MDHS Graduate Research Conference 2020

Clinical & Translational Medicine Booklet

https://mdhs.unimelb.edu.au/mdhs-graduate-research-conference-2020

mdhs-grconference@unimelb.edu.au

MESSAGE FROM THE CHAIRS

Dear Delegates,

Welcome to the virtual inaugural Medicine, Dentistry and Health Science Graduate Research Conference 2020 (MDHS GR Conference), a student conference for all biomedical graduate research students that are part of the MDHS Faculty of the University of Melbourne. The organising committee is made up of members from 11 different student society across the MDHS faculty campus. The conference schedule consists out of 12 parallel session covering a variety of interesting topics and accommodating our student talks as well as national and international keynote speakers, Science Communication workshop and a Career Panel Discussion. This event was only possible due to the generous support of the University of Melbourne and the Graduate Student Association (GSA).

We hope that MDHS GR Conference will provide you with opportunities to listen to national and international leaders talking about their ground-breaking research in different biomedical fields and communicate your research to a broad scientific audience. Despite the fact that this conference will be virtually it will give you a unique chance to meet and network with peers from different research fields engage in discussions. We hope that the MDHS GR Conference will inspire you with new possibilities for your future career by listening to our invited speakers from academia and industry.

We wish you all the best for your presentation and hope you enjoy the event and get novel project ideas, career opportunities and new connections out of it.

Martha Blank & Alexander Anderson

(Chair & Deputy-Chair of the Medicine, Dentistry and Health Science Graduate Research Conference 2020)

GENERAL PROGRAM

08.00 - 08.15 Conference Opening & Welcoming Address
Professor Alex Boussioutas and Martha Blank

08.15 - 10.00 Session 1

10.00 - 10.30 Break

10.30 - 12.30 Session 2

12.30 - 13.00 Break
Virtual Socialise

13.00 - 14.30 Science Communication Workshop
Dr. Shane Huntington

14.30 - 16.00 Break
Virtual Socialise | Networking | Games

16.00 - 17.00 Careers Panel Discussion
A/Prof. Nicholas Opie | Dr. Danijela Mirosa | Dr. Ashish Sethi
Dr. Maryam Hussain | Dr. Simranpreet Kaur

17.00 - 19.00 Session 3

19.00 - 20.00 Award Ceremony & Conference Closing
Martha Blank and Alexander Anderson

SCIENCE COMMUNICATION WORKSHOP

Dr. Shane Huntington

Dr. Shane Huntington has been providing consulting services in communication and strategy for over 20 years. As a successful broadcaster, business owner, academic and strategist he draws together experience from multiple sectors, offering clients a more detailed and analytical approach than competitors. Shane has trained thousands of people to communicate more effectively, especially in fields of research. His unique and engaging style has led to him delivering programs to some of Australia's most prestigious institutions.

CAREERS PANEL DISCUSSION

A/Professor Nicholas Opie

Synchron Founding Director and CTO
Co-Lab Head of the Vascular Bionics Laboratory, The University of Melbourne

Dr. Danijela Mirosa

Franchise Director of Oncology for the Oceanic Cluster
Takeda Pharmaceuticals

Dr. Ashish Sethi

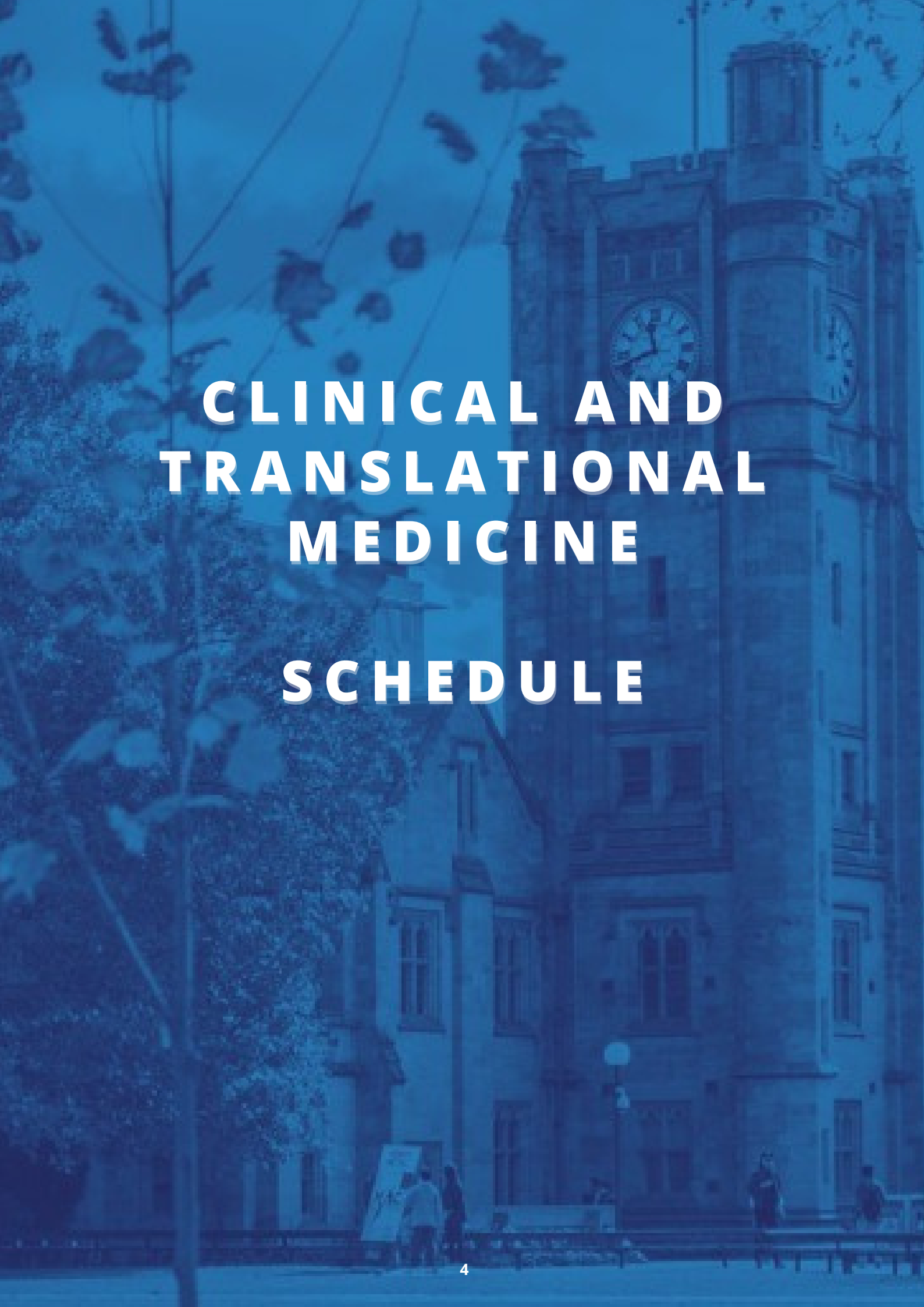
Postdoctoral Research Fellow
Department of Biochemistry & Molecular Biology, TheUniversity of Melbourne

