PharmAlliance Graduate E-Symposium

23 and 24 May 2023: UNC 7 AM|UCL 12 PM | Monash 9 PM

Day 1 Recording | Day 2 Recording

Note – recordings have been edited to remove unpublished data upon presenter request

Day 1: 23 May 2023					
Moderator	**Time – AM (UNC)**	**Time – PM (UCL)**	**Time – PM (Monash)**	**Speaker**	**Topic**
OPEN	7:00	12:00	9:00	Michael Jarstfer	Welcome and intro
Moderator: Michael Jarstfer Evaluators: Orlagh Feeney, Karolina Dziemidowicz, Kathryn Morbitzer, Catherine Tuleu, Oscar Della Pasqua	7:05	12:05	9:05	Stephany Gonzalez Tineo (UNC)	Evaluating the potency of a first-in-class covalent antagonist of the H3K9me3 reader protein MPP8 in bladder cancer
	7:10	12:10	9:10	Jingyu Zhao (UNC)	Improvement of Pseudotyped Lentivirus for T cell Targeting in CAR-T Therapy.
	7:15	12:15	9:15	Huan Wang (UCL)	Emerging variants of SARS-CoV-2 NSP10 have negligible effects on its binding to two non-structural proteins, nsp14 and nsp16
	7:20	12:20	9:20	Nicole Rose Lukesh (UNC)	Fighting the War on Self: A Microparticle Therapeutic Vaccine for Type 1 Diabetes
	7:25	12:25	9:25	Ting Fu (Monash)	Lipoxin A4 supplementation alleviates cardiac fibrosis in diabetes-associated heart disease
	10 min break				
	7:40	12:40	9:40	Dina Abushanab (Monash)	Projecting the Health and Economic Burden of Cardiovascular Disease Among People with Type 2 Diabetes, 2022-2031
	7:45	12:45	9:45		Projected Impact of Cardiovascular Disease on Type 2 Diabetes in Qatar from a Societal Perspective. A 10-Year Modeling Analysis
	7:50	12:50	9:50	Miriam Leung (Monash)	Trajectories of oral bisphosphonate use after hip fractures in Australia
	7:55	12:55	9:55	Lexy Ehlert (UNC)	Drug Price Hiking and Company Wellbeing: How Price Hikes Impact Manufacturer Stock Price and Public Interest
	10 min Break				
	8:10	1:10	10:10	John Jackson (Monash)	Funding community pharmacy dispensing: A qualitative evaluation of an existing fee-for-

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					service model and assessment of a potential performance-based model, resulting in a proposed quality-focused funding framework.
	8:15	1:15	10:15	Nouf Alsalem (UCL)	Effectiveness of patient held medication records (PHMR) in medication management across the continuum of health care. Systematic review and narrative synthesis
	8:20	1:20	10:20	Nouf Alaboud (UCL)	End-users' awareness, satisfaction, and the usability of a paediatric sepsis screening tool to support clinical decisions within an electronic prescribing system at an academic hospital in England: A survey- based study.
CLOSE	8:25	1:25	10:25	Michael Jarstfer	Closing

Day 2: 24 May 2023					
Moderator	**Time – AM (UNC)**	**Time – PM (UCL)**	**Time – PM (Monash)**	**Speaker**	**Topic**
OPEN	7:00	12:00	9:00	Joe Nicolazzo	Welcome and intro
Moderator: Joe Nicolazzo Evaluators: Orlagh Feeney, Kathryn Morbitzer, Catherine Tuleu, Michelle Halls	7:05	12:05	9:05	Brigid McInerney (Monash)	Psychotropic adverse drug event monitoring tools for use in long-term care facilities: a systematic review
	7:10	12:10	9:10	Shin Liau (Monash)	Symptomatic and Preventive Medication Use in Community-Dwelling Older People with and without Alzheimer's Disease
	7:15	12:15	9:15	Dana Alsugeir (UCL)	Risk of Osteoporotic Fractures in Menopausal Women with Common Mental Health Problems Using SSRI/SNRI antidepressants: A Cohort Study
	7:20	12:20	9:20	Monica Jung (Monash)	Prescription opioid tapering trajectories among Australians with chronic non-cancer pain: a retrospective cohort study
	Break				
	7:35	12:35	9:35	Ashley Trojniak (UNC)	Development of Biased Kappa Opioid Receptor Biased Agonists
	7:40	12:40	9:40	Yunan Peng (UCL)	Wnt signalling function in different Parkinson's disease LRRK2 cell models
	7:45	12:45	9:45	Showmika Tabassum Supti (Monash)	The impact of iron on fatty acid trafficking across the blood-brain barrier

