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Recent Advancement and Future Directions in mRNA/LNP Therapeutics

Uli Frevert

Symposium 1: mRNA Therapeutics – Its complex and more than meets the eye, Eureka Room 1, December 2, 2024, 11:15 AM - 1:15 PM

Biography:
Dr. Uli Frevert is the Head of Translational Clinical Trials for Therapeutics and Oncology at Moderna Therapeutics in Princeton, NJ, USA. His team focuses on exploratory clinical trials to advance LNP/mRNA platform knowledge and further unlock its therapeutic potential.

Dr. Frevert trained in Internal Medicine and Endocrinology and completed postdoctoral research on insulin signal transduction in Prof. Barbara Kahn's lab at Harvard Medical School. He has over 20 years of experience in Drug Discovery, Early Clinical Development, and Translational Medicine within the pharmaceutical and biotech industries.

He is also a member of the recently established mRNA Platform Incubator Network in Melbourne, Australia, an opportunity that allowed him to visit and appreciate this wonderful part of the world.

Recent Advancements and Future Directions in mRNA/LNP Therapeutics

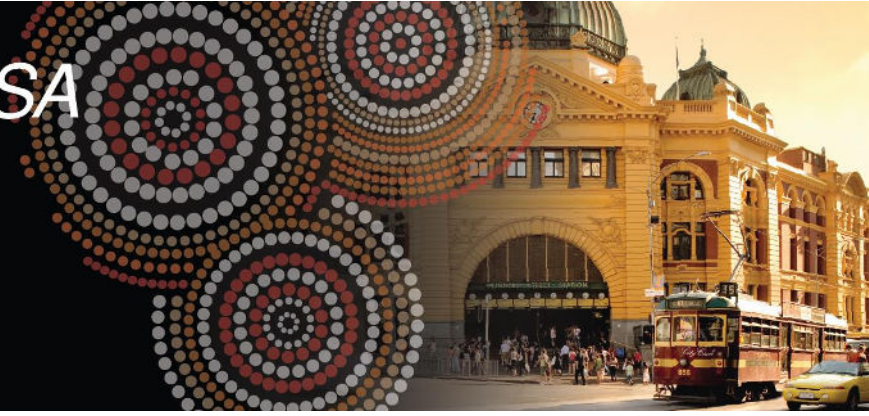
The mRNA/LNP platform has revolutionized biotechnology, achieving unprecedented impact with the rapid development and deployment of COVID-19 vaccines. Beyond vaccines, the flexibility of the mRNA/LNP approach, combined with its rapid clinical learning cycles, opens the door to innovative therapeutic strategies. These strategies include intracellular protein replacement for rare diseases, individualized neoantigen therapies in oncology, and the in vivo generation of secreted proteins with therapeutic or prophylactic effects.

While the first mRNA/LNP therapeutics are advancing rapidly through clinical development, the journey to fully unlock their potential is just beginning. Critical areas for further research include:

- Identification of key factors impacting intra- and inter-subject variability in pharmacokinetics, biodistribution, and protein expression.
- Characterization of alternative administration modes beyond intravenous infusion.
- The kinetics and impact of the biomolecular corona formation after administration.
- The application of quantitative systems pharmacology and other modelling methods to help inform our emerging understanding of mRNA/LNP clinical pharmacology.

Accumulating clinical data will enhance our understanding of the predictive translational value of cellular and animal models, further optimize LNP formulations, and identify new disease areas suited for the mRNA/LNP modality. Additionally, new clinical tools for in vivo evaluation of LNP/mRNA and protein biodistribution kinetics will aid in optimizing dosing strategies.

This presentation will explore recent advancements in mRNA/LNP therapeutics, highlighting progress and key opportunities for clinical and translational work. It will also discuss innovative industry and academic collaborations to accelerate this journey.



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Developing & manufacturing Australia first mRNA Vaccine: Lessons to inform the future of mRNA medicines

Dr Harry Al-Wassiti

Symposium 1: mRNA Therapeutics – Its complex and more than meets the eye, Eureka Room 1, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

Dr. Al-Wassiti is an early career bioengineer and researcher based at Monash Institute of Pharmaceutical Sciences. He developed the underlying intellectual properties (IP) and manufacturing technology for Australia's first mRNA vaccine. His expertise brings together pharmaceutical IP development and manufacturing technologies of nucleic acid, including mRNA. He is a chief investigator on Monash mRNACORE and a recent recipient of the ARC industry and innovation fellowship. He has strong industry-academic linkage working with multi-start ups and large pharma companies.

Developing & manufacturing Australia first mRNA Vaccine: Lessons to inform the future of mRNA medicines

Harry Al-Wassiti[1], Samantha Grimley[2], Georgia Deliyannis[2], Stewart Fabb[1], Damien Parcel[2], Dale Godfrey[2], Terry Nolan[2], Colin Pouton[1]. [1] Monash Institute of Pharmaceutical Sciences (MIPS), Monash University, Melbourne, VIC , Australia. [2] The Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia [3] The Royal Melbourne Hospital, Melbourne, VIC, Australia.

Introduction: mRNA vaccines represent a revolutionary technology with a track record of clinical success and significant future potential. At the height of the pandemic, our team developed three preclinical COVID-19 vaccine candidates. In collaboration with partners and the Australian government, we also developed and manufactured Australia's first clinical mRNA vaccine, based on a tethered receptor-binding domain (RBD).

Aims: Our aims are to develop an RBD vaccine candidate, demonstrate its therapeutic and translational utility, and establish manufacturing techniques and assessment technologies suitable for clinical translation.

Methods: We adopted various preclinical assessments, including ELISA, surrogate neutralisation assays, and methods to develop and validate the assessment of content and product purity for clinical translation (results are presented).

Results: For clinical translation, our results demonstrated strong and specific responses in RBD activity in vivo, which translated into clinical responses. Volunteers showed elevated antibody levels, as well as increased CD4+ and CD8+ T-cell responses. Additionally, we addressed manufacturing and validation challenges critical to clinical success, including those related to the mRNA entity and the lipid nanoparticle (LNP) vehicle.

Discussion: We discuss the lessons learned from the translation of mRNA therapeutics from preclinical to clinical settings, including markers of success in early preclinical stages. We also explore the future of mRNA therapeutics, particularly the challenges associated with personalised medicines, the complexities of RNA and LNP stability, and the areas of technological development needed to broaden the clinical use of mRNA vaccines and therapeutics.

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MMQPA presentation – building models to collaborate and translate mRNA therapeutics

A/Prof Cornelia Landersdorfer

Symposium 1: mRNA Therapeutics – Its complex and more than meets the eye, Eureka Room 1, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

Cornelia Landersdorfer, PhD, is an Associate Professor at the Monash Institute of Pharmaceutical Sciences, Monash University in Melbourne. She trained in clinical PK studies, bioanalysis, PK/PD modelling and microbiological studies in Germany, Australia and the USA. She leads a research group that integrates dynamic in vitro infection experiments with mechanism-based mathematical modelling to optimise dosing of antibiotics and other drugs. Her group performs the design and analysis of clinical and preclinical population PK studies. She is the Academic Deputy Director of the Monash-Moderna Quantitative Pharmacology Accelerator (MMQPA) which is focused on driving advancements in mRNA medicines. She has >140 peer-reviewed publications, and received the Georgina Sweet Award for Women in Quantitative Biomedical Sciences (2018), the Future Leader Award (2016) and Research Impact Award (2020) in the Faculty of Pharmacy and Pharmaceutical Sciences (#2 worldwide, QS world ranking), a 2022 Australian Award for University Teaching, and the 2023 Monash Graduate Supervisor of the Year award. Invited conference presentations include the European Congress of Clinical Microbiology and Infectious Diseases and American Society of Microbiology Microbe congress. Her research is supported by NHMRC, ARC, NIH and pharmaceutical industry, and has impacted on dosing guidelines and patient therapy internationally.

Building models to collaborate and translate mRNA vaccination and therapeutics

Noelia Nebot. Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia

Introduction. Beyond mRNA use in COVID-19 vaccines, this technology holds promise for other infectious diseases and therapeutic areas, such as cancer and rare diseases. This presentation explores innovative methodologies used by the Monash-Moderna Quantitative Pharmacology Accelerator (MMQPA) research group to support and accelerate the development of mRNA medicines. **Aims**. i) To share the application of Quantitative and Systems Pharmacology (QSP) mathematical models in mRNA medicines development. ii) to highlight the benefits of international industry-academic collaborative networks in maximizing therapeutic outcomes for global programs across various therapeutic areas.

Methods. The MMQPA group was established as a joint venture between the Monash University and Moderna, a biotechnology company focused on mRNA medicines. The aim of the partnership is to advance homegrown mRNA medicines. MMQPA is focused on developing platform Quantitative Pharmacology and QSP models to integrate the pharmacokinetics, pharmacodynamics, and systems biology of mRNA delivery to understand the sources of variability and the translatability of pre-clinical data to humans. Data integration from various sources, including experimental validation from ongoing experiments and clinical data, is being applied.

Results. Illustrative examples of QSP models that are currently being used for mRNA vaccinations and therapeutics will be presented. The complexity of these PBPK-QSP models will be highlighted including the many challenges in their model structure**,** function and optimisation for pre-clinical and human application. Recent advances in these models from the MMQPA team and learnings from the active collaborations across research groups will be shared.

Discussion. The MMQPA's collaborative framework sets a precedent for future research, developing platform QSP models and leveraging international subject matter expert networks to advance therapeutic areas globally.

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Trends in Korean mRNA vaccine development: future strategy of governmental projects leading industries

Prof Kevin Kee-Jong Hong

Symposium 1: mRNA Therapeutics – Its complex and more than meets the eye, Eureka Room 1, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

Prof. Kevin Kee-Jong Hong is the Director of the Korea ARPA-H "Health Security Division", also working for the Department of Microbiology at the Gachon University College of Medicine. In 2024, Prof. Hong was selected as a member of the Scientific Advisory Committee at the CEPI, also started an activity as a member of the Selection Committee at the Right Foundation. He is working as a member of National Bio-Health Innovation Committee for the government and takes a role as a board member of the Global Technology Hub for Biotechnology Foundation (GTH-B) supported by WHO. He led the national project "KmVAC (Korea mRNA Vaccine Initiative) as a director general from 2022, also worked as an executive director managing vaccine and therapeutics R&D at the Institut Pasteur Korea after spending 10 years as a government officer to manage national vaccine R&D at the Korea NIH. Prof. Hong mainly focused on the high-risk pathogen research, and he led the KNIH R&D group developing prophylactic vaccines against anthrax, tularemia, pest, avian influenza, Ebola virus, etc. He has been a researcher, and a government officer, also professor for past 25 years. he holds a Ph.D. in molecular biology from the Texas Tech University, U.S.A. after graduated Seoul National University, and completed a post-doctoral fellowship at the University of Kansas before coming back to career in Korea.

Trends in Korean mRNA vaccine development: future strategy of governmental projects leading industries

Through the COVID-19 pandemic, we are faced with a new technology that can open a new chapter in pandemic preparedness, called mRNA vaccine. While this novel vaccine technology is expected to present and lead a new paradigm in various directions and fields in the health science R&D, the priority of the Korean government's attention and investment is its ability as a rapid vaccine supply technology for the efficient responsiveness to the next pandemic situation.

Although domestic technology has not yet secured sufficient global competitiveness, Korea's strategy for mRNA vaccine development is to build a whole R&D lifecycle and an infrastructure from the development of antigens to the supply and stockpiling of vaccine products produced in domestic companies, which can make it possible to respond more independently and proactively. The national project with title of the "Korea mRNA Vaccine initiative (KmVAC)" led the industries to build up the core parts of mRNA vaccine technologies and production facilities during past two years, and now Korea secured domestic pool of R&D ventures and institutes, several production industries and some more companies supplying materials and equipment in domestic area.

The R&D strategy developing mRNA vaccines for the next stage includes several core directions described below:

- Structure-based antigen design facility for rapid and exact antigen mining,
- Dramatically quick and harmonized preclinical and clinical test system,

This presentation will show status of mRNA vaccine technologies including secured core technologies, domestic equipment and production facilities after two-year performance of the KmVAC project, also will suggest the direction for the establishment of a whole cycle R&D infrastructure in Korea near future. I hope to get plenty of ideas for collaboration between Australian and Korean institutes and companies.

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Bridging basic science and big data for drug repurposing research

A/Prof Natalie Trevaskis

Symposium 2: Drug Repurposing using real-world data; perspectives from the Asia-Pacific, Eureka Room 2, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

Natalie Trevaskis is an Associate Professor, Pharmacist and Heads the Lymphatic Medicine Laboratory at the Monash Institute of Pharmaceutical Sciences, Melbourne, Australia. Her research program is focussed on the role of lymphatics in acute, inflammatory and metabolic diseases, and drug delivery to the lymphatics to treat these diseases. She has extensive experience in biopharmaceutics, pharmacokinetics and delivery of a range of therapeutic types.

Natalie's research has resulted in ~90 peer reviewed papers (>8000 cites) including significant papers in Nature, Nature Metabolism, Nature Rev Drug Discovery, Nature Nano, Angew Chemie, J Control Rel etc. Natalie is also an inventor of 13 patents, including for a lymph-directing prodrug technology licensed to Puretech Health and Seaport Therapeutics with candidates in phase 1 and 2 clinical trials. Natalie has worked and consulted extensively with industry (Pfizer, Novartis, Astra Zeneca, Eli Lilly, Amgen, Genentech, Janssen, Protagonist, PureTech Health, Noxopharm etc.) to solve drug delivery problems.

Natalie has received several notable academic prizes including the Gold Medal for Bachelor of Pharmacy, Mollie Hollman Doctoral Medal for PhD Thesis excellence, AK McIntyre prize from the Australian Physiological Society for early career research and Future Research Leader Award for work up to 10 years post-doc at Monash University. In 2022 and 2023 Natalie was named as a Clarivate highly cited (Hi-Ci) researcher in pharmacology (top ~0.1%).

Bridging basic science and big data for drug repurposing research

Natalie L Trevaskis[1]. Monash Institute of Pharmaceutical Sciences, Monash University[1], Melbourne, VIC Australia.

Introduction. The goal of drug repurposing research is to take a drug that has completed safety and efficacy testing, and redirect it for a new therapeutic purpose[1]. Estimates suggest that up to 75% of drugs could be repurposed[2].

Aims. This presentation will highlight opportunities (including big data) and challenges to bridging the gap between basic science and clinical translation of repurposed drugs.

Methods. Three case studies from our lab will be presented: COX-2 inhibitors for type 2 diabetes, lipase inhibitors for acute pancreatitis (AP), and repurposed drugs with anti-viral activity against SARS-Cov2. The challenges we have encountered to progress these toward the clinic will be discussed.

Results. Recently we identified that dysfunction of the COX-2 pathway leads to insulin resistance in mice through promoting mesenteric lymph leakage, and that a COX-2 inhibitor could reverse lymph leakage and insulin resistance[3]. This led us to complete a nation-wide cohort study using an Australian diabetes registry which found that COX-2 inhibitor use is associated with decreased risk of diabetes treatment intensification when compared to mild opioids[4]. In AP, we found that administration of the lipase inhibitor orlistat in a novel orally bioavailable formulation reduced disease severity in rodents[5]. The patented formulation is

Discussion. Across these efforts to repurpose drugs, common challenges existed. First, there were pharmacokinetic-pharmacodynamic (PK-PD) considerations: What would be an appropriate dose, route, formulation and dosing schedule to ensure adequate drug concentrations in target tissues? Would the current clinically approved dosing regimen be efficacious and safe? Would pre-clinical and clinical safety studies need to be repeated? Next, there was consideration of intellectual property, market potential, finances, clinical and regulatory pathways, clinical equipoise and the need for clinical grade formulation manufacture. To begin to overcome these issues, it has been vital to collaborate with experts in these discrete areas such that the promise of drug repurposing may be realised.
References. 1. Begley et al (2021) Sci Transl Med. 13, eabd5524. **2.** Nosengo (2016) Nature 534, 314–316. **3.** Cao et al (2021) Nature Metab. 3 (9), 1175-1188 **4.** Tan et al (2024) Diabetes Research and Clinical Practice. 207, 111082. **5.** Lee et al (2021) Int J Pharm. 596, 120247 **6.** MacRaild (2022) Int J Mol Sci. 23 (19), 11851

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An outcome-wide approach to generate drug repurposing hypotheses using tree-based scan statistics

George SQ Tan

Symposium 2: Drug Repurposing using real-world data; perspectives from the Asia-Pacific, Eureka Room 2, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

George is completing his PhD in Pharmacoepidemiology at the Centre for Medicine Use and Safety, Monash University. His research has a methodological focus on leveraging real-world clinical data to generate and validate drug repurposing hypotheses, using traditional and emerging pharmacoepidemiologic study designs. George is also a practising pharmacist and an Assistant Lecturer at the Faculty of Pharmacy and Pharmaceutical Sciences, Monash University.

An outcome-wide approach to generate drug repurposing hypotheses using tree-based scan statistics

George SQ Tan,[1] Judith C Maro[2], Shirley V Wang[3], Sengwee Toh[2], Jedidiah I Morton[1], Jenni Ilomäki[1], Jenna Wong[2] and Xiaojuan Li[2]. Centre for Medicine Use and Safety, Monash University[1], Parkville, VIC, Australia; Department of Population Medicine, Harvard Pilgrim Health Care Institute[2], Boston, MA, United States; Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital[2], Boston, MA, United States.