Dr. Maryam Hussain

Medical Science Liaison
Boehringer Ingelheim

Dr. Simranpreet Kaur

Postdoctoral Researcher
MitoBrain Murdoch Children's Research Institute



CLINICAL AND TRANSLATIONAL MEDICINE

SCHEDULE

SCHEDULE

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09.30 – 09.45	**Development of a tissue methylation-specific cell free DNA biomarker for organ rejection following liver transplantation** Daniel Cox	12
09.45 – 10.00	**Diabetes IN-hospital, Glucose & Outcomes - The DINGO Study** Rahul Barmanray	13
SESSION 2		
10.30 – 11.00	**Generating Impact from Australia's Outstanding Medical Research** **Keynote Speaker:** Dr. Glenn Begley	
11.00 – 11.15	**Multipolar mapping with the HDG catheter compared with conventional point-by-point mapping to guide ablation for focal arrhythmias** David Chieng	14
11.15 – 11.30	**Healthy Body, Healthy Mind... Healthy Mouth? Oral microbiome composition is associated with adolescent anxiety and depression** Carra Simpson	15
11.30 – 11.45	**Experiencing genomic medicine in the workplace: secondary analysis to identify workplace learning opportunities** Alice Kim	16
11.45 – 12.00	**Multidisciplinary Care for Functional Gut Disorders Provides Superior Long Term Outcomes Compared to Standard Gastroenterologist Care: A Randomised Trial** Chamara Basnayake	17
12.00 – 12.30	**Bridging the gap between basic respiratory science and clinical medicine** **Keynote Speaker:** Prof. Daniela Traini	
SESSION 3		
17.00 – 17.30	**Gene therapy for glaucoma** **Keynote Speaker:** Prof. Keith Martin	
17.30 – 17.45	**Four-point impedance as a biomarker for bleeding during cochlear implantation** Tayla Razmovski	18
17.45 – 18.00	**Faecal Microbiota Transplantation (FMT) Therapy in Crohn's Disease:Systematic Review** Sasha Fehily	19
18.00 – 18.15	**A novel 'bundle of care' approach to cellulitis management in Western Victorian hospitals (CELLLIT)** Jaclyn Bishop	20
18.15 – 18.30	**Pelvic floor and gut-directed behavioural treatment for faecal incontinence and constipation in patients with inflammatory bowel disease** Angela Khera	21
18.30 – 18.45	**Assessing and removing the effect of unwanted technical variations in microbiome data** Muhamad Fachrul	22
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Clinical and Translational Medicine

Keynote Speakers

A/Professor Thomas Oxley
Florey Institute of Neuroscience and Mental Health
Royal Melbourne Hospital
Mount Sinai Hospital
The University of Melbourne

Session 1 08.15 - 08.45 am

Associate Professor Thomas Oxley is a vascular and interventional neurologist and world expert in brain computer interfaces. He is an Associate Professor and Laboratory Head of the Vascular Bionics Laboratory, University of Melbourne, and Clinical Instructor, attending in the Department of Neurosurgery, Mount Sinai Hospital, New York City. Dr. Oxley has performed over 1600 endovascular neurosurgical procedures, including cerebral aneurysm coiling and clot retrievals in acute stroke. He completed internal medicine, neurology residency in 2013, stroke fellowship in 2015 (Alfred and Royal Melbourne Hospitals) and interventional neurology fellowship in 2017 (Mount Sinai Hospital in New York City).
Dr Oxley completed his PhD in neural engineering in 2016 at the University of Melbourne, in signal processing, image processing and medical device development. Dr Oxley has published 102 internationally peer reviewed articles that have accumulated 6000 citations, with 18 as first or last author and has an H Index of 20. Journals include Nature Biotechnology, Nature Biomedical Engineering, New England Journal of Medicine and The Lancet. He has raised over $25 million dollars in research grant funding. Since 2012, Dr Oxley has founded three companies and raised a total of $12 million in private investment.
He is the founding CEO of Synchron. Based in Silicon Valley, Synchron is the leading implantable brain computer interface company and only one in the clinical stage. The technology includes the Stentrode, the brainPort and brainOS: a system that enables hands-free, brain-control of devices that restore communication, object grasping and mobility to patients with paralysis. The Stentrode technology has achieved widespread international media attention including an endorsement by the President of The United States, Barack Obama in 2016 as well being invited to conduct a TEDx talk in 2018. In 2019 Dr Oxley received the Australian Eureka Prize for Excellence in Interdisciplinary Scientific Research. In 2018 Dr Oxley received the Advance Global Australian of the Year, as well as Award in Life Sciences, the UNESCO Netexplo award for Innovation, and the Congress of Neurological Surgeons 2018 Innovator of the Year. In 2019 Dr Oxley was awarded the University of Melbourne Excellence Award for Team-Based Research as well as the prestigious Australian Eureka Prize for Excellence in Interdisciplinary Scientific Research. In 2020 Dr Oxley was a Victorian nominee finalist for Australian of the Year.

Large-vessel stroke as a presenting feature of Covid-19 in the young
Oxley, T.J., Mocco, J., Majidi, S., Kellner, C.P., Shoirah, H., Singh, I.P., De Leacy, R.A., Shigematsu, T., Ladner, T.R., Yaeger, K.A. and Skliut, M., 2020. *New England Journal of Medicine*, p.e60.

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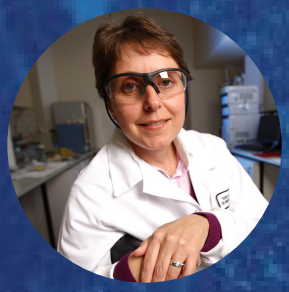

Professor Daniela Traini
Woolcock Institute of Medical Research
The University of Sydney

Session 2 12.00 - 12.30 pm

Professor Daniela Traini is an NHMRC Investigator (2020-2024; past ARC Future Fellow) and her research portfolio covers all areas of respiratory research from bench to bedside. Professor Traini leads the Respiratory Technology group at the Woolcock Institute for Medical Research and works in collaboration with Professor Young. Professor Traini is an international leader in pulmonary drug delivery. Over the last 15 years since joining the University of Sydney, and before during her 5 years in industry, she had developed a leading research program on aerosol drug delivery, ranging from powder engineering, aerosol generation and characterisation, and in vitro to in vivo correlations, including clinical translation. She has extensive experience in both academic and industrial pharmaceutics, and still retains strong link with the pharmaceutical industry. Since 2005 she has published over 220 full peer reviewed manuscripts, and has attracted more than $15 millison in competitive funding.

