG activity. 5-days post-surgery fetuses underwent sham-HI (n=9) or HI (n=9; 25min of umbilical cord occlusion) and were recovered for 21d post-insult. Alpha-1 was calculated using the PhysioNet Toolbox. Evolving injury was classified into phases: recovery (latent; 0-6h), secondary loss of oxidative metabolism (secondary; 6h-4d), and tertiary (mixed cell repair and death 4d onwards). **Results:** There was no difference in alpha-1 between sham and HI fetuses in the latent phase. In the secondary phase, alpha-1 revealed greater fractal complexity in the HI group between 21-41h (significantly lower than controls, nadir at 24h). Between 56h-4d, alpha-1 became less complex. Diurnal oscillations in alpha-1 returned between 5-7d. Thereafter, circadian oscillations became exaggerated with greater nocturnal increase in alpha-1 than controls and a gradual increase in mesor. **Discussion**: These results suggest that short-term DFA analysis can be used to discriminate between early and late stages of the secondary phase and demonstrate that diurnal oscillations in alpha-1 may be a key biomarker for the tertiary phase evolution of HI injury.
Primary Supervisor: Professor Laura Bennet

D8

Small and squishy: growth restriction in the chronically instrumented fetal sheep

King VJ[1], Dhillon SK[1], Lear BL[1], Beacom M[1], Lear CA[1], Gunn AJ[1], Bennet L[1]
[1]Department of Physiology

Background: Over 50% of fetal growth restriction (FGR) cases go undetected, yet FGR is a leading cause of adverse outcomes in pregnancy. To improve outcomes, we need better fetal biomarkers to identify FGR and evolving risks for injury. Impaired placental oxygen delivery is the major cause of FGR. Current animal models either do not permit fetal monitoring, or produce severe or inconsistent outcomes. **Objectives:** To develop a new FGR model in pregnant sheep that better models moderate FGR. **Methods:** Preterm fetal sheep were surgically instrumented for continuous physiological monitoring post-surgery. We implanted a silicone occluder around one umbilical artery (UA) within the fetal abdomen. The UA carries deoxygenated fetal blood to the placenta. UA occlusion creates placental insufficiency. 5d post-surgery, the occluder was gradually inflated over 48h, allowing progressive adaptation. Fetal blood samples were taken routinely. Experiments lasted 14d. **Results:** At occlusion onset, oxygen saturation fell from ~70% to ~40%, without acidosis or hypercapnia. Blood pressure rose from ~34mmHg to ~40mmHg and remained elevated. Oxygen saturation resolved to baseline within a week, during which time fetuses developed altered amplitude in fetal heart rate (FHR) rhythms and an acceleration of the normal gestational fall in FHR. Bodyweights were reduced for gestational age. **Discussion:** These preliminary data demonstrate the utility of the UA occlusion approach in producing moderate FGR. Observed FHR changes may reflect alterations in neural maturation and autonomic control, consistent with clinical FGR findings. Changes in patterns of FHR or FHR variability may be biomarkers of fetal condition in FGR.
Primary Supervisor: Professor Laura Bennet

D9

Do placental extracellular vesicles (EVs) have lasting effects on the maternal cardiovascular system?

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Background: The risk of cardiovascular disease (CVD) increases significantly following preeclampsia (PE), a hypertensive disorder of pregnancy. Extracellular vesicles (EVs) are lipid bilayer-enclosed structures that are extruded from cells to control the function of remote cells/organs. The placenta extrudes EVs directly into the maternal circulation which, in normotensive pregnancy protect endothelial cells from activation and alter maternal vascular tone during and after pregnancy, and vice versa. **Objectives:** To determine if preeclamptic placental EVs can enhance the cardiovascular disease of spontaneously hypertensive rats (SHR). **Methods:** We isolated EVs from cultured preeclamptic or normotensive placental explants and administered to them to female spontaneously hypertensive rats (SHR), via tail veins, at 12 weeks of age. Additional SHRs received control (bovine serum-derived) EVs. Systolic blood pressure (SBP), and cardiovascular function were monitored using a tail-cuff and high frequency ultrasound. **Results:** Our results show the SBP in animals administered preeclamptic EVs increased with age, reaching around 195 mmHg at 10 months (preliminary data, n=2). The SBP in SHRs receiving normotensive EVs (n=6) did not increase and was lower than the controls (167.12 ± 6.25 vs. 180.67 ± 6.64 mmHg; mean ± SEM). Echocardiology results show the E/A ratio, reflecting diastolic function, was higher in the normotensive than the control group (1.983±0.074 vs. 1.620± 0.064; mean ± SEM, P=0.0165). **Discussion:** Our data support placental EVs having lasting effects on the maternal cardiovascular system and confirm preeclamptic EVs as mechanistically linking preeclampsia and CVD. Our data also suggest a protective effect of EVs from normotensive placentae in vivo.
Primary Supervisor: Professor Larry Chamley

D10

Executive function and behaviour problems in school-age children after neonatal hypoglycaemia

Dai D[1], Franke N[1], Shah R[1], Nivins S[1,2], Harding J[1], McKinlay C[2], Wouldes T[3], Brown G[4]
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Background: Neonatal hypoglycaemia is associated with impaired executive function and behavioural outcomes in later childhood. However, which specific aspects of executive and behavioural functioning, and whether neonatal hypoglycaemia has an indirect effect on behaviour problems through executive function remain unknown. **Objectives:** To examine the relationship between neonatal hypoglycaemia and specific areas of executive function and behaviour in mid-childhood. **Methods:** Participants in a prospective cohort study of infants born late preterm or term at risk for neonatal hypoglycaemia (the CHYLD Study) were assessed at age 9-10 years. We assessed executive function using performance-based and questionnaire-based measures (BRIEF) and behaviour problems with the Strength and Difficulties Questionnaires (SDQ). Data are reported as adjusted mean, adjusted odds ratio (OR), and unstandardised regression coefficients (B) with 95% confidence intervals (CI). **Results:** We assessed 480 (230 girls, 250 boys; mean age=9y5mo) of 587 eligible children (82%). Children who experienced neonatal hypoglycaemia (blood glucose concentration < 2.6 mmol/L), especially if severe or recurrent, were at greater risk of parent-reported metacognition difficulties (OR 2.04 - 3.45), parent-reported peer (OR 1.76-1.90) and teacher-reported conduct (OR 1.94-2.76) problems. Both performance-based and questionnaire-based executive function were associated with behaviour problems. Metacognition difficulties mediated the relationships between severity of hypoglycaemia and peer (B=0.11, 95%CI=0.02-0.22) and conduct (B=0.10, 95%CI=0.01-0.21) problems, and between frequency of hypoglycaemia and peer problems (B=0.10, 95%CI=0.02-0.21). **Discussion:** Neonatal hypoglycaemia is associated with difficulties in specific executive functions and behaviours. The behaviour problems may be mediated by effects of hypoglycaemia on later metacognition difficulties.
Primary Supervisor: Professor Dame Jane Harding

D11

Caffeine for the reduction of intermittent hypoxaemia in late preterm infants: the Latte Dosage Trial

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Background: Intermittent hypoxaemia (IH) is more common in late preterm (34^{+0}-36^{+6} weeks gestational age (GA)) than term infants and is associated with neurodevelopmental impairment. Caffeine is an effective treatment for IH in very preterm infants (<32 weeks GA) and improves neurodevelopmental outcomes. **Objectives:** To determine the most effective and best tolerated dose of caffeine to reduce transient IH in late preterm infants. **Methods:** Phase IIB, double-blind, five-arm, parallel, randomised controlled trial. Infants born at 34^{+0}-36^{+6} weeks GA were randomised to oral caffeine citrate (5, 10, 15 or 20 mg/kg/day) or placebo. The primary outcome was the rate of IH (SpO2≥10% below baseline for ≤2 minutes) on overnight oximetry two weeks post-randomisation. Secondary outcomes included growth and sleep. **Results:** 132 infants (mean (SD), birthweight 2561(481) g; gestational age 35.7 (0.8) weeks were randomised. Caffeine reduced IH frequency at two weeks post-randomisation (IH (events/hr, median (IQR); any caffeine 3.0(1.3-6.1) vs placebo 4.0(1.8-9.8)), p=0.04). The most effective dose was 20mg/kg/day (IH (events/hr, median (IQR) caffeine 20 mg/kg/day 1.8 (0.9-4.2) vs placebo 4.0 (1.8-9.81); p=0.003). Caffeine also increased mean SpO2 (mean (SD); caffeine 20 mg/kg/day 97.2(1.0) v placebo 96.0(0.8), p<0.001), and reduced the percentage of time with SpO2 < 90% (median (IQR); caffeine 20mg/kg/day 0.5 (0.2-0.8) v placebo 1.1 (0.6-2.4), p<0.001). There were no adverse effects on growth or sleep. **Discussion:** Caffeine reduces IH in late preterm infants at 2 weeks of age, with 20mg/kg/day being most effective. Further research is warranted to investigate the effect of caffeine on neurodevelopmental outcomes in this group.

Primary Supervisor: Dr Jane Alsweiler

D12

Thyroid safety of hysterosalpingogram using oil soluble contrast medium for the woman and her offspring

Mathews DM[1], Hofman PL[1], Peart JM[2], Sim RG[2], Johnson NP[3], O'Sullivan S[4]
[1]Liggins Institute, [2]Auckland Radiology Group, [3]Repromed Fertility, [4]Endocrinology, Auckland District Health Board

Background: Hysterosalpingograms (HSG) with oil-soluble contrast medium (OSCM) increase pregnancy rates in women with infertility. However, OSCM can cause marked and prolonged iodine excess, potentially causing thyroid dysfunction in women and their babies. **Objectives:** To determine the types and pattern of thyroid function abnormalities in women undergoing OSCM HSG and their offspring. **Methods:** 150 women who underwent OSCM HSGs in the Auckland region (July 2019-December 2020) were prospectively followed up for 6 months with serial measurements of thyroid stimulating hormone (TSH), Free thyroxine (T4) and Free triiodothyronine (T3). The offspring underwent a routine newborn thyroid screening. A retrospective analysis of newborn screening TSH data was also performed on a separate cohort conceived following OSCM HSG in the past decade. **Results:** TSH levels increased after OSCM HSG with variable time to peak levels. 36% had TSH levels > 4mIU/L (above the normal range), although there were no changes in FreeT4 or FreeT3 levels consistent with a diagnosis of subclinical hypothyroidism (SCH). 2.0% had TSH>10mIU/L and required thyroxine initiation. 1% developed transient subclinical hyperthyroidism with no other cause. 47% had a biochemical pregnancy and 31 % an ongoing pregnancy. None of the newborns in the prospective (n=38) or retrospective cohort (n=146) had abnormal thyroid function at birth. **Discussion:** SCH is relatively common and thyroid monitoring is recommended for least 4 months following an OSCM HSG. However, SCH and hyperthyroidism severe enough to treat are uncommon. Current evidence suggests that neonatal hypothyroidism is not increased following OSCM HSG in the New Zealand scenario.

Primary Supervisor: Professor Paul Hofman

D13

Maternal and infant outcomes of fetal malposition. A retrospective cohort study.

Barrowclough J[1], Crowther C[1], Kool B[2]
[1]Liggins Institute, [2]School of Population Health

Background: Fetal malposition including occiput-posterior and occiput-transverse position, has a prevalence of 15-33% for women in early labour. Whilst fetal malposition resolves prior to birth for 80% of women, persistent malposition is associated with significant maternal and neonatal morbidities. Malposition earlier in labour may result in adverse outcomes but these are seldom reported. **Objectives:** To assess the incidence and outcomes of fetal malposition in the first or second stage of labour for women and their infants. **Methods:** A retrospective cohort review of 738 clinical records at a tertiary hospital in New Zealand. The cohort is described by maternal, labour, birth, and neonatal characteristics. Outcomes for women with a fetal malposition are compared to those of women with an occipto-anterior fetal position. **Results:** Occiput-posterior/transverse fetal malposition occurred in 68% (n=499) of the women and 32% of women (n=239) had an occiput-anterior fetal position in the first or second stage of labour. Fetal malposition was more likely in women with a body mass index ≥30/kg^2 or a right sided fetus. Other maternal characteristics were similar. 75% of fetuses in a malposition rotated to an anterior position by birth. Compared to women with an occiput-anterior positioned fetus, having a fetal malposition was associated with augmentation of labour with oxytocin, use of epidural analgesia, longer first stage of labour, less normal vaginal births, and increased caesarean births. No differences were observed in the neonatal outcomes being assessed. **Discussion:** Maternal outcomes of labour could be improved if interventions enable anterior fetal rotation.
Primary Supervisor: Associate Professor Bridget Kool

D14

Smaller deep grey-matter volumes at nine years in children born at risk of neonatal hypoglycaemia

Nivins S[1], Kennedy E[1], McKinlay C[1], Alsweler J[1], Harris D[1], Harding J[1], Thompson B[2], Chase G[3], Brown G[4], Woulides T[5]
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Background: Neonatal hypoglycaemia is a common metabolic disorder that may cause brain damage, most visible in the occipital region on MRI. However, it is not known whether neonatal hypoglycaemia is associated with long term changes in the brain. **Objectives:** To compare brain volumes and cortical thickness at nine years of age between children who did and did not experience neonatal hypoglycaemia. **Methods:** Children born at risk of neonatal hypoglycaemia at ≥ 36 weeks' gestation who took part in a prospective cohort study underwent brain MRI at nine years of age. Brain morphometric measures were computed using an automated pipeline using FreeSurfer. **Results:** Children who did (N=75) and did not (N=26) experience neonatal hypoglycaemia had similar combined parietal and occipital lobar volume. However, those exposed to neonatal hypoglycaemia, compared with those not exposed, had smaller caudate volume (-0.05%, 95%CI, -0.07 to -0.02; p=0.001) and thalamic volume (-0.03%, 95%CI, -0.06 to 0.00; p=0.05) as a percentage of total brain volume, and thinner occipital lobe cortex (-0.05mm, 95%CI -0.10 to 0.00, p=0.05). Boys who had experienced neonatal hypoglycaemia had smaller caudate volume, while girls had smaller combined parietal and occipital lobe volumes (p=0.02 for interaction). **Discussion:** Neonatal hypoglycaemia is associated with reduced size of specific brain regions in mid-childhood in a sex-specific manner.
Primary Supervisor: Professor Dame Jane Harding

D15

Effects of Maternal Position on Feto-Placental Blood Flow and Oxygenation in Fetal Growth Restriction.

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Background: Placental dysfunction is a key contributor to fetal growth restriction (FGR) which increases risk of stillbirth, preterm birth, neonatal mortality, and neurodevelopmental delay. Functional MRI reveals that maternal supine position reduces oxygen transfer across the placenta but is well tolerated by healthy fetuses. **Objectives:** To investigate the effect of maternal position on placental perfusion, utero-placental and feto-placental blood flow, and oxygen transfer in FGR pregnancies. **Methods:** Eight women with FGR and 26 women with healthy pregnancies (34-38 weeks gestation) underwent 1.5T MRI scans in both left lateral decubitus (LLD) and supine positions. Blood flow in the maternal internal iliac arteries and fetal umbilical vein were assessed using phase-contrast MRI. A combined diffusion-relaxation imaging protocol of the placenta (DECIDE) was used to calculate oxygenation of maternal and fetal compartments. **Results:** In FGR, supine position compared to LLD is associated with a significant reduction in the internal iliac arterial flow (24.8%, p=0.05) and a small reduction in umbilical vein flow (5.5%, p=0.67). Compared to healthy controls in LLD, supine positioning in FGR causes substantial reductions in internal iliac (29.1%, p=0.05) and umbilical vein (24.9%, p=0.02) flow. In FGR, the fetal oxygen saturation in LLD is comparable to healthy placentas in the supine position, with a further decline when FGR mothers are supine. **Discussion:** This is the first study to quantify the effect of maternal position on fetal oxygenation in FGR. Supine position during pregnancy causes a marked acute hypoxic stress that may be fatal for growth-restricted fetuses existing in chronic hypoxia.