Introduction. Most existing drug repurposing studies using real-world data focused on validating, instead of generating, hypotheses. Tree-based scan statistics (TBSS), enabled by TreeScan®, is a data mining tool that conducts scan statistics across a hierarchical tree of structured data and may be used to identify repurposing signals.
Aims. Our objective was to identify repurposing signals for sodium-glucose cotransporter-2 inhibitors (SGLT2i) by scanning across a wide range of clinical outcomes using TBSS.
Methods. We used an active-comparator, new-user design to create a 1:1 propensity-score matched cohort of SGLT2i and dipeptidyl peptidase-4 inhibitor (DPP4i) initiators between 10/1/2015 and 10/31/2019 in the Merative™ MarketScan® Research Databases. Incident outcomes were hospital and ambulatory diagnoses during the up to 2-year follow-up while on treatment. TBSS were estimated across a hierarchical tree based on ICD-10-CM diagnosis codes. We used an adjusted $p \leq 0.01$ as statistical alert to prioritise inverse associations for evaluation as repurposing signals. We varied the analyses by the size of the outcome tree, scanning level, and clinical setting for incident outcomes.
Results. There were 80,510 matched SGLT2i-DPP4i initiator pairs with 215,333 outcomes among 45,444 SGLT2i initiators and 223,428 outcomes among 45,931 DPP4i initiators. There were 18 prioritised associations ($p \leq 0.01$), which included chronic kidney

scanning at a higher level of the outcome tree increased the statistical significance of the scan statistic for liver diseases (p=0.183 to p=0.0452).
Discussion. We identified signals that align with recently approved indications of SGLT2i, as well as potential repurposing signals supported by existing evidence but requiring future validation. TBSS can be valuable to generate repurposing hypotheses for existing drugs.

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Case studies of hypothesis validation from Taiwan

Prof Edward Lai

Symposium 2: Drug Repurposing using real-world data; perspectives from the Asia-Pacific, Eureka Room 2, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

Associate Professor Edward Chia-Cheng Lai specializes in pharmacoepidemiology, with a focus on research projects using cross-center and cross-national databases. He has received solid training in research methodology. He has published approximately 90 research papers in top-tier journals, including BMJ, Annals of Internal Medicine, and Clinical Pharmacology & Therapeutics. His articles have been cited over 1,000 times. Recognized for his outstanding performance in research methodology, he was invited to become the Associate Editor of the official journal of the International Society for Pharmacoepidemiology (ISPE), Pharmacoepidemiology and Drug Safety, in 2013. He reviews over 30 research papers annually and invites more than 100 domestic and international reviewers to assist in the peer-review process, demonstrating significant academic influence.

Case studies of hypothesis validation from Taiwan

Edward Chia-Cheng Lai[1,2].
1. Population Health Data Center, National Cheng Kung University, Tainan, Taiwan.
2. School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

Introduction.
Denosumab, an antiresorptive medications in the treatment of osteoporosis, had been suggested to have potential effect on improving insulin sensitivity and glucose tolerance. Clinical evidence had suggested its effect on fasting plasma glucose, while its effect on reducing diabetes risk remain unclear.
Aims. To explore the possibility of additional benefits or new indications of the currently approved drug, we aimed to evaluate the association between denosumab usage and a lower risk of developing diabetes in patients with osteoporosis.
Methods. We conducted a nationwide cohort study using National Health Insurance Research Database (NHIRD) in Taiwan. We identified newly-received denosumab users for osteoporosis indication during 2012 and 2019. We categorized patients into two groups: treatment group and comparison group. Patients who initiated denosumab and were adherent to the denosumab treatment were allocated as treatment group. Patients who initiated denosumab but discontinued after initial dose were allocated as control group. We applied 1:1 propensity score matching to balance the baseline characteristics and to increase comparability between groups. We also conducted sensitivity analyses using negative control outcomes to estimate the effect of potential unmeasured confounders in our study.
Results. We included a total of 68,510 patients who had newly received denosumab, with mean age of 77.7 and 84.3% female population after propensity score matching. During a mean follow-up of 1.9 years, 2016 patients had incident diabetes in treatment

Discussion. In our nationwide cohort study, patients who continued denosumab for osteoporosis had a lower risk of developing diabetes than patients who discontinued denosumab regimen after initial dose. Our finding suggested a potential association between denosumab therapy and lowering risk of diabetes. The finding was also supported by several sensitivity analyses including negative control outcomes and aged-stratified analyses. The study provided clinical evidence for physicians on choosing antiosteoporosis medications while also considering lowering diabetes risk. This study could also provide a good example for exploring the possibility of additional benefits of approved drugs.
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Approaches for assessing cost-effectiveness of existing medications to potential new indications

A/Prof Wee Hwee Lin

Symposium 2: Drug Repurposing using real-world data; perspectives from the Asia-Pacific, Eureka Room 2, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

Associate Professor Wee Hwee Lin is Director of the Centre for Health Intervention and Policy Evaluation Research (HIPER) based in the Saw Swee Hock School of Public Health at the National University of Singapore. HIPER develops capacity in health technology assessments in ASEAN through short courses and project mentoring. She is a member of the International Society for Pharmacoeconomics and Outcomes Research Health Sciences Policy Council, the International Editorial Advisory Board for Journal of Patient Reported Outcomes, and the National Advisory Committee on Cancer in Singapore. A/P Wee's current work focuses on the use of real world evidence in health technology assessments. Specifically, this entails mining both structured and unstructured data in electronic medical records to evaluate cost-effectiveness of health technologies.

Approaches for Assessing Cost-Effectiveness of Existing Medications to Potential New Indications

Hwee-Lin, Wee, Saw Swee Hock School of Public Health, National University of Singapore, Republic of Singapore

Introduction. There is an increasing application of artificial intelligence and machine learning techniques to mine structured and unstructured data in electronic medical records (EMR). Such techniques can be applied to evaluate the cost-effectiveness of existing medications to potential new indications.
Aims. To describe approaches for mining EMR to evaluate the cost-effectiveness of existing medications to potential new indications.
Methods. Approaches for mining EMR include text mining, machine learning and large language models.
Results. Examples of how structured and unstructured data in EMR may be used to evaluate the cost-effectiveness of existing medications will be shared.
Discussion. Strengths and limitations of these approaches will be discussed.

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What authenticity do we need in authentic assessment?

Dr Joanna Tai

Symposium 3: Educating for careers – authentic learning and assessment in pharmacology and pharmaceutical science education, Eureka Room 3, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

Joanna Tai is Senior Research Fellow at the Centre for Research in Assessment and Digital Learning (CRADLE) at Deakin University. Her research in assessment focuses on inclusion and diversity, feedback literacies, developing evaluative judgement, and student experiences across the university and workplace. She is currently undertaking funded projects on feedback literacy (Australian Research Council) and inclusive assessment (Australian Collaborative Education Network; Council of Australasian University Leaders in Learning and Teaching).

Joanna is a Senior Fellow of the Higher Education Academy, and a member of the Australian and New Zealand Association for Health Professions Education, and the European Association for Research on Learning and Instruction. She has a background in medicine and health professions education.

What authenticity do we need in authentic assessment?

Joanna Tai, Centre for Research in Assessment and Digital Learning, Deakin University, Melbourne, Australia

There has been longstanding recognition that authentic assessment is an important assessment strategy in higher education, on the basis that assessment should test more than just the attainment of some abstract knowledge or skill. In recent years, the employability agenda has increased a pragmatic emphasis on authentic assessment, with moves to add vocational features to courses that were previously not seen as preparation for work.

The idea of authentic assessment is a rhetorically useful term that most parties can agree to be of value, without having to dig too deeply into what is meant by 'authentic'. Critiques focus on the idea that authentic assessment just means 'real life' tasks, and a focus on content rather than processes or values. It has also been suggested that authentic assessment should prepare students for the future through actively promoting social justice and contributing to the transformation of society rather than just focussing on what exists in the here and now.

This conceptual contribution draws on Ajjawi et al (2024) to extend critiques such as these while also retaining a strong commitment to the importance of authenticity in assessment. We need to consider the importance of the perception and experience of authenticity by learners themselves and ways in which learning at work takes place, the inherent relationality of tasks, and how this is not captured by typical 'authentic' tasks. We seek to shift discussion of authentic assessment into consideration of multiple forms of authenticity. The presentation will discuss *psychological authenticity*, *ontological fidelity,* and *practice theory perspectives* and how they can influence assessment design.

Ajjawi, R., Tai, J., Dollinger, M., Dawson, P., Boud, D., & Bearman, M. (2024). From authentic assessment to authenticity in assessment: Broadening perspectives. *Assessment & Evaluation in Higher Education*, *49*(4), 499–510. https://doi.org/10.1080/02602938.2023.2271193

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Working with actors, healthcare professionals and people with lived experience to develop and deliver simulated mental health assessments

Dr Sarira El-Den

Symposium 3: Educating for careers – authentic learning and assessment in pharmacology and pharmaceutical science education, Eureka Room 3, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

Dr Sarira El-Den is a Senior Lecturer, Pharmacist and Master Mental Health First Aid Instructor at The University of Sydney School of Pharmacy. Sarira is a Fellow of the UK Higher Education Academy and has led and contributed to projects that have received $6.7 million AUD in funding, primarily focusing on mental health education, psychometric testing of measurement instruments and primary care services, and often involving collaboration and co-design with people with lived experience of mental illness. Sarira was the Education Representative of the Australasian Pharmaceutical Science Association from 2018-2023 and has since become Secretary of the organization. Sarira has won multiple awards at conferences and for her teaching, and has been recognized by the Pharmaceutical Society of Australia as the NSW Early Career Pharmacist of Year (2022), and by the International Pharmaceutical Federation as a FIPWISE (Women in Science and Education) Rising Star (2022) and as a co-recipient of The Mental Health Services of Australia and New Zealand Award for Education, Training or Workforce Development (2023).

Working with actors, healthcare professionals and people with lived experience to develop and deliver simulated mental health assessments

Sarira El-Den[1]. The University of Sydney School of Pharmacy, The University of Sydney, Sydney, NSW, Australian.

Introduction. Mental illnesses greatly contribute to the global burden of disease and are a major cause of morbidity. Efforts to alleviate shortages in specialist mental health workforce often include strategies to ensure that non-specialist healthcare professionals, including those working in primary care settings, are confident and able to support people experiencing mental health problems and crises. As such, there is a need to strengthen mental health education in tertiary healthcare curricula, and ensure future healthcare professionals are provided with opportunities to practice their skills.

Aims. To present on the development and delivery of novel, authentic simulated mental health assessments to educate and assess healthcare students in how to support people experiencing mental health problems and crises.

Methods and Results. This presentation will cover almost a decade of research-driven education aimed at training healthcare students in how to confidently support people experiencing mental health problems (e.g. depression, anxiety) and crises (e.g. suicide, mania, psychosis). Through funded projects, simulated patient scenarios have been co-designed with people with lived experience of mental illness. Scenarios have been content validated with healthcare experts and marking rubrics have been psychometrically tested. After completing Mental Health First Aid (MHFA) training, pharmacy, medical, nursing and occupational therapy students have role-played the scenarios with trained actors, while being observed by peers, tutors and lived experience educators. In 2022-23, 216 simulations were conducted with MHFA-trained healthcare students, followed by self-assessment, on-the-spot performance feedback and debrief discussions. Scenarios have also been used in role-plays with registered pharmacists. Evaluations of the simulated assessments have been conducted quantitatively by analysing scores and pass/fail rates as well as comparing markers' assessments. Qualitative analyses have involved cross-country comparisons of discourse analysis, debrief analysis as well as, focus groups and interviews with students, actors and lived experience educators.

Discussion. Partnering with people with lived experience to co-design and deliver mental health education can help ensure that the content reflects the real-life experiences of consumers. MHFA participants value opportunities to practice newly-acquired skills in safe learning environments.

ASCEPT, APFP & APSA Joint Congress
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Embedding industry-relevant skills and thinking in the Pharmacology practical class

Dr Makhala Khammy

Symposium 3: Educating for careers – authentic learning and assessment in pharmacology and pharmaceutical science education, Eureka Room 3, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

Dr Makhala Khammy started out as a cardiovascular pharmacologist, obtaining her PhD at the University of Melbourne. Her postdoctoral research investigated the complex and integrated mechanisms that regulate vascular tone and contribute to blood pressure elevation. Driven by an interest in teaching, she returned to the University of Melbourne to take on a Teaching and Research role in the Department of Pharmacology. As of 2021, she is a Teaching Focused Academic in the Department of Biochemistry and Pharmacology. She is passionate about improving student engagement and the student learning experience and believes this can be aided in part by including experiential learning opportunities that encourage student agency within teaching programs, and fostering inclusive and collaborative learning environments that nurture a culture of inquiry and curiosity. A curiosity with emerging pedagogical approaches and technologies motivates her to explore, develop, and implement new strategies to enhance teaching and learning in pharmacology education.

Embedding industry-relevant skills and thinking in the Pharmacology practical class

Makhala M Khammy[1]. Dep of Biochem and Pharmacol, The University of Melbourne[1], Parkville, VIC, Australia.

Introduction. In 2020, the School of Biomedical Sciences, University of Melbourne, identified the undergraduate pharmacology practical subject as a program that could be uplifted into a definitive Capstone for the pharmacology major. Part of this uplift was to incorporate workplace experiences and practices authentic to the pharmacology discipline to enable students to develop attributes and attitudes that support work-readiness.

Aim. To design and implement a curriculum that fosters industry-relevant skills and thinking.

Methods. We redesigned the weekly practical classes to be based on scenarios that may be encountered in biomedical research or in drug discovery and development. Industry experts were engaged to deliver workshops that contextualised the practical tasks to the workplace and provided students the knowledge and strategies required to complete the tasks. The workshops were also designed to facilitate student interaction with industry practitioners and help students identify skills that were being developed through their engagement with the subject. The 12-week subject culminated in a multi-week project that required student teams to design and implement experiments to address a research question. Teams were expected to self-manage the project with the guidance of academic staff. Authentic assessments took the form of a written research proposal, a scientific abstract, and an oral presentation. The redesigned subject was implemented in 2022 and enrolled students were invited to anonymously complete a survey comprising multiple Likert items (5-point scale). We evaluated students' perception of the value of the industry workshops and the team project, and whether they felt they had developed transferable skills in the subject.

Results. Over 3 semesters between 2022-23, there were 51 respondents (19% response rate). Students had positive attitudes towards the industry workshops and team projects (78% and 84% positive approval, respectively). Moreover, students tended to agree with the statements, "the subject helped me recognise and develop graduate attributes and transferable skills" and "the subject increased my capability to problem-solve and work through new and challenging tasks (Likert item score, 4.1 and 4.3 out of 5, respectively.

Discussion. Incorporation of authentic and proximal learning activities and assessment tasks in the pharmacology practical class is feasible and has a positive impact on student's perception of their work readiness. Further curriculum redevelopment will consider additional industry engagement including assessment co-design.

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Begin with the end in mind in pharmacology and pharmaceutical sciences

Dr Maan-Yuh Lin

Symposium 3: Educating for careers – authentic learning and assessment in pharmacology and pharmaceutical science education, Eureka Room 3, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

Professor Anya Maan-Yuh Lin obtained her B.Sc. in Pharmacy and M.Sc. in Pharmacology at the National Taiwan University, Taiwan, ROC. She pursued her Ph.D. in Neuropharmacology at the University of Colorado, Health Science Center, U.S.A.. In 2016, she founded the Department of Pharmacy, a 6-year pharmacy program in National Yang Ming University (which was changed to National Yang Ming Chiao Tung University in 2021). Currently, she is the Dean/ Professor of the College of Pharmaceutical Sciences, National Yang Ming Chiao Tung University, Taiwan starting from August 1, 2022. Professor Lin has completed research projects from National Science and Technology Councils (NSTC) and published more than 80 SCI research papers in the international well-known journals (English). In addition, she has received education projects from Department of Education to promote pharmaceutical professions and STEM education. Professor Lin is the immediate past President of the Society of Taiwan Women in Science and Technology (TWiST). She organized WOMEN@NYCU to promote the network of the female faculties/scientists in the National Yang Ming Chiao Tung University, Taiwan. Furthermore, she advocated the work-life balance for women scientists in the public hearing of Legislative Yuan, Taiwan. Moreover, she was invited to share "STEM is our CHOICE" in INWES and APEC webinars (USA).

"Begin with the end in mind" in pharmacology and pharmaceutical science education.

Anya Maan-Yuh Lin, College of Pharmaceutical Sciences, National Yang Ming Chiao Tung University, Hsin-Chu, Taiwan

To improve the lives of the people on earth, the United Nations proposed 17 Sustainable Development Goals (SDGs) for the period from 2015 to 2030. Among these, SDG3 aims to establish good health and well-being for all mankind. A high quality of life, especially a healthy body and mind, is expected. Because of the rapid progress of science and technology, novel therapeutics and medical devices are being developed to meet health and medical needs. Experts with pharmacology and pharmaceutical sciences are contributing their efforts to SDG3 for a better healthcare. Cultivating experts with pharmacology and pharmaceutical sciences requires liberal arts literacy, updated knowledge in pharmacology and pharmaceutical sciences, as well as internship and leadership training. Assessments include academic activities, hand-on courses and continuing education since the lifelong learning is critical for career success. New knowledge, methodologies, technologies, and regulatory requirements are constantly evolving and should be updated for the career competencies, including precision health/medicine, regenerative medicine, artificial intelligence and machine learning, digital health technologies and regulatory sciences. For the sustainability, gendered innovation and greener environments, such as carbon reduction and green chemistry should be taken into consideration for the pharmacology and pharmaceutical sciences. In conclusion, cross-disciplinary education is the foundation for a successful career in pharmacology and pharmaceutical sciences. Experts in pharmacology and pharmaceutical sciences should be initiative and creative and always at the forefront of scientific innovation for global health of humanity.

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Resolution Pharmacology: Unveiling Nature's Healing Mechanisms

Dr Chengxue Helena Qin

Symposium 4: Advancing Drug Discovery through Modern Research on Chinese Medicine and Natural Products, Courtyard Room 1&2, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

Laboratory Head in Cardiovascular Pharmacology at Monash University, currently holding the prestigious positions of National Heart Foundation Future Fellow and Monash Talent Accelerator Fellow. Upon completing her PhD at the Department of Pharmacology & Therapeutics and the School of Chemistry (University of Melbourne), Dr. Qin advanced her career with a post-doctoral position at the Baker Institute in 2011. Recognizing her talent and leadership, she was subsequently recruited to establish her independent laboratory within the Drug Discovery Biology Theme at the Monash Institute of Pharmaceutical Sciences in 2019. Previously, she served as an MRFF REDI Industry Fellow and Baker Fellow. Dr. Qin also plays an integral role on the Board of Directors of the Australasian Pharmacologists and Toxicology Society, the Global Academic Drug Discovery Consortium, and the Australian Cardiovascular Alliance Emerging Leader (Industry Engagement portfolio).

