Alfred Research Alliance

EMCR

ALFRED RESEARCH ALLIANCE EMCR COMMITTEE PRESENTS:

EMCR SYMPOSIUM AT THE "G" 2019

Program Book and Abstract

November 7-8th 2019Lindsay Hassett Room, Melbourne Cricket Ground

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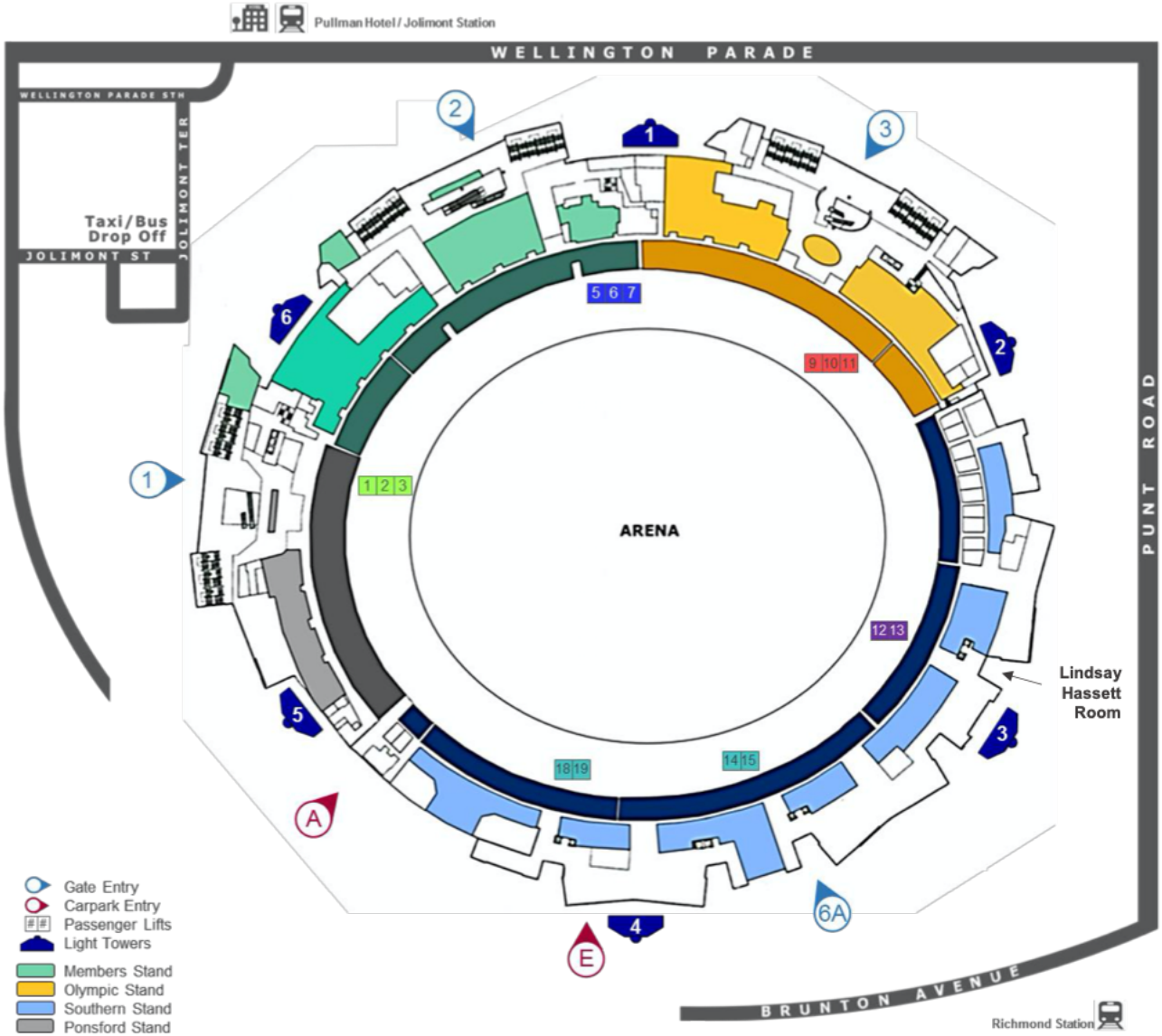

Lindsay Hassett Room

Level 2

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EMCR Symposium Program, 7-8th November 2019

Lindsey Hasset Room, Melbourne Cricket Ground, Richmond

Day 1:

08:30 AM Arrival & Registration

Welcome: 9:30-9:45 AM - A+ EMCR Committee President (Moeen Riaz)

Session 1: 9:45-10:30 AM

Keynote: Steven Rockman – Vaccine Development, Seqirus

10:30 AM Morning Tea

Session 2: 11-12:30 AM

Part 1: 11-11:45 AM - Alternate funding for research
Julie Woods (Trusts and Foundations Officer, Burnet Institute) &
Joanna Thorne (Philanthropic Gifts Coordinator, Baker Heart & Diabetes Institute)

Part 2: 11:45-12:30 PM- Panel Discussion: Careers in Research
Panel Members:

1. Steve Rockman – Vaccine Development, Seqirus
2. Jay Jha - Monash
3. Judy Gold - Burnet Institute
4. Nicola Harris – Lab Head, Monash University Immunology & Pathology

12:30 – 1:30 PM Lunch

Session 3: 1:20-3:30 PM

Part 1: 1:30-2:30 EMCR Talks (60 min)

Day 1 session 3 1:30-3:30 PM		
1:30-1:40	Jennifer Dittmer	Changes in comfort levels relating to condomless sex in samples gay and bisexual men using and not using PrEP
1:40-1:50	Howard Ho-Fung Tang	The early-life nasopharyngeal microbiome interacts with allergic and non-allergic mechanisms of childhood wheeze
1:50-2:00	Peter Daniel Fransquet	Blood based DNA methylation biomarkers of Dementia
2:00-2:10	Dinuli Nilaweera	The risk of dementia in individuals with lifetime post-traumatic stress disorder (PTSD) symptoms