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	7:50	12:50	9:50	Kai Kikuchi (Monash)	Naphthalimides: A Novel Scaffold for Sensing the Micro-Environment of Amyloids
	Break				
	8:05	1:05	10:05	Huan Yee Koh (Monash)	Physicochemical graph neural network for learning protein-ligand interaction fingerprints from sequence data
	8:10	1:10	10:10	Ameya Chaudhari (UNC)	High-Throughput in vivo discovery of organotropism of surface modified exosomes
	8:15	1:15	10:15	Effrosyni Alexandrou (UCL)	Revealing the detail in i-motif DNA structures
	8:20	1:20	10:20	Narges Mahdavian (Monash)	Altered Neuromuscular Function in the Resected Bowel of Patients with Hirschsprung Disease
CLOSE	8:25	1:25	10:25	Joe Nicolazzo	Closing

Abstracts

Stephany Gonzalez Tineo

Background: Bladder cancer (BC) is a deadly disease, and despite treatment advances metastatic BC remains incurable. Mutations in genes that encode chromatin modifier proteins are common in BC. The epigenetic reader MPP8 recognizes histone-3-lysine-9-trimethyl (H3K9me3) marks in target gene promoters, and recruits transcription factors associated with metastasis. UNC7713 was developed as a covalent antagonist to disrupt MPP8 binding to H3K9me3. We explored whether UNC7713 inhibits cell proliferation, migration, and viability in preclinical BC models.

Methods: 5637 cells were treated with ascending concentrations of UNC7713 or negative controls (UNC7716 or 0.1% DMSO). Viability was measured using CellTiter-Glo and IC50 values were calculated by a four-parameter non-linear regression model. To evaluate apoptosis versus necrosis, cells were stained with Annexin V and propidium iodide, and flow cytometry was performed. Cells were treated, then fixed with 4% paraformaldehyde and stained with DAPI to determine if UNC7713 is associated with DNA damage. To evaluate proliferation, cells were treated with UNC7713 and colonies were assessed with crystal violet. To evaluate migration, cells were treated with UNC7713, subjected to a wound healing assay, and images captured by an Olympus IX83 after 48 h.

Results: UNC7713 achieved submicromolar potency, thereby reducing cell viability in 5637 cells, and was nearly 200x more potent than UNC7716 (IC50: 0.28 vs 56.03 Î¼M). At 75 nM UNC7713 increased early apoptotic signaling over 1.8x compared to negative controls after 48 h. Concentrations of UNC7713 (75 nM, 200 nM) were associated with increased DAPI foci compared to controls. After 10 days, >60% fewer colonies were detected in UNC7713 treated cells as compared to controls. Cells treated with UNC7713 did not migrate to initiate wound closure but rather increased wound size. At 75 nM UNC7713 induced wound expansion compared to negative controls (25% wound expansion vs. 100% wound closure for

controls) at 48 h.

Conclusions: These preliminary data support further inquiry into the role of MPP8 in BC. Future studies will focus on identifying molecular mechanisms that underlie UNC7713's ability to inhibit cell proliferation, migration, and viability in preclinical models of BC.