Dr. Qin is an emerging leader in translational pharmacology, driven by a visionary pursuit to develop "pro-resolving medicines" for the treatment of cardiopulmonary diseases, one of the leading causes of death globally. Her research team is dedicated to pioneering innovative "pro-resolving" therapies, primarily focusing on advancing the pro-resolving GPCRs (e.g. FPR2) R&D program to bridge scientific discoveries with impactful clinical solutions. Dr. Qin's expertise spans molecular and integrative pharmacology, rational drug design, and the intricacies of commercialization.

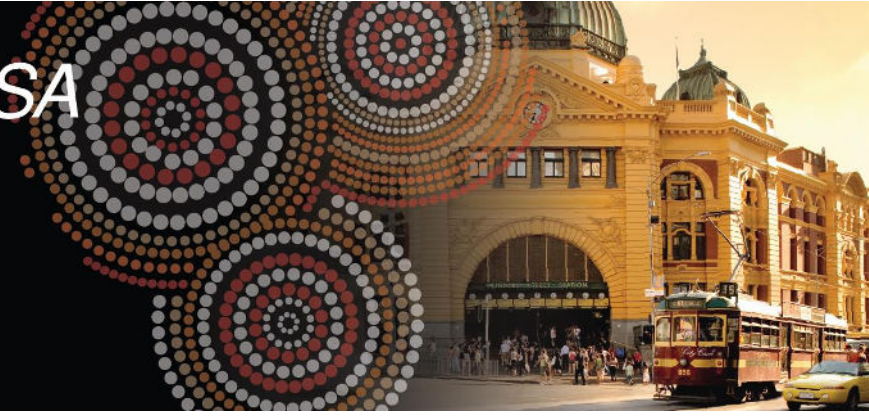
Her scholarly contributions have been featured in prestigious journals such as Nature Communications, Cardiovascular Research, Circulation, British Journal of Pharmacology, Journal of Medicinal Chemistry, and Pharmacology & Therapeutics etc. Dr. Qin has secured substantial research funding from prestigious organizations including the National Health and Medical Research Council, National Heart Foundation, National Drug Discovery Centre, Diabetes Australia, CASS Foundation, Therapeutic Innovation Australia, JDRF etc.

Dr. Qin's outstanding leadership and scholarly achievements have been duly recognized through the receipt of over 20 prestigious awards, including the Hypertension Australia Mid-Career Award (2023), Monash Talent Accelerator Fellow (2023), MRFF-Industry Fellow (2021), Future Research Leader (2020), and the Asian Australian Leadership Award (Basic Scientist, 2019), among others. For more information, please visit: https://www.monash.edu/mips/themes/drug-discovery-biology/labs/cardiovascular-pharmacology.

Resolution Pharmacology: Unveiling Nature's Healing Mechanisms

Chengxue Helena Qin. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC Australia 3052.

The active resolution of inflammation is crucial for tissue healing and repair. Inadequate resolution can lead to chronic inflammation, disrupted cellular homeostasis, and pathological tissue remodeling, particularly in cardiopulmonary diseases. Pro-resolving G-protein-coupled receptors, such as formyl peptide receptor 2 (FPR2) and its endogenous ligand annexin-A1, are integral to regulating inflammatory processes in these diseases. As key regulators of inflammation resolution, pro-resolving receptors represents a promising therapeutic target. This receptor plays a significant role in terminating the inflammatory response and



initiating tissue repair, with annexin-A1 orchestrating various cellular activities that attenuate inflammation and promote tissue regeneration. Targeting pro-resolving pathways has emerged as a potential strategy to mitigate end-stage organ remodeling and failure, thereby impeding disease progression. In addition, natural products, including herbs and their active constituents, have long been investigated for their therapeutic potential in resolving inflammation and promoting tissue repair. Integrating the principles of natural products with modern pharmacology can lead to the development of novel therapeutic strategies that leverage the body's innate inflammation resolution mechanisms. This approach offers complementary treatments that can enhance the efficacy of existing therapies and introduce new modalities for managing cardiopulmonary diseases.

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Therapeutic effects of tetramethylpyrazine nitrone in Alzheimer's disease mouse model

Prof Pui Man (Maggie) Hoi

Symposium 4: Advancing Drug Discovery through Modern Research on Chinese Medicine and Natural Products, Courtyard Room 1&2, December 2, 2024, 11:15 AM - 1:15 PM

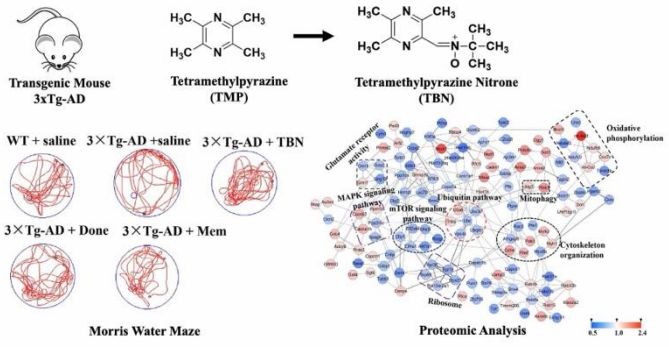
Biography:

Prof. Pui Man Maggie Hoi has a background in cardiovascular and cerebrovascular pharmacology. She graduated from Cambridge University, the United Kingdom, with a Ph.D. in Pharmacology. She currently holds the position of Associate Professor at the Institute of Chinese Medical Sciences and Faculty of Health Sciences in the University of Macau. Her research focuses on investigating endothelial dysfunctions and inflammation, particularly exploring the interactions between reactive astrocytes and microglia and their impact on brain endothelial cells, encompassing neuroinflammation in aging and pathophysiological conditions such as Alzheimer's disease (AD), stroke, and diabetes. She utilizes various transgenic animal models (mouse, zebrafish, drosophila) and multicellular co-culture models to study acute and chronic inflammatory responses in various diseases. In addition, she is also interested in drug discovery, specifically focusing on identifying anti-inflammatory small molecules and natural compounds derived from traditional Chinese medicine (TCM). She is the principle investigator for multiple research projects including projects funded by the Macau SAR Science and Technology Development Fund (FDCT), the National Natural Science Foundation of China (NSFC) (Joint scheme), the Development of Science and Technology of Guangdong Province (GDST) (Joint scheme), and the University of Macau Research Grant (UM-MYRG & UM-CRG).

Therapeutic effects of tetramethylpyrazine nitrone in Alzheimer's disease mouse model

Maggie P Hoi. SKL-QRCM & ICMS, University of Macau, Macao SAR, China.

Introduction. The pathophysiology of Alzheimer's disease (AD) is complex and multifactorial. Hallmarks of AD include extracellular accumulation of amyloid-beta (Aβ) and intraneuronal aggregation of hyperphosphorylated tau. Recent studies suggest that deleterious alterations in neurovascular cells happens in parallel with Aβ accumulation, inducing tau pathology and necroptosis. Tetramethylpyrazine nitrone (TBN) is a nitrone derivative of tetramethylpyrazine, an active ingredient from *Ligusticum wallichii* (Chuanxiong). We previously demonstrated TBN exhibited potent neuroprotective effects in experimental models of ischemic stroke [1].



Aims. The present study investigated the anti-AD properties and the underlying mechanisms of TBN.

Methods. We evaluated the therapeutic effects of TBN in transgenic mouse model (3xTg-AD) for behavioural and mechanistic studies. The hippocampal and cortical tissues were further evaluated by proteomic analysis. Donepezil (Done) and memantine (Mem) were included as controls.

Results. TBN markedly improved cognitive functions and reduced Aβ and hyperphosphorylated tau levels, promoted non-amyloidogenic processing pathways, prevented dendritic spine loss, and upregulated synaptic protein expressions, partly via modulating MAPK, mTOR and mitophagy. Proteomic analysis showed that PINK1, a key protein for mitochondrial homeostasis, was significantly upregulated by TBN treatment.

Discussion. These results suggested that TBN exerts its neuroprotective effects in AD mouse model via restoring mitochondrial homeostasis. This work is funded by FDCT/0023/2020/AFJ, FDCT/0035/2020/AGJ, MYRG-CRG2022-00010-ICMS and MYRG2022-00248-ICMS).

[1] Zhang G et al (2018) Neuromolecular Med. 20(1):97-111

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Dehydroervatamine as a Promising Novel TREM2 Agonist, Attenuates Neuroinflammation

Prof Ming-yuen Simon Lee

Symposium 4: Advancing Drug Discovery through Modern Research on Chinese Medicine and Natural Products, Courtyard Room 1&2, December 2, 2024, 11:15 AM - 1:15 PM

Biography:

Simon Ming Yuen LEE is currently Chair Professor of Biomedical Sciences in Department of Food Science and Nutrition, and State Key Laboratory of Chemical Biology and Drug Discovery, The Hong Kong Polytechnic University. Simon obtained PhD degree in biochemistry from The Chinese University of Hong Kong. His research interests lie in the discovery of drug-like agents from natural products including small molecules and biologics for use in various therapeutic areas, including brain disorder and neurodegenerative diseases. His dedication to education and research in the fields of omics, pharmacology and toxicology has leaded to over 360 scholarly articles, including Nature, Nature Genetics, Nature Communications (4×) and Science Advances. Simon is in stanford university's list of top 2% of most-cited scientists in Pharmaceutical Science and Biology (with h-index: 65 from Scopus). Simon is a life member of Clare Hall, University of Cambridge. He has served as an editorial board member for numerous international journals including Chinese Medicine, Antioxidants, Journal of Ethopharmacology, and Water Biology and Security.

Dehydroervatamine as a promising novel TREM2 agonist, attenuates neuroinflammation

Simon Ming Yuen Lee, Department of Food Science and Nutrition, and State Key Laboratory of Chemical Biology and Drug Discovery, The Hong Kong Polytechnic University, Hong Kong

Microglia plays a dual role in neuroinflammatory disorders that affect millions of people worldwide. These specialized cells are responsible for the critical clearance of debris and toxic proteins through endocytosis. However, activated microglia can secrete pro-inflammatory mediators, potentially exacerbating neuroinflammation and harming adjacent neurons. TREM2, a cell surface receptor expressed by microglia, is implicated in the modulation of neuroinflammatory responses. In this study, we investigated if and how Dehydroervatamine (DHE), a natural alkaloid, reduced the inflammatory phenotype of microglia and suppressed neuroinflammation. Our findings revealed that DHE was directly bound to and activated TREM2. Moreover, DHE effectively suppressed the production of pro-inflammatory cytokines, restored mitochondrial function, and inhibited NLRP3 inflammasome activation via activating the TREM2/DAP12 signaling pathway in LPS-stimulated BV2 microglial cells. Notably, silencing TREM2 abolished the suppression effect of DHE on the neuroinflammatory response, mitochondrial dysfunction, and NLRP3/NF-κB pathways *in vitro*. Additionally, DHE pretreatment exhibited remarkable neuroprotective effects, as evidenced by increased neuronal viability and reduced apoptotic cell numbers in SH-SY5Y neuroblastoma cells co-cultured with LPS-stimulated BV2 microglia. Furthermore, in our zebrafish model, DHE pretreatment effectively alleviated behavioral impairments, reduced neutrophil aggregation, and suppressed neuroinflammation in the brain by regulating TREM2/NLRP3/NF-κB pathways after intraventricular LPS injection. These findings provide novel insights into the potent protective effects of DHE as a promising novel TREM2 agonist against LPS-induced neuroinflammation, revealing its potential therapeutic role in the treatment of central nervous system diseases associated with neuroinflammation.

Keywords: Neuroinflammation; 19,20-dehydroervatamine; TREM2; NF-κB; NLRP3

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The intervention effect of Dengzhanshengmai Formula involves MALT1/NF-κB signaling pathway in regulating microglia-mediated neuroinflammation after cerebral ischemia

Prof Jingjing Zhang

Symposium 4: Advancing Drug Discovery through Modern Research on Chinese Medicine and Natural Products, Courtyard Room 1&2, December 2, 2024, 11:15 AM - 1:15 PM

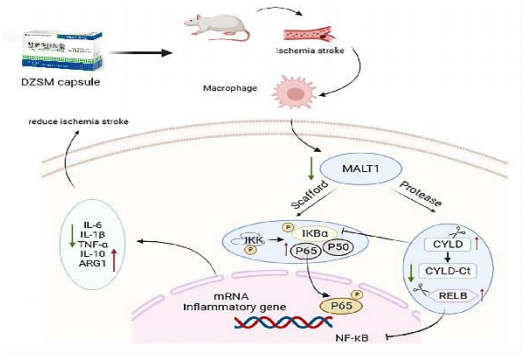
Biography:

Her main research direction is pharmacological research on traditional Chinese medicine including cerebrovascular diseases, diabetes ulcers, and craniocerebral injuries.
She received the title of North Brain Young Scholar from Beijing Brain Science and Brain Research Center (2020), and was selected for the 2021 Young Talent Promotion Project of the Chinese Society of Traditional Chinese Medicine. Hosted 6 national level projects such as the National Natural Science Foundation of China General Program. As the first author or corresponding author, she published more than 30 papers, and received 4 prizes, including the First Prize of Science and Technology of the Chinese Academy of Traditional Chinese Medicine, Additionally, she was authorized 3 invention patents, participated in the compilation of 3 monographs and invited to give presentations at international academic conferences.

MALT1/NF-κB signaling pathway in regulating microglia-mediated neuroinflammation after cerebral ischemia and the intervention effect of Dengzhanshengmai Formula

Jingjing Zhang[1], Guangzhao Cao[1,2]. Hongjun Yang[1,2] Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences[1], Beijing 100700, China; Experimental Research Center, China Academy of Chinese Medical Sciences[2], Beijing, 100700, China

Introduction. In ischemic stroke, neuroinflammation mediated by microglia polarization plays a vital role in neurological dysfunction, and targeting microglia polarization is a promising strategy for alleviating neuroinflammation and preventing cerebral ischemic/reperfusion (I/R).
Aims. In this study, we systematically investigate the mechanism of MALT1/NF-κB signaling pathway in regulating microglia-mediated neuroinflammation after cerebral ischemia and then the intervention effect of Dengzhanshengmai (DZSM) Formula on ischemic stroke.
Methods. SD rats subjected to middle cerebral artery occlusion caused ischemic stroke and the neuroprotection effect of DZSM was evaluated. To reveal the mechanism, scRNA-seq analysis combined with metabolomics analysis and bulk RNA-seq analysis was used and MALT1 inhibitor and siRNA was used to verify the role of MALT1.



Results. Collectively, siMALT1 shifted the microglia toward the protective M2 phenotype, and improved long-term functional neurological recovery. Additionally, silence of MALT1 increased the expression of TREM2 and suppressed the NOD2 and NF-κB signaling pathways, and modulated Purine metabolism and Alanine, aspartate and glutamate metabolism pathways. Importantly, DZSM inhibited MALT1/NF-κB signalling pathway to modulate microglia polarization and prevented MCAO-induced ischemic reperfusion injury. Two components (eg. Chlorogenic acid and scutellarin) in DZSM were identified to affect MALT1 and attenuated microglia-mediated inflammation
Discussion. MALT1 deficiency promoted the polarization of microglia to M2 phenotype to inhibit neuroinflammation and protect against I/R injury. Furthermore, targeting MALT1 inhibited the NOD2 and NF-κB signaling pathways and increased the expression of TREM2. And MALT1 siRNA modulated Purine metabolism and Alanine, aspartate and glutamate metabolism pathways.

Importantly, we confirmed that MALT1 was an effective target for alleviating cerebral I/R injury and shifting microglia to M2 polarization. DZSM inhibited MALT1/NF-κB signaling pathway and protected MCAO rats from ischemia/reperfusion injury.

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Genomics in advancing antimicrobial therapy in the clinical setting

Prof Ben Howden

Symposium 5: Targeting bacterial ‘superbugs’: From ward to lab, Eureka Room 1, December 3, 2024, 11:15 AM - 1:15 PM

Biography:
Professor Benjamin Howden is Director of the MDU Public Health Laboratory and Co-Director of the Centre for Pathogen Genomics at the University of Melbourne (Doherty Institute) in Melbourne. He is a leader in pathogen genomics and antimicrobial resistance research at the public health and clinical interface. He also leads capacity and capability building programs and research in these fields, focussed in the Asia Pacific Region.

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Tailoring antibiotic dosing regimens to maximize efficacy and minimize resistance by use of dynamic in vitro infection models and PK/PD approaches

A/Prof Cornelia Landersdorfer

Symposium 5: Targeting bacterial 'superbugs': From ward to lab, Eureka Room 1, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

Cornelia Landersdorfer, PhD, is an Associate Professor at the Monash Institute of Pharmaceutical Sciences, Monash University in Melbourne. She trained in clinical PK studies, bioanalysis, PK/PD modelling and microbiological studies in Germany, Australia and the USA. She leads a research group that integrates dynamic in vitro infection experiments with mechanism-based mathematical modelling to optimise dosing of antibiotics and other drugs. Her group performs the design and analysis of clinical and preclinical population PK studies. She is the Academic Deputy Director of the Monash-Moderna Quantitative Pharmacology Accelerator (MMQPA) which is focused on driving advancements in mRNA medicines. She has >140 peer-reviewed publications, and received the Georgina Sweet Award for Women in Quantitative Biomedical Sciences (2018), the Future Leader Award (2016) and Research Impact Award (2020) in the Faculty of Pharmacy and Pharmaceutical Sciences (#2 worldwide, QS world ranking), a 2022 Australian Award for University Teaching, and the 2023 Monash Graduate Supervisor of the Year award. Invited conference presentations include the European Congress of Clinical Microbiology and Infectious Diseases and American Society of Microbiology Microbe congress. Her research is supported by NHMRC, ARC, NIH and pharmaceutical industry, and has impacted on dosing guidelines and patient therapy internationally.