2:10-2:20	Artika Nath	Multivariate genome-wide association analysis of a cytokine network reveals variants with widespread immune, haematological and cardiometabolic pleiotropy.
2:20-2:30	Kathleen Ryan	Results from a large Australian PrEP demonstration study: discontinuation and subsequent HIV and other sexually transmitted infection risk
2:30-2:40	Short Break	
2:40-2:50	Aaron Osborne	Reinvesting in targeted HIV programs to improve the response to the rising HIV prevalence among MSM in Kosovo
2:50-3:00	Nompilo Moyo	The association between nursing skill mix and outcomes for patients in a mental health setting: a feasibility study
3:00-3:10	Filip Djordjevic	Experiences of stigma among people at risk of, or living with, hepatitis C
3:10-3:20	Jessica Borger	Differential Regulation of B Cell Development, Activation and Function by the Hematopoetic Cell Kinase (Hck)
3:20-3:30	Michael Traeger	Changes in the Hepatitis C Cascade of Care among Individuals Attending Primary Health Services Before and After the Introduction of Direct-acting Antiviral Treatment

3:30PM – 4:00 PM Afternoon Tea

Session 4: 4:00-5:00 PM

Monash University and Burnet Institute Bioinformatics Team: Nick Wong, and Mar Quiroga

5:00 pm: Day 1 close, 2020 Mentorship program (EMCR Committee)

5:15-6:15 pm: Keith Millar Room Networking drinks/Happy Hour

6:00-9:00 pm Conference Dinner

Day 2:

9:00 AM Arrival & Registration

Session 1: 9:30- 10:30 AM

Keynote: Paul Zimmet - Department of Diabetes, Monash University

10:30 AM Morning Tea

Session 2: 11-12:30 AM

Part 1: 11-12 AM Prof Karin Vespoor – Text mining for Biomedicine, Melbourne University

Part 2 EMCR Talks

Day 2 session 2 12:00-12:45 PM		
12:00-12:10	Dr Frances Ampt	Impact of a mobile phone-based sexual and reproductive health intervention on unintended pregnancy and contraceptive use among female sex workers in Mombasa, Kenya
12:10-12:20	Matthew Snelson	Advanced Glycation End product-Induced Albuminuria and Changes in Gut Microbiota and Metabolome are Attenuated by Resistant Starch in a Mouse Model of Type 2 Diabetes
12:20-12:30	Clarissa Moreira	Prevalence and predictors of early stunting among infants in Papua New Guinea
12:30-12:40	Abdul Waheed Khan	Inhibition of histone methyltransferase EZH2; a novel target for vascular complications of diabetes

12:45-1:30 PM Lunch

Session 3: 1:30-3:30 PM

Part 1 EMCR Talks

Day 2 session 3 1:30-2:30 PM		
1:30-1:40	Guillaume Méric	Correcting index databases improves metagenomic studies
1:40-1:50	Feby Savira	Inhibition of apoptosis signal regulating kinase 1 in rats with cardiorenal syndrome
1:50-2:00	Daniela K. van Santen	The longitudinal HIV cascade of care among gay and bisexual men with a new HIV diagnosis in Australia between 2012 and 2018
2:00-2:10	Christina Begka	Segmental delivery of bleomycin via mini-bronchoscopy induces lobe-specific fibrosis in mice
2:10-2:20	Akram Zamani	What happens after paediatric traumatic brain injury?

2:20-2:30	Lakshanie C. Wickramasinghe	Development of a clinically relevant mouse model of Bronchopulmonary dysplasia

Part 2: 2:30-3:30 PM Dr Miranda Smith – Project Officer for APPRISE, Peter Doherty Institute
Title: Preparedness and Collaboration in Infectious Disease Research

3:30-4PM Afternoon Tea

Session 4: 4-4:30PM Awards Session

Announcement of Best Paper Awards and Best Speaker prizes
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Closing by the EMCR Committee

4:30-05:00pm Conference concludes

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Abstract

Jennifer Dittmer
Position: RA

Changes in comfort levels relating to condomless sex in samples gay and bisexual men using and not using PrEP

Authors:
Dittmer J[1], Wilkinson A[1,2], Asselin J[1], Draper B[1], Quinn B[3], Holt M[4], Hellard M[1,2,5], Stoové M[1,2]

[1]Burnet Institute, [2]School of Public Health and Preventive Medicine, Monash University, [3]Australian Institute of Family Studies, [4]Centre for Social Research in Health, University of New South Wales, [5]Department of Infectious Diseases, Alfred Health and Monash University

Background: Increasing prominence of biomedical HIV prevention has raised concerns about changing attitudes towards HIV prevention among gay and bisexual men (GBM). We examined changes in levels of comfort with condomless sex with casual partners among HIV negative GBM.
Methods: HIV-negative GBM completing online surveys in 2016 and 2018 were asked questions about comfort having condomless sex with: any Casual Partner (CP); HIV-negative CP (CPNeg); CP using PrEP (CPPr); HIV-positive CP (CPPos); and HIV-positive CP with undetectable viral load (CPUVL). We compared proportions reporting being comfortable/very comfortable having condomless sex, stratified by participants currently using PrEP or not.
Results: PrEP use was reported among 84 (11%) of 754 respondents in 2016 and 122 (37%) of 326 respondents in 2018. Comfort with condomless sex was greatest for GBM using PrEP and increased for any CP (39% to 61%; p=0.003), CPNeg (64% to 84%; p=0.001), and CPPr (71% to 92%; p<0.001). There was no significant increase in comfort among GBM using PrEP with CPPos (30% to 32%; p=0.736) or CPUVL (49% to 60%; p=0.118). GBM not using PrEP reported significant increases in comfort with CPPr (24% to 34%; p=0.007), CPPos (2% to 6%; p=0.006), and CPUVL (6% to 19%; p<0.001). There was no significant increase in comfort among GBM not using PrEP with any CP (7% to 9%; p=0.213) or CPNeg (30% to 33%; p=0.397).
Conclusion: Comfort with condomless sex increased significantly across many partner types. Among PrEP users, high levels and increases in comfort suggesting underlying trust in PrEP were not extended to condomless sex with people living with HIV (PLHIV), even those with suppressed virus. While comfort with condomless sex with PLHIV with suppressed virus increased among GBM not using PrEP, trust in this prevention strategy remained low. Improving knowledge to inform HIV prevention strategies among GBM remains a challenge.