Jingyu Zhao

Introduction: Chimeric antigen receptor (CAR) T cells have shown considerable promise as personalized cellular immunotherapy. However, the complex and lengthy manufacturing processes in generating CAR T cell products ex vivo result in substantial delays in production and high costs. To overcome these limitations, we develop a lentiviral system for in vivo engineering of CAR-T cells by using lentivirus pseudotyped with Nipah virus (NiV) and Measles virus (MV) glycoprotein, coupled with a proprietary combo of transduction enhancers to redirect lentivirus tropisms to CD3+ T cells and transduce these non-activated T cells.

Method: To redirect Lentivirus tropism, we linked anti-CD3 scFv to the exposed C terminus of the Nipah and Measles virus glycoprotein. To improve the transduction efficiency in non-activated T cells, we tested a library of transduction enhancers and selected the combination of poloxamer 407 (P407) and vectofusin-1 (VF-1).

Results: Engineered NiV and MV upon VF-1 and P407 application are able to specifically and efficiently transduce T-cells in whole PBMCs without any activation or stimulation in vitro. Non-activated PBMCs transduced by NiV and MV efficiently express CD19-CAR and kill B cell lymphoma cells in vitro.

Conclusions: These findings underscore our ability to transduce effective CD19-CAR T-cells directly from non-activated PBMCs and provide evidence that in vivo engineering of CAR-T cells is a promising approach for personalized cancer immunotherapy.

Discussion: Despite these promising results, we seek to evaluate this new in vivo CAR-T system in NSG mouse model with human B cell lymphoma and confirm the potency and safety of P407 and VF-1 application in vivo.

Huan Wang

The coronavirus SARS-CoV-2 protects its viral RNA from being recognized by host immune responses by methylation of its 5' end, also known as capping. This process is carried out by two enzymes, NSP16 containing 2'O-methyltransferase and NSP14 through its N7 methyltransferase activities, which are essential for the replication of the viral genome as well as evading the host's innate immunity. The non-structural protein 10 (NSP10) acts as a crucial cofactor and stimulator of NSP14 and NSP16. To further characterise the role of NSP10, we carried out a comprehensive analysis of >7 million globally collected whole-genome sequences (WGS) of SARS-CoV-2 obtained from the Global Initiative Sharing All Influenza Data (GISAID) and compared it with the reference genome Wuhan/WIV04/2019 to identify all currently known variants in NSP10. T12I, T102I, and A104V in NSP10 have been identified as
the three most frequent variants and characterised using biophysical and structural methods. In contrast to other non-structural proteins such as NSP1 and NSP12, the RNA-dependent RNA polymerase, a well-characterised and important drug target, NSP10 is significantly less prone to mutation due to its crucial

role in replication. The functional effects of the variants were examined for their impact on the binding affinity and stability of both NSP14-NSP10 and NSP16-NSP10 complexes. These results highlight the limited changes induced by variant evolution in NSP10 and reflect on the crucial roles NSP10 plays during the SARS-CoV-2 life cycle. These results also indicate that there is limited capacity for the virus to overcome inhibitors targeting NSP10 via the generation of variants in inhibitor-binding pockets.

Nicole Rose Lukesh

Introduction: Type 1 Diabetes (T1D) is an autoimmune disease affecting millions worldwide [1]. Autoreactive cells (Th1) recognize self-antigens as foreign and facilitate selective destruction to insulin-producing pancreatic beta cells [2]. Our goal is to retrain the immune system by co-delivering a diabetic self-peptide (p31) and a tolerogenic drug rapamycin (Rapa) to induce an antigen-specific regulatory T cell (Treg) population. Regulatory cells can suppress autoreactive cells in an antigen-specific manner, avoiding global immunosuppression. Soluble peptide therapies have shown little clinical success, in part due to their small size and their ability to be degraded. Therefore, the use of a microparticle (MP) system to encapsulate peptides can enhance efficacy by protecting cargo and promoting cellular uptake.

Methods: Acetalated dextran (Ace-DEX) MPs co-encapsulating p31 and Rapa were formed as described previously [3]. Non-obese diabetic (NOD) mice (10-12 weeks) were injected subcutaneously with Ace-DEX MPs to optimize Rapa dose in an adoptive transfer model and to assess the effects of our MP treatment on T cell phenotypes in a 28-day preclinical model.