Tailoring antibiotic dosing regimens to maximize efficacy and minimise resistance by use of dynamic *in vitro* infection models and PK/PD approaches

Cornelia B Landersdorfer[1]. Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus)[1], Melbourne, VIC, Australia.

Antimicrobial resistance is rising in Australia and worldwide. Resistance can emerge rapidly, even against recently approved antibiotic compounds, when they are administered to patients in non-optimised dosing regimens. Therefore, it is important to develop novel approaches that inform the rational selection of antibiotic dosing regimens, in monotherapy and combinations, and account for patient factors and bacterial characteristics, to maximise bacterial killing, minimise resistance emergence and translate optimised regimens to the clinic.

Well-designed dynamic *in vitro* infection models combined with latest data analysis and pharmacokinetic/ pharmacodynamic modelling approaches enable us to evaluate a range of antibiotic dosing regimens and inform the selection of those most likely to be successful in patients, for clinical trials during pre-registration development and routine use of the antibiotic after registration. The dynamic *in vitro* studies expose bacterial pathogens to the concentration-time profiles of one or multiple antibiotics that are observed in patients following administration of relevant dosing regimens. They allow us to frequently quantify the total and resistant bacterial counts, as well as genomic, transcriptomic and metabolomic changes in response to treatment.

Mechanism-based and quantitative and systems pharmacology models that are developed based on the data generated in dynamic *in vitro* infection models contribute to a better understanding of the interplay of interactions between the pathogen, antibiotic and patient. They can be used to quantify the effect of certain bacterial and patient factors on the bacterial response to treatment. When combined with population pharmacokinetic models for the patient population of interest, they can be used to predict likely treatment outcomes and support the clinical translation of optimised dosing regimens.

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Structure activity relationships VS. structure-toxicity relations: a key battle in the design of lipopeptide antibiotics

Tony Velkov

Symposium 5: Targeting bacterial 'superbugs': From ward to lab, Eureka Room 1, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

A/Prof Velkov is a world leading expert in several aspects of antibiotic pharmacology, including their mode of action, chemistry, structure-activity relationships and toxicity. His innovative research is encompassed by complementary and integrated streams that encompass the 'lab bench to bedside' doctrine and efficiently translate his multidisciplinary research to clinical practice and pharmaceutical products. Specifically, A/Prof Velkov's team has been highly engaged in research across the following fields:

(1) Pharmacology, chemical biology and structure-activity relationships (SAR) of lipopeptide and teixobactin antibiotics;

(2) Novel antibiotic resistance mechanisms;

(3) Pharmacology and neurotoxicology of polymyxin antibiotics;

(4) Development of novel resistance-resistant teixobactin depsi-peptide antibiotics as dry powder and hydrogels formulations for the treatment of multi-drug resistant lung and wound infections;

(5) Development of synergistic polymyxin-nonantibiotic combinations against Gram-negative 'superbugs'.

Structure activity relationships VS. structure-toxicity relations: a key battle in the design of lipopeptide antibiotics

Tony Velkov[1] and Jian Li[2]
[1]Monash University, Department of Pharmacology, Clayton, Australia.
[2]Monash University, Department of Pharmacology, Clayton, Australia.

Resistance to the last-resort antibiotic colistin is now widespread and new therapeutics are urgently required. We report the first in toto chemical synthesis and pre-clinical evaluation of octapeptins, a class of lipopeptides structurally related to colistin. The octapeptin biosynthetic cluster consisted of three non-ribosomal peptide synthetases (OctA, OctB, and OctC) that produced an amphiphilic antibiotic, octapeptin C4, which was shown to bind to and depolarize membranes. While active against multidrug resistant (MDR) strains *in vitro*, octapeptin C4 displayed poor in vivo efficacy, most likely due to high plasma protein binding. Nuclear magnetic resonance solution structures, empirical structure-activity and structure- toxicity models were used to design synthetic octapeptins active against MDR and extensively drug-resistant (XDR) bacteria. The scaffold was then subtly altered to reduce plasma protein binding, while maintaining activity against MDR and XDR bacteria. In vivo efficacy was demonstrated in a murine bacteremia model with a colistin-resistant *Pseudomonas aeruginosa* clinical isolate.

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Optimising the use of antimicrobials in patients – what have we achieved?

A/Prof Andrea Kwa

Symposium 5: Targeting bacterial 'superbugs': From ward to lab, Eureka Room 1, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

Dr Andrea Kwa, a distinguished pharmacist clinician -scientist, has had a remarkable journey fueled by her curiosity. She excels in translational science, where she conducts evidence-based research and translate discoveries into practical applications, ensuring top-tier patient care. She specialised in critical care medicine, infectious diseases, and antimicrobial resistance research, specifically in in-vitro wet bench translational (phage therapy, antibiotics combination testing), population PKPD studies, molecular diagnostics in anti-fungal and antibacterial resistance, epidemiology/outcomes studies and health services research (specifically AI/ML for AMR management) to guide antimicrobial stewardship. To date, she has authored more than 120 publications.

Optimising the use of antimicrobials in patients – what have we achieved?

Andrea L Kwa

Antimicrobial optimization efforts have significantly improved patient care through several key interventions. Implementing antimicrobial stewardship programs has led to more appropriate drug selection, optimized dosing strategies, and reduced duration of therapy. Evidence shows decreased antimicrobial consumption while maintaining or improving clinical outcomes across multiple healthcare settings. Key achievements include the development of rapid diagnostic testing protocols, implementation of prospective audit and feedback systems, and creation of clinical decision support tools integrated into electronic health records. These initiatives have reduced antimicrobial resistance rates, decreased healthcare costs, and fewer adverse drug events. Regular monitoring of prescribing patterns and patient outcomes has enabled continuous refinement of optimization strategies. The collaborative approach between infectious disease specialists, clinical pharmacists, and primary care teams has proven essential to sustained success in antimicrobial optimization.

As antimicrobial resistance (AMR) intensifies globally, innovative strategies are needed to maximize the efficacy of existing antibiotics. Precision medicine provides a powerful framework for enhancing antibiotic effectiveness, particularly by leveraging combination therapies, therapeutic drug monitoring (TDM), and adjunctive phage therapy. Combination antibiotic testing identifies synergistic drug pairs that can more effectively target resistant pathogens, thus preserving the efficacy of existing antibiotics and potentially restoring susceptibility to certain drug-resistant strains. Therapeutic drug monitoring allows clinicians to optimize antibiotic dosing at an individual level, adjusting doses to maximize bacterial eradication while minimizing toxicity risks, thereby safely pushing drug exposure to its therapeutic limits. Phage therapy, the use of bacteriophages to specifically target bacterial pathogens, offers a complementary strategy that can eradicate bacteria which produce biofilm. In concert, these precision approaches enable a multifaceted and highly tailored response to AMR, potentially prolonging the clinical utility of current antibiotics and improving outcomes for patients with resistant infections.

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Innovative 5-HT2A Receptor Potentiators with Distinct Pharmacological Profiles vs. Psychedelic 5-HT2AR Agonists for Pharmacotherapy of Psychostimulant Use Disorder

Prof Kathryn Cunningham

Symposium 6: Neuropharmacological Frontiers:Transformational Addiction Therapeutics, Eureka Room 2, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

Dr. Cunningham has catalyzed translational research advances in neuropsychopharmacology with a particular emphasis on the mechanisms underlying substance use disorders (SUDs), and small molecule discovery in GPCR targets for therapeutics. Her research has been continuously funded by NIH and foundations, and she has published 180+ manuscripts. She has life-long commitment to diversity, equity and inclusion as a driver of excellence in science and has been recognized with the ASPET-Astellas Award for Translational Pharmacology, the Marian W. Fischman Memorial Award, the Paul Vanhoutte Award for Excellence in Science, and the University of Texas STARs Award. She is an active educator and board member for community organizations and fosters awareness and knowledge of diagnosis and treatment for SUDs and mental health disorders.

Innovative 5-HT$_2$ Receptor Potentiators for Substances Use Disorders (SUDs)

Kathryn A. Cunningham, Christina R. Merritt, Jia Zhou, Noelle C. Anastasio[1,2]. [1]Department of Pharmacology and Toxicology and [2]Center for Addiction Sciences and Therapeutics at the John Sealy School of Medicine at the University of Texas Medical Branch, Galveston, TX, U.S.A.

Introduction. The serotonin 5-HT$_2$R family of three GPCRs (5-HT$_{2A}$R, 5-HT$_{2B}$R, 5-HT$_{2C}$R) exhibit ~80% homology in orthosteric 5-HT binding pockets with each receptor governing myriad biological functions. Achieving subtype selectivity for ligands that bind 5-HT$_2$Rs is a long-held focus of pharmacological sciences in the quest to discover new therapies. In particular, the 5-HT$_{2A}$R and 5-HT$_{2C}$R are modulators of cortical circuitry that regulates vulnerability to SUDs, and vital targets for neurotherapeutic discovery.

Aims. We have crystalized strategies to explore 5-HT$_{2A}$R and 5-HT$_{2C}$R function with small molecule allosteric modulators. We are addressing a critical gap in knowledge for these 5-HT receptor systems.

Methods. A fragment-based, rational drug design approach was employed optimize novel molecule series which were evaluated in 5-HT-induced signaling assays in h5-HT$_{2C}$R, h5-HT$_{2A}$R and h5-HT$_{2B}$R cells *in vitro*. We evaluated metabolic properties, blood-brain barrier access and profiles in a broad-panel receptor screen. *In silico* molecular docking with receptor X-ray crystal structures explored positive allosteric modulator (PAM) binding sites and select compounds were evaluated in proof-of-concept studies in rodents.

Results. Molecules with selectivity as 5-HT$_{2A}$R or 5-HT$_{2C}$R or dual 5-HT$_{2A}$R/5-HT$_{2C}$R positive allosteric modulators (PAMs) have been identified with on-target properties, acceptable pharmacokinetic and brain penetration parameters as well as negligible displacement of orthosteric sites of ~50 GPCRs and transporters. *In silico* analyses suggest binding to less conserved, extracellular sites vs. the orthosteric 5-HT site. Efficacy profiles of PAMs were explored in unconditioned and conditioned behavior assays, and the findings are consistent with more constricted 5-HT$_2$R agonist-like actions vs. a full 5-HT$_2$R-specific agonist.

Discussion. Optimization of 5-HT$_{2C}$R, 5-HT$_{2A}$R and dual 5-HT$_{2C}$R/5-HT$_{2A}$R PAMs provide key pharmacological tools to promote greater understanding of the function and roles of these receptors in brain diseases and provide new prospects to develop selective, novel candidate medications with distinct profiles at these closely related receptors.

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Opioid Withdrawal Contributes to the Development of Compulsive Drug Use: Prospects for New Pharmacotherapeutics in Opioid Use Disorder

Prof Elena Bagley

Symposium 6: Neuropharmacological Frontiers:Transformational Addiction Therapeutics, Eureka Room 2, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

Professor Bagley completed a PhD at The University of Sydney in 2001. She was a C.J Martin Fellow from 2001 to 2006. During this time she was a postdoctoral fellow in the laboratory of Professor Gary Westbrook at the Vollum Institute (Oregon, USA) and at the Pain Management Research Institute (University of Sydney). Professor Bagley's established her research laboratory in the Brain and Mind Institute (2010-2011), moved to Pharmacology in 2011 and Sydney Pharmacy School in 2021 and has a laboratory in the Charles Perkins Centre.

Her laboratory primarily focuses on synapses, which are the point of communication between brain cells and is interested in normal synaptic function and synapse dysfunction. Synaptic dysfunction is emerging as a key player in many brain disorders. Of particular interest are the synaptic changes or plasticity that may be responsible for chronic pain states, addiction and anxiety disorders and the role that endogenous opioids may play in these diseases.

Opioid withdrawal contributes to the development of compulsive drug use: Prospects for New Pharmacotherapeutics in Opioid Use Disorder

Elena E. Bagley, Gabrielle C. Gregoriou, Sahil Patel, Muskaan Kalra, Neda Refiei, Roger Wang, Rakulan Santhakumar. Charles Perkins Centre & Sydney Pharmacy School, Faculty of Medicine and Health, University of Sydney, NSW, Australia.

Introduction. During opiate withdrawal, several reward learning processes can direct future behaviour towards relapse and compulsive drug use. These processes are mediated by plasticity at glutamatergic thalamic and orbitofrontal projections to the lateral amygdala and also rely upon activation of amygdala mu opioid receptors in the basolateral amygdala.

Aims. It is currently unknown how activation of amygdala mu opioid receptors participates in the reward processes that drive relapse and the underlying plasticity, which limits the development of treatments for addiction.

Methods. We used optogenetics and patch-clamp electrophysiology in rat brain slices taken from opioid treated rats.

Results. We found that the induction of plasticity at excitatory inputs onto pyramidal neurons in the lateral amygdala was tightly controlled by GABAergic inhibition (potentiation with GABA signaling blocked = 39 ± 14 %, n = 7 vs. potentiation with GABA signaling intact = -2 ± 10 %, n = 6). Further, we found that application of met-enkephalin (10µM), an opiate peptide that activates mu opioid receptors, gates the induction of plasticity at these inputs, presumably by supressing GABAergic signalling in the lateral amygdala.

Discussion. These findings provide an explanation as to why relapse-triggering reward processes rely on activation of mu receptors in the amygdala during withdrawal and highlight amygdala mu opioid receptors as a potential target for novel ways to stop the development of compulsive opioid use.

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The Promise of FKBP51 Antagonists to Mitigate Opioid Relapse Vulnerability

Prof John Neumaier

Symposium 6: Neuropharmacological Frontiers:Transformational Addiction Therapeutics, Eureka Room 2, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

John F. Neumaier, M.D., Ph.D. graduated from Reed College and then completed his medical and doctoral degrees at the University of Washington. After completing his residency in Psychiatry at the University of Washington, he joined their faculty as an Assistant Professor in 1994. He is currently Joint Professor in the Departments of Psychiatry and Pharmacology, and Head of the Division of Psychiatric Neurosciences. In 2020 he became Director of Mental Health Research at the Puget Sound VA Medical Center. He is the president of the International Society for Serotonin Research. Dr. Neumaier's research focuses on the study of complex emotional behaviors involving learning, motivation, and stress responses and he uses a variety of molecular, pharmacological, and behavioral strategies in rodent models of stress, reward mechanisms, and drug withdrawal. In addition to research, Dr. Neumaier practices psychiatry and focuses on treatment resistant mood disorders using psychopharmacology, behavioral interventions, and neuromodulation.

The Promise of FKBP51 Antagonists to Mitigate Opioid Relapse Vulnerability

John F Neumaier. Departments of Psychiatry and Pharmacology, University of Washington, Seattle, WA, USA

Introduction. Polymorphisms in the FKBP5 gene increase the vulnerability to psychiatric and substance use disorders. This seems to be mediated mainly by increased expression of the gene, which codes for the protein FKBP51, which can short-circuit normal feedback regulatory mechanisms. This protein is a critical regulator of steroid receptor signalling and FKBP51 antagonism has been found to reduce stress responses and relapse to alcohol and cocaine seeking in animal models. Since physiological and emotional stress and negative emotion can exacerbate opioid seeking, we are testing SAFit2, a highly selective FKBP51 antagonist, in several rodent models of fentanyl seeking as well as models that combine mild traumatic brain injury (mTBI) and chronic fentanyl administration on subsequent opioid seeking.

Aims. The goal of these studies is to assess whether inhibiting FKBP5 signalling with SAFit2 reduces fentanyl seeking and withdrawal along with concomitant emotional symptoms of stress and drug withdrawal.

Methods. In the first study, male and female C57Bl6 mice are exposed to mTBI or sham condition three times using a well validated blast overpressure method, followed by chronic fentanyl administered by minipump for four weeks. Four weeks later, emotional and oral fentanyl seeking is measured during treatment with SAFit2 or vehicle. In the second study, operant self-administration of oral fentanyl is used in rats to assess the impact of SAFit2 on several parameters of fentanyl taking and seeking.

Results. Repeated swim stress or mTBI increases FKBP5 expression in multiple brain regions. SAFit2 reduces the negative emotional state associated with repeated stress. Oral fentanyl self-administration strategies are a reliable and accessible model for investigating opioid seeking; these methods work well in both mice and rats using operant and two-bottle choice methods. The results of SAFit2 administration on fentanyl seeking after repeated mTBI and chronic noncontingent fentanyl as well as its effects on operant self-administration of oral fentanyl will be presented.

Discussion. Inhibition of FKBP5 signalling is an important new strategy for blunting the impacts of stress on drug seeking and has been shown to reduce relapse to seeking of alcohol, cocaine, and now opioids. Future development of FKBP5 antagonists is a promising new approach to the treatment of chronic stress disorders and may also lead to lower risks of substance abuse as well.

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Serotonin Modulation of Transition to Compulsive Cocaine Intake: Implications for Therapeutics

Yue Li

Symposium 6: Neuropharmacological Frontiers:Transformational Addiction Therapeutics, Eureka Room 2, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

Yue Li graduated from her PhD project at Zhejiang University in 2017. From 2018 to 2022, Yue worked as a postdoc at University of Geneve under the supervision of Christian Luscher. In December 2022, Yue joined the Institutes of Brain Science at Fudan University as principal investigator. Yue Li's lab focuses on how serotonin modulates synaptic plasticity and shapes behavior.