Howard Ho-Fung Tang
Position: Post-doctorate

Title: The early-life nasopharyngeal microbiome interacts with allergic and non-allergic mechanisms of childhood wheeze

Authors: HHF Tang[1,2], A Lang[3], M Evans[3], DJ Jackson[3], R Lemanske[3], J Gern[3], SM Teo[1,2], LM Judd[4], P Holt[5], P Sly[6], KE Holt[4,7], M Inouye[1,2,8]

[1]Systems Genomics Laboratory, Cambridge-Baker Systems Initiative, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia

[2]Department of Public Health & Primary Care, Cambridge-Baker Systems Initiative, University of Cambridge, Cambridge, UK

[3]Departments of Paediatrics / Biostatistics & Medical Informatics, University of Wisconsin-Madison, Madison, Wisconsin, USA

[4]Department of Infectious Diseases, Central Clinical School, Monash University, Melbourne, Victoria, Australia

[5]Telethon Kids Institute, Perth Children's Hospital, Nedlands, Western Australia, Australia

[6]Child Health Research Centre, University of Queensland, South Brisbane, Queensland, Australia

[7]London School of Hygiene and Tropical Medicine, London, UK

[8]Alan Turing Institute, London, UK

Recent research has demonstrated potential links between host microbiota and subsequent health and disease. Our aim was to determine such links in relation to childhood wheeze and asthma. We used data from two paediatric cohorts – CAS from Australia and COAST from USA. Both cohorts featured children with a family history of allergy, monitored from birth to mid-childhood via routine measurements of nasopharyngeal microbiome (16S V4 rRNA sequencing, viral PCR), and comprehensive phenotyping of respiratory illness (symptoms, asthma diagnosis) and sensitization to common allergens. Hierarchical clustering was used to derive clusters of nasopharyngeal samples with similar bacterial compositions. Multiple factor analysis with K-means clustering was employed to generate trajectories of children with similar patterns of colonization across time.

We reaffirmed that known respiratory pathogens, both bacterial (*Streptococcus*, *Moraxella*, *Haemophilus* spp.) and viral (RSV, rhinovirus), were associated with acute respiratory illness in both cohorts, and that these interacted with allergic sensitization to have subsequent effects on asthma risk. Furthermore, in COAST, healthy colonization with a specific *Staphylococcus* taxon in the first 2mths of life was associated with increased sensitization to common allergens as well as increased frequency of asthma diagnosis. These associations were absent in CAS.

In conclusion, the microbiota of the infant nasopharynx has significant effects on future asthma risk. Such effects may be shared or differ across human populations. Our study establishes the importance of investigating microbe-immune system interactions with respect to allergy and asthma, and opens up the possibility of microbiota monitoring or modulation to treat or prevent disease.

Peter Daniel Fransquet
Position: PhD Student

Title: Blood based DNA methylation biomarkers of Dementia

Authors: PD Fransquet[1], J Phung[1], P Lacaze[1], E Parker[1], J Lockery[1], R Saffery[2], R Shah[3], M Ernst[4], A Murray[5], E Storey[1], R Wolfe[1], C Reid[1,6], M Nelson[1,7], J McNeil[1], RL Woods[1], J Ryan J[1,8]
[1]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Victoria, Australia[2]Disease Epigenetics, Murdoch Childrens Research Institute, and The University of Melbourne, Parkville, 3052 Victoria, Australia [3]Department of Family Medicine and Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago[4]Department of Pharmacy Practice and Science, College of Pharmacy, and the Department of Family Medicine, Carver College of Medicine, University of Iowa, Iowa City[5]Berman Center for Outcomes and Clinical Research, Hennepin Healthcare Research Institute, Hennepin Healthcare; Division of Geriatrics, Department of Medicine, University of Minnesota, Minneapolis[6]School of Public Health, Curtin University, Australia[7]Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia[8]INSERM, U1061, Neuropsychiatrie, Recherche Clinique et Epidémiologique, Univ. Montpellier, Montpellier 34000, France

Dementia currently has no definitive biomarker for diagnosis. DNA methylation (DNAm) is implicated in dementia, and has potential to act as an early biomarker of the disease. The aims of this study are to determine whether a unique DNAm signature exists in the peripheral blood of individuals with dementia, and whether a discernible DNAm signature is present prior to diagnosis. The ASPREE study recruited 19,114 generally healthy individuals, predominantly over 70y/o, from the community. Cognitive tests were administered at baseline and at follow-up visits (approx. 3yrs). Incident dementia was adjudicated according to DSM-IV criteria. Epigenome-wide DNAm profiles (of 761,967 methylation sites) were generated using 49 blood samples at follow-up and 160 at baseline. Initial analysis compared DNAm between 25 dementia cases and 24 controls (follow-up). Further analysis compared the DNAm of individuals at baseline, when all participants were without dementia diagnosis, where 73 would go on to receive a dementia diagnosis, and 87 remained cognitively healthy. We identified 3955 differentially methylated regions (DMRs) ($p<0.01$) between cases and controls (adjusted for batch, age and sex), and 1060 DMRs between pre-diagnosis individuals (at baseline) and controls. Thirty-three DMRs overlapped between follow-up and baseline analyses, including genes implicated in neurodegenerative diseases such as Alzheimer's and macular degeneration, as well as genes associated with neurotransmission and neurotoxicity. DNAm signatures measured in blood have the potential to be early biomarkers of dementia. Future studies using larger sample sizes are needed to verify findings, and explore the functional significance of these DNAm marks in dementia pathophysiology.

Dinuli Nilaweera
Position: PhD student

Title: The risk of dementia in individuals with lifetime post-traumatic stress disorder (PTSD) symptoms

Authors: Dinuli Nilaweera[1], Rosanne Freak-Poli[1], Karen Ritchie[2,3], Isabelle Chaudieu[2], Marie-Laure Ancelin[2], Joanne Ryan[1,2]

[1]School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

[2]INSERM, University of Montpellier, Montpellier, Languedoc-Roussillon, France

[3]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, Midlothian, Scotland

Increasing evidence suggests that stress may be a risk factor for dementia. However, the specific impact of post-traumatic stress disorder (PTSD) symptoms on the incidence of dementia in community-dwelling older individuals, requires further investigation. The aim of this study is to determine whether lifetime PTSD symptoms are associated with incident dementia. Data for this study were derived from the ongoing French-based longitudinal ESPRIT study of later-life neuropsychiatric disorders. Lifetime PTSD symptoms were assessed in 1,700 individuals using Watson's PTSD Inventory. Cognitive function was measured in 5 cognitive domains, including global cognition. Incident dementia was ascertained over 17 years according to DSM-IV criteria. Logistic regression analysis was used to determine the association between PTSD and cognitive function at baseline, and cox-proportional hazards models were used to determine the association between PTSD and incident dementia. Various sociodemographic, lifestyle, psychiatric, and health factors were controlled for. An unexpected finding was the association between lifetime PTSD symptoms without re-experiencing symptoms, and a decreased risk of low cognition at baseline, in comparison to no PTSD (global OR: 0.67 [95% CI: 0.52-0.87], executive function OR: 0.69 [95% CI: 0.51-0.93]). Furthermore, PTSD without re-experiencing symptoms was associated with a decreased risk of incident dementia (HR: 0.63 [95% CI: 0.44-0.91). These findings suggest that lifetime PTSD without re-experiencing symptoms may be protective against low cognition and incident dementia. Whilst direct causal relationships cannot be established, future research is need to investigate the potential for post-traumatic growth and biological mechanisms, which may play a role in mediating these associations.