Gomes Dos Reis, L., **Traini, D.** (2020). Advances in the use of cell penetrating peptides for respiratory drug delivery. Expert Opinion on Drug Delivery, 17(5), 647-664

Clinical and Translational Medicine

Keynote Speakers

Dr. Glenn Begley
BioCurate

Session 2 10.30 - 11.00 am

Dr. Begley has over 20 years basic research and clinical experience in medical oncology and haematology. His research focused on regulation of hematopoietic cells and translational clinical trials. His early research first described human G-CSF, and in later clinical studies, first demonstrated G-CSF-"mobilised" blood stem cells hastened hematopoietic recovery. This finding revolutionised the approach to bone-marrow transplantation worldwide. He has published over 200 papers (>25,000 citations; h-index 77) and his TED-x seminar "The Complex Biology of Cancer" has >100,000 views.
In 2002 he re-located to the USA. From 2002-2012 was Vice-President and Global Head of Hematology/Oncology Research at Amgen California, responsible for building, directing and integrating Amgen's 5 research sites. He subsequently served as Chief Scientific Officer and Senior Vice President at Akriveia Therapeutics, California (2016-2027; now Xilio Therapeutics) and TetraLogic Pharmaceuticals, Pennsylvania (2012-2016); as Non-Executive Director Oxford BioTherapeutics (2012-2017). At Amgen, he highlighted the issue of research integrity and scientific reproducibility, and presented on this subject to President Obama's Science Council, the White House, USA National Institutes of Health, USA Academies of Science, USA National Institute of Standards and Technology, Wellcome Trust, Australian NHMRC, numerous Universities, research Institutes, companies, and in multiple public forums.
His honours include being elected as the first Foreign Fellow to the American Society of Clinical Investigation in 2000, to the Association of American Physicians (2008), to the Research "Hall of Fame" at his alma mater, the Royal Melbourne Hospital (2014), and to the Australian Academy of Health and Medical Sciences (2014).

Raise standards for preclinical cancer research.
Begley CG &Ellis LM. Nature 483:531-533 (2012)

Professor Keith Martin
Dept. of Ophthalmology
The University of Melbourne

Session 3 5.00 - 5.30 pm

Professor Keith Martin is the Managing Director of the Centre for Eye Research Australia and Ringland Anderson Professor and Head of Ophthalmology at the University of Melbourne. Until January 2019, he was Head of Ophthalmology at the University of Cambridge, Deputy Director of the University's John van Geest Centre for Brain Repair and an Affiliate Principal Investigator at the Wellcome Trust - MRC Cambridge Stem Cell Institute. He was also Academic Lead for Ophthalmology and Lead Clinician for Glaucoma at the Cambridge University Hospital. Professor Martin is working to develop new treatments for eye disease using stem cells, gene therapy and other techniques. He is co-founder of Quethera, a Cambridge-based gene therapy company which has developed a gene therapy for glaucoma that is currently progressing towards human clinical trials with a major pharmaceutical company. His other current main research interest is in regeneration and repair of the optic nerve. Clinically, Professor Martin specialises in the medical and surgical management of complex glaucoma. He was President of the World Glaucoma Association from 2018-20.

Neuroprotection of retinal ganglion cells by a novel gene therapy construct that achieves sustained enhancement of brain-derived neurotrophic factor/tropomyosin-related kinase receptor-B signaling.
Osborne A, Khatib TZ, Songra L, Barber AC, Hall K, Kong GYX, Widdowson PS, **Martin KR.** *Cell Death Dis*. 2018 Sep 26;9(10):1007.

ABSTRACTS

CLINICAL AND TRANSLATIONAL MEDICINE

Analysing different missense mutation phenotypes in PTEN

Stephanie Portelli[1,2,3], Douglas E.V. Pires[1,2,3,4] & David B. Ascher[1,2,3]

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[2] Computational and Systems Biology, Bio21 Institute, University of Melbourne, 30 Flemington Rd, Parkville VIC 3052
[3] Computational Biology and Clinical Informatics, Baker Heart and Diabetes Institute, Melbourne VIC 3004
[4] School of Computing and Information Systems, University of Melbourne, Melbourne, VIC 3010

Introduction: PTEN germline missense mutations are associated with a range of phenotypes, ranging from autism spectrum disorder to cancer. While PTEN's role in cancer is related to its tumour suppressor activity in the Akt pathway, the mechanism causing autism-related phenotypes remains unclear. In this work, I have used protein structure, data analysis and machine learning techniques to identify possible differences in autism-causing, cancer-causing and non-pathogenic mutations within PTEN.

Methods: A dataset containing 22 non-pathogenic, 41 autism-causing and 57 cancer-causing mutations was compiled from the literature and online databases. Biophysical measurements of mutational effects were calculated, describing changes in protein stability and dynamics, ligand affinity, molecular interactions, and
conservation. Additionally, an experimental cellular fitness score for each mutation was obtained from the literature. All features were compared across the different phenotype classes through structural analysis, statistical analysis, and unsupervised and supervised machine learning techniques.

Results: Structurally, the distribution of mutations was not observed to be phenotype dependent, suggesting the involvement of multiple pathways. Statistically comparing all pathogenic with non-pathogenic mutations showed that pathogenicity was driven through changes in protein stability, with pathogenic mutations localizing at conserved regions and buried within the protein core. Comparing cancer-causing and autism-causing mutations highlighted that cancer-causing mutations led to a larger reduction in experimental lipid-phosphatase activity, suggesting a more subtle autism-related mechanism. This was reflected in principal components analysis, which illustrated a distinction between benign and pathogenic mutations, where major components included information on conservation and protein stability changes. However, other tested unsupervised machine learning techniques, including t-SNE and U-MAP, did not distinguish between the classes, highlighting disease complexity.

Using these insights, we developed a 3-class supervised machine learning predictor that uses structural and functional mutation information to
distinguish between cancer-causing, autism-causing and non-pathogenic mutations. When tested with an independent blind test, our model showed an accuracy of 61% when considering all features. Our initial model primarily struggled with identifying autism-causing mutations, likely due to their subtle molecular consequences. This provides a strong suitable model for further optimization.

Conclusion: Appropriately distinguishing the different phenotype classes remains an important unanswered question within the PTEN-research community. In this work, we used different techniques to highlight possible differences in mutational properties across the classes, which can suggest possible mechanistic effects for each disease state presented in the clinic. We hope that this work provides the background comprehensive information required to guide research effortstowards a clinical application.

CLINICAL AND TRANSLATIONAL MEDICINE

Characterizing a self-sustained electrical status epilepticus model of epileptogenesis of chronic mesial temporal epilepsy in c57bl/6 mice

P Thergarajan[1,2], TJ O'Brien[1,2,3],NC Jones[1,2] & I Ali [1,2]

[1] Department of Medicine, The Royal Melbourne Hospital, The University of Melbourne;
[2] Department of Neuroscience, Central Clinical School, Monash University;
[3] Department of Neurology, Alfred Hospital, Melbourne

Introduction: Status epilepticus (SE) rat models are well-validated models of chronic mesial temporal lobe epilepsy (MTLE) in translational epilepsy research; however, are much less established in mice. Mice offer experimental advantages; in particular, the availability of transgenic strains in c57bl/6 mice can provide novel insights about neurobiological mechanisms and provide easy access to tools for genetic modification to test potential therapeutic targets. This study aimed to validate the Self-Sustained Electrical Status Epilepticus (SSSE) model of chronic MTLE in c57bl/6 mice, characterizing cognitive and behavioural comorbidities, neuroinflammation as well as the number of spontaneous recurrent epileptic seizures.