Primary Supervisor: Professor Peter Stone

D16

Antenatal and perinatal risk factors for unintentional injury among young children

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Background: Unintentional injuries are a common cause of infant morbidity and mortality. Falls, struck by/against, burn, and foreign body ingestion are leading injury mechanisms among infants because of their limited coordination and exploratory nature with an inability to predict danger. In New Zealand (NZ), little is known about the risk factors for unintentional among this age group. **Objectives:** To identify antenatal and perinatal risk factors unintentional injury among infants (0-9 months) in NZ. **Methods:** A secondary data analysis was conducted utilising data from Growing up in NZ cohort. Predictors of injury in infants were identified using the domains of the theoretical life-course framework of child injury prevention: perinatal, maternal, family context, household physical environment and neighbourhood and community factors. Log-linear binary regression models were fitted to determine variables from each domain that were significantly related to child injury. **Results:** Among those who were included (N=6304), 51.8% (n= 3344/6304) were male, from European mothers (55%), and lived in a household with medium or high levels of deprivation (37.2% and 37.3%, respectively). Up to age 9-months, mothers reported that 6.4% (n=406/6,304) of infants had sustained an injury. After controlling for the effect of all domains, increased maternal depression score was consistently associated with increased risk of injury (risk ratio (RR)=1.03 (95%CI 1.01-1.05)). **Discussion:** Antenatal maternal depression was identified as a risk factor of unintentional infant. Understanding perinatal and antenatal risk factors of infant injury will assist in implementing injury prevention programs or modifying the existing policies among these vulnerable age groups.

Primary Supervisor: Associate Professor Bridget Kool

Oral Presentations: Room E

E1

The genetics of lymphatic vessel growth and guidance

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[1]Department of Molecular Medicine and Pathology

Background: The lymphatic vasculature system is essential for tissue fluid homeostasis. Abnormal growth of lymphatic vessels is associated with lymphoedema, allograft rejection and cancer metastasis. To uncover novel molecular mechanisms involved in lymphatic growth, the Astin lab isolated zebrafish mutants from a forward genetic screen with defective lymphatic vessel patterning. Two mutants displayed abnormal growth of the otolithic lymphatic vessel (OLV), a vessel in the otic vesicle (inner ear). One mutant with overgrowth of the OLV has loss-of-function mutations in *patched1* (*ptch1*) (an inhibitor of Hedgehog-signaling). The other unmapped mutant *OLV-less* (*oll*), lacks the OLV. **Objectives:** To uncover the causative mutation(s) of the *oll* mutant and to confirm that the candidate mutations in the two mutants cause their OLV phenotypes. **Methods:** Whole Genome Sequencing and mapping of *oll* was conducted. An antisense *ptch1* morpholino was injected into wild-type embryos, while mutant embryos were exposed to low dose cyclopamine (Hedgehog inhibitor). **Results:** Knockdown of *ptch1* in wild-type animals phenocopies the *ptch1* mutant. Exposure to cyclopamine rescued the *ptch1* mutant. The *oll* mutant is currently being sequenced and mapped. **Discussion:** I have confirmed that loss of *ptch1* results in overgrowth of the OLV. Development of the OLV is likely indirectly influenced by Hedgehog-signaling through its known role in otic vesicle patterning. This study will contribute new knowledge to how lymphatic vessel growth is regulated which will help pave the way for new therapies.
Primary Supervisor: Dr Jonathan Astin

E2

Characterization of a Novel Group A Streptococcus Virulence Factor: Spy0433

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Background: Group A Streptococcus (GAS) is a bacterium that causes diseases in humans. Several vaccine candidates are in preclinical or early clinical phases, but no GAS vaccine has yet been licensed. Therefore, characterization of novel virulence factors is urgently needed to identify new vaccine candidates. Spy0433 is a recently identified secreted GAS protein that was shown to interact with complement protein C1qC and with myeloperoxidase (MPO), suggesting a potential role in host immune evasion. **Objectives:** To generate recombinant Spy0433 (rSpy0433), confirm binding to host proteins, and to examine the function of the protein interactions. **Methods:** The spy0433 gene was cloned into pET-32a-3c plasmid and expressed in *Escherichia coli* BL21(DE3). rSpy0433 was purified by immobilized metal affinity chromatography (IMAC) using a nickel-nitrilotriacetic acid (Ni^{2+}-NTA) column. Purified rSpy0433 was immobilized onto Sepharose beads by amide coupling and analysed for binding to human plasma proteins using a pull-down assay. Inhibition of complement was tested using a commercial kit. Inhibition of MPO chlorination and peroxidation activities was investigated using a MPO Activity Assay kit. **Results:** rSpy0433 was generated with a purity of >95%. Pull-down assays with human plasma did not confirm binding to human proteins as previously reported. No inhibition was observed in all three complement pathways. MPO displayed a dose dependent inhibition in the chlorination assay but not in the peroxidation assay. **Discussion:** Spy0433 has an inhibitory effect on MPO which might facilitate bacterial evasion from host immune responses.
Primary Supervisor: Professor Thomas Proft

E3

Discovering determinants of sensitivity and resistance to duocarmycin analogues using functional genomic CRISPR-Cas9 screening

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Background: The duocarmycins are cytotoxic agents which alkylate DNA causing cell death. Therapeutic potential of duocarmycin derivatives is currently being explored in preclinical or clinical trials. However, the precise mechanism of action and sensitivity determinants to this class of drugs remains unclear. Discovering genetic biomarkers for sensitivity of cancer cells to duocarmycin derivatives is essential for clinical progression. **Objectives:** To determine mechanism of action and sensitivity determinants to duocarmycin derivatives: aminoCBI and phenolCBI. **Methods:** Cell lines were modified to express inducible Cas9 (iCas9), a DNA nuclease which inactivates a gene after complexing with gene-specific single guide RNA (sgRNA). Clones were generated and validated by polymerase chain reaction (PCR), Sanger sequencing and phenotypical assay. Clones will be transduced with a sgRNA library that targets DNA damage genes and treated with aminoCBI and phenolCBI. Finally, the sgRNAs conferring sensitivity and resistance will be identified by DNA sequencing of surviving cells. Literature searching for top candidates will enable hit calling. **Results:** PCR and sequencing confirmed integration of iCas9 in clones. Small-scale cell culture in the presence of incrementally increased drug concentrations determined the optimal dosing schedule. The CRISPR screen will help in understanding repair mechanisms of duocarmycin exerted DNA damage, and which genes, when knocked out, confer resistance/sensitivity to the agent. **Discussion:** Identifying predictive biomarkers to duocarmycins is required for patient stratification in future clinical trials. It will also assist in better understanding of DNA damage repair mechanisms invoked by alkylation, enabling better prediction of the clinical response to duocarmycin-based therapies.

Primary Supervisor: Dr Barbara Lipert

E4

Withdrawn

E5

Understanding the Innate Immune Response to Group A Streptococcus Pili

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Background: The global disease burden of Group A Streptococcus (GAS) infections and complications highlights the need for a vaccine. One proposed vaccine candidate is GAS pili. GAS pili are flexible, hair-like structures anchored to the cell surface. GAS pili are able to stimulate the production of protective antibodies, but the innate immune response involved is yet to be defined. **Objectives:** Investigate the interaction between GAS pili and components of innate immunity to characterise the implication of pili based vaccines on the immune system. **Methods:** Pilus recombinant proteins were utilised to investigate the pili's immunomodulation capacity. The interactions between pili and toll-like-receptors (TLRs) expressed on reporter cell lines was studied using flow cytometry and by measuring protein production. Cytokine production in response to pili was analysed using ELISA and monocytes. **Results:** Protein production downstream of TLRs in reporter cell lines indicated specificity of pili for TLR2, and interactions between the receptor and pili subunits was confirmed via binding assays. In the monocytic cells, pili induced production of pro-inflammatory cytokines such as TNFα . While the whole structure played a role in stimulating an innate immune response, the tip subunit had higher affinity receptor binding and induced higher levels of cell stimulation. **Discussion:** These results indicate that GAS pili are ligands of TLR2, which primes the immune system for enhanced antibody production downstream of activation. Pili are also able to induce cytokines which help upregulate antibody production, such as TNFα. This helps solidify the pili as a GAS vaccine candidate, as well as raise its potential as an adjuvant for other vaccines.

Primary Supervisor: Dr Catherine Tsai

E6

The pathogenesis of tonsillar hyperplasia in children

Clark ST[1], Johnston J[1], Waldvogel-Thurlow S[1], Biswas K[1], Douglas R[1], Radcliff F[2]
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Background: The surface area of human palatine tonsils is extensive. Bacterial microcolonies in tonsillar crypts have been implicated as a target of host inflammatory cells, resulting in chronic inflammation and substantial morbidity. Antibiotics remain the primary medical treatment for tonsillar hyperplasia (TH), despite a lack of consensus about its microbiology and pathogenesis. **Objectives:** To determine the underlying immunological and microbiological factors contributing to paediatric TH. **Methods:** Paired tonsils were collected from 24 children undergoing tonsillectomy in the Auckland region. Immunofluorescence techniques were used to identify inflammatory cells and lymphocytes. Fluorescence *in situ* hybridisation (FISH) protocols were used to identify the spatial distribution of aerobic and anaerobic bacterial species within tonsillar microcolonies. **Results:** Bacterial microcolonies were identified in 92% of patients. *Bacteroides spp.* and *Fusobacterium spp.* had the highest average percentage coverage within the microcolonies identified (33.6 ± 14.8% and 26.3 ± 7.9% respectively) and were both consistently located in the periphery of the microcolonies. In comparison, *Pseudomonas spp.* and *H. influenza* had the lowest average percentage coverage (33.6 ± 14.8% and 26.3 ± 7.9%) and were consistently located in the centre of the microcolonies. *Streptococcus spp.* had an average percentage coverage of 10.5 ± 8.1% and were most commonly identified in small peripheral clusters. **Discussion:** This is the first study to determine the abundance and arrangement of multiple aerobic and anaerobic bacterial species in tonsillar microcolonies. These novel findings offer new and important insights into the microbiology and pathogenesis of TH and may provide promising avenues for developing effective treatments.

Primary Supervisor: Professor Richard Douglas

E7

Ethnicity, deprivation and access to endoscopic sinus surgery

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Background: Resource constraints limit the provision of care to patients with chronic rhinosinusitis (CRS) in New Zealand. CRS may be under-appreciated among Māori and Pacific people or those of lower socioeconomic status (SES) due to barriers in access to healthcare. **Objectives:** As part of a wider goal to tackle health inequities in our population, our objective was to explore issues around access to rhinology services in New Zealand. **Methods:** A single surgeon retrospective study of all cases of comprehensive endoscopic sinus surgery (ESS) at Waikato Hospital between January 2017 - December 2019 was performed. A total of 177 patients were included. The ethnic composition and deprivation status of study patients were compared to the Waikato District Health Board population. Access to ESS was measured by calculating patients' waiting time and distance from hospital. **Results:** Minority ethnic groups such as Māori, Pacific people and Asians were under-represented in ESS whilst Europeans were over-represented (p=.002). More than the expected number of the most deprived and least deprived patients underwent ESS. Distance travelled to reach hospital did not differ significantly across ethnicities (p=.09), or deprivation scores (p=.64). Multiple regression model found that ethnicity, deprivation score and distance from hospital did not significantly predict the waiting time for clinic or surgery (p =.55, p=.27). **Discussion:** This is the first study to describe the demographics of patients undergoing ESS in New Zealand. Our results highlight racial inequities and encourages all clinicians to customise their care in order to address these inequities.
Primary Supervisor: Dr Andrew Wood

E8

Sinonasal tissue remodelling during chronic rhinosinusitis

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Background: Literature suggests that early surgical intervention in chronic rhinosinusitis (CRS) may bring about better long-term outcomes. CRS is a sinonasal disease with unknown aetiology, characterised by long-term inflammation with epithelial and interstitial tissue remodelling. Remodelling is described as a structural change in the tissue with cyclical deposition as well as degradation of collagen. In asthmatic patients remodelled tissue may result in an irreversible system however, similar evidence is lacking in CRS disease. We hypothesise that CRS patients who are receive early surgical intervention exhibit less severe tissue remodelling when compared with patients who underwent surgery many years after diagnosis with CRS. **Objectives:** Our objectives are to characterise unique tissue remodelling features in CRS and to identify early and late histological features of disease. **Methods:** We analysed sinonasal tissue harvested during functional endoscopic sinus surgery from 40 CRS patients and 20 controls. Histological staining and slide imaging had been performed to establish a novel remodelling scoring system. **Results:** Tissue remodelling was observed in CRS tissue with some features like sero-mucous glandular hyperplasia, thickening of the basement membrane, extracellular matrix expansion and epithelial denudation. The novel tissue remodelling scoring system was established and validated against early and late disease of CRS. **Discussion:** Establishing a robust tissue remodelling scoring system provides an indicator of the duration of disease which may aid surgeons decide how early to surgically treat CRS patients. This can then be applied to other body sites in the future.
Primary Supervisor: Professor Richard Douglas

E9

Qualitative and quantitative analysis of bacterial microcolonies in the tonsils of patients with tonsillar hyperplasia

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Background: Tonsillar hyperplasia (TH) can cause a spectrum of clinical presentations, ranging from obstructive sleep apnoea to recurrent tonsillitis. Current treatment options are limited to antibiotics and tonsillectomy. Recent studies have identified bacterial microcolonies in tonsillar tissue, but their pathogenic role is unclear. **Objectives:** To determine the spatial distribution and association of immune cells and bacteria within human tonsil tissue. **Methods:** Tonsils were collected from 35 patients undergoing tonsillectomy for TH. Tissue sections were stained using fluorescent *in-situ* hybridization (FISH) targeting *Streptococcus* spp., *Haemophilus influenzae* and *Fusobacterium* spp., and immunohistochemistry (IHC) to identify T and B lymphocytes. Microcolonies from adjacent sections were micro-dissected using a laser. The bacterial load in these microcolonies will be determined using Droplet Digital PCR. **Results:** We successfully developed a combined FISH and IHC protocol that allows for the simultaneous visualization of clinically relevant bacteria and immunocytes within tonsil tissue. Preliminary data suggests *Streptococcus* spp. was the most prevalent and detected in 91% of microcolonies, followed by *H. influenzae* (64%), then *Fusobacterium* spp. (55%). A higher abundance of B lymphocytes co-localised with bacterial microcolonies when compared with T lymphocytes ($p<0.05$). **Discussion:** It is unclear whether bacterial microcolonies represent foci for chronic inflammation or commensalism. Our observation of lymphocyte migration into the tonsillar crypt towards bacterial microcolonies does not match typical lymphocyte behaviour. We hypothesise this immune response may contribute to TH pathogenesis. It is important to develop a greater understanding of the role of these phenomena to better inform treatments in the future.

Primary Supervisor: Professor Richard Douglas

E10

The chronic rhinosinusitis microbiota: a one year longitudinal observational study

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Background: Chronic rhinosinusitis (CRS) is characterised by inflammation of the paranasal sinus mucosa and can be associated with acute infections. Over 90% of CRS patients are prescribed antibiotics, often repeatedly. However, the role of the microbiota in CRS remains poorly understood. Previous studies investigating CRS have used culture-based methods. Increasingly, studies utilising gene sequencing approaches have shown that the airway microbiota is much more complex. We hypothesise that microbial dysbiosis (unbalanced microbial communities) contributes to CRS disease severity. **Objectives:** To follow the natural progression of the CRS microbiota and assess for correlations with acute infections, seasonal variations, medications, and surgery. **Methods:** Eighteen CRS patients were recruited from Auckland District Health Board. Endoscopically guided nasal swabs were collected regularly over one year for bacterial 16S ribosomal RNA gene sequencing. Samples were sequenced on the Illumina MiSeq platform. Additional samples, including bacterial culture swabs, were collected during acute infectious exacerbations. **Results:** The microbiota was diverse across participants and was significantly affected by acute infectious exacerbations, medications, surgery and patient co-morbidities. Several acute infectious exacerbations were associated with substantial shifts in microbial composition with an increased relative abundance of potentially pathogenic organisms. Bacterial culture results were available for twelve acute infectious exacerbations. Compared to sequencing data, 7/12 culture results missed potential pathogens, including *Haemophilus influenzae*, E*scherichia coli*, C*ronobacter sakazakii*, and M*oraxella* species. **Discussion:** These results suggest that microbial dysbiosis plays a significant role in CRS disease pathoaetiology and that longitudinal gene sequencing can potentially enhance pathogen detection and antibiotic stewardship in clinical practice.