Serotonin Modulation of Transition to Compulsive Cocaine Intake: Implications for Therapeutics

Yue Li[1]. Institutes of Brain Science, Fudan University[1], Shanghai, SH, China

Introduction. Compulsive drug use despite adverse consequences defines addiction. While mesolimbic dopamine signaling is sufficient to drive compulsion, psychostimulants such as cocaine also boost extracellular serotonin by inhibiting reuptake.
Aims. In this study, we aimed to identify the role of serotonin in compulsive cocaine intake.
Methods. We used SERT Met172 knockin (SertKI) mice carrying a transporter that no longer binds cocaine to abolish serotonin transients during cocaine self-administration. Conversely, we used selective serotonin reuptake inhibitor (SSRI) to pharmacologically elevate serotonin during optogenetic dopamine self-stimulation paradigm (oDASS).
Results. SertKI mice showed an enhanced transition to compulsive cocaine take, while SSRI treatment during oDASS reversed the inherently high rate of compulsion. The bidirectional effect on behaviour is explained by presynaptic depression of orbitofrontal cortex to dorsal striatum synapses induced by serotonin via 5-HT1B receptors.
Discussion. Our study identified the synaptic mechanism underlying how serotonin curbs cocaine addiction, and may help to refine approaches in addiction treatments.

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Exploring sex differences in various preclinical models of cardiometabolic disease

Dr Miles De Blasio

Symposium 7: Sex differences in cardiovascular disease, Eureka Room 3, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

Dr Miles De Blasio leads the Cardio-Metabolic Physiology (CMP) laboratory at Monash University and is focussed on learning more about the metabolic alterations that occur in the heart, and the influence of the surrounding pericardial fat in the setting of diabetes and obesity. He is an expert in the endocrine and metabolic basis of diabetes and obesity and the impact that these have on cardiac metabolism and function. He is also interested in understanding how diabetes and obesity impair cardioprotective adiponectin signalling which leads to lipotoxic cardiomyopathy.

Exploring sex differences in various preclinical models of cardiometabolic disease

Miles De Blasio. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences. Monash University, Melbourne, VIC, Australia.

Cardiometabolic disease, including conditions such as type 2 diabetes (T2D), cardiovascular disease, diabetic cardiomyopathy and metabolic syndrome, is a leading cause of morbidity and mortality due to a high risk of developing heart failure (HF). While both men and women are affected by these conditions, sex-specific differences in prevalence and outcomes have been consistently observed, however treatment for HF remains the same regardless of sex.

Sex differences in cardiometabolic disease are driven by a complex interplay of hormonal, genetic, and environmental factors. Women are disproportionately affected by cardiometabolic disease, with higher rates of metabolic syndrome and type 2 diabetes compared to men. Conversely, men are more likely to experience cardiovascular events and mortality from cardiometabolic disease.

The clinical implications of sex-specific differences in cardiometabolic disease are significant. Sex-specific treatment approaches are needed to account for these differences in pathophysiology and to optimise treatment outcomes. Clinically, sex differences in cardiometabolic disease presentation can have important implications for diagnosis and management. Understanding the sex-specific pathophysiology of cardiometabolic disease is crucial for developing effective prevention and treatment strategies that take into account the unique characteristics of each sex and to improve outcomes for both men and women affected by cardiometabolic disease.

This talk will focus on the sex-specific differences in preclinical mouse models of diabetic cardiomyopathy and heart failure with preserved ejection fraction (HFpEF).

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Unravelling sex differences in the phenotype of pulmonary hypertension to enhance insights into therapeutic approaches

Peng-Cheng Wang

Symposium 7: Sex differences in cardiovascular disease, Eureka Room 3, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

Peng-Cheng (Stan) Wang, has a Bachelor of Life Science (Chinese Culture University, Taiwan) and a Master of Science (Taipei Medical University, Taiwan). He completed his PhD in 2024 and continues his academic career as a post-doc in the Cardiovascular & Pulmonary Pharmacology Group (CPPG) in the Department of Pharmacology at Monash University. His research focuses on sex differences in the pathophysiology and treatment of pulmonary hypertension and exploring new therapeutic targets and cell-based treatments (e.g. human amniotic epithelial cell (hAEC)-derived exosomes) for the diseasse. His studies utilise the gold-standard sugen/hypoxia pre-clinical murine model of pulmonary hypertension, in which endpoint hemodynamic measures include right ventricular systolic pressure and mean arterial blood pressure together with histological and molecular analysis to examine pulmonary and cardiac remodelling and inflammation. Stan is a chief investigator on a recently awarded Heart foundation, Vanguard Grant which is focused on targeting IRAP as a novel therapy for pulmonary hypertension.

Unravelling sex differences in the phenotype of pulmonary hypertension to enhance insights into therapeutic approaches

Peng-Cheng Wang[1], Mingyu Zhu[1], Celine Shi[1], Jerusha Mather[1], Kristen Bubb[2], Brad Broughton[1], and Barbara K. Kemp-Harper[1]. Department of Pharmacology[1], Department of Physiology[2], Monash University, Melbourne, VIC, Australia.

Introduction. Pulmonary arterial hypertension (PAH) is an incurable, fatal disease characterised by elevated mean pulmonary arterial pressure, remodelling of the pulmonary vasculature and right ventricular hypertrophy that ultimately leads to right heart failure and death. The prevalence of PAH is higher in females, yet the disease is more severe in males, hence they generally have a poorer long-term prognosis. As such, preclinical models of PAH are needed which replicate these sex differences and facilitate the screening of novel therapeutics in males and females.

Aims. To compare the time course of development of PAH and associated inflammatory processes in male and female mice using the gold-standard sugen/hypoxic (SuHx) model.

Methods. Male and female C57BL/6 mice (9-15 weeks old) were subjected to either normoxic (NmOx: 21% O_2) or SuHx conditions (10% O_2, plus vascular endothelial growth factor inhibitor SU5416, 20mg/kg, s.c.) for 14, 21, 35 and 42 days. Endpoint measurements included: right ventricular systolic pressure (RVSP), RV to left ventricle plus septum ratio (RV/LV+S), lung vessel wall thickness (Masson's trichrome), pulmonary macrophage analysis ($CD68^+$ immunofluorescence) and pro-inflammatory gene expression (RT-qPCR).

Results. The PAH phenotype, as ascertained by significant increases in both RVSP (~11 mmHg) and RV hypertrophy (RVH, ~50%), was established by day 21 in male and day 14 in female mice ($p<0.05$, n=6-8). PAH severity progressed in male SuHx mice, with a secondary increase (~30%) in RVSP and RVH and ~67% increase in pulmonary vessel wall thickness at day 42. By contrast, PAH and pulmonary vascular remodelling remained stable from day 14 onwards in female mice. Inflammation was evident in male SuHx mice at day 35 with an increase (1.8-fold) in lung macrophage infiltration and IL-6 (6-fold) and TNFα (3-fold) expression observed. In female SuHx mice, lung macrophage number and TNFα expression was unchanged, yet a modest increase in IL-6 (2-fold) was observed at day 42.

Discussion. The murine SuHx model of PAH emulates sex differences in PAH patients, with PAH established earlier in female mice and progressing in severity in male mice. A prominent inflammatory component in male mice may underly these differences, such that anti-inflammatory therapeutics may have greater efficacy in males with PAH.

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Resolution of inflammation: sex driving differences

Prof Amrita Ahluwalia

Symposium 7: Sex differences in cardiovascular disease, Eureka Room 3, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

Amrita Ahluwalia is currently Dean for Research at Barts & The London, Faculty of Medicine & Dentistry Queen Mary University of London. Professor Ahluwalia is an active biomedical researcher with a career spanning over 25 years. Her current research work focuses on delineating mechanisms of vascular homeostasis, differences in vascular homeostasis between men and women and particularly the effect of both nitrite and nitrate in influencing cardiovascular function in health and disease. Ahluwalia's group were the first to demonstrate, in 2004, that nitrite is cytoprotective in the heart as well as leading translational research into the delivery of dietary nitrate to lower blood pressure and improve outcome in hypertensive and coronary artery disease patients. Prof Ahluwalia has led numerous initiatives supporting Equality and Diversity in the Academic Biomedical research environment. In particular she has led establishment of a suite of guidelines seeking to raise the bar upon reproducibility and transparency in biomedical research.

RESOLUTION OF INFLAMMATION IN CARDIOVASCULAR DISEASE: SEX MATTERS

Amrita Ahluwalia. Barts & The London Faculty of Medicine & Dentistry, Queen Mary University of London, London, UK

Vascular inflammation is now understood to play an important role in both initiating and perpetuating cardiovascular disease. Males and females are both subject to this disease process however substantial evidence exists suggesting that the mediators, pathways and magnitude of the distinct phases of the immune process are different between the sexes. Ours and others evidence demonstrates sex differences in the incidence of cardiac and vascular disease and confirms biological differences in inflammatory initiation and resolution between men and women. I will discuss our data investigating sex differences in vascular function and the initiation and resolution of inflammatory responses, with a view to proposing potential targets for pharmacological intervention that might prove useful in improving cardiovascular disease outcomes in both sexes.

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Sex differences in susceptibility to ventricular arrhythmias

Dr. Junko Kurokawa

Symposium 7: Sex differences in cardiovascular disease, Eureka Room 3, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

Junko Kurokawa is a professor of Department of Bio-informational Pharmacology, Faculty of Pharmaceutical Sciences, University of Shizuoka where she teaches and does research on the cardiac physiology and pharmacology. Dr. Junko Kurokawa obtained her BSc (1993) and PhD (1998) at Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, the University of Tokyo in Japan (supervised by Prof. Taku Nagao). Dr. Kurokawa did postdoctoral work at Georgetown University (with Prof. Martin Morad) and Columbia University (with Prof. Robert S Kass), before starting a faculty position at Tokyo Medical and Dental University, Medical Research Institute (Department of Bio-informational Pharmacology, with Prof. Tetsushi Furukawa). Junko's work has been focused on regulation of cardiac ion channels by signaling molecules, cAMP, NO and sex hormones, and has published work specifically on mechanisms associated with drug-induced ventricular arrhythmias. In 2016, Dr. Kurokawa was appointed a professor in Pharmaceutical School at University of Shizuoka.

Her current research aims to identify novel molecular mechanisms of sex differences in regulation of ion channels involved in the pathophysiological function of the heart as well as other organs.

In this symposium, the title of her talk is "Sex differences in susceptibility to ventricular arrhythmias.

Sex differences in susceptibility to ventricular arrhythmias

Junko Kurokawa[1] and Masami Kodama[1]. Department of Bio-Informational Pharmacology, Faculty of Pharmaceutical Sciences, University of Shizuoka[1], Shizuoka, SHIZUOKA, Japan; Department Name, Organisation[2], Shizuoka, SHIZUOKA, Japan.

Introduction. It has been known that women have a greater TdP (torsade de pointes) risk than men in both congenital and acquired long QT syndrome. The sex difference becomes evident only when compared with adult men and adult women at the follicular phase, implying androgen and progesterone (P4) have protective effects on TdP. Accumulating clinical evidence suggests that testosterone and progesterone shorten QT intervals. We have found that both sex hormones produced NO which up-regulates the I_{Ks} channel currents and suppressed L-type Ca^{2+} channel currents ($I_{Ca,L}$) (1, 2). However, the molecular mechanisms underlying the sex difference in TdP susceptibility remain unclear.

Aims. To understand the sex difference in TdP occurrence, we analysed the molecular mechanisms of ion channel regulation by these sex hormones.

Methods and Results. With patch-clamp experiments in guineapig ventricular myocytes, we have demonstrated that a nitric oxide (NO) production induced by stimulation of cardiac progesterone receptors through a non-genomic pathway suppresses L-type Ca^{2+} currents ($I_{Ca,L}$) under cAMP-stimulated conditions. This suggests a cross-talk between NO and cAMP/PKA signaling. Our pharmacological analysis in this study revealed that the cross-talk is mediated by phosphodiesterase 2 (PDE2) located at the lipid rafts of T-tubules in cardiac myocytes. To visualize cAMP/PKA activities in living cells, we employed FRET-based cAMP/PKA biosensors anchored to membrane rafts or non-raft regions, respectively. The FRET analysis suggested a subcellular localization of the cross-talk.

Discussion. These results suggest that a compartmentalized PKA activity may involve a cross-talk between the non-genomic PRs pathway and beta-ARs pathway to regulate $I_{Ca,L}$. These data may explain a sex difference in QT intervals and dynamic changes of arrhythmia risk in women during the menstrual cycle, and can be a clue to avoid the potentially lethal arrhythmias in long QT syndromes.

References. 1. CX Bai, J Kurokawa, et. al., Circulation 2005;112;1701-1710. 2. H Nakamura, J Kurokawa, et. al., Circulation 2007;116;2913-2922.

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Cubic Nanostructure and Cholesterol Enhance Lipid Nanoparticle Mediated mRNA Transfection in Macrophages

Dr Maggie Zhai

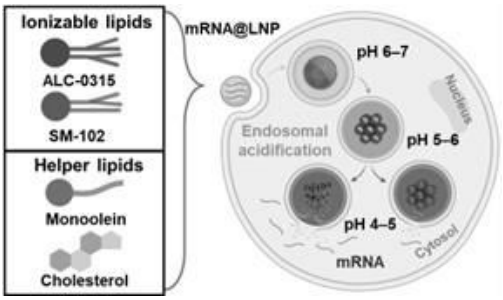
Symposium 8: Unveiling the next wave of therapies for chronic lung diseases, Courtyard Room 1&2, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

Dr Jiali (Maggie) Zhai is a Senior Research Fellow in School of Science, RMIT University. Her research interests focus on developing lipid and polymer nanoparticle delivery platforms for targeted delivery of bioactives and therapeutics, including mRNAs, proteins, chemotherapeutics, antimicrobials and imaging agents. She has pioneered the use of high throughput materials screening approach and synchrotron time-resolved X-ray scattering technique to elucidate the mechanisms of drug delivery, endosomal escape and structure-function relationship of nanoparticle delivery platforms.

Cubic Nanostructure and Cholesterol Enhance Lipid Nanoparticle Mediated mRNA Transfection in Macrophages

Haitao Yu[1], Joshua Iscaro[2], Natalia Martinez[1], Hao Wang[2], Calum Drummond[1], Steven Bozinovski[2], Jiali Zhai[1]. School of Science, RMIT University[1], Melbourne, VIC, Australia; School of Health & Biomedical Sciences, RMIT University[2], Melbourne, VIC, Australia. (please abbreviate state)



Introduction. Macrophages are unique immune cells attracting growing attention as a potential candidate for cell-based therapy for infectious diseases and cancer. Low endosomal escape of mRNAs delivered by lipid nanoparticle (LNP) delivery platforms remains a formidable barrier for efficient transfection to lung macrophages which have implications for many chronic lung diseases.

Aims. The aim of the current study is to investigate the effect of components and structures of LNP delivery platforms on the transfection efficiency of mRNAs in lung resident macrophages. Ultimately, the study aims to develop next-generation LNP delivery platforms for more efficient mRNA delivery to immune cells with exceptional endosomal escape.

Methods. By using high-throughput LNP formulation and physicochemical characterisation, LNPs with pH-responsive properties were screened for their ability to deliver mRNAs, and the transfection efficiency in various model cell types including primary alveolar macrophages from the lung lumen and human primary monocyte derived macrophages.

Results. We show that the ionisable lipid component, cholesterol, and the pH-responsive cubic structure are the key factors influencing the mRNA transfection efficiency (Yu, et al. 2023). We also show that the protein corona of mRNA-LNPs after incubating with the bronchoalveolar lavage fluid altered the mRNA transfection efficiency.

Discussion. The study provides insights on mRNA transfection in lung macrophages. In vivo work are currently under exploration focusing on non-invasive administration route.

Yu, H., et al., (2023) Journal of the American Chemical Society, 145, 24765-24774

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Developing calcaratarin D, a labdane diterpenoid, as therapeutics for chronic lung diseases

Prof Fred Wong

Symposium 8: Unveiling the next wave of therapies for chronic lung diseases, Courtyard Room 1&2, December 3, 2024, 11:15 AM - 1:15 PM

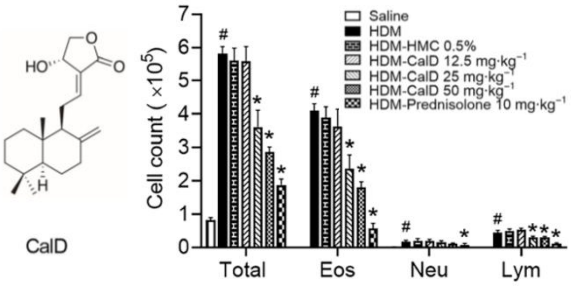
Biography:

Professor W.S. Fred was the Head of the Pharmacology Department (2014-2020), and Assistant Dean and Vice Dean of Research (2009-2014) of the Yong Loo Lin School of Medicine, National University of Singapore. He is the Director of the Drug Discovery and Optimization Platform in the Yong Loo Lin School of Medicine. He is the Principal Investigator of the Singapore-HUJ Alliance for Research and Enterprise (SHARE). He is the founding President of the Singapore Pharmacological Society. His research interest is to identify therapeutic targets and to discover and develop novel drug molecules for the treatment of chronic airway inflammation including asthma, COPD and pulmonary fibrosis. Professor Wong is ranked the top 2% of scientists worldwide in 2022 and 2023.

Developing calcaratarin D, a labdane diterpenoid, as therapeutics for chronic lung diseases

WS Fred Wong[1,2,3], W Liao[1]. Department of Pharmacology[1,3], Drug Discovery and Optimization Platform[2] and Singapore-HUJ Alliance for Research and Enterprise[3], National University of Singapore, Singapore 117600

Introduction. Calcaratarin D (CalD), a *normal*-labdane diterpenoid, is isolated from a medicinal plant called *Alpinia calcarata*. Our initial screen revealed potent anti-inflammatory effects of CalD on LPS-induced macrophage production of TNF-α, IL-6, and IL-1β. Structure-activity relationship study showed that the α,β-unsaturated γ-butyrolactone moiety of the labdane scaffold is critical for CalD's actions.



Aims. This study was to test the anti-inflammatory effects of CalD in animal models of asthma and idiopathic pulmonary fibrosis (IPF), and to investigate mechanisms of action underlying its protective effects.

Methods. We developed house dust mite (HDM)-induced asthma mouse model and bleomycin-induced IPF mouse model. CalD doses were given by mouth. Bronchoalveolar lavage fluid (BALF), lung lobes and blood were collected for analysis. Isolated macrophages were further studied for mechanisms of action of CalD. Separate cohorts of mice were used to study lung functions in asthma and in IPF.