METHODS:
SSSE was induced in c57bl/6 mice via a bipolar electrode implanted in the ventral hippocampus and followed by continuous video electroencephalography (vEEG) monitoring. Tissues were collected at three timepoints, 1-day, 7-days and 16-weeks post-SE for gene expression analysis. Additionally, at the chronic
timepoint animals underwent a series of behavioural tests to examine depression, anxiety and cognitive behaviours.

RESULTS:
Sixty percent of animals that underwent SSSE developed spontaneous seizures within the first month, with a latency to first seizure between 2-15 days.
Another 25% animals progressively developed spontaneous seizures over the time course following SE. The seizures were predominantly non-convulsive. During the chronic epilepsy period, post-SSSE mice displayed memory impairments, evidenced by less time spent in the novel arm ($p=0.0001$) as compared to controls in the Y-maze test. In addition, total immobility time on tail suspension test was higher ($p=0.0174$) and preference for sucrose consumption was lower ($p=0.0003$) in SSSE animals when compared to the controls suggesting behavioural despair and anhedonia in these animals. Expression of mRNA for inflammatory cytokines was upregulated at 1-day timepoint and then subsequently decreased to normal at 7-days and 16-weeks.

CONCLUSION:
Our study provides evidence that a SSSE model in c57bl/6 mice can induce chronic epileptic seizures consistent with those seen in patients chronic MTLE
with high reproducibility, as well as able to simulate the cognitive and behavioural comorbidities in these patients. SSSE model has face validity for human epilepsy and could be a model of choice for investigating mechanisms that regulate risk to epilepsy or testing preventive therapies.

Early prediction of incident liver disease using conventional risk factors and gut microbiome-augmented machine learning models

Yang Liu[1,2], Guillaume Meric[1,3], Aki S. Havulinna[4,5], Shu Mei Teo[1,6], Matti Ruuskanen[7,8], Jon Sanders[9], Karin Verspoor[10], Susan Cheng[11], Mo Jain[9,12], Pekka Jousilahti [4,7], Leo Lahti[7,8], Teemu Niiranen[7,8], Veikko Salomaa[4], Rob Knight [9,12,13] & Michael Inouye[1,2,6,14-18]

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[3] Department of Infectious Diseases, Central Clinical School, Monash University, Melbourne, Victoria 3004, Australia
[4] Department of Public Health Solutions, Finnish Institute for Health and Welfare, Helsinki, Finland
[5] Institute of Molecular Medicine Finland, University of Helsinki, Helsinki, Finland
[6] Cambridge Baker Systems Genomics Initiative, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. (7)Department of Medicine, Turku University Hospital and University of Turku, Turku, Finland
[8] Department of Future Technologies, University of Turku, Turku, Finland
[9] Department of Pediatrics, School of Medicine, University of California San Diego, La Jolla, California, USA
[10] School of Computing and Information Systems, University of Melbourne, Melbourne, Australia
[11] Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA
[12] Center for Microbiome Innovation, University of California San Diego, La Jolla, CA, USA
[13] Department of Computer Science & Engineering, Jacobs School of Engineering, University of California San Diego, La Jolla, CA, USA
[14] Health Data Research UK Cambridge, Wellcome Genome Campus and University of Cambridge, Cambridge, UK
[15] British Heart Foundation Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
[16] British Heart Foundation Centre of Research Excellence, University of Cambridge, Cambridge, UK
[17] National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge and Cambridge University Hospitals, Cambridge, UK
[18] The Alan Turing Institute, London, UK

Introduction:
Liver disease is a leading cause of death and is increasingly common in aging populations. The aetiology of liver disease is complex and includes several inter-related risk factors, such as obesity, age and excess alcohol consumption. Recently, the role of the human gut microbiome—the collection of microorganisms residing in the gastrointestinal tract—has been increasingly recognized in various aspects of liver disease. However, the potential of gut microbiota for prospective risk prediction of liver disease has not been assessed.

Methods:
This study included the gut metagenomics sequencing and phenotype data of 7,231individuals (55% female) with 15 years of electronic health record (EHR) follow-up from the FINRISK 2002 cohort. The gut microbial compositions were characterized using shallow shotgun metagenomics sequencing and classified by GTDB taxonomy. We developed machine learning models to investigate the potentials of baseline gut microbial features in predicting 15-year follow-up incident risk of liver disease and evaluated the prediction performance with area under the receiver operating characteristic curve (AUC). To further validate the prediction results, we performed survival analysis for time to disease onset using predicted disease risks.

Results:
Separately, conventional and microbiome risk factors showed comparable predictive capacity for incident liver disease. However, microbiome-augmentation of conventional risk factor models using machine learning models resulted in significantly improved performance, with AUC of 0.834 for incident liver disease and 0.956 for alcoholic liver disease. Similarly, disease-free survival analysis showed better stratification using microbiome-augmented risk models than conventional risk factors alone. Investigation of predictive microbial signatures revealed previously unknown bacterial taxa for incident liver disease, as well as those previously associated with hepatic function and disease.

Conclusion:
Our study assesses the potential clinical validity for adding the gut metagenome to conventional risk factors for prediction of incident liver disease.

CLINICAL AND TRANSLATIONAL MEDICINE

Development of a tissue methylation-specific cell free DNA biomarker for organ rejection following liver transplantation

Daniel RA Cox[1,2], Nicholas Low[1,2], Su Kah Goh[2], Christopher Christophi[1,2], Adam Testro[3], Alexander Dobrovic[4] & Vijayaragavan Muralidharan[1,2]

[1] The University of Melbourne, Department of Surgery – Austin Precinct, Level 8 Lance Townsend Building, Studley Rd, Heidelberg, Melbourne, Victoria 3084, Australia
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[3] Liver Transplant Unit, Department of Gastroenterology & Hepatology, Austin Hospital, Studley Rd, Heidelberg, Melbourne, Victoria 3084, Australia
[4] Translational Genomics and Epigenomics Laboratory, University of Melbourne, Department of Surgery – Austin Precinct, Level 7 Harold Stokes Building, Studley Rd, Heidelberg, Melbourne, Victoria 3084, Australia

Introduction: Graft-derived cell-free DNA (gdcfDNA) quantification is an emerging, minimally-invasive tool for monitoring organ health and detecting acute cellular rejection (ACR) following liver transplantation (LT). Issues with the scalability of laboratory workflows, which usually require genotyping of both donor and recipient, have slowed its translation into clinical use. Recent work has illustrated that patterns of DNA methylation are unique to the tissue of origin. We describe the development and application of a hepatocyte methylation-specific cfDNA (MS-cfDNA) biomarker to quantify gdcfDNA without the requirement for genotyping.