Artika Nath

Post-doctoral researcher - Baker Heart and Diabetes Institute

Multivariate genome-wide association analysis of a cytokine network reveals variants with widespread immune, haematological and cardiometabolic pleiotropy.

(Nath et al., 2019. American Journal of Human Genetics, in press)

Artika P. Nath[1,2,3,*], Scott C. Ritchie[1,2], Nastasiya F. Grinberg[4], Howard Ho-Fung Tang[1], Qin Qin Huang[1,5], Shu Mei Teo[1,2], Ari V. Ahola-Olli[7,8], Peter Würtz[9,10], Aki S. Havulinna[8,11], Kristiina Santalahti[12], Niina Pitkänen[6], Terho Lehtimäki[13], Mika Kähönen[14], Leo-Pekka Lyytikäinen[13], Emma Raitoharju[13], Ilkka Seppälä[13], Antti-Pekka Sarin[8,11], Samuli Ripatti[8,15,16], Aarno Palotie[8,16,17,18,19], Markus Perola[8,11], Jorma S Viikari[20], Sirpa Jalkanen[12], Mikael Maksimow[12], Marko Salmi[21], Chris Wallace[4,22], Olli T. Raitakari[6,23], Veikko Salomaa[11], Gad Abraham[1,2,5], Johannes Kettunen[11,24,25,26], Michael Inouye[1,2,5,27,*]

Abstract

Background: Cytokines are essential regulatory components of the immune system and their aberrant levels have been linked to many disease states. Despite increasing evidence that cytokines operate in concert, many of the physiological interactions between cytokines, and the shared genetic architecture that underlie them, remain unknown. **Aim:** To identify and characterise genetic variants with pleiotropic effects on circulating cytokines. **Methods:** Using three population-based cohorts (N=9,263), we performed multivariate genome-wide association scans for a correlation network of 11 circulating cytokines, then combined our results in meta-analysis. Next, we performed Bayesian colocalisation analysis by integrating publicly available GWAS summary statistics with the cytokine network associations. **Results:** We identified a total of 8 loci significantly associated with the cytokine network, of which two (*PDGFRB* and *ABO*) had not been detected previously. Integration of publicly available GWAS summary statistics with the cytokine network associations using Bayesian colocalisation analysis, revealed shared causal variants between the eight cytokine loci and other traits; in particular, cytokine network variants at the *ABO, SERPINE2,* and *ZFPM2* loci showed pleiotropic effects on the production of immune-related proteins; on metabolic traits such as lipoprotein and lipid levels; on blood-cell related traits such as platelet count; and on disease traits such as coronary artery disease and type 2 diabetes. **Conclusions:** Our findings add a new dimension to our understanding of the genetics underlying human cytokine responses and inflammatory processes in cardiometabolic diseases.

Kathleen Ryan
Position: Post-Doc

Results from a large Australian PrEP demonstration study: discontinuation and subsequent HIV and other sexually transmitted infection risk

Kathleen Ryan, Jason Asselin, Luxi Lal, Long Nguyen, Matthew Penn, Brian Price, Norm Roth, Simon Ruth, BK Tee, Michael West, Jeff Wilcox, Kit Fairley, Margaret Hellard, Jennifer Hoy, Mark Stoove, Edwina Wright

Background
The PrEPX demonstration study used existing health services to emulate the 'real world' provision of HIV PrEP prior to government subsidisation in Australia in April 2018. We describe PrEPX participants who discontinued receiving study drug prior to the study ending, examine factors associated with discontinuation and describe these participants' ongoing HIV and sexually transmitted infection (STI) risk.
Methods
Study drug dispensing data from pharmacy logs, HIV/STI testing and behavioural survey data from four study clinics participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) system were extracted for the duration of PrEPX (26Jul 2016-30Apr2018). PrEPX participants were provided 90 pills per study drug dispensing event, and study discontinuation was classified as participants who were dispensed their last study drug before October 2017, seven months prior to study completion and missing at least two scheduled study prescriptions. Cox proportional hazards estimated covariates associated with discontinued study participation. HIV/STI diagnosis rates >100 days after last study drug dispensed are described and differences in HIV/STI positivity between study and post-study periods were assessed using Chi squared analyses.
Results
This analysis included 2451 participants; 515 (21.0%) discontinued study participation with a median time from last study drug dispensed to study end of 367days (IQR:272-499). PrEP naiveté (aHR1.67 95%CI: 1.11-2.48), age < 30 years (aHR1.65, 95%CI: 1.09-2.50), and reporting consistent condom use with casual partners (aHR1.52 95%CI: 1.01-2.30) at enrolment were associated with discontinuing study participation. Of these 515 participants, 130 (25.2%) accessed post-study testing at ACCESS sites; four participants (3.3%) were diagnosed with HIV during the observation period. Mean time between last study drug dispensed and HIV diagnosis was 338 days (range 140-466 days). STI positivity was similar between pre and post-study periods for chlamydia (8.5%, 8.3%, p=0.9), gonorrhoea (10.4%, 9.9%, p=0.9), and syphilis (0.5%, 1.3%, p=0.5).
Conclusions
Approximately 20% of participants in this analysis discontinued study participation. Four HIV diagnoses and similar STI positivity between study and post-study periods suggest ongoing HIV and STI acquisition risk and unmet HIV prevention need. Greater understanding of barriers to PrEP retention and factors affecting accurate risk perception are needed to maximise the HIV prevention benefits of PrEP.

Aaron Osborne

Position: Research Assistant

Title: Reinvesting in targeted HIV programs to improve the response to the rising HIV prevalence among MSM in Kosovo

Authors: Aaron J Osborne,[1] Edona Deva,[2] Arta Berisha,[2] Flora Robelli,[2] Arber Nuhiu,[3] David P Wilson,[1,4-6] Sherrie L Kelly[1]

[1]Burnet Institute, Melbourne, Victoria, Australia

[2]Community Development Fund, Pristina, Kosovo

[3]Center for Social Group Development, Pristina, Kosovo

[4]Monash University, Melbourne, Victoria, Australia

[5]Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia

[6]University of Maryland, Baltimore, Maryland, USA

Background: HIV prevalence among men who have sex with men (MSM) has increased in Kosovo from no detected cases in 2011 to 2.8% in 2018. Currently 60% of Kosovo's HIV response is donor funded; however, the country is transitioning to be fully domestically funded by 2022. As such, it is imperative to optimally invest these limited available resources to maximize health outcomes.