Results. CalD was effective against HDM-induced allergic asthma and bleomycin-induced IPF. CalD was found to reduce BALF eosinophil, M2 macrophages, airway inflammation and hyperresponsiveness in allergic asthma, probably via inhibition of JAK-STAT and FoxO1/IRF4 pathways. CalD was able to reduce BALF lymphocytes and M2 pro-fibrotic macrophages, lung collagen deposition and epithelial-mesenchymal transition (EMT), and improve lung functions in IPF, probably via inhibition of the Wnt/β-catenin pathway and YAP/TAZ signaling.

Discussion. CalD is a novel labdane diterpenoid anti-inflammatory molecule equipped with α,β-unsaturated γ-butyrolactone moiety capable of protecting against allergic asthma and IPF. (National Research Foundation of Singapore NRF2020-ITC002-0001 and NUHS DDOP-E-559-00-0004-01)

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Exploration of CD151 as a therapeutic target in asthma

A/Prof Thai Tran

Symposium 8: Unveiling the next wave of therapies for chronic lung diseases, Courtyard Room 1&2, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

Thai Tran is an Associate Professor in the Department of Physiology and Infectious Disease Translational Research Program at the National University of Singapore (NUS). She leads a dynamic research group investigating how the microenvironment (extracellular matrix including laminin and its adaptor protein, CD151) interacts with cells of the lung and how dysregulation of this interaction contributes to lung pathophysiology. Within this theme, her laboratory has two major areas of research focus: (A) Role of laminin and CD151 in lung disease pathophysiology (including asthma, influenza infection, and lung cancer) through molecular, cellular, and disease model approaches and (B) Identification of novel therapeutic targets of lung diseases. Thai is also the Education Director for the Life Sciences, Vice-President of the Singapore Pharmacological Society, NUS Medicine Faculty Academic Advisory Committee member, and Associate Professorial Faculty Promotion and Tenure Committee member. She has won awards in research (NUS Medicine Young Researcher of the Year Award 2019), teaching (NUS Medicine Faculty Teaching Excellence Award, 2016 and 2019), and graduate mentoring (NUS Medicine Graduate Mentor of the Year Award 2018).

Exploration of CD151 as a therapeutic target in asthma

Thai Tran[1,2], Department of Physiology[1], Infectious Disease Translational Research Program[2], National University of Singapore, Singapore 117593.

Introduction. Mechanisms underlying the self-limiting effects of glucocorticoids in reducing airways hyperresponsiveness (AHR) have predominantly focused on the inflammatory aspects of asthma pathophysiology. However, inflammation and the resulting mechanical phenotype (including AHR) associated with disease presentation remain poorly understood. We previously implicated tetraspanin, Cluster of Differentiation 151 (CD151), as a pivotal factor in AHR (Qiao et al., 2017, J Allergy Clin Immunol 139:82-92).
Aim. To determine whether GCs regulate CD151 expression to impact AHR in vitro and in vivo models of asthma.
Methods. We employed a constellation of experimental tools, including collagen gel contraction assay, traction force microscopy, atomic force microscopy, magnetic twisting cytometry, and precision-cut lung slice technology, to determine the role and functional significance of GCs on CD151 expression in airway smooth muscle (ASM) cells from both non-asthmatic and asthmatic individuals. We also assessed the presence of CD151 in human bronchial biopsy samples in GC-naïve versus GC-treated asthmatics from two clinical study cohorts, SAGE (Woodruff et al., 2007 PNAS 104: 15858-63) and MAST (Solberg et al., 2012 AJRCCM 186: 965-74).
Results. The GC, dexamethasone (Dex), induced increases in CD151 protein abundance in a concentration-dependent and GC-receptor-dependent manner, indicative of a general class effect of GCs. Interestingly, Dex increased cell stiffness at baseline and following histamine stimulation in ASM cells, irrespective of asthmatic status. This stiffening effect was blocked by CD151 siRNA. Clinically, compared to GC-naïve asthmatics, GC-treated asthmatics exhibited elevated CD151 expression after 1- or 8-week treatment, concomitant with a reduced PC20 value, indicating enhanced AHR.
Discussion. Our study highlights a hitherto unexpected influence of anti-inflammatory GCs on the mechanical phenotype of ASM through the upregulation of CD151, shedding light on a potential novel mechanism underlying GC resistance. These insights could be significant in deciphering asthma patient responses to GC therapy and may extend to other inflammatory disease conditions that employ GC treatment. (Academic Research fund - T1-BSRG 2014-04 and MOE2019-T2-1-059).

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Clinical dose estimation for anti CXCR4 i-body-Fc fusion AD-214 for the treatment of fibrotic diseases

Dr Jason Lynch

Symposium 8: Unveiling the next wave of therapies for chronic lung diseases, Courtyard Room 1&2, December 3, 2024, 11:15 AM - 1:15 PM

Biography:

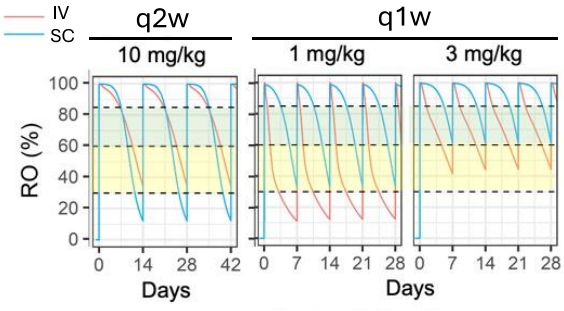
Dr Jason Lynch is a Senior Scientist at AdAlta Ltd based at La Trobe University's Bundoora Campus. Jason leads several R&D initiatives at AdAlta, including steering the clinical advancement of AdAlta's lead i-body, AD-214, for the treatment of fibrotic diseases. Jason has a BSc (Hons) degree in Pharmacology from the University of Edinburgh, UK and a PhD in Biomedical Science from the University of Queensland. Jason's PhD studies and postdoctoral work at QIMR Berghofer Medical Research Institute led to several novel insights into the pathogenic mechanisms underlying the development of severe bronchiolitis and its link to subsequent asthma. After completing his PhD, Jason undertook further postdoctoral training at Massachusetts General Hospital and Harvard Medical School where developed a designer probiotic bacteria for targeted drug delivery into the gastrointestinal tract and solid tumours.

Clinical dose estimation for anti CXCR4 i-body-Fc fusion AD-214 for the treatment of fibrotic diseases

Jason P Lynch[1], Louise Organ[1], Timothy C Oldham[1], Lionel Renaud[2], Bastien Casini[2], Mattias Machacek[2], Michael Foley[1,3]
AdAlta Ltd[1], Melbourne, VIC, Australia; Lyo-X AG[2], Basel, Switzerland; Department of Biochemistry and Chemistry, La Trobe University[3], Melbourne, VIC, Australia.

Introduction. i-bodies are small, stable, human scaffolds inspired by shark single domain antibodies. i-body-Fc-fusion AD-214 has picomolar affinity for CXCR4, a GPCR upregulated in fibrosis. AD-214 has been specifically designed for fibrotic disease, has demonstrated anti-fibrotic activity in preclinical models and was well tolerated in Phase I clinical trials. AD-214 maintained high receptor occupancy (RO, blocking) for up to three weeks after IV infusion in Phase I.

Aims. Demonstrate RO by AD-214 and efficacy are causally linked. Develop a PK/PD model of AD-214 administration. Determine IV and SC dosing regimens that maintain the RO levels required to achieve efficacy.



Methods. AD-214-CXCR4 RO and efficacy was measured using an *ex vivo* SDF-1α induced primary human T cell migration assay, a model fibrotic process. A PKPD model of IV AD-214 administration was developed and validated. Preclinical PK results and reasonable assumptions allowed this to be extrapolated to SC AD-214 administration.

Results. *Ex vivo* studies correlating RO and inhibition of a model fibrotic process at achievable serum concentrations are reported. PK and RO simulations based on models fitting the Phase I data enabled dose regimens to be assessed against target RO for potential to achieve therapeutic efficacy. As shown in the Figure above, the model predicts q2w ≥10 mg/kg and q1w ≥1 mg/kg IV or SC to achieve target RO (dotted lines).

Discussion. Taken together these studies are strongly suggestive that not only is a clinically feasible q2w intravenous dosing regimen likely to be efficacious, an even more convenient q1w subcutaneous administration regimen may also be efficacious.

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Novel insights into the Gut Phageome in Hypertension

Dr Antony Vinh

Symposium 9: The role of the gut microbiome in cardiometabolic disease, Eureka Room 1, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

A/Prof Antony Vinh is a Principal Research Fellow in the Department of Microbiology, Anatomy, Physiology and Pharmacology at La Trobe University, where he leads the Hypertension and Diabetes Division within the Centre for Cardiovascular Biology and Disease Research. He earned his Ph.D. from Monash University in 2008 and completed postdoctoral training at Emory University's Division of Cardiology, specializing in immunity and hypertension. Since joining La Trobe University in 2017, his research program has received continuous funding from the NHMRC. A/Prof Vinh's work has significantly advanced our understanding of the roles of inflammasomes, interleukin-18, and B cells in hypertension and kidney damage, and he has recently expanded his research to explore alternative pathways, including the gut microbiome, with a specific focus on the gut virome and bacteriophages.

Novel insights into the Gut Phageome in Hypertension

Antony Vinh[1,2]. Centre for Cardiovascular Biology and Disease Research, La Trobe University[1], Bundoora, VIC, Australia. Department Microbiology, Anatomy, Physiology and Pharmacology, La Trobe University[2], Bundoora, VIC, Australia.

The gut microbiome is a complex community of microorganisms residing in most, if not all, animal species. Loss of commensal bacteria in the gut (dysbiosis) promotes inflammation and diseases like hypertension. While there has been much focus on restoring gut health with pro- or pre-biotics, only scant attention has been paid to identifying environmental/biological factors that initially drive dysbiosis. This is remiss, as elimination of such factors should be a superior strategy for restoring a healthy microbiome than current approaches of reintroducing/regrowing bacteria in the same environment that depleted the host's own bacteria. Phages are viruses that infect bacteria. They outnumber bacteria in the gut by 10:1, yet their role in dysbiosis and hypertension remains unknown. Phages normally exist in a dormant state but can be induced into a lytic state by environmental stressors, causing bacterial death. Using metagenomic analyses, we compared the gut phageome of healthy mice to that of hypertensive mice. Several phage strains were highly abundant in hypertensive mice but absent in healthy mice, including a family of phages that target an important genus of commensal bacteria, *Faecalibacterium*. *Faecalibacterium* are major producers of beneficial short chain fatty acids, and their depletion is a feature of dysbiosis in many chronic diseases, including hypertension. Targeted elimination of culprit phages will thus promote recovery of a healthy microbiome, alleviating hypertension symptoms and end organ complications.

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Leveraging gut microbes as natural pharmacists to lower blood pressure

A/Prof Francine Marques

Symposium 9: The role of the gut microbiome in cardiometabolic disease, Eureka Room 1, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

Professor Francine Marques is a National Health and Medical Research Council Emerging Leader, Viertel Charitable Foundation, and National Heart Foundation Fellow. She leads the Hypertension Research Laboratory at Monash University. She has published more than 120 peer-reviewed papers in top journals such as Nature Reviews Cardiology, Nature Medicine, Nature Cardiovascular Research and Circulation, and has secured $10 million in competitive funding as a principal investigator. She won 28 awards including the 2019 American Heart Association Hypertension Council Goldblatt Award, 2020 High Blood Pressure Research Council of Australia and 2021 International Society of Hypertension Mid-Career Awards, and the 2021 Australian Academy of Science Gottschalk Medal. She was a finalist for 11 awards, including the Eureka Prize Emerging Leader in Science. The purpose of her research team is to build exceptional scientists that help improve cardiovascular health, using translational approaches to lower blood pressure via the gut microbiome.

Leveraging gut microbes as natural pharmacists to lower blood pressure

Francine Z. Marques[1]
[1]Hypertension Research Laboratory, School of Biological Sciences, Faculty of Science, Monash University, Melbourne, Australia

Introduction. Cardiovascular disease and stroke account for 25% of all deaths in Australia. A key risk factor for these diseases is high blood pressure. Diet is an essential player in preventing these diseases – for example, diets high in salt are associated with higher blood pressure, while diets high in fibre are associated with lower blood pressure. Besides decades of clinical and epidemiological evidence, the mechanisms driving the association between dietary fibre and lower cardiovascular disease and stroke rates remained unclear.

Aims. We aim to identify the mechanisms behind this association to develop and implement new therapies to lower blood pressure and, thus, cardiovascular disease and stroke.

Discussion. Our research has pioneered the concept that dietary fibre protects against these diseases by manipulating the gut microbiota. We identified gut microbiota-derived metabolites called short-chain fatty acids (SCFAs) involved in this protection. Here, we will present pre-clinical and clinical data on how we could manipulate the gut microbiota and levels of SCFAs to lower the prevalence of cardiovascular disease, stroke, and hypertension, discuss some of the mechanisms involved, and how we are targeting them to develop new treatments.

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Alterations in gut microbiota composition, plasma lipids, and brain activity, suggest inter-connected pathways influencing malnutrition-associated cognitive and neurodevelopmental changes

Prof Justin O'Sullivan

Symposium 9: The role of the gut microbiome in cardiometabolic disease, Eureka Room 1, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

*Justin M. O'Sullivan PhD is a Professor and Director of the Liggins Institute at the University of Auckland. He has honorary appointments at the Garvan Institute of Medical Research (Australia), University of Southampton (UK) and A*STAR Singapore Institute for Clinical Sciences. Justin's research group is currently focused on establishing rapid genome sequencing for clinical care, understanding how disease associated mutations in non-coding DNA affect gene regulatory networks and the pathways that underlie disease development, the role of the microbiome in brain and behaviour development, and the role of microbiome restoration in clinical care.*

Alterations in gut microbiota composition, plasma lipids, and brain activity, suggest inter-connected pathways influencing malnutrition-associated cognitive and neurodevelopmental changes.

Portlock, T.[1] *et al.* O'Sullivan, J.M.[1] on behalf of the M4EFaD consortium.
[1]The Liggins Institute, The University of Auckland, New Zealand.

Introduction. Malnutrition affects over 30 million children annually and has profound immediate and enduring repercussions, with nearly half of child deaths under five linked to malnutrition. Survivors face lasting consequences, including impaired neurocognitive development, leading to cognitive and behavioural deficits, impacting academic performance and socioeconomic outcomes.
Aims. The objective of this study was to identify gut microbiome mediated associations between Moderate Acute Malnutrition (MAM) and cognitive development.
Methods. The study was performed as part of the M4EFaD intervention, a community based clinical trial within the Mirpur slum, Dhaka, Bangladesh[1,2]. Random Forest and network analyses were used to identify non-overlapping connections between the gut microbiome, plasma lipids, electroencephalogram power spectral density data, and behavioural outcomes from children with MAM and well-nourished controls.
Discussion. Integrative multi-omics analysis highlights inter-connected pathways between features of gut microbiome, microbial metabolism, plasma lipids and either brain activity (EEG PSD) or cognitive function. These pathways provide testable hypotheses to optimise MAM associated behavioural and brain development changes. Causality between gut microbiome, plasma metabolite changes, and MAM phenotype remains unclear, necessitating further research.

[1] Shama T et al. (2024) Multidimensional evaluation of the early emergence of executive function and development in Bangladeshi children using nutritional and psychosocial intervention: A randomized controlled trial protocol. PLoS ONE 19(3): e0296529. https://doi.org/10.1371/journal.pone.0296529
[2]Theo Portlock, Talat Sharma et al. Alterations in gut microbiota composition, plasma lipids, and brain activity, suggest inter-connected pathways influencing malnutrition-associated cognitive and neurodevelopmental changes., 04 April 2024, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-4115616/v1]

ASCEPT, APFP & APSA Joint Congress
1–4 Dec 2024
Melbourne Convention & Exhibition Centre, Australia

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Gut microbiota metabolite trimethylamine N-oxide impairs β-cell function and glucose tolerance

Prof Pingping Li

Symposium 9: The role of the gut microbiome in cardiometabolic disease, Eureka Room 1, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

Pingping Li got her Ph.D. degree in pharmacology at Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College (CAMS & PUMC) in 2006. Then she moved to University of California San Diego for her postdoc, assistant project scientist, and assistant adjunct professor. Dr. Li set up a new lab and built a research team as an independent PI at CAMS & PUMC in 2015. She has been dedicated to studying the pathogenesis of type 2 diabetes for more than 15 years and made several findings regarding to the critical role of immune cells and the identification of therapeutic targets in inflammation, insulin resistance, and diabetes. In total, she has published more than 70 papers and filed 20 patents. As first or corresponding author, Dr. Li's papers have been published in several journals including Cell (3 papers), Nature Medicine, Nature Metabolism, Cell Metabolism, Nature Communications, and Hepatology. The purpose of her research team is to build exceptional scientists that help to improve human health, using in vitro and in vivo approaches to uncover new molecular mechanisms, new drug target, and their therapeutic applications for insulin resistance and associated metabolic disorders, including obesity, type 2 diabetes, and fatty liver disease. She was awarded Distinguished Professor of Peking Union Medical College (2015), 1000 Talent Youth in China (2016), Outstanding Youth of the National Natural Science Foundation of China (2016), and QiuShi Outstanding young scientist award (2017).

Gut microbiota metabolite trimethylamine N-oxide impairs β-cell function and glucose tolerance

Lijuan Kong[1,2,3,#], Qijin Zhao[1,2,3,#], Xiaojing Jiang[1,2,3,#], Jinping Hu[1], Qian Jiang[1,2,3], Li Sheng[1], Xiaohong Peng[4,5], Shusen Wang[6], Yibing Chen[1,2,3], Yanjun Wan[1,2,3], Shaocong Hou[1,2,3], Xingfeng Liu[1,2,3], Chunxiao Ma[1,2,3], Yan Li[1], Li Quan[5], Liangyi Chen[4,5], Bing Cui[1,3], Pingping Li[1,2,3]✉.