Methods: The design and laboratory development of this hepatocyte MS-cfDNA blood-based biomarker is described. Initially, it was piloted in a small cohort of patients post-LT; blood was collected at 8 time-points, up-to 6 weeks post-LT. cfDNA was extracted from plasma and underwent bisulfite modification. Droplet-digital PCR (ddPCR) was used to quantify gdcfDNA using the MS-cfDNA assay. A gdcfDNA biomarker employing donor/recipient genotyping was used to cross-validate results. In a second, larger cross-sectional cohort; blood was collected from 51 patients at the time of liver biopsy for suspected ACR. Absolute quantification of plasma MS-cfDNA by ddPCR was correlated with biopsy and clinical outcomes.

Results: The MS-cfDNA biomarker was successful in quantifying gdcfDNA post-LT and mapping trends of organ injury. In a small cohort of LT patients (n=3) who underwent longitudinal monitoring of gdcfDNA for 6 weeks post-transplant, the MS-cfDNA biomarker had significant linear correlation in values (R2 = 0.99) to an established gdcfDNA assay requiring genotyping. 51 LT patients undergoing liver biopsy for suspected ACR were recruited to the cross-sectional study. 37 had evidence of rejection on biopsy; 20 required treatment for ACR. Receiver operator characteristics and the area under the curve (AUC) were used to analyse the diagnostic performance of the MS-cfDNA biomarker and conventional biomarkers for ACR; liver function tests (LFTs). Increasing derangement in LFTs was not a statistically significant indicator of ACR. MS-cfDNA outperformed LFTs in the diagnosis of ACR requiring inpatient treatment (MS-cfDNA AUC 73.0%, p 0.01, 95% CI 55.4-90.6% vs ALT AUC [best performing LFT] 66.5%, p 0.08, 95% CI 47.7-85.3%).

Conclusions: A MS-cfDNA biomarker can be used for monitoring gdcfDNA post-LT. Hepatocyte MS-cfDNA at a level <33% of total cfDNA was a strong negative predictor for ACR requiring treatment (NPV = 88.1%, specificity = 96.8%). MS-cfDNA analysis has a major advantage over previous gdcfDNA quantification techniques; it does not require genotyping, lending it greater feasibility for translation into transplantation care.

CLINICAL AND TRANSLATIONAL MEDICINE

Diabetes IN-hospital, Glucose & Outcomes - The DINGO Study

Rahul D Barmanray[1,2], Mervyn Kyi[1,2], Leon Worth[2], Peter G Colman[2], Candice Hall[2], Vicky Gonzalez[2] & Spiros Fourlanos [2]

[1] The University of Melbourne, Parkville, VIC, Australia
[2] The Royal Melbourne Hospital, Parkville, VIC, Australia

Background: Hyperglycaemia in hospital is associated with increased morbidity and mortality. In 2019 the Royal Melbourne Hospital became the first Australian hospital to implement networked blood glucose meters (NBGM) across all wards, enabling immediate uploads of capillary glucose data to assist remote glucose monitoring and glucometric data collection. DINGO is a large prospective observational study aiming to comprehensively characterise the glucometric landscape in an Australian hospital. We aimed to investigate the relationship between in-hospital hyperglycaemia and key clinical outcomes in hospital.

Methods: Between October 2019 and March 2020, 10,701 patient admissions of ≥24 hours duration were identified. In 5,210 admissions, ≥2 blood glucose (BG) measures were recorded. Using alternation to ensure equal representation from discharges throughout the week we investigated 2,605 patient admissions, including 60,493 BG measures. Comprehensive glucometric data and clinical outcomes arising in hospital (including healthcare-associated infections [HAI], acute coronary syndrome [ACS], stroke, acute kidney injury [AKI], mortality and length of stay [LOS]) were audited from the clinical record and NBGM network server. For each admission the presence of in-hospital hyperglycaemia (IHH, ≥2 BGs ≥11.1 mmol/L) was determined and outcomes compared with admissions with no IHH.

Results: The IHH group comprised 1,048 patients with 92% pre-existing diabetes and the no IHH group comprised 1,557 patients with 51% pre-existing diabetes. HAIs were significantly more prevalent in the IHH group (10.7 vs. 8.1%, p=0.029) as well as multiple other in-hospital clinical outcomes (ACS, AKI and LOS) (Table 1). There was no significant difference for inpatient mortality between the groups (Table 1). Multivariable analyses will be performed to evaluate for an independent relationship between in-hospital hyperglycaemia and in-hospital complications.

Conclusion: The institution of a whole-of-hospital NBGM system enabled investigation of the relationship between glucometrics and clinical outcomes. IHH was associated with increased adverse clinical outcomes including HAIs, ACS, AKI and LOS.

CLINICAL AND TRANSLATIONAL MEDICINE

Multipolar mapping with the HDG catheter compared with conventional point-by-point mapping to guide ablation for focal arrhythmias

David Chieng[1,2,4], Anandaroop Lahiri[6], Hariharan Sugumar[1,2,4], Ahmed Al-Kaisey[3,4], Ramanathan Parameswaran[3,4], Robert D Anderson[3,4], Sandeep Prabhu[1,2,4], Liang-Han Ling[1,2,4], Joseph B Morton[3,4], Alex J McLellan[1,3] , Geoffrey Lee[3,4], Jonathan M Kalman[3,4,5] , Andrew D McGavigan[6,7] & Peter M Kistler [1,2,4,5]

[1] The Baker Heart Research Institute, Melbourne, Vic, Australia
[2] The Alfred Hospital, Melbourne, Vic, Australia
[3] Royal Melbourne Hospital, Melbourne, Vic, Australia
[4] University of Melbourne, Melbourne, Vic, Australia
[5] Monash Health, Melbourne, Vic, Australia
[6] Flinders Medical Centre, Adelaide, Australia
[7] Flinders University, Adelaide, South Australia, Australia

Introduction: Multipolar catheters provide high density mapping which may reduce procedural duration and improve success of catheter ablation (CA) for focal arrhythmias. The high density grid (HDG) catheter is a 16 electrode mapping catheter with bipole recordings at orthogonal splines. The aim of this study is to compare the clinical and procedural features from a cohort who underwent CA for focal arrhythmias using multipolar mapping (MPM) with an age and case matched cohort using point by point (PbyP) mapping.

Methods: Consecutive patients undergoing CA for focal arrhythmias between October 2018 and January 2020 guided by MPM were compared with PbyP mapping with the ablation catheter over a similar period. Demographics, procedural features and outcomes were compared.

Results: 54 patients (27 in MPM vs 27 in PbyP mapping) underwent CA for 68 focal arrhythmias (26 atrial and 42 ventricular). In the MPM group the electrogram at the successful site was significantly earlier (39 +/- 11 ms) than in the PbyP group (33 +/- 7 ms; p =0.02). In the MPM group the mapping time (35 +/- 24 mins vs 53 +/- 31 mins in PbyP; p= 0.03) and procedural duration (126 +/- 42 mins vs 153 +/- 39 mins in PbyP, p = 0.02) were significantly shorter. There was no significant difference in radiofrequency and fluoroscopy times, acute procedural success, and arrhythmia recurrence.