Methods: Optima HIV, a resource optimization model, was used to estimate the impact of reallocating 30% of Kosovo's spending on non-targeted HIV programs, including management and enabling environment programs, towards prevention and treatment, including implementation of pre-exposure prophylaxis (PrEP) targeting MSM in Pristina. PrEP implementation was modeled using low ($109) and high unit costs ($865). We estimated the number of new HIV infections and HIV-related deaths that could be averted by 2022.

Results: Optimized investment analysis suggests scaling up antiretroviral therapy (ART) and MSM programs, particularly the HIV testing component, through to 2022. PrEP should be implemented if it can be provided at a low unit cost. If 30% of non-targeted spending were to be optimally reallocated, it is estimated that an additional 29% of new HIV infections and 40% of HIV-related deaths could be averted by 2022. At a low unit cost, the PrEP program could avert an additional 3% of new HIV infections.

Conclusion: More HIV infections and HIV-related deaths can be averted by prioritizing scale-up of treatment, and HIV testing among MSM. PrEP should only be implemented if it can be delivered at a sufficiently low unit cost.

Speaker Name: Nompilo Moyo
Position: Ph.D. student

Title: The association between nursing skill mix and outcomes for patients in a mental health setting: a feasibility study

Authors: N Moyo[1], M Jones[2], R Gray[1]
1 La Trobe University, Bundoora, Victoria 3086, Australia.
2 Department of Rural Health, University of South Australia, North Terrace, Adelaide, South Australia 5000, Australia.

ABSTRACT

Background: Research examining nursing skill mix has focused primarily on medical and surgical patient outcomes. No studies have explored association of Mental Health Nurse to registered nurse ratio and clinical outcomes in acute mental health settings.

Aim: We want to establish the feasibility of extracting and linking nurses and psychiatric inpatient data. This will help us to understand if mental health nurse exposure reduces relapse in people with Serious Mental Illness (SMI) in acute inpatient settings.

Method: A retrospective observational study in Victoria, Australia. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) will guide this study. Patient-level data will be extracted from Client Management Interface (CMI) and RiskMan (Incident Reporting System). Nurse-level data will be extracted from the hospital payroll system (Kronos). Patient information will include demographic and clinical characteristics such as diagnosis, untoward incidence, length of stay, admission and discharge dates. Formal educational qualification, demographic data, and nursing roster data will be extracted about nurses working in the participating hospital over the 12-month study period. The data will be used to calculate an estimate of the amount of mental health nursing care each patient received, nursing skill mix ratios, and number of readmissions.

Results: Patient and nurse data will be linked. We will produce tables summarising the extracted data.

Conclusion: Our study will establish the feasibility of extracting and linking nurse and patient data in an acute inpatient ward. This will help us understand if we can test the association of Mental health nurses and patient relapse.

Filip Djordjevic

Position: Research Assistant

Experiences of stigma among people at risk of, or living with, hepatitis C

Authors: Filip Djordjevic[1,2], Kathleen E Ryan[1,3,4], Jack Gunn[1], Bridget Draper[1,3], Sophia Schroeder[1,3], Chloe Layton[1], Judy Gold[1], Paul Dietze[2], Margaret Hellard[1,3,4], Mark Stoove[1,3], Alisa Pedrana[1,3], on behalf of the EC Victoria Partnership.
[1]Disease Elimination Program, Burnet Institute, Melbourne, Australia, [2]Behaviours and Health Risks Program, Burnet Institute, Melbourne, Australia, [3]Department of Infectious Diseases, The Alfred and Monash University, Melbourne, Australia, [4]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia
Presenter's email: filip.djordjevic@burnet.edu.au

Introduction and Aims:

In Australia, people who inject drugs (PWID) are a priority population for hepatitis C (HCV) elimination efforts, yet barriers to treatment uptake remain. We describe the prevalence of injection drug use (IDU)-related stigmatisation and differential treatment from service providers among a newly established cohort of PWID in Victoria, Australia.

Design and Methods:

The EC Experience Cohort is a prospective cohort study nested in the EC Victoria Partnership, which is driving hepatitis C elimination strategies across the state. EC Experience aims to recruit >700 participants from eight EC sites to explore barriers and predictors of HCV testing and treatment uptake, including stigma indicators. Interviewer-administered questionnaires at baseline assessed health service utilisation, experiences of stigma due to IDU and experiences of differential or poor treatment by various service providers.

Results:

By August 2019, 190 participants had been recruited from two community health centres and one large private practice. Of those who reported attending health services on fewer than three occasions, 57% had experienced IDU-related stigma, compared to 67% of those attending health services more frequently. When asked about experiences of stigmatisation from service providers in the previous 12 months, 9% reported ever being treated poorly or differently by NSP and community health workers. In comparison, experiences of poor or differential treatment from GPs, nurses and specialists were reported by 26%, 35% and 39% respectively (see Figure 1).

Jessica Borger
Postdoc

Differential Regulation of B Cell Development, Activation and Function by the Hematopoetic Cell Kinase (Hck)

Jessica G Borger[1*], Erica Brodie[1], Mhairi J Maxwell[1¥], Timothy A Gottschalk[1], Justine Mintern[2], Maverick Lau[1,3], Evelyn Tsantikos[1] and Margaret L Hibbs[1]

[1]*Monash University; Department of Immunology and Pathology, Melbourne, Australia*

[2]*The Department of Biochemistry and Molecular Biology, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Parkville, Australia*

[3]*University of Melbourne; Department of Pharmacology and Therapeutics, Melbourne, Australia*

[¥]*Present address: CSL Limited, Parkville, Victoria, Australia*

Hematopoietic cell kinase (Hck) is a member of the highly conserved Src family of protein tyrosine kinases (SFKs) which mediate cellular activation, survival, differentiation, adhesion and migration. Hck is restricted to cells of the hematopoetic lineage, in particular myeloid cells and has been shown to be involved in the secretion of growth factors and pro-inflammatory cytokines, neutrophil migration and polarisation of macrophages towards an alternatively activated phenotype. We have now identified the expression of Hck in primary B lymphocytes. Transgenic mice ($Hck^{F/F}$) habouring a knock-in mutation in *Hck*, had reduced survival rates compared to wild-type counterparts, developing IgG autoreactive antibodies with age. We identified within the spleen that Hck plays a critical role in the developmental pathway of B cells, with $Hck^{F/F}$ mice and $Hck^{F/F}$ bone marrow chimeras displaying significantly altered transitional, marginal zone and follicular B cell populations. SFKs are known to play key roles in initiating signal transduction through the B cell antigen receptor (BCR) and indeed there was a significant reduction of IgM on $Hck^{F/F}$ B cells, correlating with aberrant signalling and cellular activation. These studies for the first time identify an unexpected role for Hck in B cells, with future investigations aiming to delineate the role for Hck in B cell signal transduction.