State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College[1], Beijing, China. Diabetes Research Center of Chinese Academy of Medical Sciences[2], Beijing, China. CAMS Key Laboratory of Molecular Mechanism and Target Discovery of Metabolic Disorder and Tumorigenesis[3], Beijing, China. College of Future Technology, Institute of Molecular Medicine, National Biomedical Imaging Center, Peking University[4], Beijing, China. Beijing Key Laboratory of Cardiometabolic Molecular Medicine, Peking University[5], Beijing, China. Tianjin First Central Hospital[6], Tianjin, China.

Introduction. Type 2 diabetes (T2D) is a global health problem. Decreased β-cell function, manifested as decreased glucose-stimulated insulin secretion (GSIS), and β-cell mass is the predominant factors for progression to T2D.

Aims. Diabetes is associated with higher trimethylamine N-oxide (TMAO) plasma levels in mice and humans. This study is to investigate whether TMAO at a pathological dose directly impairs β-cell function in vivo.

Methods. For gain-of-function studies, we used choline diet feeding to increase TMAO levels in C57BL/6J mice. For loss-of-function studies, genetic knockdown of Fmo3, the TMAO producing enzyme, was performed in C57BL/6J choline diet-fed mice and antisense oligomers of Fmo3 was injected in diabetic db/db mice.

Results. TMAO at a similar concentration to that found in diabetes could directly decrease GSIS in MIN6 cells and primary islets from mice or humans. Elevation of TMAO levels impairs GSIS, β-cell proportion, and glucose tolerance in male C57BL/6J mice. TMAO inhibited calcium transients through NLRP3 inflammasome-related cytokines and induced Serca2 loss, and a Serca2 agonist reversed the effect of TMAO on β-cell function in vitro and in vivo.. Additionally, long-term TMAO exposure promotes β-cell ER stress, dedifferentiation, and apoptosis and inhibits β-cell transcriptional identity. Inhibition of TMAO production improves β-cell GSIS, β-cell proportion, and glucose tolerance in both male db/db and choline diet-fed mice.

Discussion. These observations identify a role for TMAO in β-cell dysfunction and maintenance, and inhibition of TMAO could be an approach for the treatment of T2D.

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Using real-world data: Can CYP2C19 genotype predict an individuals' response to voriconazole?

Dr Sophie Stocker

Symposium 10: Interindividual variability in disposition and response to infectious disease therapy, Eureka Room 2, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

Dr Stocker, a Senior Lecturer at the School of Pharmacy, Sydney University, also holds an Honorary Senior Hospital Scientist appointment in the Department of Clinical Pharmacology and Toxicology at St Vincent's Hospital, Sydney, Australia. Dr Stocker received her PhD from the University of Sydney and performed postdoctoral studies at the University of New South Wales and the University of California San Francisco. Dr Stocker joined the Ethnopharmacology group at GlaxoSmithKline in 2012 and then the Department of Clinical Pharmacology and Toxicology at St Vincent's Hospital, Sydney in 2015. In 2020, Dr Stocker joined the School of Pharmacy at the University of Sydney.

Dr Stocker's research focuses on understanding variability in response to medicines and how this can be managed to optimise patient care. Her research program involves the application of clinical pharmacology, ethnopharmacology, pharmacogenomics, pharmacometrics, implementation science, health service delivery and qualitative research to optimise medicine use in several therapeutic areas including anti-infectives, gout, diabetes and transplant medicine. She is internationally recognised for implementation of precision dosing software and other precision medicine approaches.

Dr Stocker has co-authored more than 120 papers and holds several committee positions in national and international societies. She has gained recognition of leadership internationally (Victor Armstrong Young Investigator Award, 2022), and nationally (CERTARA Young Investigator and the APSA Emerging Leader Award, 2020).

Using real-world data: Can CYP2C19 genotype predict an individuals' response to voriconazole?

Eman Wehbe[1], Leping Kong[1], Thulashigan Sreeharan[2], Gaurav Sutrave[3], Debbie Marriott[2,4], Jan-Willem Alffenaar[1], Christine Lu[1], Sophie Stocker[1] on behalf of the researcher group. Sch of Pharm, FMH, Univ of Sydney[1], Sydney, NSW; St Vincent's Clin Sch, Facul of Med, Univ of NSW[2], Sydney, NSW; Westmead Instit for Med Research, Univ of Sydney[3], Sydney, NSW; Dept of Clin Microbiol & Infect Dis, St Vincent's Hosp[4], Sydney, NSW.

Introduction. Up to 40% of patients who receive the antifungal drug voriconazole are exposed to suboptimal drug concentrations and 30% prematurely discontinue therapy due to adverse effects. This variability in pharmacokinetics is, in part, influenced by genetic variation in CYP2C19.

Aims. To investigate whether CYP2C19 genotype can predict suboptimal exposure or drug-related adverse effects to voriconazole, necessitating a switch to alternative antifungal therapy.

Methods. Data on voriconazole administration (dosing history, plasma drug concentrations), drug-related adverse effects, and alternative antifungal use were obtained from electronic medical records of patients administered voriconazole (1 May 2019 – 31 May 2024) at Westmead Hospital, St Vincent's Hospital, and Royal North Shore Hospital, Sydney. Buccal swabs were collected to determine CYP2C19 genotype. Voriconazole trough concentrations (Cmin) were predicted (InsightRx Nova Inc.). Data analysis was conducted using GraphPad Prism 9.5.1.

Results. Of the 186 patients, most were male (56%), on average (SD) 55 (16) years old and received voriconazole for prophylaxis. Most patients were CYP2C19 intermediate (35%, 66/186) or normal (33%, 62/186) metabolisers followed by rapid (21%, 39/186), ultrarapid (8%, 15/186) and poor metabolisers (2%, 4/186). Despite receiving the same daily dose (400 mg/day), CYP2C19 ultrarapid metabolisers had lower Cmin (0.4 [0.2-0.7] mg/L) compared with normal (1.6 [0.1-5.0] mg/L) and intermediate (1.5 [0.1-4.2] mg/L) metabolisers ($p<0.01$ and $p<0.01$, respectively). Overall, 42% (79/186) were switched from voriconazole to an alternative antifungal. The occurrence of drug-related adverse events was associated with a 3-fold (OR 3.46, 95%CI 1.77-7.01) increased odds of switching. Switching to alternative antifungal therapy and the incidence of drug-related adverse effects were not associated with CYP2C19 genotype.
Discussion. Switching from voriconazole to alternative antifungal therapy due to drug-related adverse effects is common. In this cohort, CYP2C19 genotype was associated with voriconazole exposure but not the incidence of drug-related adverse effects most likely due to very low presence of CYP2C19 poor metabolisers.

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Factors which influence pharmacokinetic variability that affect target attainment in patients with drug-resistant bacterial infections in South East Asia

A/Prof Cornelia Landersdorfer

Symposium 10: Interindividual variability in disposition and response to infectious disease therapy, Eureka Room 2, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

Cornelia Landersdorfer, PhD, is an Associate Professor at the Monash Institute of Pharmaceutical Sciences, Monash University in Melbourne. She trained in clinical PK studies, bioanalysis, PK/PD modelling and microbiological studies in Germany, Australia and the USA. She leads a research group that integrates dynamic in vitro infection experiments with mechanism-based mathematical modelling to optimise dosing of antibiotics and other drugs. Her group performs the design and analysis of clinical and preclinical population PK studies. She is the Academic Deputy Director of the Monash-Moderna Quantitative Pharmacology Accelerator (MMQPA) which is focused on driving advancements in mRNA medicines. She has >140 peer-reviewed publications, and received the Georgina Sweet Award for Women in Quantitative Biomedical Sciences (2018), the Future Leader Award (2016) and Research Impact Award (2020) in the Faculty of Pharmacy and Pharmaceutical Sciences (#2 worldwide, QS world ranking), a 2022 Australian Award for University Teaching, and the 2023 Monash Graduate Supervisor of the Year award. Invited conference presentations include the European Congress of Clinical Microbiology and Infectious Diseases and American Society of Microbiology Microbe congress. Her research is supported by NHMRC, ARC, NIH and pharmaceutical industry, and has impacted on dosing guidelines and patient therapy internationally.

Factors which influence pharmacokinetic variability that affect target attainment in patients with drug-resistant bacterial infections in South East Asia

Cornelia B Landersdorfer[1], Roger L. Nation[1]. Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus)[1], Melbourne, VIC, Australia.

Traditionally, an empirical ‘one-size-fits-all’ approach has been applied to antibiotic dosing. This approach may lead to suboptimal antibiotic exposures, risking treatment failure, emergence of resistance and/or toxicity, particularly for compounds with a narrow therapeutic window. Polymyxin antibiotics including colistin are last-line agents which are commonly used in South East Asia to treat infections caused by drug-resistant bacteria and have a narrow therapeutic window.

We aimed to generate an increased understanding of sources of interindividual variability that affect antibiotic exposures and thereby target attainment, with a focus on polymyxins.

Mathematical models that characterise the population pharmacokinetics and interpatient variability of antibiotics in patient groups from South East Asia were developed and evaluated. These included patient groups at high risk of mortality from an infection, such as paediatric patients, the critically ill, and those requiring kidney support. These patient groups often display different pharmacokinetics compared with the general patient population. The models evaluated the impact of patient covariates on the antibiotic exposure profiles achieved with a given dosing regimen.

Subsequently they were used in simulations to inform the selection of dosing regimens which maximise target attainment and the probability of successful treatment outcome.

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Understanding how drug-pathogen interactions influence variability in drug response

Dr Kashyap Patel

Symposium 10: Interindividual variability in disposition and response to infectious disease therapy, Eureka Room 2, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

Kashyap Patel (PhD) is employed by GSK, Australia, where he contributes to model-informed drug development in the department of Clinical Pharmacology Modelling and Simulation. He has over 14 years of experience in pharmacometrics, both in academia and in industry. Kashyap graduated from The University of Auckland in 2009, and has had previous appointments at Monash University, and as a CRO. He has routinely provided quantitative rationale and regulatory support for small molecules and biologics across a range of therapeutic areas, including oncology and infectious diseases. Additionally, he has frequently developed models using adult data with extrapolation to inform paediatric dosing.

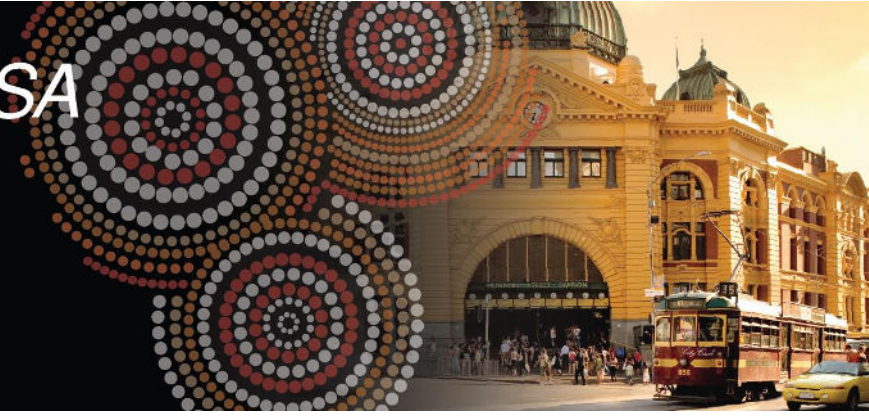
Understanding how drug-pathogen interactions influence variability in drug response

Kashyap Patel[1], Frances Stringer[1]. Clinical Pharmacology Modelling and Simulation, GSK[1], Australia.

Optimal treatment of pathogenic infections requires an understanding of the interplay between drug exposure, time-course of infectious agent, and pharmacological response. Each of these components can be integrated into semi-mechanistic population pharmacokinetic-pharmacodynamic (PK-PD) models that quantify the relationships between drug exposure and response, and further characterize the influence of between-subject variability. These models can also provide an understanding of patient-specific factors that contribute to differences in PK-PD, thereby facilitating individualized dosing recommendations that optimize therapeutic benefit.

This session will discuss respiratory viral infections and the utility of semi-mechanistic PK-PD models that support drug development and regulatory decisions. Initially, models that characterize the time-course of the virus life-cycle will be presented using representative examples for influenza [1], respiratory syncytial virus (RSV) [2] and COVID-19 [3]. This aspect will additionally demonstrate the substantial variability in viral kinetics (VK) due to inter-individual differences and measurement of virus titer. The antiviral effect is then quantified by integrating VK models with a population PK model to describe the relationships between dose, drug concentration, and viral load decline. Other pharmacological components such as biomarker kinetics and clinical symptom scores may be further incorporated, where available.

Once developed, these integrated VK-PK-PD models can then be applied to the prediction and variability of antiviral drug response across a range of dosing regimens of interest. Simulations from the model can identify the dose, time of treatment initiation, and



duration of treatment that could maximize therapeutic response. Furthermore, these models can be applied to the extrapolation of PK and pharmacological effect in vulnerable populations, including pediatric and elderly populations.

Lovern et al (2017) Curr Pharm Rep 3: 294-300
Patel et al (2017) J Antimicrob Chemother 74: 442-452
Patel et al (2021) Br J Clin Pharmacol 87: 3425-3438

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NAT2 and isoniazid: evidence and road map for implementation

Prof Jan-Willem Alffenaar

Symposium 10: Interindividual variability in disposition and response to infectious disease therapy, Eureka Room 2, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

Prof Alffenaar is a hospital pharmacist and clinical pharmacologist at the School of Pharmacy, Faculty of Medicine and Health at the University of Sydney. He is member of the leadership team of the University of Sydney Infectious Diseases Institute. He is an internationally recognized expert in PKPD with a special interest in anti-TB agents and current President of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology. He is a member of the WHO's Technical Advisory Group on TB drug dosing. Prof Alffenaar led systematic reviews for WHO on the PKPD of second line TB drugs which informed the WHO TB treatment policy review meeting in 2018 and later in 2022. He has significant experience in dose optimization strategies of TB drugs in adults as well as children.

NAT2 and isoniazid: evidence and road map for implementation

Jan-Willem Alffenaar[1,2,3]. [1]School of Pharmacy, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia. [2]Westmead Hospital, Sydney, NSW, Australia. [3]Sydney Institute of Infectious Diseases, University of Sydney, Sydney, NSW, Australia.

Introduction.
Tuberculosis (TB) is the leading infectious cause of death globally. Failure to effectively end the global TB pandemic resulted in 10.6 million people developing TB and 1.3 million TB-related deaths in 2022. Treatment failure and exposure associated side effects are related to the large individual variability in pharmacokinetics. N-acetyltransferase type 2 (NAT2) is a polymorphic enzyme involved in metabolism of the first-line TB drug isoniazid resulting in slow, intermediate or rapid metabolism.
Aims. to understand the clinical impact of NAT2 polymorphisms and develop a road map for implementation of pharmacogenomic guided dosing.
Methods. Effects of slow and fast acetylators on side effects and treatment failure are investigated and hurdles for implementation are explored.
Results. Clinical evidence to support implementation of N-acetyltransferase type 2 testing to guide dosing of isoniazid is presented and practical solutions to overcome implementation hurdles are proposed.
Discussion. High level evidence of the impact of pharmacogenomic guided dosing of isoniazid on efficacy, safety, tolerability as well as cost-effectiveness are needed to change TB treatment guidelines.

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Gen AI and pedagogy- approaches, perspectives and strategies

Prof Danny Liu and Prof Tim Fawns

Symposium 11: AI in Education: Innovations and Applications, Eureka Room 3, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

Danny is a molecular biologist by training, programmer by night, researcher and academic developer by day, and educator at heart. A multiple international and national teaching award winner, he works at the confluence of artificial intelligence, learning analytics, student engagement, educational technology, and professional development and leadership. He is a Professor of Educational Technologies in the DVC Education Portfolio at the University of Sydney, co-chairs the University's AI in Education working group, and leads the Cogniti.ai initiative that puts educators in the driver's seat of AI.

Tim Fawns is Associate Professor (Education Focused) at the Monash Education Academy. Tim's research interests are at the intersection of digital, professional (particularly medical and healthcare) and higher education, with a focus on relations between technology and education. Tim's research covers a broad range of practices (including curriculum design, assessment, teaching practice, evaluation and more), emphasising complexity within online, blended and hybrid education. He has recently contributed to TEQSA's Assessment reform for the age of artificial intelligence guidance document and played a leading role in a range of sector-wide events to help institutions respond to the opportunities and challenges of artificial intelligence.

Gen AI and pedagogy- approaches, perspectives and strategies

Tim Fawns[1], Danny Liu[2]. Monash Education Academy, Monash University[1], Melbourne, VIC, Australia; Educational Innovation, University of Sydney[2], Sydney, NSW, Australia.

In this session, Tim and Danny will engage in a conversation about how higher education can move forward in negotiating the possibilities and risks of Generative Artificial Intelligence technologies. They will discuss institutional responses, student perspectives, approaches to assessment and the need for holistic responses to curriculum reform.

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Strategies for designing assessment using and because of Gen AI

Angelina Lim and Thao Vu

Symposium 11: AI in Education: Innovations and Applications, Eureka Room 3, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

Dr. Thao Vu is the Senior Educational Designer, a member of the Faculty Education Executive, and Chair of the Faculty Assessment Sub-Committee in the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University. She is also an active member of Monash's inaugural Learning Circle on Artificial Intelligence in Education, which aims to provide guidance and examples for Monash educators on integrating AI into education. Thao has been invited to design and lead interactive sessions on Assessment Design and AI for faculty educators and hundreds of Chief Examiners at Monash. She has developed and executed a range of innovative and collaborative educational design initiatives that have resulted in award-winning outcomes in learning, teaching and assessment quality, student experience, and student retention. As an education researcher, Thao is currently leading projects focused on assessments, digital learning including GenAI in education, and health professions education.