Conclusion: Multipolar mapping with the HDG catheter for focal tachycardias identified earlier activation times and was associated with shorter mapping and procedure duration with equivalent success to PbyP mapping.

CLINICAL AND TRANSLATIONAL MEDICINE

Healthy Body, Healthy Mind...Healthy Mouth? Oral microbiome composition is associated with adolescent anxiety and depression

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Introduction: Adolescence is marked by high rates of oral disease and the emergence of depression and anxiety disorders, although this co-occurrence is not well understood. Mental well-being and oral health may be associated via changes to the billions of microorganisms that inhabit the mouth (i.e., the oral microbiome), due to poorer maintenance of toothbrushing routines, higher secretion of the stress hormone cortisol into the mouth, and/or elevation of systemic inflammatory markers. The present study provides the first investigation of the associations between the oral microbiome with depression and anxiety symptoms by employing objective gene sequencing technology. This technique measures the microbial DNA in the sample to infer the species present, without relying on biased bacterial growth techniques.

Methods: Adolescents (N = 66) aged 14–18 years (69.70% female) self-reported oral health, depression and anxiety symptoms. Four saliva samples were assayed for cortisol and the systemic inflammatory marker C-reactive protein (CRP), and one sample was used to estimate the oral microbiome using 16S rRNA gene sequencing. The R packages phyloseq and MaAsLin2 were utilised to conduct multivariate statistical analyses, controlling for age, sex, and corrected for multiple comparisons.

Results: The total number of bacterial species in the mouth (alpha diversity) was not associated with anxiety or depression symptoms. Relationships were instead isolated to specific bacterial groupings including Spirochaetaceae, Actinomyces, Treponema, Fusobacterium and Leptotrichia spp. Several host mood-microbial relationships were moderated by proposed mechanisms, including salivary cortisol and CRP. The most consistent finding was a significant positive association between members of the Spirochaetes bacterial group with anxiety and depression. These pro-inflammatory species have been previously associated with Alzheimer's disease and Syphilis, and are among the small number of
bacteria with the ability to cross the blood-brain-barrier.

Conclusion: Oral microbiome composition, but not diversity, was associated with adolescent anxiety and depression symptoms. Longitudinal studies would improve mechanistic understanding of how pro-inflammatory oral Spirochaetes are associated with mental health, and may elucidate the directionality of these cross-sectional findings. This research indicates that adolescence remains an essential developmental period to identify early targets for intervention.

CLINICAL AND TRANSLATIONAL MEDICINE

Experiencing genomic medicine in the workplace: secondary analysis to identify workplace learning opportunities

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Introduction: Genomic medicine is impacting the clinical practice of the wider medical workforce, but the literature reports that medical specialists without clinical genetics training do not feel adequately prepared. Traditionally, continuing professional development has addressed this deficiency through the delivery of workshops, short courses but more recently there has been a shift towards more active and experiential forms of learning. A recent Australian interview study by our group [1] reported a positive perception of the impact of experiential learning, particularly in the context of the workplace, on preparing medical specialists to practice genomic medicine. However, no research has yet been
conducted to qualitatively explore how medical specialists experience learning about genomics in the workplace. The current study aimed to address this gap by exploring workplace learning of genomics.

Methods: Adequate data was present in an accessible data corpus of de-identified interview transcripts with medical specialists across Australia to conduct qualitative secondary analysis. A dataset with Victorian medical specialists was selected from this using purposive sampling. Thematic analysis was performed, guided by the theory of "co-participation at work" [2], to deductively identify how medical specialists experienced genomics in the workplace and the learning opportunities that afforded them. A coding framework was developed and iteratively refined by the research team to inductively identify themes and sub-themes.

Results: The data set represented 29 hospital-based medical specialists from 11 specialties, varied career stages, patient types and levels of genomics experience and research involvement. Three major themes were identified in how medical specialists experienced - and potentially learned about - genomics in the workplace: 1) during (established) clinical work practice; 2) engaging with opportunities within the workplace (contextual affordances); and 3) pursuing opportunities external to practice (agentic pursuits). These workplace experiences were influenced by a range of individual, professional and contextual factors. Some experiences were recognised as "informal" opportunities for learning by participants whilst many were not.

Conclusion: The secondary data analysis revealed workplace experiences can be utilised to contribute towards practice-related understanding and competence in genomics. Further research is required to explore how medical specialists learn about genomics from their workplace experiences and what factors may influence these experiences.

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CLINICAL AND TRANSLATIONAL MEDICINE

Multidisciplinary Care for Functional Gut Disorders Provides Superior Long Term Outcomes Compared to Standard Gastroenterologist Care: A Randomised Trial

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Introduction: Functional gastrointestinal disorders (FGIDs) are common and costly to treat. Most specialist care is provided by a gastroenterologist, yet a minority of patients symptomatically improve. Although proven effective, psychological, behavioural and dietary therapies are not provided routinely. In a randomized trial we found that multidisciplinary care resulted in superior symptom, psychological and cost outcomes in short-term, compared to standard gastroenterologist-only care1. We now evaluate longer-term outcomes.

Methods: In a single-centre, pragmatic trial consecutive new referrals of patients with Rome IV criteria-defined FGIDs were randomised 1:2 to a gastroenterologist-only standard-care (SC) or co-located multidisciplinary (MD) clinic, MD comprising gastroenterologists, dieticians, gut-hypnotherapists, psychiatrists and physiotherapists. In the MD clinic all patients saw a gastroenterologist and were seen by allied clinicians as needed. We now present longer-term outcomes, 12-months after clinic discharge. Outcomes included global symptom improvement ("slightly better"(4/5) or "much better"(5/5) on a 5-point Likert), gut symptoms [GISSI, IBS:IBS-SSS], psychological well-being (HADS), quality of life (Euro-QOL:EQ-5D) and cost. Analyses included all patients with outcomes available at 12-months (modified intention-to-treat).

Results: 143 discharged study patients (46 SC, 97 MD) were included in the long-term follow up analysis. 59% had IBS and 27% functional dyspepsia. 62% of MD patients saw allied clinicians during clinical care. Median time from first appointment to long term follow up was 563 days (IQR:474 – 642). Patients in Standard Care (SC) were less likely to achieve global symptom improvement: 65% SC (30/46) vs 76% MD (74/97); P=0.17. Patients scoring "much better" was 20% SC (9/46) vs 37% MD (36/97); P=0.04. Median IBS-SSS score at 12-months in IBS patients was worse in SC, 193 SC (IQR:106-275) vs 130 MD (IQR:68-221); P=0.03. ≥50% reduction in GISSI sub-scores from baseline was superior in MD for abdominal discomfort, dyspepsia, constipation, diarrhoea (all P<0.04). Median HADS scores
decreased from baseline to 12-months in MD but not SC: SC 15 vs 12 (P=0.24), MD 14 vs 10 (P<0.01). Quality of life improved in MD at 12-month follow up,
median EQ-5D VAS: SC 70 vs 70 (P=0.58), MD 68 vs 75 (P<0.01). Patients in the standard clinic were more likely to see their GP for gut symptoms during the 12 months post clinic discharge 57% SC vs 32% MD; P=0.005.