Primary Supervisor: Professor Richard Douglas

E11

Stoma-Output Reinfusion Device for Ileostomy Patients: A Feasibility Study

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Background: Ileostomy patients suffer considerable morbidity prior to and following reversal. Dehydration and prolonged post-operative ileus are common. Chyme reinfusion is a solution but widespread use has been limited due to lack of specialized equipment and low patient acceptance. **Objectives:** The aim of this feasibility study was to assess user experience, device performance and clinical outcomes of a novel chyme reinfusion device in ileostomy patients. **Methods:** The device is comprised of a custom enteral feeding tube inserted into the downstream ileostomy limb and connected to a compact pump within the stoma appliance. To activate the pump, a hand-held driver unit is held adjacent but external to the stoma appliance, achieving magnetic coupling and facilitating bolus chyme reinfusion. Adult patients with a defunctioning ileostomy were eligible. The primary outcome was to demonstrate device feasibility indicated by the endpoints of successful chyme reinfusion and improvement in user-experience feedback scores. Secondary outcomes included safety, technical and clinical factors. **Results:** Nineteen patients were enrolled with 549 patient-days of device-use captured. The final five patients who used a late version of the custom feeding tube all achieved successful chyme reinfusion and had improved median user-experience feedback scores compared to the initial seven patients using off-the-shelf gastrostomy tubes. Other clinical benefits included reduced net stoma losses. Thirteen patients experienced at least one minor device-related adverse event. Two serious device-related adverse events were recorded (both led to design alterations). **Discussion:** A novel chyme reinfusion device was refined and found to be user-friendly, safe, and effective in ileostomates.
Primary Supervisor: Professor Ian Bissett

E12

The impact of sleeve gastrectomy for weight loss on the gastric conduction system

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Background: Sleeve gastrectomy is commonly performed for the treatment of obesity and type 2 diabetes. The stomach's greater curvature is removed, which includes the normal gastric pacemaker region, but the long-term impact of gastric pacemaker resection on gastric conduction has never been evaluated. Abnormalities of gastric conduction could contribute to side effects such as reflux, nausea and food intolerance. **Objectives:** To determine the impact of sleeve gastrectomy on the gastric conduction system. **Methods:** Participants were >3 months post-surgery, or normal controls who hadn't undergone gastric surgery. Gastric conduction was measured non-invasively using a novel medical device (64 electrode stretchable electronics array and wearable reader) (Alimetry, NZ). Recordings comprised a 30-minute baseline (fasted), followed by a meal, and a post-meal recording for 4 hours. Gastrointestinal symptoms were measured using an App, and validated quality of life questionnaires were employed. **Results:** 11 patients and 24 non-operative normal controls were analysed to date. There was a reduced mean intrinsic frequency after surgery (2.29 vs 2.91 cycles per minute; $p<0.0001$), but unstable frequency was noted in 9/11 patients indicating pacemaker instability. Mean amplitude was lower in the post-sleeve group (23.2 vs 38.0 μV; $p=0.01$). The dominant symptom in 9/11 patients was 'excessive fullness' after eating (median 2, range 0 - 8 on a Likert Scale from 0-10). **Discussion:** After sleeve gastrectomy, the gastric conduction system remodels at a reduced conduction frequency. However, frequency instability occurs in many patients. Further analyses will define gastric wave propagation patterns and correlate symptoms to gastric activity.
Primary Supervisor: Professor Greg O'Grady

E13

Smart surgical planning for anatomical ACL reconstruction

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Background: Anterior Cruciate Ligament (ACL) tears are among the most prevalent knee injuries in sport. The clinical outcome after ACL reconstructive surgery (ACLR) is dependent on the graft's placement. However, data on the ideal anatomical location in 3D is limited, which has prevented surgeons from objectively agreeing on the best graft tunnel sites. The lack of a definitive target can make ACLR challenging for low-volume surgeons. **Objectives:** To develop a computational workflow for characterizing the anatomical attachment sites of the femoral and tibial ACL footprints in a dataset of healthy knee MRIs (n=185) to aid ACLR planning and execution. **Methods:** Healthy knee MRIs were segmented and processed to obtain triangulated surface meshes of the femurs, tibias, and ACLs. An algorithm was developed to programmatically quantify the footprints from the surface meshes as a function of clinical morphometric measurements. These data were used to train a 3D neural network using a patch-based approach to automate segmentations for pre-operatively predicting patient-specific footprints from their MRI. **Results:** The neural network segmented the MRIs with Dice scores >90% (femur) and >85% (tibia). The footprint centroids were tightly clustered. The femur centroids ranged between 3-19% of intercondylar notch height and 39-48% of lateral condyle depth. For the tibia, centroids ranged between 32-37% (anterior-posterior plane) and 48-54% (medial-lateral plane). **Discussion:** The results suggest that the clinically acceptable zone in ACLR needs to be more restrictive than documented in literature. An objective graft position exists and provides a benchmark for which surgical performance can be analyzed and improved.

Primary Supervisor: Dr Marco Schneider

E14

Remote Patient Monitoring with Wearable Sensors following Knee Arthroplasty

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Background: Post-operative monitoring of patients following knee arthroplasty is essential to identify patients on a sub-optimal recovery course. Traditional patient-reported outcomes measures (PROMs) are highly subjective and are shown to poorly correlate with actual physical function. Inertial Measurement Units (IMUs) provide a low-cost, portable solution to obtain objective functional measures for three-dimensional gait analysis. **Objectives:** To demonstrate the feasibility and reliability of ankle-worn IMUs in monitoring post-operative recovery in knee arthroplasty patients. **Methods:** Fourteen patients undergoing primary knee arthroplasty for osteoarthritis were prospectively enrolled. Remote patient monitoring in the community was performed pre-operatively and weekly from post-operative weeks 2 to 6. IMU measures included: cumulative impact load, bone stimulus, impact load asymmetry. PROMs included: Oxford Knee Score, EuroQol Five-dimension with EuroQol visual analogue scale. **Results:** On average, significant improvements were seen in the bone stimulus (P=0.002) and cumulative impact load (P=0.035) from post-operative Week 2 by Week 4 and Week 6, respectively. The impact load asymmetry value trended towards equal impact loading between the operative and non-operative limb, but did not reach significant difference (P=0.308). Of note, PROMs scores (Oxford Knee Score) did not always reflect the same trend as the IMU-derived limb usage. **Discussion:** This study demonstrates the feasibility of a reliable, low cost and low-maintenance workflow system to remotely monitor post-operative progress in knee arthroplasty patients. By providing quantitative data, this complementary tool will be highly useful to clinicians to identify and intervene on 'at risk' outlier patients early in their recovery period.

Primary Supervisor: Associate Professor Paul Monk

E15

Investigating mechanisms of failure for unicompartmental knee arthroplasty.

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Background: Rates of knee arthroplasty are increasing due to increasing obesity and an ageing population. The majority of patients have isolated compartment disease and are eligible for a unicompartmental (partial) knee arthroplasty (UKA) instead of total knee arthroplasty (TKA). UKA has advantages over TKA including cost-effectiveness, fewer complications and faster recovery; however UKAs have higher revision rates and consequently low surgeon usage. A better understanding of why UKAs fail can lead to improved clinical outcomes. **Objective**: We aimed to identify reasons for UKA failure over time. **Methods**: A systematic review of literature published between 2000 and 2020 was conducted. A retrospective audit of UKA outcomes was conducted using New Zealand Joint Registry data combined with electronic patient notes from four large centres (Auckland, Counties Manukau, Canterbury and Waitematā District Health Boards) between 2000 and 2017 (n=2196). **Results/Discussion**: A total of 24 cohort studies was identified from the literature. The retrospective audit included 2100 UKAs, with a 6.6% implant failure rate. Reasons for failure were similar in the systematic review and patient cohort. The most common reasons were aseptic loosening (24%) and OA progression (30%). Early failures were due to infection, bearing dislocation and fractures, whereas late-term failures were due to osteoarthritis progression in the unreplaced compartments. Aseptic loosening was common in mid-term failures. **Conclusion**: The main modes of failure are aseptic loosening and OA progression. Biologically, these are associated with inflammation in surrounding tissues. Further research will focus on investigating the role of underlying inflammatory mechanisms in UKA patient outcomes.
Primary Supervisor: Dr Simon Young

E16

Novel mechanisms of postoperative ileus and acute colonic pseudo-obstruction revealed by high resolution manometry

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Background: Gastrointestinal motility disorders such as postoperative ileus (POI) and acute colonic pseudo-obstruction (ACPO) result in a large clinical burden. Few effective therapies exist, reflecting a limited understanding of the underlying pathophysiology. These conditions are often assumed to result from gastrointestinal hypomotility, though little evidence exists supporting this. **Objectives:** Use high-resolution colonic manometry to define motility patterns in POI and ACPO. **Methods:** High-resolution manometry catheters with 36 sensors at 1cm intervals were used to measure distal colonic motility. Seven patients undergoing right-sided colectomy had preoperative, intraoperative, and postoperative recordings for 4 days after surgery. One patient with ACPO underwent 24 hours of recordings following endoscopic decompression. Manometry data were analysed according to a published classification system. **Results:** Postoperatively, the distal colon became markedly hyperactive, dominated by cyclic motor patterns occurring at 2-4 cycles per minute (cpm) (81.8% vs. 24.1% pre-operatively, $p<0.001$). This returned to preoperative levels over the first 4 days after surgery. No patient passed stool before this hyperactivity resolved. High-amplitude propagating sequences were absent in early postoperative recordings, and their return temporally correlated with gut recovery. Abnormal high-amplitude 0.5-1 cpm activity was observed in one patient with prolonged POI. In ACPO, the distal colon was hyperactive with disorganised non-propagating activity with dominant frequencies at 2-6 and 8-12cpm. Correlation with computed tomography imaging suggested these contractions may act as a functional obstruction. **Discussion:** POI and ACPO result from hyperactive distal colonic motility patterns, which likely slow colonic transit. Further work is now needed to develop targeted therapeutic strategies.
Primary Supervisor: Professor Greg O'Grady

Elevator Pitch

EP1

Magnetic Resonance Imaging (MRI) of brain motion for non-invasive assessment of abnormal intracranial pressure

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Background: Raised intracranial pressure (ICP), or intracranial hypertension, is a common problem in neurosurgical and neurological practice. If left untreated, raised ICP can severely compromise brain perfusion and oxygenation, potentially leading to permanent brain injury or death. The lack of a reliable and non-invasive method of assessing ICP hinders clinical management, particularly for patients with chronic, ICP-linked conditions. Amplified MRI (aMRI) is a novel imaging technique with the potential to provide an accurate and non-invasive measure of ICP. The technique observes the subtle, cardiac-driven motion of brain tissue. When combined with a detailed mechanical model, aMRI could allow for the estimation of ICP-related quantities. **Objectives:** To develop and validate an MRI-based non-invasive method of estimating ICP. **Methods:** Using the aMRI technique, patterns of brain motion were observed in ovine models at baseline and elevated levels of ICP. Various levels of artificially elevated ICP were achieved by continuously injecting saline solution through an intraventricular catheter. The ovine MRI data will be used to create a proof-of-concept mechanical model, describing how cardiac-driven brain motion is affected by elevated ICP and allowing for MRI-based assessment of ICP. **Results:** Preliminary results show that an increase in ICP is associated with reduced cardiac-driven motion in the spinal cord, brainstem and cerebellum. **Discussion:** ICP-dependant changes in lower-brain motion indicate the possibility of deriving an imaging-based index of ICP. Further experiments will assist the creation of a mechanical model of the brain, allowing for a diagnostic understanding of the link between brain motion patterns and ICP levels.

Primary Supervisor: Dr Samantha Holdsworth

EP2

Pathological load of phosphorylated α-synuclein and phosphorylated tau in the human olfactory mucosa

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Background: Dementia is a devastating condition that affects more than 50 million people worldwide. Parkinson's disease (PD) and Alzheimer's disease (AD) are neurodegenerative conditions associated with neuronal loss, and aggregation of phosphorylated α-synuclein and Tau, respectively. Patients with either disorder might present with dementia and olfactory dysfunction (OD). OD and early olfactory bulb (OB) involvement in the neurodegenerative conditions are well established. However there is a little research on the olfactory epithelium (OE) and its involvement in the OD of PD and AD patients. **Objectives:** To assess the presence and patterns of expression of the pathological proteins phosphorylated α-synuclein (PD), and phosphorylated tau (AD) in the OE between neurologically normal and dementia cases. **Methods:** Central OE sections of three dementia and four neurologically normal cases were immunofluorescently stained with UEA1 and phospho S129 or AT8. Analysis used integrated density per area as measure of density load of pathology and olfactory sensory neurons (OSNs). **Results:** The density loads of the pathological aggregates and OSNs were randomly distributed across the OE in every case. There is no difference in AT8 and phosphor S129 density load between neurologically normal and dementia cases (P-value=0.6286; P-value=0.6286, respectively). **Discussion:** The analysis method allowed for the preservation of the localization of the staining along the OE. For the first time it was possible to assess pathology load and its distribution in relation to the anatomical structure of the OE. This project demonstrates the first systematic study of pathology in olfactory mucosa in humans.