Michael Traeger
Position: PhD student

Title: Changes in the Hepatitis C Cascade of Care among Individuals Attending Primary Health Services Before and After the Introduction of Direct-acting Antiviral Treatment

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Introduction: Realisation of global hepatitis C elimination targets will require widespread access to treatment as well as localised responses at the health-service level to increase testing among populations at risk of infection.

Methods: De-identified data were retrospectively extracted from eighteen Victorian clinics participating in the *ACCESS* project. We compared changes in HCV cascades of care before and after the introduction of DAA treatments in March 2016. Two retrospective cohorts were constructed based on clinical consultations between March2013-February2016 (pre-DAA period), or between March2016-February2019 (post-DAA period). Proportion of individuals hepatitis C antibody/RNA tested and proportion RNA-positive during each period were calculated. Individuals were classified as having reached one of four stages in cross-sectional care cascades after each period respectively; (1) ever RNA-positive; (2) genotype/viral load-tested; (3) initiated treatment; (4) cured (RNA-negative>24 weeks [pre-DAA] or >8 weeks [post-DAA] post-treatment-initiation).

Results: 113,248 individuals were included in the pre-DAA period; 13,784 (12.2%) were HCV-tested, and 1,918 (13.9%) were RNA-positive within the period. 139,082 individuals were included in the post-DAA period; 14,507 (10.4%) were HCV-tested and 2,070 (14.3%) were RNA-positive during the period. The pre-DAA cascade included 2,515 individuals ever RNA-positive; 1,977 (78.6%) were HCV viral load/genotype-tested; 19 (0.8%) initiated treatment; and 12 (0.5%) were cured. The post-DAA cascade included 3,713 individuals ever RNA-positive; 3,276 (88.2%) were HCV viral load/genotype-tested; 1,674 (45.1%) initiated treatment; and 863 (23.2%) were cured.

Conclusion: Marked improvements in the HCV cascade of care were observed following universal access to DAA treatments in Australia, particularly at the treatment and outcome cascade stages.

Dr Frances Ampt

Position: PhD student

Title: Impact of a mobile phone-based sexual and reproductive health intervention on unintended pregnancy and contraceptive use among female sex workers in Mombasa, Kenya

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Background:
Female sex workers (FSWs) in sub-Saharan Africa experience high rates of unintended pregnancy. The "WHISPER or SHOUT" cluster-randomised controlled trial was developed to test a mobile phone intervention to prevent unintended pregnancy (WHISPER), compared to a control group receiving nutrition-related messages (SHOUT) among FSWs in Mombasa.

Methods:
The WHISPER intervention consisted of several SMS per week for 12 months, promoting contraceptive use and related health behaviours. Sex work venues (clusters) were randomly sampled with a probability proportionate to venue size. FSWs aged 16–35 years who owned a mobile phone and were not pregnant were eligible and followed up every 6 months. Discrete-time survival models compared unintended pregnancy incidence between arms. Secondary outcomes, including contraceptive use and knowledge, were assessed using multi-level models.

Results:
Ninety-three sex work venues were randomly sampled, and 882 FSWs enrolled. Incidence of unintended pregnancy was 15.09 per 100 person-years, with no difference between the two groups (hazard ratio:0.98, 95%CI:0.69-1.39, p=0.894). The WHISPER intervention improved knowledge over time (likelihood ratio test (LR)=14.43, p<0·001) and dual method use (LR=6.47, p=0.039). There was no difference in long-acting reversible contraceptive (LARC) use between groups (LR=2.15, p=0.34).

Conclusions and Recommendations:
This mHealth intervention did not have the hypothesised impact on unintended pregnancy or LARC use, although it did have an effect on knowledge and shorter-acting methods, including condoms. Complementary interventions, including to improve the supply of LARCs and address structural influences on FSWs' health, may be needed to impact biological outcomes in this population.

Matthew Snelson
Position: Post-Doctoral Research Fellow

Advanced Glycation Endproduct-Induced Albuminuria and Changes in Gut Microbiota and Metabolome are Attenuated by Resistant Starch in a Mouse Model of Type 2 Diabetes

Authors: Matthew Snelson[1], Sih Min Tan[1], Karly Sourris[1], Runa Lindblom[1], Vicki Thallas-Bonke[1], Mark E Cooper[1], Melinda T Coughlan[1]
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Excess intake of dietary advanced glycation endproducts (AGEs) contributes to chronic renal injury. This study investigated whether excess consumption of dietary AGEs promotes gut dysbiosis and exacerbates renal injury in diabetic mice, and if this could be ameliorated with resistant starch (RS) supplementation. Six-week-old diabetic mice (db/db) and non-diabetic mice (db/m) were randomised to receive a low AGE (LAGE, unbaked rodent chow) or a high AGE diet (HAGE, baked at 160°C for 1h) ± 12.5% RS for 10 weeks. 24-hour urine was collected for the assessment of albuminuria. Cecal digesta were collected for an untargeted metabolomics screen and microbiota analysis. The HAGE diet exacerbated albuminuria in diabetic mice which was attenuated by RS. In db/db mice, a HAGE diet was associated with an increase in the Firmicutes/Bacteroidetes (F/B) ratio, which was ameliorated by supplementation with RS. High-AGE-fed db/db mice had a unique cecal metabolome with a marked increase in metabolites from the phenylalanine, tryptophan and tyrosine pathways. RS protected against HAGE-induced albuminuria and reversed changes observed in the microbiome and cecal metabolome. This study supports the notion that dietary AGEs contribute to DKD via alterations in gut homeostasis and indicates a potential renoprotective role for RS.

Clarissa Moreira

PhD student

Title: Prevalence and predictors of early stunting among infants in Papua New Guinea

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Background

Papua New Guinea (PNG) has one of the highest rates of stunting globally with nearly half of all children affected. Insufficient data exists to measure progress towards the WHO Global Nutrition Target of a 40% reduction in child stunting by 2025. Key risk factors for stunting in PNG are unknown. Using data from a longitudinal study of mothers and infants in rural East New Britain (ENB) province, PNG we investigated the prevalence and predictors of stunting.