Conclusion: In the longer-term follow-up of this randomised, controlled trial multi-disciplinary care was significantly superior to standard gastroenterologist-only care in relation to symptoms, psychological state, quality of life and healthcare utilization 12-months after care was completed.

CLINICAL AND TRANSLATIONAL MEDICINE

Four-point impedance as a biomarker for bleeding during cochlear implantation

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Introduction: The preservation of cochlear structures and natural hearing has become the standard of care for cochlear implantation (CI). Currently in cochlear implant surgery, there is no method for real-time detection of cochlear injury, which may include the infiltration of blood from a damaged lateral wall. Blood in the cochlea creates a hostile environment, causes a larger inflammatory response, and may lead to the loss of natural hearing. Four-point impedance (4PI) can be used to distinguish different biological mediums and may be useful to detect intra-cochlear bleeding as it occurs.

Methods: The aim of this work is to monitor 4PI directly from the intracochlear electrodes on the implant, and to correlate these measurements with hearing preservation. 51 adults with some natural acoustic hearing prior to surgery underwent cochlear implantation. Cochlear health was monitored in real-time during implantation using electrocochleography, and 4PI was measured immediately after insertion. In a preclinical setting, 4PI was measured from custom-built cochlear implants in 13 ears from 9 tri-colour guinea pigs, before and after injection of blood into the cochlea.

Results: The results from the clinical study showed elevated 4PI values correlated significantly with a loss of residual, natural hearing. 13 / 51 patients showed elevated 4PI, with an associated loss of residual hearing and an increased rate of post-operative dizziness. In the animal study, 4PI instantaneously increased after blood injection and remained high thereafter, at a similar magnitude to that seen in clinical patients. 2 control ears did not show this increase.

An alternative explanation for elevated 4PI values is the narrowing of the cochlea from the base to apex, causing an increase in impedance. To test this, 4PI was measured throughout the insertion of a commercially available cochlear implant into a 3D printed human cochlear model. As hypothesised, the 4PI increased slightly on electrodes from base to apex. However, this increase was an order of magnitude smaller than the clinical results, suggesting that cochlear geometry is an unlikely explanation for clinically elevated 4PI.

Conclusion: Four-point impedance is a new marker for the detection of cochlear injury associated with increased rates of post-operative hearing loss and vestibular dysfunction. The magnitude of 4PI elevation is consistent with intra-cochlear bleeding. 4PI may be implemented into commercially available intraoperative monitoring protocols during CI surgery.

CLINICAL AND TRANSLATIONAL MEDICINE

Faecal Microbiota Transplantation (FMT) Therapy in Crohn's Disease: Systematic Review

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Background: The gastrointestinal microbiota is the key antigenic drive in the inflammatory bowel diseases. Randomised controlled trials (RCTs) in ulcerative colitis have established faecal microbiota transplantation (FMT) as an effective therapy.

Aims: To conduct a systematic review to evaluate the efficacy of FMT in Crohn's disease.

Methods: A systematic literature search was performed through to August 2020 [MEDLINE; Embase]. Studies were included if they reported FMT administration in patients with Crohn's disease, and reported on clinical outcomes.

Results: Fifteen studies published between 2014 and 2020, comprising 13 cohort studies and two RCTs, were included in the analysis. One RCT in 21 patients, of single-dose FMT following steroid-induced remission, showed higher rate of steroid-free clinical remission in the FMT group. Another RCT, two-dose FMT in 31 patients, showed no difference in clinical or endoscopic endpoints when comparing FMT via gastroscopy to colonoscopy. Clinical response rates in the early follow up period were higher following multiple FMT than with single FMT. FMT dose did not appear to influence clinical outcomes, nor did whether FMT was fresh or frozen. FMT delivered via upper gastrointestinal route demonstrated higher early efficacy rates than the lower gastrointestinal route but on follow-up beyond eight weeks this difference was not maintained. No serious adverse events were reported.

Conclusion: Preliminary studies suggest that FMT may be an effective therapy in Crohn's disease. However large controlled trials are needed. No serious safety concerns have been identified. Systematic review registration number: CRD42020163791.

CLINICAL AND TRANSLATIONAL MEDICINE

A novel 'bundle of care' approach to cellulitis management in Western Victorian hospitals (CELLLIT)

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Introduction: Cellulitis is a common condition that impacts on health service resources. In Australia in 2017–18, there were 68,664 separations for cellulitis, representing 9% of potentially preventable hospitalisations. An analysis of the National Antimicrobial Prescribing Survey (NAPS) data (2014–16) indicated that antimicrobials for cellulitis were more often prescribed inappropriately in regional and remote hospitals compared to major-city hospitals (25.7% v 19.0%, p = <0.001). The aim of this study was to improve the appropriateness of antimicrobial therapy for cellulitis by implementing a cellulitis bundle of care in three regional health services.

Methods: An adult lower limb cellulitis plan incorporating the bundle elements was co-designed across three Victorian health services, and its impact analysed using a pre/post study design. Adults with ICD-10-AM codes for lower limb cellulitis or erysipelas admitted as inpatients of the three hospitals between 1 May 2019 to 30 November 2019 (baseline) and 1 March 2020 and 31 October 2020 (post) were identified. Patients were excluded if they were; not prescribed an antimicrobial, admitted to ICU, transferred to or from another facility or pregnant or if they had already contributed data to the study. The primary outcome was the percentage of antimicrobial prescriptions assessed as appropriate on day 1 of antimicrobial therapy using the NAPS appropriateness definitions. Secondary outcomes, including readmission to the same hospital with cellulitis within 30 days of discharge, were also collected.

Results: Overall, 31 % (28/90) patients with lower limb cellulitis were commenced on the cellulitis plan. The baseline appropriateness of antimicrobial therapy at Day 1 was 79% (144/183 antimicrobial prescriptions). Preliminary post implementation data collection shows that this increased to 91% (30/33) when a patient was commenced on the cellulitis plan and decreased to 75% (61/81) when the cellulitis plan was not
commenced. The readmission rate with cellulitis within 30 days of discharge at baseline was 3.6% (6/166). In the post implementation phase, 4.3% (1/23) with a cellulitis plan and 12.5% (6/48) without a cellulitis plan were readmitted within 30 days of discharge with cellulitis.

Conclusion: Preliminary results suggest that a cellulitis plan can increase the appropriateness of antimicrobial prescribing at Day 1 and reduce readmission for cellulitis within 30 days.

CLINICAL AND TRANSLATIONAL MEDICINE

Pelvic floor and gut-directed behavioural treatment for faecal incontinence and constipation in patients with inflammatory bowel disease

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Introduction: A significant number of patients with inflammatory bowel disease (IBD) continue to experience bowel symptoms despite achieving disease remission. Increased bowel frequency, urgency, faecal incontinence, evacuation difficulty, abdominal pain, bloating and anorectal pain can affect up to 52% of patients with inactive IBD. Gut-directed behavioural treatment is effective for managing constipation or faecal incontinence in patients without IBD but there is limited evidence for its efficacy in patients with quiescent IBD.