Primary Supervisor: Professor Maurice Curtis

EP3

Incorporating sweat gland organoids into a human 3D printed skin matrix

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Background: Patients whose skin is irreversibly damaged or diseased often require skin grafts to aid healing. While the grafts' main role of an environmental barrier is achieved, grafted skin lacks important secondary functions performed by appendages i.e. hair, sweat glands (SG) and sebaceous glands. Of these functions, temperature regulation is most important, primarily carried out by SGs. **Objectives:** We plan to create grafts with SGs by inducing SG self-aggregation and organisation in autologous synthetic skin by harnessing 3D bio-printing technology to mimic an in vivo microenvironment to stimulate normal cell function. **Methods:** Preliminary experiments determine if SG cells are present in vitro cultured skin. Following this the cells are sorted and mixed with gelatine-based bio-ink for printing. Separate inks for SG cells and two other cell types found in skin, fibroblasts and keratinocytes, will be printed to mimic SG architecture in skin. **Results:** We have characterised normal skin via IHC for comparison to the future 3D printed model, and SG cells have been identified residing as singular cells in culture up to 2 weeks post whole skin digest via ICC and flow cytometry. Current research is determining whether skin cells grow well in/on the bioink and which printing speeds, pressures and cross-linking variables produce optimal printed products. **Discussion:** The current progress of this project is in preparation for 3D printing and current data proposes a favourable outcome of the product. In the future, this method has the possibility of being translated to create other skin appendages and revolutionise wound healing.
Primary Supervisor: Dr Vaughan Feisst

EP4

A Multidisciplinary Approach to Understanding the Pathophysiology of Endometriosis

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Background: Endometriosis is the most common gynaecological disease afflicting 10-15% of people with a uterus. It can cause debilitating pelvic pain and infertility, leading to a reduced quality of life and limiting study and work opportunities for sufferers. Endometriosis is vastly under-researched; there is no clear understanding of its pathophysiology or genetic basis. Current methods of treatment have limited effectiveness in alleviating pain and infertility associated with the disease. Primary culture of endometriotic tissue is an invaluable research tool for understanding this biologically complex disease since it closely mimics *in vivo* characteristics. Currently, there are no universal protocols for the culture of endometriosis tissue. **Objectives:** To search through published literature and collate variations in processing, purification, and conditions of primary endometriotic cell culture. **Methods:** Systematic literature search through three databases (MEDLINE, Scopus, embase). **Results:** Since 1989, over 300 articles with successful methods of primary endometriotic culture have been published. Some studies cultured both stromal and epithelial components of lesions; but majority only purified and cultured stromal cells. Most protocols begin with mechanical and enzymatic digestion with variations in the types of chemicals used. Cells are then filtered to remove debris and other cell types; a few studies employ methods to remove erythrocytes and leukocytes. Most primary cells are cultured in Dulbecco's Modified Eagle Medium. **Discussion:** Results will be used to publish a summary of primary endometriosis culture methods to support endometriosis research around the world. They will also inform optimisation of a protocol for tissue collected for my PhD project.
Primary Supervisor: Dr Cherie Blenkiron

EP5

Atrial Fibrillation after cardiac surgery; An analysis of New Zealand Cardiac Surgery Registry data

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Background: Atrial fibrillation (AF) is the commonest complication after cardiac surgery; occurrence is associated with adverse outcomes. **Objectives:** To describe incidence and preoperative predictors of new-onset AF after cardiac surgery. **Methods:** Analysis of registry data from patients without previous AF having coronary artery bypass grafting (CABG) and/or valve surgery at Auckland City Hospital 2019-2021. Logistic regression was used to identify independent predictors. **Results:** The overall incidence of new onset AF was 28.5% (n=465) in 1630 patients, and higher after combined CABG/valve surgery compared to isolated CABG (42.1% vs. 25.2%). Patients that developed AF were older (67.2 vs. 62.1, p<0.001), with higher body mass index (BMI) (30.2 vs. 29.4, p=0.01) and EuroSCORE II (1.96 vs.1.63, p<0.001). Māori and European ethnicities had the highest incidence (35.1% and 32.0% respectively), with significant difference in mean age between ethnic subgroups (56.9±13.5 Māori vs. 67.7±10.3 European). The final multivariate model included age (OR 1.05, 95%CI 1.035-1.058, p<0.001), BMI (OR 1.04, 95%CI 1.02-1.06, p<0.001), history of congestive heart failure (OR 2.08, 95%CI 1.47-2.95, p<0.001), valve surgery (isolated valve OR 1.51, 95%CI 1.16-1.95, p=0.002; CABG/valve OR 1.59, 95%CI 1.11-2.28, p=0.01) and Māori ethnicity (OR 1.55, 95%CI 1.078-2.218, p=0.02). **Discussion:** Increasing age, valvular heart disease and heart failure are well-known risk factors for AF. These findings suggest BMI is an additional, easily measurable factor to identify patients at higher risk. Furthermore, there is new evidence that Māori are at high risk of postoperative AF despite being significantly younger at time of surgery.

Primary Supervisor: Dr Cynthia Wensley

EP6

Withdrawn

EP7

Investigating the functional anatomy of the terminal thoracic duct and lymphovenous junction using ultrasonography

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Background: The thoracic duct (TD) drains the majority of the body's lymph. Lymphatic dysfunction can lead to a sequelae of disease processes. The fine balance between lymph drainage and homeostasis hinges on the lymphovenous junction (LVJ). The mechanism underpinning movement of lymph from the TD into the draining vein is not well understood. **Objectives:** 1. To visualise the terminal thoracic duct (TTD) and assess the presence of a lymphovenous valve in healthy subjects 2. To examine it in full inspiration and full expiration to assess for functional changes during the ventilatory cycle. **Methods:** The cervical portion of the terminal thoracic duct was scanned in 33 healthy volunteers with ultrasound. The rate of TTD and LVV identification was recorded. The internal diameter of the TTD was measured in the supine position, with full inspiration and expiration, and in the Trendelenburg position. **Results:** In 20 (61%) of 33 examinations, the TTD was visualised. An LVV was seen in 4 of the 20 cases (20%). The average diameter of the TTD in the supine position was 1.7mm (0.8-3.1mm). The diameter increased both in full inspiration (1.8mm [0.9-3.2mm]) and in Trendelenburg position (1.8mm [1.2-3.1mm] p value=<0.001). The smallest average diameter of the TTD was seen in full expiration (1.6mm [0.7-3.1] p value=<0.001). **Discussion:** Homeostatic lymph drainage requires a functional lymphovenous junction (LVJ). It does appear that respiration and position change influence lymphatic flow in the TTD. This knowledge may help to manipulate lymph flow and augment lymph related disease processes.

Primary Supervisor: Dr Ali Mirjalili

EP8

Visualisation of PEGylated Nanocarrier for Thymopentin in Immunodepression Modulation

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Background: Thymopentin (TP5) is an immunomodulatory agent with a long history using in modulating immunodepression. However, its clinical effectiveness is limited by its poor stability and permeability. We hypothesise that the nanocarrier technology will provide an alternate strategy aiming to enhance the TP5 stability and permeability. **Objectives:** To fabricate a TP5 loaded nanocarrier system and visualise its morphological features using electron microscopies. **Methods:** TP5 was loaded into PEGylated niosomes using thin film hydration method, then optimised by central composite designs. The TP5-PEG-niosomes was conducted by cryogenic transmission electron microscopy (Cryo-TEM) and verified by cryogenic scanning electron microscopy (Cryo-SEM). It was characterised by particle size, zeta potential, entrapment efficacy (EE) %, *in vitro* drug release and *ex vivo* intestinal degradation studies. **Results:** TP5-PEG-niosomes exhibit a spherical shape and regular porous surface under Cryo-TEM and Cryo-SEM. It is physical stable with nano-scaled particle size at 145 nm, surface charge of -30.6 mV and EE% of 76.5%. The sustainable drug release profile was achieved using PEGylated niosomes, wherein 71% of TP5 was released in 24 hours with a Higuchi-diffusion mechanism. It displayed a superior protection under *ex vivo* intestinal contents for 6 hours compared with control. **Discussion:** TP5 can be stabilised by PEGylated niosomes physiochemically. Chemically, the nano-scaled structure and PEGylation of niosomes can prevent TP5 from intestinal degradation and prolong blood circulation time. Physically, the uniform surface charge of niosomes can provide electrostatic repulsion amongst particles avoiding aggregation. Future work will focus on both *in vitro* and *in vivo* assays for its biological activities in immunological therapies.

Primary Supervisor: Associate Professor Jingyuan Wen

EP9

What Makes a Good Sulfatase Substrate? Application in the Design of Antibody-Drug Conjugate Linkers.

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[1]Auckland Cancer Society Research Centre

Background: Antibody-drug conjugates (ADCs) are an emerging class of targeted cancer therapy consisting of a monoclonal antibody, a linker, and a cytotoxic "payload". The linker must be stable in circulation yet labile within target cells. Enzyme-cleavable linkers have emerged as an effective strategy, utilising intracellular enzymes to trigger payload release. Sulfatases hydrolyse sulfates and while selective for their natural substrates also hydrolyse synthetic arylsulfates. Recently, promising sulfatase-cleavable linkers have been reported. How sulfatases bind their substrates is poorly defined; thus, improved understanding of substrate recognition is needed to design optimal sulfatase-cleavable linkers. **Objectives:** To synthesise a library of model sulfatase-cleavable linkers. To generate an empirical structure-activity-relationship (SAR) of sulfate hydrolysis and payload release. **Methods:** A series of model linkers will be synthesised with a fluorescent payload. Payload fluorescence is quenched until release. An enzyme-activity assay will screen model-linkers against human arylsulfatase A (hARSA). Mass spectroscopy and fluorometry will measure rates of sulfate hydrolysis and payload release. **Results:** We have developed synthetic methodology suitable for preparation of an array of model sulfatase-cleavable linkers. Seven linkers are in the synthetic pipeline, with one analogue completed. A further three have progressed to the penultimate step. **Discussion:** Formation of the carbamate linkage proved less facile than anticipated. A model study was conducted to discover best conditions and was successfully applied to our target substrates. Future work will synthesise another 10-15 analogues and screen model-linkers against hARSA. Results will be compared to substrate structure and correlated to enzyme structure to generate an empirical SAR.

Primary Supervisor: Dr Moana Tercel

EP10

Functional interpretation of enhancer mutations driving the onset and progression of melanoma

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Background: The advent of next-generation sequencing and GWAS (genome-wide association study) has led to the identification of thousands of somatic and germline variants associated with tumorigenesis. However, most of these variants are found in the non-protein-coding part of the genome, making functional interpretation difficult. It is hypothesised that mutations in the non-coding genome are concentrated in regulatory elements called enhancers, where they cause tumorigenesis through alteration of regulatory mechanisms, leading to abnormal gene expression. To provide a functional interpretation of how non-coding mutations impact tumorigenesis in melanoma. **Methods:** Based on the CoDeS3D pipeline, developed in the O'Sullivan lab, we integrated information from melanoma GWAS with skin-specific markers of the 3D structure of DNA (Hi-C), expression quantitative trait loci (eQTLs), and other co-localising features (e.g. methylation) to identify the genes dysregulated by non-coding mutations in skin. We then clustered the genes by their known protein-protein interactions to investigate the biological relevance of these mutations in the onset and progression of melanoma. **Results:** The computational approach enabled the identification of novel enhancer-promoter connections between somatic/germline non-coding mutations and target genes. This functional interpretation may lead to the discovery of new biological pathways specific to the development of melanoma. **Discussion:** While previous studies have developed various approaches to tackle this problem, most have focused on identifying close-range connections (e.g. in the promoter or other nearby regions). Our integrative approach enabled the identification of long-range connections, adding to a more complete understanding of the biological mechanisms that drive tumorigenesis.

Primary Supervisor: Professor Justin O'Sullivan

EP11

THE ROLE OF CD44 IN NEURODEVELOPMENT: INTERACTIONS WITH HYALURONAN DURING RAT HIPPOCAMPAL NEURITE OUTGROWTH

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Background: Within the last decade, the importance of successful neuronal development within the hippocampus has been extensively highlighted. Specifically, molecular and structural abnormalities have been linked to neurodevelopmental disorders showing common patterns of dysregulation within neuronal processes. Recent work suggests hyaluronan (a major component of the extracellular matrix) is critical for regulating development of neurites, although exact mechanisms are unknown. Its receptor, CD44, has therefore been suggested to play a role in early neurodevelopment. A cell-surface glycoprotein, CD44 regulates various cellular processes throughout the body, such as cellular growth and migration. Therefore, both molecules have sparked interest as potential therapeutic targets for neurodevelopmental disorders, which can only be achieved once their underlying physiology is uncovered. The aim of this study is to elucidate the contribution of CD44 to hippocampal neurite outgrowth and morphology related to hyaluronan signaling. **Methods:** Dissociated hippocampal neuron cultures (E18 rats) were transfected using Lipofectamine3000, with DNA constructs containing shRNA-interference sequences that knockdown CD44 receptor expression, and were compared with scrambled sequences. mApple Fluorescent reporter expression was used to identify transfected cells, and trace neuronal morphology using Neurolucida360. Preliminary datasets were blinded, traced and processed using Sholl analysis, with findings intended towards clarifying an underlying role of CD44-hyaluronan signaling in neurodevelopment. **Results:** Preliminary results indicate CD44 knockdown could promote higher complexity of neurite arbors and longer processes. **Discussion:** If future outcomes are aligned with preliminary results, this could suggest that CD44 plays an inhibitory role in the growth of rat hippocampal neurons, via pathways involving hyaluronan.

Primary Supervisor: Dr Justin Dean

EP12

Machine learning to identify the functional targets of genetic contributions to diseases with different heritability

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[1]Liggins Institute

Background: Juvenile idiopathic arthritis (JIA), Crohn's disease (CD), and systemic lupus erythematosus (SLE) are all relatively common autoimmune (AI) diseases that affect millions of people worldwide. These diseases have varying levels of estimated heritability (JIA-highly heritable, CD-medium heritability, SLE- low heritability). Several GWAS studies have identified SNPs that are associated with the development of these diseases. However, which specific SNPs in which tissues make the greatest contribution to disease risk remain poorly understood. Understanding this would enable the identification of potentially effective therapeutic targets with greater specificity and reduced side effects. To identify particular SNP-gene-tissue combinations that make significant contributions to the risk of developing JIA, CD, and SLE. **Methods:** Utilize a machine learning algorithm that integrates individual disease case/control genotypes with tissue-specific eQTL data on diseases associated SNPs to identify the SNPs and tissue that make the greatest contribution to the development of these diseases. For disease with high heritability (JIA), the algorithm was able to pinpoint particular SNP-gene-tissue combinations that make significant contributions to the disease risk. By contrast, for medium and low heritability diseases (CD and SLE), the identified SNP-gene-tissue combinations are consistent between individuals but each makes a much smaller individual contribution to the risk. **Discussion:** The result generated from this study help to identify key genetic factors and tissues that contribute most to the development of these diseases. Furthermore, this study also shed light on the genetic mechanism behind their different heritability.

Primary Supervisor: Professor Justin O'Sullivan

EP13

EAAT2 expression in the Alzheimer's disease hippocampus, subiculum, entorhinal cortex and superior temporal gyrus.

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Background: Alzheimer's Disease (AD) is a neuropathological disorder characterized by the presence and accumulation of amyloid-beta plaques and neurofibrillary tangles. Glutamate dysregulation and the concept of glutamatergic excitotoxicity is postulated to play a major role in the progression of AD. Alterations in glutamate uptake have been implicated in AD, with dysfunction of the excitatory amino acid transporter 2 (EAAT2), the main glutamate uptake transporter reported. Several animal and few human studies have examined EAAT2 expression in multiple brain regions in AD, but studies of the hippocampus, the most severely affected brain region, are scarce. **Objectives:** To determine whether EAAT2 expression patterns are altered in the human AD hippocampus, subiculum, entorhinal cortex and superior temporal gyrus compared to control post-mortem tissue. **Methods:** Fluorescent immunohistochemistry and confocal microscopy were used to quantify the density of EAAT2 in the anatomical areas mentioned above. Density measurements were compared between AD and control cases. 3, 3',-Diaminobenzidine (DAB) immunohistochemistry was also used to examine expression patterns qualitatively. **Results:** No significant EAAT2 density changes were observed between control and AD cases. However, there was a qualitative translocation of EAAT2 staining evident from DAB immunohistochemistry in AD, with reduced immunoreactivity along astrocytic cell bodies and increased diffuse staining in the neuropil. **Discussion:** The spatial expression changes observed here may contribute to glutamatergic dysfunction and subsequent neuronal damage in AD. Our findings warrant further investigation into the potential of the EAAT2 transporter as a therapeutic target in AD.

Primary Supervisor: Dr Andrea Kwakowsky

EP14

Arylformamidase: a prospective drug target for potentiating cancer immunotherapy

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Background: Arresting the production of an immunosuppressive metabolite called kynurenine represents one of the most promising strategies to sensitise cancer patients to curative immunotherapies. However, two decades of efforts to inhibit enzymes IDO1 and TDO (idoleamine- and tryptophan 2,3-dioxygenase) that catalyse the first step of kynurenine formation has generated disappointing results in the clinic. This is likely attributed to dose-limiting toxicities and challenges in blocking both IDO1/TDO necessary to fully arrest kynurenine formation. We propose a transformative approach to arrest kynurenine production by inhibiting arylformamidase (AFMID) which appears to be the only enzyme catalysing the final step of kynurenine production. **Objectives:** To test if genetic inactivation of AFMID ends kynurenine production in IDO1 and TDO-expressing ovarian (SKOV3) and brain (A172) cancer cell lines in the absence of toxicity. **Methods:** To mimic an AFMID inhibitor, I will inactivate AFMID by mutating its catalytically essential active site residue using CRISPR/Cas9 gene editing. The impact of AFMID inactivation on tryptophan metabolism and cell growth will be determined by liquid chromatography, immunoblotting for IDO/TDO and cell viability, thymidine-uptake and tryptophan metabolite detecting assays. **Results:** I have optimised AFMID gene editing and developed a high-throughput fluorescence assay for parallel detection of tryptophan metabolites that will be critical for selection of AFMID-inactivated single cell clones. **Discussion:** This work will illuminate the role of AFMID in tryptophan catabolism of cancer cells. This study will feed into subsequent research aiming to validate AFMID as a new therapeutic target with potential to broaden immunotherapeutic success to more cancer patients.