Methods

Between 2015 and 2018, 699 mothers were recruited during pregnancy. At delivery, one, 6- and 12-months post-partum mothers were interviewed and samples and measurements taken from mothers and their infants to test for infections and nutrient deficiencies. Height for age z scores were calculated using WHO reference standards with <-2 the cut-off for stunting. Predictors of stunting were investigated using mixed multilevel models.

Results

The prevalence of stunting at 6 months was 23% for boys and 20% for girls, increasing to 33% for boys and 23% for girls at 12 months. Mother's height, education level, malaria infection during pregnancy and infant birth weight and length were significant predictors of stunting at 6 and 12 months. Breastfeeding and complementary feeding indicators were not associated with stunting.

Conclusions

Stunting in ENB among infants <12 months is lower than previous national estimates but remains unacceptably high with life-long consequences. Prenatal maternal factors were the strongest predictors of infant stunting suggesting that improving the health of mothers is key to preventing stunting among PNG infants.

Abdul Waheed Khan
Research Fellow

Title: Inhibition of histone methyltransferase EZH2; a novel target for vascular complications of diabetes

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Posttranslational modifications of histones, for instance acetylation and methylation of specific lysine residues play a critical role in regulating gene expression in health and disease. The Enhancer of zeste homolog 2 (EZH2) methylates lysine 27 of histone H3 (H3K27me3). Gene promoters enriched for H3K27me3 are tightly associated with gene repression. EZH2 is potentially important factor in ROS generation and inflammation. Epigenetic changes are amenable to pharmacological intervention. GSK126 is an EZH2 specific small-molecule inhibitor. This study validates targeting EZH2 by GSK126 as a novel target for vasoprotection in the context of diabetes.

Methods: Human aortic endothelial cells (HAECs) stimulated with high glucose (HG) and GSK126 and HAECs isolated from patients with diabetes grown in media containing GSK126 were examined for superoxide anion ($O2^-$) production by electron spin resonance (ESR) and gene expression changes by RT qPCR. Chromatin immunoprecipitation (ChIP) was performed to determine levels of H3K27me3 on gene promoters.

Results: Inhibition of EZH2 with GSK126 blunted HG-induced H3K27me3. EZH2 inhibition abolished the generation of $O2^-$ by HG. GSK126 prevented HG-induced downregulation of ROS-scavenging enzymes SOD1 and SOD2. ChIP analysis showed that these gene expression changes were regulated by EZH2-mediated H3K27me3. We also identified that EZH2 regulates NOX4 expression via transcription factor JunD. GSK126 stimulation of HAECs also prevented HG-induced NF-κB p65 binding activity and subsequent overexpression of inflammatory molecules MCP1 and IL6. Moreover, these findings were validated in HAECs of diabetic origin.

Conclusion: Targeting EZH2 may attenuate oxidative and inflammatory transcriptional programmes and thus prevent vascular disease in diabetes.

Guillaume Méric
Position: Post-doc

Correcting index databases improves metagenomic studies

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Assessing the taxonomic composition of metagenomic samples is an important first step in understanding the biology and ecology of microbial communities in complex environments. Despite a wealth of algorithms and tools for metagenomic classification, relatively little effort has been put into the critical task of improving the quality of reference indices to which metagenomic reads are assigned. Here, we inferred the taxonomic composition of 404 publicly available metagenomes from human, marine and soil environments, using custom index databases modified according to two factors: the number of reference genomes used to build the databases, and the monophyletic strictness of species definitions. Index databases built following the NCBI taxonomic system were also compared to others using Genome Taxonomy Database (GTDB) taxonomic redefinitions. We observed a considerable increase in the rate of read classification using modified reference index databases as compared to a default NCBI RefSeq database, with up to a 4.4-, 6.4- and 2.2-fold increase in classified reads per sample for human, marine and soil metagenomes, respectively. Importantly, targeted correction for 70 common human pathogens and bacterial genera in the index database increased their specific detection levels in human metagenomes. We also show the choice of index database can influence downstream diversity and distance estimates for microbiome data. Overall, the study shows a large amount of accessible information in metagenomes remains unexploited using current methods, and that the same data analysed using different index databases could potentially lead to different conclusions. These results have implications for the power and design of individual microbiome studies, and for comparison and meta-analysis of microbiome datasets.

Feby Savira
Position: PhD student

Title: Inhibition of apoptosis signal regulating kinase 1 in rats with cardiorenal syndrome

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Cardiorenal syndrome (CRS) is a major health burden worldwide with suboptimal options for effective therapies. The present study assessed the therapeutic potential of apoptosis signal-regulating kinase 1 (ASK1) inhibition, a cellular stress-driven pathway, in a rat model of CRS. Adult male Sprague-Dawley rats underwent surgery for myocardial infarction (MI) (week 0) followed by 5/6 subtotal nephrectomy (STNx) at week 4 to induce CRS. At week 6, MI+STNx animals were randomised to receive either 0.5% carboxymethyl cellulose (Vehicle, n=15, Sham=10) or ASK1 inhibitor GSK2261818A (G226) (15mg/kg daily, n=11). Cardiac and renal function was assessed by echocardiography and glomerular filtration rate (GFR) respectively, prior to treatment at week 6 and endpoint (week 14). Haemodynamic measurements were determined at week 14 prior to tissue analysis. G226 treatment significantly improved the absolute change in left ventricular (LV) fractional shortening and posterior wall thickness compared to Vehicle. G226 also attenuated the reduction in preload recruitable stroke work. Increased myocyte cross sectional area, cardiac interstitial fibrosis, immunoreactivity of cardiac collagen-I and III and cardiac TIMP-2 activation, were significantly reduced following G226 treatment. Although we did not observe improvement in GFR, G226 significantly reduced renal interstitial fibrosis, diminished renal collagen-I and –IV, kidney injury molecule-1 immunoreactivity as well as macrophage infiltration and SMAD2 phosphorylation. In conclusion, inhibition of ASK1 ameliorated LV dysfunction and diminished cardiac hypertrophy and cardiorenal fibrosis in a rat model of CRS. This suggests that ASK1 is a critical pathway with therapeutic potential in the CRS setting.