This prospective study aimed to determine whether physiotherapist-led gut-directed behavioural treatment, including pelvic floor muscle training, decreases the severity of functional gut symptoms in patients with quiescent IBD. A secondary aim was to evaluate the effect of the training program on quality of life and psychological well-being.

Methods: Consecutive patients, referred from the hospital IBD clinic, were screened for eligibility. Included patients had bothersome bowel symptoms and quiescent IBD (ulcerative colitis, Crohn's disease or an ileoanal pouch for ulcerative colitis). Active IBD was excluded by endoscopy, imaging, faecal biomarker or disease activity score as indicated, to ensure remission or stable mild IBD. Treatment included pelvic floor muscle training, defaecation retraining, urge resistance strategies, modification of maladaptive toileting behaviour and other practical management strategies, in two to six sessions over 6 months.

Patients were assessed before and after treatment completion using a patient rating of improvement (1=substantially worse, 7=substantially better), Patient Assessment of Constipation-Symptoms (PAC-SYM), St Marks faecal incontinence score (FIS), Inflammatory Bowel Disease questionnaire (IBDQ), EuroQol quality of life measure (EQ), Hospital anxiety and depression score (HADS).

Results: Thirty-four patients (median age 38 years; 24 female) were included (18 ulcerative colitis, 13 Crohn's disease, 3 ileoanal pouch). The median symptom duration was 3.5 years. Twenty-nine (83%) patients completed treatment with 21 of the 29 (72%) reporting moderate or substantial improvement (patient rating of 6 or 7). Paired t-tests compared scores before and after treatment. Symptom scores improved significantly at the end of treatment in the PAC-SYM ($P<0.001$) and FIS ($P<0.001$). The IBDQ disease-specific quality of life score also significantly improved ($P=0.008$). The EQ and HADS scores did not change significantly.

Conclusion: This study demonstrated significant improvement, in more than two-thirds of patients with quiescent IBD, after physiotherapist-led gut-directed behavioural treatment for bothersome bowel symptoms. This is consistent with reported response rates in the non-IBD population and provides evidence supporting the use of this safe therapy to ease the symptom burden on patients already living with a chronic disease.

Assessing and removing the effect of unwanted technical variations in microbiome data

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Introduction: In the past couple of decades, microbiome sequencing has emerged as an important dimension in elucidating human health. Gut microbiome in particular have been found to mediate metabolism, and its link to various diseases have made it an attractive therapeutic target. However, the varying technologies and experimental approaches used in different studies often lead to irreproducible results due to unaccounted unwanted technical variations. Such variations, often unknown, may interfere with true biological signals — possibly resulting in misleading biological conclusions.

Methods: This study aims to characterize the major source of technical variations in microbiome data and to demonstrate how a state-of-the art approach can minimize the impact of these unwanted variations on downstream analyses. We analyzed a total of 184 pig faecal samples encompassing 60 specific combinations of unwanted variations as well as wanted biological factors. We used RUVIII.nb, a GLM-(generalized linear model) based tool utilizing Negative Binomial distribution to estimate and adjust for the unwanted variation in the highly sparse raw microbiome counts data and compared it to existing approaches for normalizing microbiome data.

Results: A number of estimated unwanted factors correlates well with the known experimental factors, with storage conditions and freeze-thaw cycles considerably affecting samples. We noted how thawing seems to affect microbial taxa of class Bacteroidia the most, among other effects of batch variations. We also benchmarked the performance of RUVIII.nb against other popular batch correction methods, namely ComBat, ComBat-seq, RUVg, and RUVs. After correction, both ComBat and ComBat-seq still struggled to remove the overall unwanted variations, whereas RUVg overcorrected and lost biological information in the process. RUVIII.nb and RUVs performed similarly consistent across our sensitivity and specificity metrics.

Conclusion: Our analysis suggests careful consideration in experimental design is essential to ensure accurate biological reading of microbial taxa of interest, and that the inclusion of technical replicates is necessary in efficiently removing unwanted variations.

CLINICAL AND TRANSLATIONAL MEDICINE

Cation leak underlies neuronal hyperexcitability in an HCN1 developmental and epileptic encephalopathy

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Introduction: Pathogenic variants in HCN1, including the recurrent de novo HCN1 M305L variant, are associated with developmental and epileptic encephalopathies (DEEs) – severe, pharmacoresistant epilepsies which often have poor prognoses. The pathophysiological mechanisms underlying how HCN1 dysfunction causes epilepsy are unclear. We engineered the homologue Hcn1 M294L heterozygous knock-in (Hcn1M294L) mouse to explore the disease mechanism underlying HCN1 DEE.

Methods: We first conducted a range of behavioural and seizure assays to characterise the Hcn1M294L mouse and confirm that it accurately models HCN1 DEE. These experiments included electrocorticography, a thermogenic seizure assay, immunohistochemistry for markers of brain excitability, and a Barnes maze learning assay. We subsequently explored the molecular mechanism through which the M305L variant causes HCN1 channel dysfunction using two-electrode voltage-clamp recordings from Xenopus laevis oocytes. Finally, we used whole-cell electrophysiology of layer V somatosensory cortical pyramidal neurons from Hcn1M294L and wild-type mice to study the impact of the mutant channel on neuronal properties and output.

Results: The Hcn1M294L mouse recapitulated the major phenotypic features of patients with HCN1 M305L DEE, including having spontaneous seizures, increased susceptibility to heat-induced seizures, and a learning deficit. The brains of Hcn1M294L mice displayed increased morphological markers of seizures including GFAP and NeuropeptideY. Hcn1M294L mice showed clear spiking on electrocorticogram and were also prone to sudden death. Lamotrigine exacerbated seizures and increased electrocorticographic spiking in the Hcn1M294L mice, whereas sodium valproate reduced spiking, mirroring drug responses reported in a patient with the HCN1 M305L variant. Functional analysis in Xenopus laevis oocytes revealed that the HCN1 M305L variant displayed a loss of voltage dependence, resulting in a constitutively open channel which led to cation leak at depolarised membrane potentials. Consequently, Hcn1M294L layer V somatosensory cortical pyramidal neurons were significantly depolarised at rest. These neurons adapted through a depolarising shift in action potential threshold. However, despite this compensation, these neurons fired action potentials more readily from rest and displayed an increased frequency of spontaneous synaptic events, suggesting local network scale excitability.

Conclusion: These data provide a mechanistic model that links molecular, cellular and network dysfunction causing the neuronal hyperexcitability seen in patients with HCN1 DEE. The Hcn1M294L mouse provides a strong preclinical model of HCN1 DEE, including accurately recapitulating
responses to anti-epileptic drugs, suggesting that this mouse model could be used to test potential drug treatments for this condition.

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