Primary Supervisor: Dr Petr Tomek

EP15

Effect of Perioperative Slow-Release Opioid Use on Long-Term Opioid Dispensing Following Total Knee Arthroplasty

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Background: Total knee arthroplasty (TKA) is a common procedure which leads to significant amounts of post-operative pain. Sustained-Release (SR) opioids during the early postoperative period has been associated with increased rates of opioid prescribing following discharge. **Objectives:** To determine the impact of perioperative SR opioid use on total inpatient opioid consumption, and longer-term outpatient dispensing for 3-months following TKA. **Methods:** Patients undergoing unilateral TKA between 1st January and 31st December 2018 at Counties Manukau Health were retrospectively identified. Participants were stratified into two groups by inpatient use or avoidance of strong SR opioids. The primary outcome was the percentage of patients receiving prescriptions for opioid medications at thirty-day intervals for 3-months after discharge. **Results:** There were 232 patients eligible for inclusion. The baseline demographics of both groups were similar. In the SR opioid use group, the majority (79%) received Oxycontin. Total inpatient opioid consumption between Post-Operative Days zero and three was lower in the SR opioid avoidance group, although this was not statistically significant (157.5 vs 167.5mg Oral Morphine Equivalent [OME], p=0.14). Outpatient postoperative opioid dispensing was significantly greater in patients who received inpatient SR opioids from 0-30 days (p=0.01). Dispensing of oxycodone was significantly higher in the SR opioid use group at one- and two-months (p=0.01 and 0.03 respectively). **Discussion:** The post-operative use of SR opioids is not routinely recommended following TKA. Their use is associated with greater overall inpatient opioid use, with prolonged opioid dispensing during and after the expected recovery period, and potential for significant harm.

Primary Supervisor: Dr Nicholas Lightfoot

Posters

P1

Analyses of whole-genome CRISPR/Cas9 screens identify genetic dependencies in NRAS-mutant melanoma

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Background: New Zealand has the highest incidence of malignant melanoma in the world. Of particular clinical concern are melanomas with mutations in the *NRAS* gene, which are associated with a poor prognosis and for which there are no therapeutic agents specifically approved. Therefore, there is an unmet need for novel strategies for the therapy of *NRAS*-mutant melanoma. **Objectives:** Through this research we aim to identify genetic dependencies in *NRAS*-mutant melanoma, which will potentially uncover novel drug targets to overcome the challenges of treating melanoma patients with *NRAS* mutations. **Methods:** Whole-genome CRISPR/Cas9 dropout screens were conducted in a collection of New Zealand Melanoma (NZM) cell lines that were established from NZ melanoma patients and maintained at physiological oxygen conditions (5% O_2). *NRAS*-mutant and *NRAS*-wild-type NZM cell lines were transduced with the full-genome Brunello lentiviral sgRNA library. The knockout libraries have been screened for 28 days and quantitated with next-generation sequencing. Whole-genome sequencing data for NZM and additional 28 melanoma cell lines, which are available on the Cancer Cell Line Encyclopaedia (CCLE) database, were analysed with optimised bioinformatic pipelines. **Results:** Bioinformatic analyses revealed a list of genes that are deleterious to the fitness of each *NRAS*-mutant cell line when knocked out. Prospective gene candidates will be further validated as essential genes for *NRAS*-mutant melanoma cells through *in vitro* and *in vivo* individual gene knockout studies. **Discussion:** The identification of genetic dependencies alongside *NRAS* mutations may provide potential new drug targets for the development of therapeutic strategies for the treatment of *NRAS*-mutant melanoma.
Primary Supervisor: Dr Stephen Jamieson

P2

Tonabersat Rescues Inflammation in an Experimental Mouse Model of Multiple Sclerosis through Connexin-43 Hemichannel Blockade

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Background: Multiple sclerosis (MS) is a chronic and inflammatory disease of the central nervous system. Blockade of Connexin-43 (Cx43) hemichannels has been seen to prevent inflammasome activation and the secretion of several pro-inflammatory cytokines. The exact role of Cx43 in MS is not clear but may serve as a potential new therapeutic target for reducing disease severity and progression. **Objectives:** To examine whether the Cx43 hemichannel blocking drug, Tonabersat, reduces inflammation in an Experimental Autoimmune Encephalomyelitis (EAE) mouse model of MS. **Methods:** Paraffin-embedded brain sections were immunolabelled for microglial marker ionized calcium-binding adapter molecule 1 (Iba-1), astrocyte marker glial fibrillary acidic protein (GFAP), and inflammasome activation marker NLR family pyrin domain containing 3 (NLRP3). Clinical scores were used for behavioural analysis. **Results:** We observed prominent expression of the markers across the corpus callosum, motor cortex, and striatum region of the mouse brains in EAE mice. Integrated density of Iba1 and GFAP, and the number of activated microglia and astrocytes, were significantly increased in EAE mice while EAE-Tonabersat treated mice showed an inflammatory profile similar to control mice. Behavioral analysis showed a significant improvement in the scores of the EAE-Tonabersat treated mice compared with the EAE mice. Qualitative assessment revealed diminished expression of NLRP3 in Tonabersat-treated mice relative to EAE mice. **Discussion:** We have demonstrated that Cx43 hemichannel blockade reduces inflammation, overall alleviating the clinical outcome, in an EAE mouse model of MS. These findings suggest Tonabersat may be a potential pharmacological candidate for the treatment of MS.
Primary Supervisor: Dr Andrea Kwakowsky

P3

The delivery and content of communication strategies in biosimilar transitions: A systematic review with meta-analysis

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Background: Effective patient-provider communication is crucial when changing patients to new treatments. Patients may be asked to change from an original biopharmaceutical (bio-originator) to a highly similar version (biosimilar) to generate cost savings for the healthcare system. However, communicating this treatment change to ensure that patients accept and adhere to biosimilars remains a significant challenge. **Objectives:** This review investigates communication strategies used to educate patients taking bio-originators on transitioning to biosimilars. It also explores whether willingness to transition and treatment persistence differs for the delivery of the communication strategy and the amount of content provided. **Methods:** MEDLINE, Embase, Scopus, and relevant conference databases were systematically searched. Communication strategies from 33 studies (88% were observational cohort studies) published from 2012-2020 were synthesized and willingness to transition, persistence, and subjective adverse events explored. **Results:** Patients only received verbal information in 11 studies. The remaining 22 studies also provided written information. Cost-saving was the main reason provided for the transition. Patients were most willing to transition when receiving written and verbal information (χ^2=5.83, p=.02) or written information that only addressed a few concerns (χ^2=16.08, p<0.001). There was no significant difference for persistence or subjective adverse events (*p's*>.05). **Discussion:** Patients who received verbal and written information were more willing to transition to biosimilars. Initial documents should contain basic information, and healthcare providers should use consultations or telephone calls to address patient concerns. More randomized controlled trials are needed to explore communication strategies.

Primary Supervisor: Professor Keith Petrie

P4

In vivo fibre photometry in freely behaving mice: A technique to measure hippocampal neuronal activity.

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Background: Fibre photometry is a powerful technique that has enabled neuroscientists to record changes in fluorescent signals as a measure of neural activity dynamics of a particular population of neurons in the brains of freely living animals. Despite the wide use of this versatile tool, the lack of a structural protocol for its construction and interpretation of data has limited its progress. **Objectives:** This research will design a fibre photometry system, develop a protocol for its application, and investigate the effects of virus-based (GECI) expression in CA1 region of the hippocampus**.** **Methods:** C57BL6 mice were stereotactically injected bilaterally in the CA1 hippocampal region with genetically encoded Ca^{2+} indicator GCaMP6s and GCaMP6f to monitor neuronal activity**.** We custom built a fibre photometry set-up to monitor neural activity from inhibitory GABAergic neurons. Signal processing and data analysis was performed offline using MATLAB (version 2018b, Mathworks). **Results:** When mice were injected with GCaMP6s and GCaMP6f, we detected changes in calcium response (dF/F), a bulk to tissue measurement over time-varying fluorescence in the CA1 hippocampal region. No calcium response was observed in our control GFP mice. **Discussion:** The successful virus-based GECI expression in the hippocampus and the recorded neuronal activity indicates that this custom-made fibre photometry device is reliable and effective for neuronal activity detection, which will help neuroscientists carry out functional and behavioural studies in the future.

Primary Supervisor: Dr Andrea Kwakowsky

P5

Hysterosalpingogram with oil soluble contrast medium causes iodine excess and improve pregnancy rates

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Background: Hysterosalpingograms (HSG) using oil-soluble contrast medium (OSCM) improve pregnancy rates in women with unexplained infertility. The commonly used OSCM has a high iodine content and a long half -life with a potential to cause a prolonged iodine excess state. **Objectives:** To determine the pattern of iodine excess in women undergoing OSCM HSGs. **Methods:** 150 women underwent OSCM HSG and had serial measurements of urine iodine (UI) for 6 months. **Results:** 46% (69/150) had biochemical pregnancy with a marked drop in pregnancy rates over 40 years old (50% ≤40 years and 15% >40 years). 31% (47/150) completed pregnancy.

1. The rate of iodine deficiency was unexpectedly high in this infertile cohort (47.3% deficient (urine iodine< 100 mcg/L)).
2. Of those women ≤40 years, 77% of the deficiency group became pregnant versus 21% of iodine sufficient women ($p<0.0001$) within the next 6 months.
3. There was a marked increase in average iodine post HSG. This was quite variable with peak iodine excess occurring anywhere between 1 week and 3 months. Peak iodine levels were not associated with conception.
4. Qualitative radiological assessment of peritoneal retention was predictive of iodine excess and those with more extensive spill had higher urinary iodine concentration ($p<0.0001$)**.**

Discussion: OSCM HSG improves pregnancy rates in women under 40 and especially those with iodine deficiency. Iodine deficiency is prevalent in women with unexplained infertility suggesting iodine deficiency contributes to unexplained infertility and the beneficial effect of OSCM are in part due to treatment of this iodine deficiency.

Primary Supervisor: Professor Paul Hofman

P6

Differential expression of ectonucleotidase enzymes in carotid bodies of Spontaneously Hypertensive versus Wistar rats

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Background: The carotid bodies (CBs) are the primary chemoreceptor organs that contribute to the homeostatic maintenance of multiple bodily functions. Purinergic signalling via P2X receptors plays a crucial role in modulating the CB afferent discharge and the upregulation of P2X3 receptors on petrosal sensory neurons is partly responsible for aberrant CB tonicity and hyperreflexia in the Spontaneously Hypertensive rat (SHR). While genes that modulate levels of synaptic nucleotides such as adenosine triphosphate (ATP) that acts on purinergic receptors, contribute to CB plasticity during acute and chronic hypoxia, whether these genes are differentially expressed in the CBs of SHRs compared to normotensive Wistar rats is unknown. **Objectives:** To determine whether ATP degrading ectonucleotidase enzymes are differentially expressed in the CBs of SHRs relative to Wistar rats. **Methods:** Using droplet digital PCR (ddPCR), we examined expression levels of ectonucleotidases including; ectonucleoside triphosphate diphosphohydrolases 2-3 (***Entpd2-3***), ecto-5'-nucleotidase (***Nt5e***) and ectonucleotide pryophosphatase/phosphodiesterase 1 (***Enpp1***) in CBs extracted from 4-week old pre-hypertensive SHRs and age-matched Wistar rats. **Results:** Preliminary ddPCR results suggest an upregulation of ***Enpp1*** (n=5) mRNAs in CBs of SHRs relative to Wistar rats (n=6). In contrast, expression of ***Entpd-2 and Entpd-3*** appear downregulated in SHRs relative to Wistar rats (n=5) and no change in ***Nt5e*** mRNAs (n=5) was observed between the strains. **Discussion:** Our results suggest a differential expression of genes involved in ATP degradation in the CBs of SHRs compared to that of Wistar rats. Whether this results in altered ATP bioavailability in the SHR is still to be determined.

Primary Supervisor: Professor Julian Paton

P7

Aortic wall shear stress estimation using deep learning on 4D Flow MRI

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Background: Wall shear stress (WSS) affects vessel wall remodeling and atherosclerosis. While 4D flow MRI allows WSS calculation, it is limited by resolution and noise, resulting in underestimated WSS. Meanwhile, computational fluid dynamics (CFD) enables accurate physics-based simulation, but is time consuming, requires patient-specific parameters, and is not clinically practical. **Objectives:** We demonstrate the power of deep learning (DL) to estimate WSS from surrogate aortic flow datasets generated by CFD. **Methods:** Fourty-three aortic geometries were extracted from 4D Flow MRI for CFD simulatons. A pipe-like quadrilateral mesh was used as a template for the aortic surface mesh. The template was registered to each aortic geometry and two layers of internal coordinates and velocity vectors were extracted from the CFD simulations. Using these input data, we trained a U-Net based DL algorithm to estimate a WSS flatmap. **Results:** The predicted WSS had good accuracy (absolute error of 0.70 ± 1.2 Pa and relative error of 3.0 ± 3.7 % on CFD test cases). WSS patterns showed 0.86 ± 0.02 similarity. For in-vivo cases (n=43), the predictions exhibited good correlation (0.67 ± 0.06) with the commonly used parabolic fitting method. **Discussion:** This work demonstrated the feasibility of estimating WSS from 4D Flow MRI using a DL network trained on surrogate datasets derived from CFD. Inference speed is 26 cases per minute on a CPU for a typical 4D Flow MRI. This approach leverages computational models to overcome limitations in the clinical setting and can be incorporated into a fully automated analysis tool.

Primary Supervisor: Professor Alistair Young

P8

Are alpha-synuclein “strains” the solution to novel therapeutics for Parkinson’s disease?

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Background: The accumulation of alpha-synuclein (α-syn) is a major histopathological hallmark of Parkinson’s disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). How α-syn is involved in different conditions with diverging clinical phenotypes remains elusive. Recent studies suggest that α-syn can misfold into several structural variants (strains), each with different biochemical and functional properties. Hence, the existence of strains may underlie the clinical heterogeneity observed among patients with PD, DLB, and MSA. To investigate the impact of different α-syn strains in these diseases, our lab used RNA-sequencing to identify gene expression changes after treatment with two α-syn strains (Fibrils and P65). This project aims to validate the significant gene expression at the protein level on human brain tissues and primary brain cells using immunofluorescence. **Methods:** We performed immunofluorescence on the middle temporal gyrus of PD and healthy brains and patient-derived pericytes. Based on the RNA seq data we selected 31 candidate genes. We optimised the antibodies targeting the corresponsding protein using a combination of different antigen retrieval buffers (i.e., Tris-EDTA, citrate and/or hydrochloric acid). **Results:** 14/31 antibodies showed specific cell-type specific labelling. Preliminary data indicates a differential labelling between PD and control brains for seven markers. **Discussion:** Initial literature screening revealed that 5/7 marker five have no previous links with PD opening up new potential avenues for PD caused by different alpha syn strains. we will validate these antibodies further on tissue microarrays containing a mixture of 54 PD and healthy cases.