Speaker: Daniela K. van Santen
Position: post-doc

The longitudinal HIV cascade of care among gay and bisexual men with a new HIV diagnosis in Australia between 2012 and 2018

Daniela K. van Santen[1,2], Jason Asselin[1], Denton Callander[3], Michael Traeger[1], Noah Haber[4], Carol El-Hayek[1], Basil Donovan[3], James McMahon[2], Kathy Petoumenos[3], Hamish McManus[3], Margaret Hellard[1,2,5], Rebecca Guy[3]*, Mark Stoove[1,2]* on behalf of the TAIPAN investigators

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Background: Most studies assessing the HIV cascade typically perform cross-sectional analyses, which do not capture the time individuals take to transition to subsequent stages. We aimed to assess the longitudinal HIV cascade of care in Australia, along with trends in transition times.

Methods: We used linked data from gay and bisexual men (GBM) attending clinics captured by the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS). Eligible participants had evidence of a new HIV diagnosis between 2012-2018. We estimated stages: 1) diagnosis test interval, from last HIV-antibody negative test to HIV diagnosis (in a subset of GBM with a previous HIV-negative test recorded); 2) diagnosis to linkage to care, defined as the first CD4 T-cell count and/or HIV viral load (VL) measurement; 3) Linkage to care to antiretroviral therapy (ART) initiation; and 4) ART initiation to viral suppression (VL <200 copies/ml). We used Kaplan-Meier methods to estimate time to stages 2-4 conditional on reaching a previous stage, and Cox-Proportional hazard models to assess trends.

Results: Among 10,042 ever HIV positive GBM, 1,866 were diagnosed during follow-up. Stage 1: Among 849 GBM, median diagnosis interval was 7.3 months (Interquartile range=2.9-20.4). Stage 2: median time to linkage to care was 5 days (95%CI: 5-6). Stage 3: median time ART initiation was 35 days (95%CI: 33-41). Stage 4: median time to viral suppression was 66 days (95%CI: 62-76). The cumulative probability at one-year post-stage eligibility of ART initiation and viral suppression significantly increased over calendar periods: from 59.7% and 67.4% in 2012-2013 to 96.0% and 80.5% in 2016-2018, respectively.

Conclusion: Among newly-diagnosed GBM in Australia HIV cascade transitions occur rapidly, with considerable improvement seen in time to viral suppression over the observation period. In countries like Australia with high cross-sectional cascade estimates, longitudinal analyses are better to assess improvements over time and provide crucial information lacking in cross-sectional analysis.

Christina Begka
Post-doc

Segmental delivery of bleomycin via mini-bronchoscopy induces lobe-specific fibrosis in mice

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Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease characterised by compromised lung structure due to fibrosis and progressive tissue damage. Intranasal (i.n.) or intra-tracheal (i.t.) administration of bleomycin, a pro-fibrotic drug, induces lung fibrosis in mice by causing epithelial cell apoptosis and inflammation followed by an aberrant wound repair response. However, these administration methods result in generalized fibrosis and do not faithfully recapitulate the fibrosis observed in IPF patients. With the use of a miniature bronchoscope equipped with a camera and an irrigation channel, we have established a segmental lung lobe bleomycin delivery model. In addition, we have performed lobe-specific broncho-alveolar lavage (BAL), allowing the evaluation of inflammation and fibrosis in individual lobes of the lung. Histological evaluation of lungs showed fibrosis and collagen deposition exclusively in the treated lobe, while the untreated lobe remained healthy. Flow cytometric analysis of BAL fluid (BALF) and lung digests demonstrated a pronounced increase in CD4+ T cells from day 7 to 21 and an increased B cell frequency from day 14, compared to the untreated lobe. We observed the formation of tertiary lymphoid structures in the lung tissue, similar to those reported in the lungs of IPF patients. Overall, we have established a novel model of site-specific fibrosis in mice, that faithfully recapitulates characteristics of IPF, allowing the future analysis of mechanisms underlying disease progression and chronicity.

Akram Zamani
Post-doc

Losing Friends?
What happens after paediatric traumatic brain injury?

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Traumatic brain injury (TBI) is particularly prevalent in the paediatric population (age 1-4 years). This is also an age when the brain is vulnerable to insult, in part due to the ongoing development of new white matter (WM) tracts. Following paediatric TBI, neurobehavioural deficits emerge at adulthood and are likely to reduce quality of life. To understand the neuropathology of paediatric TBI, we use diffusion weighted imaging (DWI) to characterise the extent of WM disruption after a mouse paediatric TBI model and use a battery of behavioural tests to identify the deficits seen at a later stage. Controlled cortical impact (CCI) or sham-surgery is performed on male C57Bl/6 mice at postnatal day 21 and MRI scanning is acquired at 4, 7 and 28 days post injury and behavioural tests are performed at day 70 post injury. DWI metrics such as FA, RD and AD are used to evaluate the WM changes that follows. We found loss of integrity in axons and myelin damage in a number of WM regions, and a change in social behaviour in adulthood. Using this study, we aim to identify if WM degeneration precedes the onset of such deficits and if we can use this to predict the behavioural dysfunction the emerge later in life.

Lakshanie C. Wickramasinghe

PhD Candidate

Development of a clinically relevant mouse model of Bronchopulmonary dysplasia

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INTRODUCTION: Bronchopulmonary Dysplasia (BPD) is a severe lung disorder affecting premature infants requiring life-saving oxygen therapy. Currently, no cure exists and the treatments to prevent disease complications are inadequate, therefore better treatment strategies are urgently required. Due to the lack of gold-standard, clinically accurate animal model of BPD development, novel targets for therapeutic intervention remain unexplored. This study aims to develop a new supplemental oxygen mouse model of acute and chronic BPD, based on the key lung developmental stages affected in preterm infants with BPD.
METHODS: Neonatal C57BL/6 mice pups were exposed to 75% oxygen for 5, 8 or 14 days from postnatal day PD1 to PD5,8 or 14 and /or kept in room-air conditions until PD40 to develop early and late-stage BPD. Mice lungs were assessed at PD14 and PD40 to examine the effect of differential supplemental oxygen schemes on the development of alveolar septal wall thickening and airspace enlargement. Mice housed solely in room-air served as disease free controls. Lung paraffin sections stained with H&E were used for morphometric analysis of structural changes.
RESULTS: At PD14 and PD40, C57BL/6 mice exposed to oxygen from PD1 to PD14 had the greatest septal wall thickening and airspace enlargement, respectively, compared to the PD1 to PD5 and PD1 to PD8 supplemental oxygen protocols. The age-matched room air controls showed no changes to alveolar structure at PD14 or PD40.
CONCLUSION: Supplemental oxygen exposures in the first 14 days of murine postnatal life can be used to accurately model key features of human BPD.