Dr. Angelina Lim is a senior lecturer at Faculty of Pharmacy and Pharmaceutical Sciences, Monash University. Her key interests are simulation, authentic assessment, generative artificial intelligence, antimicrobial stewardship and paediatric endocrinology. Angelina's main expertise lies in designing and evaluating Objective Structured Clinical Examinations. Angelina has embarked on many pharmacy related career paths, starting with hospital pharmacy, then community pharmacy (still practicing), public health sector and research. She still maintains links with the Murdoch Children's Research Institute (MCRI) working on projects in disability and paediatric endocrinology. Angelina is dedicated to teaching and education research and aims to use evidence based pedagogical approaches to drive her teaching and curriculum design.

Strategies to (re)design assessments in the era of Artificial Intelligence (AI)

Angelina Lim[1], Thao Vu[1], Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia

Introduction. In the context of a rapidly evolving educational landscape influenced by artificial intelligence (AI), designing assessment methods that provide trustworthy evidence of student learning and equip students with the knowledge and skills to be prepared for a future where AI is ubiquitous is essential. This presentation explores strategies to design assessments in pharmacy education, addressing both task-level and unit-level assessments.

Aims. The primary aim of the presentation is to share strategies and examples for redesigning assessments at both the task and unit levels to ensure valid student learning outcomes and significant educational impacts in a pharmacy course.

Methods. The presentation will consist of two main sections: the first covering the redesign of assessments at the task level, including strategies for both graded and non-graded assessments; and the second focusing on a holistic approach to assessment planning at the unit and course levels. Both sections will present evidence from the literature and educational design practices, as well as examples from our own context.

Results. By the end of the presentation, participants will gain insights into effective strategies and examples for designing assessments that ensure trustworthy evidence of student performance and support students' learning. They will also understand the significance of integrating AI literacy and evaluative judgment into the curriculum and see practical applications of these strategies within the context of pharmacy education.

Discussion. We will discuss the implementation of these strategies in terms of what is working, what is not working, impacts and solutions moving forward in our context.

Vu, T., Swiecki, Z. & Seligmann, A. (2024). Positioning Artificial Intelligence (AI) in assessments may seem hard but here are some ways to start the journey. Monash Teaching Community. https://teaching-community.monash.edu/ai_assessment/

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Towards an efficient future: The integration of artificial intelligence in education

Pranav Runwal

Symposium 11: AI in Education: Innovations and Applications, Eureka Room 3, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

I am an interdisciplinary PhD candidate at Monash University, collaborating with the Walter and Eliza Hall Institute of Medical Research and The Brain Cancer Centre. My research focuses on bioengineering nanobodies to cross the blood-brain barrier, aiming to improve therapeutic outcomes for brain cancer patients. I also serve as a lead teaching associate at the Monash Faculty of Pharmacy and Pharmaceutical Sciences. I have been involved in promoting the use of AI in education, facilitating workshops across six diverse Monash faculties, two national universities, and at national and international conferences. Additionally, I have designed AI-enhanced assignments, now implemented for final-year formulation science students at Monash University, further integrating innovative learning methodologies into the curriculum.

Towards an efficient future : The integration of artificial intelligence in education

Pranav Runwal. Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, VIC, Australia

Introduction. Artificial intelligence (AI) has emerged as a powerful tool in the field of education, revolutionising how we approach both teaching and educational administration. The integration of AI technologies offers unprecedented opportunities for personalised learning, enhanced student engagement, and more efficient management of educational processes. My talk delves into the transformative application of generative AI across diverse academic disciplines, showcasing significant advancements in pedagogy and administrative efficiency.

Aims. To showcase the potential of AI in curating educational material and design of alternative assignments that promote critical thinking and problem solving

Methods. Tools such as Chat-GPT (4o), Perplexity AI, Invideo.io, Heygen.io and Bland.ai were synergistically used to create learning outcomes, learning material, short-style assignments, extended assignments, creation of dynamic hypothetical datasets, creation of AI assisted educational videos and creation of AI agents to facilitate simulations for Observed structured clinical examination (OSCEs)

Results. This presentation will share insights from over 15 specific AI applications and detail different AI tools that have revolutionized the creation of educational content and examination materials, as well as innovative approaches to student interaction.

Discussion. This work underlines generative AI's role in fostering dynamic, efficient, and engaging educational environments, illustrating its significant promise for advancing educational methodologies.

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Animating basic sciences: AI Crafted Clinical Cases for Deep Learning Engagement

Prof Priyia Pusparaiah

Symposium 11: AI in Education: Innovations and Applications, Eureka Room 3, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

Associate Professor Priyia Pusparajah is an accomplished academic with a rich background in both clinical and biomedical sciences. As a paediatrician, medical educator, and researcher, she brings a comprehensive perspective to medical education. Currently serving as the Co-Director of PreClinical Medicine at Monash University, Priyia is dedicated to enhancing the medical curriculum by integrating basic and clinical sciences. Her innovative approach focuses on creating authentic and engaging learning experiences through a variety of active learning modalities.

In recognition of her contributions, Priyia was awarded the Malaysian Society of Pharmacology and Physiology's Young Teachers Award for Physiology in 2016. She also received a Commendation in the Monash Malaysia Pro-Vice Chancellor Awards for Education Excellence: Innovations in Teaching and Learning in 2019. She endeavours to inspire and shape the future of medical education.

Animating basic sciences: AI Crafted Clinical Cases for Deep Learning Engagement

Priyia Pusparajah. School of Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, VIC, Australia

Introduction: Incorporating clinical cases in teaching materials for biomedical science courses has been shown to enhance student engagement and improve content retention.

Discussion: While evidence supports the use of clinical cases, creating them presents challenges. Many academics who teach biomedical science have limited clinical experience, making it daunting to develop authentic cases relevant to the course content. Clinicians also face a range of challenges in crafting or curating cases suitable for different academic levels and disciplines. Limited time for creating teaching materials makes this task even more challenging. Generative AI offers a practical solution, providing a time-efficient way to generate a diverse range of cases across various topics and pathological conditions. These AI-generated cases benefit from review by clinical content experts to ensure accuracy and authenticity. Having a baseline AI generated case significantly saves time and facilitates collaboration between basic scientists and clinicians.

Conclusion: Generative AI can efficiently produce clinical cases suited for teaching across various subjects, facilitating the process of case creation to enhance student learning in biomedical science courses. This may also enhance interdisciplinary collaboration between academics from the clinical and biomedical sciences.

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A comparison of nanoparticle gene therapy to drug therapy with small molecule CFTR modulators in the treatment of cystic fibrosis

Dr Shafagh Waters

Symposium 12: Novel inhalable gene and drug delivery strategies to combat respiratory diseases, Courtyard Room 1&2, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

Dr. Shafagh Waters (BSc, MSc (Disc.), PhD) is a Scientia Senior Lecturer at the University of New South Wales (UNSW) and an Honorary Senior Scientist at Sydney Children's Hospital. She completed her PhD at the Australian National University (ANU), followed by postdoctoral fellowships at UNSW from 2013 to 2016. During this time, she received prestigious international fellowships for gene therapy research at City of Hope in the USA and training in organoid medicine in Lisbon, Portugal. She established her independent research lab in 2016.

Dr. Waters leads an NHMRC-funded research program focused on adult stem cell biology for cystic fibrosis (CF), supported by 32 grants, 21 of which she serves as Chief Investigator (CIA), including partnerships with national and international industry collaborators. Her work has led to the development of an Australian national biobank for stem-cell-derived airway and gut organoids, a high-throughput platform for testing therapeutic interventions on patient-derived organoids, and the implementation of organoid-guided clinical trials for cystic fibrosis. In these trials, patient-derived organoids are used to identify the most effective treatments, directly guiding personalized therapy for CF patients.

A founding member of the NSW Non-Animal Technologies Network, Dr. Waters combines her expertise in organoid disease modeling with advanced work in creating complex organoids that incorporate vascularization and immune cells. Her research also includes developing co-culture systems to study interactions between airway organoids and pathogens. During the COVID-19 pandemic, this approach was adapted to explore the innate immune response to SARS-CoV-2, providing crucial insights into host-pathogen interactions.

In recognition of her contributions to science and public engagement, Dr. Waters was awarded the NSW Young Tall Poppy Science Award in 2022, acknowledging her outstanding research achievements and commitment to science communication.

Lentiviral gene therapy and stem cell transplantation in cystic fibrosis: A comparative analysis with CFTR modulator therapy

Shafagh A Waters
School of Biomedical Sciences, UNSW Sydney, Sydney, NSW, Australia.

Introduction. Cystic fibrosis (CF) is caused by pathogenic variants in the CFTR gene, leading to impaired CFTR protein function. CFTR modulators such as elexacaftor/tezacaftor/ivacaftor (ETI) improve outcomes for many patients but are ineffective for some. Lentiviral (LV) gene therapy offers a promising alternative by delivering functional CFTR to airway basal cells. Additionally, stem cell transplantation into the sinus represents a potential approach to restore CFTR function in a common site of CF-related morbidity.

Aims. This study compares CFTR function in organoids derived from CFTR gene-corrected stem cells and uncorrected stem cells treated with CFTR modulators. It also investigates the transplantation of eGFP-transduced stem cells into the sinus of a rabbit model as proof of principle for cell engraftment and differentiation.

Methods. Primary airway basal cells from CF patients were transduced with a lentiviral vector carrying the wild-type CFTR gene. Organoids derived from these gene-corrected cells were compared to those from uncorrected cells treated with CFTR modulators for CFTR channel function, cilia beat frequency, and epithelial integrity. In a separate experiment, eGFP-transduced

stem cells were transplanted into the rabbit sinus using a matrix bioscaffold to assess engraftment and differentiation. Mucociliary function was evaluated using in vivo micro-optical coherence tomography (μOCT).
Results. Organoids derived from gene-corrected cells showed improved CFTR function, with an additive effect observed when combined with ETI treatment. Transplanted eGFP-transduced cells in the rabbit model successfully engrafted, differentiated into functional epithelium, and improved mucociliary transport compared to control grafts without stem cells.
Discussion. This study highlights the potential of LV gene therapy to restore CFTR function in organoid models and demonstrates the feasibility of stem cell transplantation in the sinus. While gene-corrected cells were not transplanted, eGFP-transduced cells provided proof of concept for the successful engraftment and differentiation of airway basal cells. Further studies are needed to explore clinical applications in CF patients.

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Impact of airway surface perturbations and infection on the efficacy of inhaled gene therapy

Dr Alexandra McCarron

Symposium 12: Novel inhalable gene and drug delivery strategies to combat respiratory diseases, Courtyard Room 1&2, December 4, 2024, 10:30 AM - 12:30 PM

Biography:
Dr Alexandra McCarron is a research fellow in the Cystic Fibrosis Airway Research Group at the University of Adelaide. She is passionate about transforming the lives of those with cystic fibrosis and improving their quality of life and longevity. Dr McCarron's research is focussed on advancing lung-targeted genetic therapies for cystic fibrosis. She is currently developing novel ways to enhance the delivery of these therapies, aiming to improve their overall effectiveness.

Challenges and progress in developing lung-directed genetic therapies for cystic fibrosis

Alexandra McCarron[1, 2, 3]
1. Adelaide Medical School, The University of Adelaide, South Australia, Australia.
2. Robinson Research Institute, The University of Adelaide, South Australia, Australia.
3. Department of Respiratory and Sleep Medicine, Women's and Children's Hospital, South Australia, Australia.

Cystic fibrosis (CF) is a genetic disease that affects the lungs and is characterised by frequent infections, airway mucus obstruction and progressive lung function decline. Genetic-based therapies aim to restore the defective CF gene in airway cells, thus preserving lung health. One promising approach under development for airway gene therapy employs use of a lentiviral vector gene delivery system. While significant progress has been made in the field, the lungs pose unique challenges when delivering genetic therapies. Naturally-occuring airway barriers significantly impede uptake and subsequent efficacy of these therapies. A critical area of research focuses on overcoming these barriers to enhance the efficacy of lung-directed genetic therapies.
Three studies were performed to assess or improve the effectiveness of gene therapy in rat airways. (1) Physical perturbation of the airways was performed prior to gene therapy delivery. This was found to provide significant increase in gene uptake by up to 1000-fold. (2) CF lungs are frequently infected with biofilm-producing bacteria and contain mucus that can impede the uptake of some gene delivery vehicles. Rats infected with bacteria were found to have comparable gene expression levels to uninfected rats, suggesting lentiviral vectors are not inhibited by CF lung conditions. (3) Neonatal life stage of gene therapy delivery was investigated to assess the benefits of early intervention in CF rats. Electrophysiological assessments revealed sustained therapeutic correction for up to 12 months.
This work highlights three key areas of research in assessing and improving the efficacy of lung-directed gene therapies for CF. Continued progress will be essential to advance this approach toward first-in-human clinical trials.

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Inhalable bacteriophage therapy to treat respiratory diseases

Prof Hak-Kim Chan

Symposium 12: Novel inhalable gene and drug delivery strategies to combat respiratory diseases, Courtyard Room 1&2, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

Hak-Kim Chan, Professor in Pharmaceutics, is leading the Advanced Drug Delivery Group at the Sydney Pharmacy School, University of Sydney. Kim is a world leader in respiratory drug delivery, with a research program ranging from powder production by novel processes, particle engineering and aerosol formulation, to scintigraphic imaging of lung deposition and clinical outcome. He is a Fellow of American Association of Pharmaceutical Scientists, was Vice President of Asian Federation for Pharmaceutical Science, Executive Editor of Advanced Drug Delivery Reviews, and recipient of the 2023 Career Achievement Award of The International Society for Aerosols in Medicine.

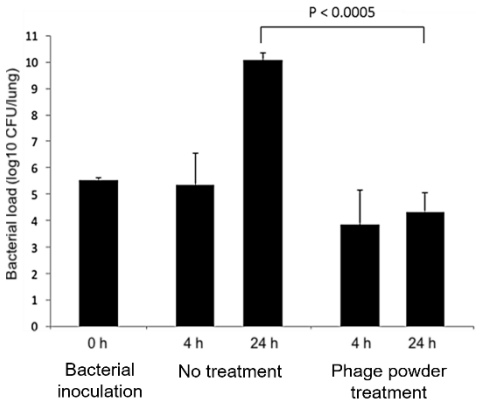
Inhalable bacteriophage therapy to treat respiratory diseases

Hak Kim Chan. Sydney Pharmacy School, University of Sydney, Sydney, NSW, Australia

Introduction. Antibiotic resistance is one of the greatest threats to human health globally. *Pseudomonas aeruginosa* was identified as one of the three highest priority pathogens requiring urgent attention for new, effective antibiotics. *P. aeruginosa* causes difficult-to-treat lung infections, particularly in immunocompromised and cystic fibrosis (CF) patients. Bacteriophages (phages) are being investigated world-wide as a potential treatment for multidrug-resistant (MDR) infections.

Aims. This talk will cover phage therapy *in vitro* and animal efficacy studies conducted by the presenter with his collaborators.

Methods. Pseudomonal phages were formulated for inhalation delivery, followed by efficacy studies in an acute mice lung infection model.



Results. Phages were prepared in stable aerosol dosage forms of liquid or powder, which showed phage amplification in the lungs along with significant bacterial killing when administered intra-tracheally.

Discussion. Bacteriophages are a new generation of biologics for combating MDR superbugs. It is safe and efficacious to deliver phage powders in a murine acute lung infection model with MDR *P. aeruginosa*. We can use various aerosol technology platforms and advanced formulation expertise to deliver stable, safe and efficacious phages. Synergy of phages with antibiotics is a huge advantage that can be further leveraged over antibiotics alone.

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Next Generation Carrier Particles for Therapeutics Delivery to the Lung: Challenges and Opportunities

Clive Prestidge

Symposium 12: Novel inhalable gene and drug delivery strategies to combat respiratory diseases, Courtyard Room 1&2, December 4, 2024, 10:30 AM - 12:30 PM

Biography:

Clive Prestidge is the University of South Australia's Professor of Pharmaceutical Science, leading the internationally recognised Nanostructure and Drug Delivery research group and co-Director for the Centre for Pharmaceutical Innovation. He has an extensive track record in nanomaterials for drug delivery and the development of nano-biomaterials for outcomes in Health and Medicine. He has supervised over 50 PhD and MSc students and authored around 300 international journal articles. He is an inventor of several technology platforms, and has been extensively involved in patenting, licencing, spin off companies and partnering with industry to advance commercialisation/clinical translation

Next Generation Carrier Particles for Therapeutics Delivery to the Lung: Challenges and Opportunities.

Clive Prestidge, Paul Joyce, Kara Paxton, Anthony Wignall, Santhni Subramaniam. Centre for Pharmaceutical Innovation, Clinical and Health Science, University of South Australia, Adelaide, South Australia, Australia

Introduction. Pulmonary medicines are highly desirable to directly treat diseases of the lung, e.g. infections, inflammation, and cancer, and are increasingly being approved for clinical use. However, effective delivery of therapeutic agents to the lung is challenging due to the complex lung physiology and the biological barriers to facilitate effective cellular targeting.

Aims. To develop nanocarriers and hybrid microparticles that can improve the delivery of both small molecule and biological drugs to the lung and catalyse the next generation of pulmonary medicines. Improve understanding of cellular targeting within the lung and the role of the lung corona in directing the biodistribution of such nanocarriers.

Methods. Particle engineering approaches have been used to synthesise novel lipid and polymer based nanocarriers that are applicable to lung delivery by either dry powder inhalation or nebulisation. In vitro and in vivo studies of relevance to lung delivery have been performed. The lung protein corona associated with pulmonary delivery nanocarriers has been characterised using mass spectroscopy.

Results. Case studies will be presented to demonstrate the importance of nanostructure, chemistry, and size in controlling lung uptake, biodistribution, safety and efficacy and how the biomolecule corona mediates pulmonary delivery of nanomedicine. E.g. liquid crystal lipid nanoparticles and polymer-lipid hybrid microparticles for antibiotic delivery to the lung - overcoming biofilm and intracellular infections.

Discussion. Smart nanocarrier design can facilitate effective lung delivery and facilitate clinical translation in pulmonary medicines.

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