Primary Supervisor: Dr Victor Dieriks

P9

Immunohistochemical mapping of huntingtin protein distribution using human brain tissue microarrays

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Background: Huntington's Disease (HD) is a monogenic neurodegenerative disease stemming from a mutation in the *huntingtin* gene. This results in the production and accumulation of mutant huntingtin protein (HTT). Despite being a pathological hallmark of HD, there are limited studies characterising protein distribution, expression, and localization of both normal and mutant HTT in the human brain. **Objectives:** This study will provide a comprehensive profile of HTT protein immunoreactivity in human brain tissue microarrays (HBTMAs) by utilising a range of antibodies specific to various regions along the HTT protein sequence. **Methods:** Immunohistochemistry was performed on HBTMAs using 9 antibodies to detect HTT protein (2B7, 2E10, 4C9, EPR5526, MAB2168, MAB5490, MAB5492, MW1, MW8). The immunolabeled HBTMAs were imaged using the automated V-slide scanner and analysed using Metamorph. **Results:** All antibodies resulted in diffuse, cytoplasmic HTT staining throughout both control and HD human brains. Punctate HTT aggregates were immunolabelled with MAB2168, MAB5490, MAB5492, MW8 and 4C9, while plaque-like inclusions were labelled by 2E10 and MW1. EPR5526 immunolabelled cell-specific HTT expression while 2B7 demonstrated neuropil immunoreactivity. **Discussion:** Through this study, we are gaining a better understanding of the complexity of HTT expression patterns in both the control and HD human brain. By advancing our knowledge of HTT protein expression in the control brain, we can better understand how expression is altered in HD. By doing so, we gain a better understanding of how the disease affects the brain, but also hope to contribute to the development of novel therapeutics targeting pathologically-relevant mutant HTT.

Primary Supervisor: Dr Malvindar Singh-Bains

P10

Can psychological factors and colonic motility predict postoperative complications? An observational pilot study

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Background: Prolonged postoperative ileus (PPOI) describes delayed bowel function recovery and oral intake intolerance following surgery. Compared to non-colonic, colonic patients have a two-fold greater risk of experiencing PPOI, thereby lengthening hospital stays and increasing complication risk and costs. Evidence suggests heightened preoperative anxiety may contribute to PPOI by dysregulating gastrointestinal motility patterns. **Objectives:** This study aimed to evaluate the feasibility of a large observational study investigating the role of psychological factors on gut electrophysiology and function recovery following major colonic and non-colonic surgery. **Methods:** An observational pilot study was conducted at Auckland City and North Shore Hospitals. Nine colonic and nine non-colonic surgical patients were recruited. Surgical anxiety, optimism, depression, stress, and expectations were assessed at baseline. Baseline, preoperative and postoperative colonic electrophysiology and electrodermal activity were measured using Body Surface Mapping Electrocolonography (BSM EColG) and Empatica E4 wristband. Primary outcomes were protocol and device feasibility. **Results:** Eligibility rates, recruitment rates and sample retention were acceptable in both patient groups. Self-reported measures were appropriate and performed well except the repeated state anxiety measure. Both devices were acceptable, appropriate, uncomplicated to place and worn for the full study duration in most patients. Empatica E4 data quality was moderate. EColG demonstrated acceptable connectivity. **Discussion:** These results demonstrate study method feasibility. However, it is recommended that changes in preoperative state anxiety are assessed using short semi-structured interviews. A large observational study is currently underway, with an aim to recruit 80 patients. An additional surgical service has been added to increase recruitment.

Primary Supervisor: Dr Elizabeth Broadbent

P11

The role of genetic variation and childhood adversity on telomere attrition and psychosocial wellbeing

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Background: Telomeres are DNA sequences located at the ends of chromosomes that protect DNA from damage. However, with each cell cycle, telomeres undergo natural attrition and are therefore, negatively associated with ageing. Telomere length and attrition has both a genetic and environmental component (e.g. oxidative stress accelerates attrition). As adversity has been linked to increased oxidative stress, it may also influence telomere length and attrition with subsequent biological consequences. To determine the effect of genetic variation and adversity on telomere length and attrition in early childhood and whether these are associated with psychosocial wellbeing at 8-years.
Data has been collected from ~5000 children from the *Growing Up in NZ* (GUiNZ) study which has followed participants from the antenatal period onwards. DNA has been extracted from saliva samples obtained at 4.5 and 8-years. Relative telomere length has been measured by qPCR and initial statistical analyses have been performed to determine the effect of adversity on telomere length at 4.5-years. **Results:** Children with greater exposure to adversity often demonstrated longer telomeres at 4.5-years compared to children with less exposure to adversity. Additionally, anxiety at 8-years showed a significant positive association to telomere length at 4.5-years (*P*=.01). **Discussion:** These results suggest that children who experience adversity are more likely to demonstrate biological resilience through increased telomere length. This may act as a protection mechanism to balance the effects of oxidative stress on telomere attrition. Future investigations will include observation of telomere attrition across early childhood and the involvement of genetic variation.
Primary Supervisor: Dr Caroline Walker

P12

Unravelling the contribution of individual genes to tumour microenvironment stress tolerance in an unbiased fashion

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Background: The tumour microenvironment is often hypoxic and low in nutrients due to the chaotic and leaky tumour vasculature. To proliferate in these conditions, tumour cells have altered metabolism and this in turn leads to extracellular accumulation of acidic metabolites, resulting in tumour acidosis. Adaptations used by tumour cells to survive and thrive in the presence of these microenvironmental stressors are thus potential tumour-selective therapeutic targets. **Objectives:** This project aims to identify genes that confer tolerance to the physical tumour microenvironment stressors in an unbiased manner in order to gain greater insight into tumour microenvironment biology and possibly provide novel drug targets. **Methods:** Whole-genome pooled CRISPR-Cas9 knockout screens were performed in UT-SCC-54C, a head and neck squamous cell carcinoma cell line. UT-SCC-54C cells were first transduced with the whole-genome Brunello guide RNA (gRNA) library. The resultant knockout cell populations were then subjected to chronic hypoxia, glucose deprivation or acidosis, with screens for each stressor carried out on two independent transduction replicates. Sequencing of gRNAs and bioinformatics analyses of the gRNA counts have identified gene knockouts that are altered in frequency under the respective stressors. **Results:** A list of gene knockouts which displayed significant survival advantage or disadvantage under the isolated stressors has been obtained for each screen. Prospective gene candidates generated from the screens are currently undergoing validation. **Discussion:** These data have led to novel information by identifying cellular pathways that contribute to tumour microenvironment stress tolerance in unexpected or previously unknown ways.
Primary Supervisor: Dr Tet Woo Lee

P13

Characterisation of microglia and astrocyte phenotypes in the Alzheimer's disease human brain

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Background: Alzheimer's disease (AD) is the most common neurodegenerative disease with no existing cure. Morphological and functional changes in astrocytes and microglia have been implicated in AD. Previous *in vitro* and human transcriptomic studies in tissue have identified key molecular pathways which may be associated with these cell types and AD progression. **Objectives:** This project aims to characterize whether differences in glial protein intensity or localization occurs in the middle temporal gyrus of the AD human brain using immunohistochemistry on human brain tissue microarrays (TMAs). **Methods:** Using TMAs which contains up to 60 tissue core samples from control and AD donors, immunohistochemistry with astrocytic (Glial fibrillary acidic protein (GFAP), inwardly rectifying K+ channel 4.1 (Kir4.1), aquaporin-4 (AQP-4), glutamate transporter-1 (GLT-1), glutamine synthetase (GS), and aldehyde dehydrogenase family member L1 (ALDH1L1)) and microglial (StAR Related Lipid Transfer Domain Containing 13 (STARD13), Autophagy related 7 (ATG7), N-Acylsphingosine Amidohydrolase 1 (ASAH1)), and Myosin-Ie (MYO1E)) antibodies were used to investigate protein expression in the control and AD brain. Image acquisition was conducted using the V-slide automated scanning microscope. The software MetaMorph will be used to quantify cell number, protein expression, and morphology. **Results:** We have optimized various astrocytic and microglial antibodies. Preliminary results indicate a qualitative increase in Kir4.1, AQP-4 protein expression, qualitative decrease in GLT-1 expression in AD astrocytes, and differential expression of microglial markers, which will be further investigated in future studies. **Discussion:** Preliminary results demonstrate interesting and novel astrocytic and microglial protein targets of therapeutic relevance for human AD.

Primary Supervisor: Dr Amy Smith

P14

The effects of general anaesthesia on the circadian clock

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Background: General anaesthesia (GA) affects the circadian clock, however, whether this occurs through a direct effect on clock genes or via neurotransmitters such as GABA is less understood. Here we investigated the effects of light and GA on behaviour and $GABA_A$ receptor ($GABA_AR$) expression in the suprachiasmatic nucleus (SCN). **Objectives:** To determine the concurrent effects of GA and light on locomotor activity rhythms and corresponding changes in $GABA_AR$ expression in the SCN in a mammalian model. **Methods:** Behavioural studies on C57BL/6 mice examined time-dependent effects of light (400 lux) and GA (1.5% isoflurane) on wheel-running activity at different circadian times (CT) over a 24-hour period (n=60). Immunohistochemical analysis of α1, β3, and γ2 $GABA_AR$ subunit expression in the SCN was quantified in mice exposed to light and GA at the same CTs (n=20). **Results:** Behavioural phase shifts persisted in anaesthetized mice exposed to light, suggesting that either: (1) isoflurane exerts its own phase shifts on the clock while blocking light-induced shifting or (2) isoflurane does not entirely block light-induced phase shifts. In the SCN, γ2 subunit expression was increased following light and GA treatment compared to light-alone, although not statistically significant. The α1 subunit expression was significantly increased at times of large behavioural phase delays for light and GA treatment ($p = 0.0352$) and light-alone ($p = 0.0057$). **Discussion:** This study shows there is a time-dependent relationship between light and GA on the clock and demonstrated functional differences in $GABA_AR$ activity in response to GA and phase shifting.

Primary Supervisor: Dr Guy Warman

P15

Development and validation of a high-performance liquid chromatography-ultraviolet method for the quantification of ergothioneine

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Background: Ergothioneine is a non-essential dietary amino acid implicated to play important physiological roles obtained solely from diet. Uptake of ergothioneine is facilitated via the organic cation transporter protein (OCTN1). Red blood cells (RBCs) act as sites of ergothioneine accumulation. A fully validated high performance liquid chromatography-ultraviolet (HPLC-UV) method has not been developed for ergothioneine quantification in cell lysate extract. **Objectives:** The aim of the study was to develop and validate a bioanalytical method, in accordance to US Food and Drug Administration (FDA) guidelines, for the quantification of ergothioneine in cell lysate extract and application in the quantification of ergothioneine in human RBCs. **Methods:** The method was validated for the quantification of ergothioneine in HEK293 cell lysate extract according to the criteria defined by the US Food and Drug Administration Guidance for Industry Bioanalytical Method Validation. The method was applied to measure ergothioneine uptake in HEK293-hOCTN1 cells and accumulation in human RBCs. Ergothioneine in samples were analysed via HPLC-UV. **Results:** The assay was validated over a quantitative range of 3-300μM. Calibration curves were linear (R^2 =0.99), inter- and intra- accuracy (91.7-110.2%) and precision (0.05-10.4%) were validated. Ergothioneine uptake was only observed in HEK293 cells transfected with hOCTN1 and an approximate 15-fold variation in ergothioneine accumulation was seen in human RBCs. **Discussion:** A simple HPLC-UV based assay was developed and validated for ergothioneine quantification in cellular extract. The results demonstrated hOCTN1 mediated ergothioneine uptake and wide variation in RBC ergothioneine accumulation, providing insight into the physiological role and impact of ergothioneine.

Primary Supervisor: Professor Mark McKeage

P16

KCC2 expression in the human Alzheimer's disease medial temporal lobe

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Background: Alzheimer's disease (AD) is a neurodegenerative disorder that currently has no cure. Hallmarks of the disease include declining cognitive function and neuronal death in the hippocampus and cerebral cortex. The co-transporters K+–Cl – co-transporter 2 (KCC2) and Na-K-Cl (NKCC1) regulate intracellular chloride levels. Mouse models of AD and other neurological disorders have demonstrated altered neuronal KCC2 and NKCC1 expression that makes GABA, the primary inhibitory neurotransmitter, switch to excitatory resulting in cognitive impairment. The excitatory/inhibitory equilibrium is a delicate feature of the brain that needs to be maintained to avoid pathological consequences. **Objectives:** To characterise KCC2 expression density in the human hippocampus between control and AD cases. We hypothesize that altered expression of KCC2 in the AD human medial temporal lobe might be a contributing factor to the excitatory/inhibitory balance disruption and cognitive deficit observed. **Methods:** Coronal tissues sections of the hippocampus, subiculum, entorhinal cortex, and superior temporal gyrus (STG) of healthy (n=8) and AD post-mortem human (n=8) brains were analysed by using free-floating fluorescent immunohistochemistry and confocal laser-scanning microscopy. **Results:** There was significant downregulation of KCC2 levels (p=0.0006) in the STG when comparing control healthy cases to AD cases. Other brain regions examined showed no altered KCC2 expression. **Discussion:** These results suggest there is a disturbed excitatory/inhibitory balance in the STG region. Our findings could provide a possible novel avenue of treatment for AD.

Primary Supervisor: Dr Andrea Kwakowsky

P17

Seeing is Believing in Ocular Biomaterials

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Background: It is estimated that only 1 in 70 people worldwide who require a corneal transplant will receive one due to the chronic shortage of cadaveric donor corneal tissue. **Objectives:** Current work aims to develop and characterise corneal stromal equivalents to supplement the insufficient supply of cadaveric corneal tissue required for sight-restoring corneal transplant surgery. **Methods:** A rabbit study is being conducted to test the biocompatibility of lens crystallin protein films developed by our group for ocular therapeutics. Corneal health will be scored according to a modified McDonald-Shadduck Scoring System, along with immunohistochemical analysis of the corneal stroma. Collagen and silk-based stromal equivalents will be characterised and hybridised with lens crystallin proteins. Q-CMD analysis will investigate protein absorption and cell-binding potential, while a custom microtensile testing rig will assess the mechanical properties of prototype materials. Biocompatibility testing will be undertaken with human keratocytes and corneal epithelial cells. Patterning and surface modification will also be trialled. **Results:** Preliminary animal study results show lens crystallin protein films are more resistant to degradation on the ocular surface than the current gold standard materials. Polymer brushes have been produced to act as control surfaces from Q-CMD. Several clamp designs have been modelled and 3D printed for the microtensile testing rig, allowing the elasticity of porcine corneas to be assessed. **Discussion:** Lens crystallin proteins are proven to produce materials that are transparent, biocompatible and robust. When incorporated into stromal materials, they should improve these characteristics and allow us to replicate native tissue for surgical use.

Primary Supervisor: Dr Laura Domigan

P18

Validity of magnetic resonance spectroscopy combined with echo-planar spectroscopic imaging for measurement of neuroinflammation

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Background: Psychiatric disorders affect a significant percentage of the New Zealand population. These disorders are associated with educational difficulties, decreased productivity, and reduced quality of life, yet their pathophysiological mechanisms are not fully elucidated. Recent studies support the pathogenic role of neuroinflammation; however, there are no accepted methods that can reliably measure these inflammatory processes in patients. **Objectives:** Magnetic resonance imaging (MRI) is a versatile, non-invasive neuroimaging technique that demonstrates sensitivity to brain inflammation. Using magnetic resonance spectroscopy in conjunction with echo-planar spectroscopic imaging (MRS/EPSI), we aimed to measure brain metabolites in order to derive calculations of whole-brain and regional brain temperature, which may increase in cases of neuroinflammation. **Methods:** The validity of MRS/EPSI was tested using a safe experimental model of human brain inflammation – intramuscular administration of typhoid vaccine. Healthy volunteers participated in a double-blind, placebo-controlled study including MRI scans before and three hours after vaccine/placebo administration. **Results:** Preliminary results demonstrate increases in whole-brain temperature following administration of the Typhoid vaccine and placebo. Regions of the brain associated with neuroinflammation appear to increase in temperature following the vaccine administration. **Discussion:** The potential applications of these non-invasive methods for the measurement of neuroinflammation may prove to be crucial in identifying subgroups of psychiatric patients with neuroinflammation who would be most likely to respond favourably to certain classes of treatments, and to improve monitoring of neuroinflammatory-related disease activity.

Primary Supervisor: Dr Joanne Lin

P19

Should Pacific people be homogenised when considering their need for CVD health services?

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Background: Pacific people experience inequities in the burden of cardiovascular disease (CVD) globally. Health services responsible for meeting the health needs of Pacific people, including those in NZ, generally homogenise this group in terms of health service delivery. **Objectives:** To determine whether there are differences in the epidemiology and management of CVD between Pacific groups. **Methods:** We conducted a systematic review to determine whether the epidemiology and management of CVD among Pacific people varies according to Pacific-specific ethnicity or place of birth. The review covered the period 1959–February 2021. Key words were cardiovascular, pacific, pacific-specific, epidemiology, management, equity. The full review protocol is available at https://osf.io/x7nr6/. **Results:** Twenty-three texts were identified, of which only six were of good quality. Much of the literature was outdated and interpreted from non-Pacific perspectives. There was little literature on the management of CVD by Pacific-specific ethnicity and/or place of birth. The findings of included literature indicate that there do appear to be differences in the epidemiology and management of CVD by Pacific-specific ethnicity or place of birth. The most recent NZ-based report estimated the prevalence of ischaemic heart disease (IHD) as highest among Cook Islands Māori (138 per 1,000 age-standardised population ($p<0.001$)) and lowest among Niuean (107.8) in metro-Auckland. **Discussion:** Health services need a contemporary, Pacific-led understanding of the epidemiology and management of CVD among Pacific people to determine the appropriate configuration and monitoring of services to address the CVD health needs of Pacific peoples in NZ.

Primary Supervisor: Dr Vanessa Selak

P20

Understanding the Role of the GABA Signaling System in the Human Cerebral Vasculature

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Background: Alzheimer's disease (AD) is a neurodegenerative disease characterized by neuronal and cerebrovascular dysfunction. Emerging evidence shows that γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter of the mammalian brain, has a role in cerebrovascular dysfunction. Pericytes, an essential neurovascular component involved in microvascular regulation and stability, undergo AD-associated dysfunction through mechanisms yet to be established. A better understanding of how GABA may influence angiogenesis will provide a novel mechanism underlying AD-related pathology. **Objectives:** To assess pericytic proliferation and integrity, and GABAergic receptor (GABAR) subunit assembly and activity in AD-affected and healthy human brain pericytes. **Methods:** Immunocyto- and histochemistry were performed on human brain primary pericytes (hPCs) and pericytes in AD-affected and healthy post-mortem middle temporal gyri (MTG) to assess GABAR subunit composition, with siRNA knockdown to determine subunit function. Electrical cell-impedance sensing (ECIS) and phosphorylated extracellular signal-regulated kinase (pERK) immunoassay were performed to test for hPC vasomotor responses and pERK alterations following GABAergic treatment. **Results:** We demonstrated hPC expression of $GABA_A$ receptor α_3, β_1, β_3, ε, and γ_3 subunit, with β_3 subunit knockdown reducing hPC proliferation. No AD-related post-mortem subunit expression changes were observed on the neurovasculature. Though no GABA-mediated effects on hPC contractility were observed, we detected GABAergic reduction of pERK. **Discussion:** In hPCs, we revealed a possible proliferative role for the $GABA_A$ receptor β_3 subunit, and GABAergic modulation of pERK, a multifaceted downstream signalling event of the $GABA_B$ receptor. Thus, cerebrovascular pericytic function and viability can be regulated by GABA, and potentially compromised by AD-related GABA signalling dysfunction.

Primary Supervisor: Dr Andrea Kwakowsky

P21

A strain-specific approach: Identification of novel therapeutic targets associated with distinct alpha Synuclein polymorphs

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Background: Synucleinopathies are a collective of neurodegenerative diseases characterised by lesions of misfolded α-synuclein (αSyn) aggregates. These deposits localise within specific cellular populations and regions of the brain leading to Parkinson's Disease (PD), Dementia with Lewy bodies, or multiple system atrophy. A recent shift in research found that αSyn fibrils exist as polymorphs with different characteristics. Current literature suggests specific fibril polymorphs are associated with distinct synucleinopathies. As such, they may explain differences in disease pathology, onset, and progression, in addition to being a possible therapeutic target. **Objectives:** The study aims to identify the expression of potential protein targets associated with the Ribbons and P91 polymorphs of αSyn through the validation and optimization of 42 antibodies. **Methods:** Antibody validation was determined using fluorescent labelling on formalin-fixed paraffin-embedded healthy control and PD brain tissue, and fixed pericytes treated with Ribbon or P91 polymorphs of αSyn. Optimization of antibody labelling included alterations to antigen retrieval using Tris-EDTA, citrate buffer and hydrochloric acid. **Results:** Initial observations indicate that 13 of the 42 antibodies have been successful. Nuclear and perinuclear staining is associated with four antibodies, while seven are related to neuronal components localized to the cytoplasm. Two antibodies show possible astrocytic or microglial links. **Discussion:** Of the 13 successful antibodies, NUCKS1 is associated with PD pathogenesis, although its definite mechanism remains unknown. Further validation of protein targets will be determined by testing successful antibodies on tissue micro-arrays containing PD, healthy control, and progressive supranuclear palsy cases.

Primary Supervisor: Dr Victor Dieriks

P22

Withdrawn

P23

The role of phages in Fecal Microbiota Transplant

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Background: The gastrointestinal tract of humans is inhabited by numerous microorganisms which have been connected to gastrointestinal diseases. Fecal Microbiota Transplant (FMT) from a healthy donor to an unhealthy recipient attempts to treat these diseases by modifying the microbial composition. Bacteriophages are viruses that infect bacteria and have been connected to gut health and FMT treatment efficacy. Gut phage taxonomy, functions and interactions with bacteria are still poorly understood. **Objectives:** To investigate the role of phages in FMT, we will extract phages from the Gut Bugs Trial stool samples, a clinical trial investigating how FMT affects the weight of obese recipients. We will determine their composition, degree of transfer and engraftment, and biological interaction with bacteria. **Methods:** We have developed a protocol to extract phage DNA with emphasis on unbiased DNA recovery. We will use Oxford Nanopore Technologies (ONT) long-read DNA sequencing for identification and quantification of near-complete phage genomes. The role of phages in FMT will be inspected through metagenomic analysis. **Results:** Phage DNA was extracted from 1 g of stool at 8.88 ± 1.69 ng/µl mean concentration, obtaining 171 ± 31 ng of total DNA, meeting ONT input requirements. **Discussion:** We expect to increase our knowledge of the behaviour of phages in the gut and FMT, focusing on their ecological interactions with bacteria, thought to be of pivotal importance in gut health. This will lead to a more comprehensive understanding of the aetiology of gastrointestinal pathologies, potentially improving FMT donor selection criteria and, henceforth, its efficacy.
Primary Supervisor: Dr Tommi Vatanen

P24

Mutant Huntingtin Aggregates and Neuroinflammation in the Huntington's disease Midcingulate Cortex

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Background: Huntington's disease (HD) is a neurodegenerative disorder that can result in motor, mood and cognitive symptoms. HD mood symptomatology correlates with neuronal death in the cingulate cortex. Neuroinflammation, involving reactive glial cells and inflammatory mediators in the brain parenchyma, may influence HD pathophysiology. Accumulation of mutant huntingtin (mHTT) aggregates has been linked to neuroinflammation and neuronal loss. Importantly, the degree to which neuroinflammatory changes are detrimental to neurons and influence HD pathology is not well understood. **Objectives:** Our aims were to quantitatively identify microglial activation in HD in the midcingulate cortex. We also assessed if a correlation was present between neuroinflammation and mHTT aggregate burden. **Methods:** Using fluorescent immunohistochemistry, we stained HD and control post-mortem human midcingulate cortex tissue with HLA DP/DQ/DR, an inflammatory marker, and Iba-1, labelling microglia. We qualitatively and quantitatively assessed activation and morphology, indicating neuroinflammation, and mHTT levels - linking neuroinflammation and mHTT burden. We are currently investigating neuroinflammatory pathway activation in HD using western blotting. **Results:** We found increased activated microglial morphologies across all HD cases (53.82%), and increased ramified microglia in control cases (67.41%). HD cases showed decreased ramified and ameboid microglia. Activated microglia were localised close to neurons containing mHTT aggregates in HD, which positively correlated with mHTT burden. Total microglia number did not increase in HD cases. **Discussion:** Total microglia remaining constant between HD and control cases suggests ramified microglia change to activated states in HD, increasing neuroinflammation. Our data also indicates an association between mHTT burden and neuroinflammation in HD.
Primary Supervisor: Dr Andrea Kwakowsky

P25

Best method of delivering transgene for imaging widespread brain activity in live mice

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Background: Widefield calcium imaging is a popular method to study cellular activity in the brain. This requires widespread expression of a genetically encoded calcium indicator, such as GCaMP7. **Objectives:** To determine the best method for widespread transfection of GCaMP7 for in vivo calcium imaging in mouse cortex. **Methods:** Three different methods of delivering calcium indicator were investigated: adult stereotaxic injections into the right auditory cortex of mice at 4 weeks old, injections into the lateral ventricle of mouse pups at postnatal day 1 (p1) and injections into the right transverse sinus at p1. Imaging of tone-evoked fluorescence over the auditory cortex was done after a minimum of 3 weeks post-injection. **Results:** Ventricular injections have low successful recordings over the auditory cortex as transfection tends to be localised to the injection site, which is outside the imaging window. Adult stereotaxic injections have good localised transfection over the imaging window with good signal-to-noise ratio, however, some cortical damage was seen at the injection site. Transverse sinus injection have good widespread cortical transfection seen as early as 5 days post-injection and as late 10 weeks post-injection. However, the fluorescence emission was much lower compared to the other methods. **Discussion:** Transverse sinus injections was shown to have the best transfection of GCaMP7 over a large cortical surface, however the emission was low meaning stronger excitation was needed to get good signal-to-noise ratio. Despite the trade-off, this method is capable of imaging brain activity from post-natal developing mouse pups to the whole adult brain.

Primary Supervisor: Dr. Juliette Cheyne

P26

Investigating the influence of hypoxia on cGAS-STING signalling in macrophages

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Background: Hypoxia is a common, immunosuppressive feature of the tumour microenvironment which contributes to disease progression and therapy resistance. Cyclic GMP-AMP synthase (cGAS) is a dsDNA-sensing protein that induces antitumour type 1 interferon (IFN) via the downstream effector, stimulator of interferon genes (STING). Recently, it has been reported that hypoxia downregulates signalling through the cGAS-STING pathway in breast cancer cells and tumours. **Objectives:** We aim to determine: (i) whether hypoxia impairs cGAS-STING signalling in macrophages and (ii) whether cGAS-STING signalling is activated by atovaquone, an anti-parasitic drug that reduces hypoxia in lung cancer.

To evaluate the effect of hypoxia on cGAS-STING activity we used macrophage models differentiated from human THP-1 cells engineered with a dual NFkB and ISG54 reporter system (THP-1 Dual). To confirm any observed changes in reporter activity, RT-qPCR was used to quantify the transcriptional regulation of selected cGAS-STING-induced transcripts, and ELISA was used to assay protein secretion of CXCL10. Additionally, other cells of monocytic lineage will also be investigated. THP-1 Dual cells were treated with relevant tumour concentrations of atovaquone and cGAS-STING activity assessed by RT-qPCR. **Results:** A time-dependent suppression of cGAS-STING-induced genes (*IFNB1, CXCL10, IFIT1*) was observed in hypoxia but not normoxia. Atovaquone-treatment did not appear to induce cGAS-STING activity in THP-1 Dual cells. **Discussion:** In vitro hypoxia suppresses antitumour IFN response in macrophage models. Eliminating hypoxia by suppressing tumour oxygen consumption may increase antitumour immunity and enhance T cell checkpoint therapy.

Primary Supervisor: Dr Dean Singleton

P27

Effects of P2X Agonists and Antagonists in an *In-vitro* Rat Model of Cochlear Synaptopathy

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Background: According to the World Report on Hearing (2021), hearing loss affects more than 1.5 billion people globally. The majority is due to sensorineural hearing loss (SNHL) due to pathologies in the inner hearing organ, the cochlea. P2X receptors (P2XR's) are ligand-gated cation channels activated by extracellular ATP. While many P2Xs are expressed in mammalian cochlea, their function is not fully understood. **Objectives:** To investigates the expression of P2XRs near cochlear synapses, and effects of manipulating P2X signalling on these synapses *in vitro*. **Methods:** Wistar rat (P5-14) cochleaes were either immediately fixed or incubated for 2 hours in the presence of glutamate agonists (0.05mM of Kainic acid and 0.01mM of NMDA) to model excitotoxic pathology *in vitro* with/without P2X agonist and antagonists. Cochleae's were fixed with 4% paraformaldehyde, analysed by immunohistochemistry. **Results:** The *in vitro* culture model was first established. The effect of P2X agonist/antagonists on the cochlear synapse coupling and innervation will also be reported. P2X isoform specific expressions were found in the proximity of the cochlear synapses. **Discussion:** Recent studies have reported the loss of synaptic connections between auditory neurons and sensory cells, or "cochlear synaptopathy" to be key pathological events associated with SNHL in both human temporal bones and animal models. However, molecular mechanism of synaptopathy remains unclear. The outcome from this study implicates the role of P2X receptors as non-selective cation channels involved in the cochlear synaptopathy.

Primary Supervisor: Professor Peter Thorne

P28

Withdrawn

P29

Assembly of a bioelectronic implant ("Backpack") for recording and stimulating the rat spinal cord.

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Background: Spinal cord injury (SCI) is a severely debilitating condition that affects up to 500,000 people worldwide with no established ways of reversing the effects of this condition. One experimental method to meet this end is by using bioelectronic implants that can both exogenously apply electrical fields aimed to regenerate damaged neurons and record neuronal activity to monitor the injury and effects of the electric fields. **Objectives:** The aim is to assemble a bioelectronic implant that is designed to both record neuronal activity and stimulate electric fields originating from the subdural space in the rat spinal cord. This will be done by bringing together its custom made, prefabricated units. **Methods:** Using microsoldering techniques, connections are made between a customized electrode array on a polyimide probe, a printed circuit board (PCB) and an Omnetics connecter. The PCB and Omnetics connector are sealed inside a custom built, 3D printed "backpack". The majority of the polyimide probe protrudes from the backpack assembly with the electrode array at the far end. A catheter is attached to the tip of this polyimide implant/ probe in order to aid the electrode positioning in the subdural space of the spinal cord. **Results:** The microsoldering techniques were reliable in establishing conductive paths between the electrodes and the appropriate channels of the Omnetics plug with no shorting across channels. **Discussion:** The bioelectronic implant is functional to take recordings directly from the spinal cord of rats. Future work will seek to modify the electrodes to optimise them for stimulation.

Primary Supervisor: Dr Bruce Harland

P30

Association between birth-size and brain volumes at nine years in children born late-preterm and at-term

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Background: Altered brain development is common after preterm birth, and reduced brain volume in childhood has been associated with functional impairments. However, there are few data about the relationship between perinatal factors and brain volumes in mid-childhood. **Objectives:** We examined the association between size at birth and brain volumes at nine years of age. **Methods:** Children born at 36 to 42 weeks' gestation at risk of neonatal hypoglycaemia underwent brain magnetic resonance imaging (MRI) at nine years of age. Volumes of total brain, total cortical grey matter and cerebral white matter, subcortical grey matter, and regional structures (frontal, parietal, occipital, and temporal lobes, cerebellum, cerebrospinal fluid) were analysed using the FreeSurfer tool. Relationships between brain volumes and gestational age at birth, birth weight, and head circumference were analysed using linear regression. **Results:** Among 101 children (49 boys), shorter gestation length ($R2=0.10$, $p<0.001$), lower birth weight ($R2=0.13$, $p<0.001$), and smaller head circumference ($R2=0.17$, $p<0.001$) were associated with smaller total brain volume at nine years of age. The associations with birth weight and head circumference remained significant after accounting for gestational age at birth. There was also a positive association between these perinatal factors and most other brain volumes studied, except for the cerebellum, occipital lobe, and cerebrospinal fluid volumes. **Discussion:** Size at birth is associated with brain volumes at nine years of age, suggesting that both growth before and timing of birth might be important for later brain size.

Primary Supervisor: Prof Dame Jane Harding

P31
Withdrawn

P32
Investigating effects of RXFP4 and INSL5 gene variants found in Polynesian populations

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Background: Relaxin family peptide receptor 4 (RXFP4) and insulin-like peptide 5 (INSL5) form a receptor-ligand pair expressed mainly in the gastrointestinal tract. INSL5-RXFP4 have functions related to food intake, colon motility, energy and metabolism. Two single nucleotide polymorphisms in these genes were identified to be enriched in Polynesian populations. The T6N variant in RXFP4 is found with a minor allele frequency (MAF) of 0.15 while the R114S variant in INSL5 has a MAF of 0.04. **Objectives:** To investigate the roles of RXFP4-INSL5 and potential effects of the gene variants. **Methods:** Phenotypes associated with the variants were analysed in a healthy Polynesian male cohort. Publicly available single cell sequencing datasets were used to identify patterns of RXFP4 expression. *In vitro* assays were performed to study functions of the genes and effects of the variants. **Results:** RXFP4 expression is limited to a subset of enterochromaffin cells, the biggest source of peripheral serotonin. RXFP4 overexpressing Colo320 cells had decreased levels of TPH1, the enzyme catalysing the rate-limiting step of serotonin synthesis. The R114S variant in INSL5 was hypothesised to affect peptide cleavage during protein synthesis and result in a partially processed non-functional hormone. Differences in band sizes and intensity were observed by Western blotting between INSL5 wild-type and variant overexpressing cells. **Discussion:** We have potentially identified a new role for RXFP4-INSL5 system in serotonin synthesis that could mechanistically link to the phenotypes associated with these gene variants and provide information on how this system could be a novel therapeutic target for metabolic diseases.
Primary Supervisor: Professor Peter Shepherd

P33

Melanocortin-4 receptor activated calcium signalling is a potential new platform for screening anti-obesity therapeutics

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Background: Obesity, a global epidemic, has no safe and effective treatments. The human melanocortin-4-receptor (hMC4R) is a critical regulator of body weight and is a prime target for anti-obesity therapeutics. Yet, the signalling mechanisms for hMC4R regulation of body weight is unknown.
This project aimed to understand hMC4R activated calcium signalling by comparing this between hMC4R Loss of function (LoF) variants that cause human obesity and Gain of function (GoF) variants that protect from developing obesity. **Methods:** We developed a high-throughput Fura-2 ratiometric fluorescent assay to quantitatively measure intracellular calcium *in vitro*. The hMC4R-wildtype (WT) was compared with two LoF variants (H76R and L250Q), one overweight-associated variant (H158R) and two GoF variants (V103I and I251L). Basal and α-melanocyte stimulating hormone (α-MSH) activation of hMC4R exogenously expressed in HEK293 cells were studied. Data were analysed using non-parametric sum of squares f-test from three independent experiments. **Results:** The LoF variants exhibited significantly increased ($p<0.0001$) basal calcium and were sensitive to low dose α-MSH stimulated calcium compared with WT (H76R: $p=0.0019$; L250Q: $p=0.0066$; H158R: $p = 0.0009$). The GoF variants exhibited significantly decreased ($p<0.0001$) basal calcium and sensitivity to α-MSH-stimulated calcium was unchanged compared with WT ($p=0.0001$). **Discussion:** Three patterns for hMC4R-induced calcium signalling were observed, (1) Normal body weight, (2) Obesity/overweight-associated, (3) Obesity-protected. We predict increased intracellular calcium associated with hMC4R causes obesity, and decreased intracellular calcium associated with hMC4R protects from developing obesity. In the future, hMC4R induced calcium signalling could be used to screen for potential anti-obesity therapeutics.
Primary Supervisor: Dr Kathleen Mountjoy

P34

Optogenetic modulation of GABAergic system improves Aβ-induced memory deficits

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Background: Accumulation of beta amyloid (Aβ), neurofibrillary tangles and disrupted excitatory neurotransmission are considered the major factors underlying cognitive deficits observed in Alzheimer's disease (AD). Recent evidence indicates that remodelling of the inhibitory y-aminobutyric acid (GABA) signalling system and the resulting excitatory/inhibitory imbalance also contribute to cognitive impairments in AD; in particular, Aβ-induced elevation of extracellular GABA level and disruption of inhibitory function in the hippocampus. However, how GABAergic modulation affects AD pathogenesis is still not fully understood. **Objectives:** Investigate whether modulation of GABAergic inhibition can restore cognitive deficits in Aβ-injected mice. **Methods:** Using a novel wireless implantable optogenetics device, animals were given optogenetic stimulus targeted to the GABAergic interneurons in the hippocampus during learning and memory behavioural tasks, and long-term recognition and spatial memory were assessed. **Results:** We found that continuous light stimulation during both the learning and recall phases of the behavioural tasks reversed memory deficits in Aβ-injected animals, including the inability to recognise object and location novelty. We also found that optogenetic modulation prior to developing AD symptoms also reversed cognitive deficits. **Discussion:** These results support the critical role of GABAergic system in AD pathogenesis and advance our understanding of the potential for GABAergic modulation as a therapy for AD.
Primary Supervisor: Dr Andrea Kwakowsky

P35

The development of a hydrogel-based ultrasound-triggered delivery system for neurotrophic growth factors

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Background: Growth factors have recently been explored as therapeutic agents for tissue engineering. Neurotrophic growth factors (NF), specifically, have been shown to support and direct the regrowth of nerve cells and have potential for the treatment of a range of disease states and injuries. However, key challenges in using NFs include their short half-life *in vivo* and their potential for off-target effects. These challenges could be overcome by the temporal and spatial control of NF delivery to their target site. **Objectives:** The objectives of this research are to create a delivery system where i) release of NF is sustained and ii) release of NF can be triggered by ultrasound. **Methods:** A model drug (FITC-lysozyme) was loaded into hydrogel-based drug delivery systems and different loading strategies explored. The release of the model drug was compared with and without ultrasound stimulation. **Results:** Premixing FITC-lysozyme with the hydrogel precursors was the most efficient loading approach for gelatin methacryoyl (GelMA) and poly(N-isopropylacrylamide) (pNIPAM). Sustained FITC-lysozyme release from the hydrogels was observed, and release rates were increased by ultrasound stimulation. **Discussion:** These results suggest that GelMA and pNIPAM are suitable delivery system for the controlled delivery of NFs to their target site. In the future, these hydrogel-based ultrasound-triggered delivery systems will be loaded with NFs and NFs will be released in a controlled manner to support the regrowth of nerve cells.
Primary Supervisor: Dr Brad Raos

P36

Association Between Quality of Recovery and Postoperative Opioid Use Following Elective Total Knee Arthroplasty

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Background: Opioid analgesics are commonly prescribed following Total Knee Arthroplasty (TKA) to manage postoperative pain and improve overall patient recovery. Persistent opioid use following surgery can lead to short- and long-term adverse effects. **Objectives:** To investigate whether patient-reported quality of recovery metrics following TKA are predictive of longer-term opioid use. **Methods:** We retrospectively identified patients who underwent unilateral TKA at Counties Manukau Health between 1st January and 31st December 2018. Quality of Recovery-15 (QoR-15) scores collected from Post-Operative Days (POD) one and two were summated. Patients were stratified into three groups by QoR-15 scores (<25th, 25-75th, >75th percentile). The primary outcome was the proportion of patients requiring strong opioids at one-month following discharge. Secondary outcomes were patient- and system-centred recovery metrics. **Preliminary Results:** There were 364 patients eligible for inclusion, of whom 202 (55.5%) completed QoR-15 surveys. Baseline demographics between groups were similar except for gender. There was no statistically significant difference between QoR-15 scores and overall inpatient opioid consumption (POD0-3) ($p=0.818$). In the $<25^{th}$ group, 87.9% received either morphine or oxycodone at one-month following discharge, compared to 56.3% in the $>75^{th}$ group ($p=0.005$). Correlation between summated QoR-15 scores and Days Alive and Out of Hospital at thirty-days, and Hospital Length of Stay revealed significant associations ($p=0.005$, $p<0.001$ respectively). **Discussion:** There is an association between QoR-15 scores and longer-term opioid dispensing after TKA, which suggests that patient-reported outcomes of early recovery may impact on later recovery trajectory and pain experience. Further modelling will be conducted for refine this analysis.
Primary Supervisor: Dr Nicholas Lightfoot

P37

Exercise training and chemoreflex sensitivity: endurance trained athletes versus untrained individuals.

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Background: Increased central and peripheral chemoreflex sensitivity is present in several disease states (e.g., hypertension). Therapeutic approaches targeting heightened peripheral chemoreflex sensitivity are currently limited to surgical or pharmacological interventions, and non-invasive alternatives are needed. **Objectives:** To determine whether a history of endurance exercise training attenuates chemoreflex sensitivity in young, healthy individuals. **Methods:** Eleven endurance trained athletes (6 men and 5 women, 25±7 yr, body mass index [BMI] 22±1 $kg.m^{-2}$, peak oxygen consumption [VO_2peak] 66.4±9.1 $mL.kg^{-1}.min^{-1}$ [mean±SD]) and eight untrained individuals (3 men and 5 women, 29±6 yr, BMI 24±4 $kg.m^{-2}$, VO_2peak 47.6±9.0 $mL.kg^{-1}.min^{-1}$) were recruited based on their exercise training history and peak oxygen consumption during an incremental maximal exercise test. All participants performed a hyperoxic hypercapnic rebreathing protocol, from which central chemoreflex sensitivity was taken as the slope of the relationship between minute ventilation (V_E) and end-tidal partial pressure of carbon dioxide. A steady-state 5-min isocapnic hypoxia protocol was also administered, and peripheral chemoreflex sensitivity determined from the increase in V_E during the final minute expressed relative to the fall in oxygen saturation (SpO_2%). **Results:** Central chemoreflex sensitivity was attenuated in the endurance trained vs. untrained groups (2.52±0.92 $L.min^{-1}$. $mmHg^{-1}$ vs. 4.39±1.97 $L.min^{-1}$. $mmHg^{-1}$ respectively, p=0.014), while peripheral chemoreflex sensitivity was not different between groups (-0.17±0.09 $L.min^{-1}.\%^{-1}$ vs. -0.44±0.66 $L.min^{-1}.\%^{-1}$, p>0.05). **Discussion:** These preliminary findings suggest that central, but not peripheral, chemoreflex sensitivity is lower in endurance exercise trained individuals. Future studies are required to determine whether exercise training is an effective strategy for reducing chemoreflex sensitivity in clinical populations.

Primary Supervisor: Dr James Fisher

P38

Neuroinflammation in the Human Cingulate Cortex in Huntington's disease

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Background: Huntington's disease (HD) is a genetic neurodegenerative disease in which patients present with several symptoms including the loss of motor control, behavioural and psychiatric symptoms, and cognitive decline. The cingulate cortex plays a vital role in learning, memory, and emotion processing. Previous research in our laboratory suggests that the cingulate cortex is affected in HD, and mood symptoms in HD cases are linked with major cell loss in the anterior cingulate cortex. Significant evidence of neuroinflammatory changes in HD is evident in the literature and has been hypothesised to promote cell death. Microglia and astrocytes are non-neuronal cells which contribute to an inflammatory response. **Objectives:** The objective of our study was to examine microglial and astrocytic changes in the middle cingulate cortex in HD. **Methods:** We carried out immunohistochemistry experiments to detect astrocytes and microglia and examine changes in cell number and morphology. Our experiments were carried out on human brain tissue sections of the cingulate cortex from both HD brains and healthy control brains. **Results:** We identified the presence of morphological changes in microglia and astrocytes in HD and quantitative analysis of these alterations are in progress. **Discussion:** Understanding the role of astrocytes and microglia in the human cingulate cortex and how they correlate to cell death and symptomology may help us understand the underlying mechanisms of cell death in HD. Ultimately, a better understanding of the inflammatory environment in HD will aid the development of targeted therapies for the disease.

Primary Supervisor: Dr Andrea Kwakowsky

P39

Why do gout patients not take allopurinol?

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Background. Gout is one of the most prevalent inflammatory diseases. Urate-lowering therapy with allopurinol is the most effective agent for controlling this progressive disease. However, continuation rates for ULT are very low. **Objective.** To examine the reasons for non-adherence to urate-lowering therapy and the differences between adherent and non-adherent patients with regards to their motivations to not take allopurinol. **Methods.** A total of 69 patients with gout completed the Intentional Non-Adherence Scale (INAS) as well as clinical and demographic data. Patients were classified as adherent or not based on meeting serum urate target. **Results.** Among the most frequently endorsed reasons for not taking their urate lowering medication was because they wanted to lead a normal life (23.2%) or thought of themselves as a healthy person again (20.2%). Patients also reported that they did not take their medicine as way of testing if they really needed allopurinol (21.7%). Non-adherent patients endorsed significantly more INAS items as reasons for not taking their medicine, had higher medicine-related concerns and had higher levels of testing treatment ($p < 001$). Younger patients, single and non-NZ European also endorsed more reasons for not taking their allopurinol ($p < 001$). **Discussion.** Major reasons behind the decision not to take allopurinol relate to wanting to lead a normal life and the strategy of testing treatment to see if patients could reduce the dose without getting symptoms. The results provide some indications to clinicians about how urate lowering treatment may be framed for patients in order to improve adherence.

Primary Supervisor: Professor Keith Petrie

P40

Bufalin-doxorubicin combination therapy to target trastuzumab-resistant HER2 positive breast cancer

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Background: Human epidermal growth factor 2 receptor positive (HER2+) breast cancer patients usually have a poor clinical prognosis. Although the anti-HER2 antibody trastuzumab significantly improves patients' survival, it poses high drug resistance (60-70%). An effective therapy against trastuzumab-resistant HER2+ breast cancer is needed. Bufalin, a Chinese Traditional Medicine isolated from toad venom, has shown anti-cancer effects against various types of breast cancer; and inhibition of P-glycoprotein to increase intracellular doxorubicin concentrations. **Objectives:** This study aims to investigate the cytotoxicity of bufalin in combination with doxorubicin to trastuzumab resistant HER2+ cancer in a cell-line model. **Methods:** A trastuzumab resistant HER2+ cell line (BT474-R) was developed by continuously exposing BT474 to 10 μg/ml (IC_{50} ~10 μg/ml) for 30 days, then 15 μg/ml for 5 months. The combined cytotoxic effect of bufalin and doxorubicin at various molar ratios were assessed by MTT assay. **Results:** The trastuzumab-resistance of BT474-R was confirmed as treatment with the antibody at 10 μg/ml did not affect the cell growth rates (doubling times 7.4 vs 7.9 days). In both BT474 and BT474-R, the combination index of bufalin and doxorubicin at molar ratio of 1:10, 1:1 and 1:0.1 were less than 1, and the half-maximal inhibitory concentration (IC_{50}) of the combination therapies were significantly less ($p=0.002$) than bufalin and doxorubicin monotherapies, indicating strong synergism between those two drugs. **Discussion:** This study demonstrated a synergistic effect of bufalin and doxorubicin against HER2+ cell lines independent of trastuzumab sensitivity. The mechanisms of trastuzumab drug resistance and the drug combination are under investigation.

Primary Supervisor: Associate Professor Zimei Wu