Results and Discussion: In our adoptive transfer mouse model of diabetes, we identified both a dose-dependent host endogenous increase of Tregs in disease-related organs and an increase in the ratio of tolerogenic cells to the number of autoreactive cells. Our optimized dose was then used in a preclinical model of diabetes. We observed an increase in Tregs found in peripheral blood by day 27. This aligned with the influx of Tregs found in the pancreatic islets. Future studies will focus on further optimization by titrating the peptide dose.

Lay Summary: p31/Rapa Ace-DEX MP treatment increased the presence of Tregs in disease-related organs; these cells can suppress destructive effects of autoreactive T cells. Our Ace-DEX MP platform has the potential to provide a therapeutic effect in T1D patients by educating the immune system to suppress autoreactive attacks.

1 Gregory, G. A. et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol 10, 741-760, doi:10.1016/S2213-8587(22)00218-2 (2022).
2 Marrack, P., Kappler, J. & Kotzin, B. L. Autoimmune disease: why and where it occurs. Nat Med 7, 899-905, doi:10.1038/90935 (2001).
3 Chen, N., Kroger, C. J., Tisch, R. M., Bachelder, E. M. & Ainslie, K. M. Prevention of Type 1 Diabetes with Acetalated Dextran Microparticles Containing Rapamycin and Pancreatic Peptide P31. Adv. Healthcare Mater. 7, 1800341, doi:10.1002/adhm.201800341 (2018).

Ting Fu

Introduction: Chronic low-grade inflammation is a hallmark of diabetic heart disease. Lipoxin A4 (LXA4), an endogenous lipid mediator biosynthesized from arachidonic acid, promotes the resolution of

inflammation by limiting responses to pro-inflammatory mediators and promoting macrophage polarization. Further, levels of LXA4 in patients after acute myocardial infarction are negatively correlated with the risk of further adverse cardiovascular events (Chen et al., 2023). We hypothesized that LXA4 supplementation may protect against diabetic heart disease in mice.

Aim: To investigate the potential therapeutic effects of LXA4 on diabetic heart disease.

Methods: Male (n=88) ApoE-/- mice (6-week-old) were injected with vehicle or streptozotocin (55 mg/kg/day i.p. for 5 days) to induce diabetes. After 10 weeks of diabetes, mice were randomly received either LXA4 (5 Î¼g/kg i.p.) or vehicle (0.02% ethanol) twice/week for a further 6 weeks. At the end of the study, mice were culled and organs were harvested for analysis.
Results. Diabetic (DM) mice had elevated HbA1c (DM 11.9Â±0.2% cf. NDM 4.6Â±0.1% P<0.0001), lower final body weight (DM 25.6Â±0.7g cf. NDM 32.3Â±0.4g P<0.0001) and increased cardiac fibrosis (DM 3.1Â±0.4% cf. NDM 1.6Â±0.2% area collagen P = 0.001). Interestingly, LXA4 supplementation decreased cardiac collagen deposition in the left ventricle of diabetic mice.

Discussion: These data show that LXA4 modulates cardiac fibrosis in diabetic heart disease, suggesting it may be a target for drug treatment.

Lay-Summary: Diabetic-associated heart disease is one of the leading causes of developing heart failure in diabetic patients. The lack of effective treatments, especially for diabetic patients, may be due to the lack of targeting the underlying pathological mechanism, which is a clear unmet clinical need. We tested whether LXA4 can protect diabetic animals from cardiac fibrosis. We found that diabetic mice had significantly elevated blood sugar levels and reduced body weight. Interestingly, diabetic mice exhibited increased cardiac fibrosis, and LXA4 supplementation reduced that effect.
Chen R, Li J, Zhou J, et al. (2023) Pharmacological Research, 187:106618.

Dina Abushanab

Objective: As the majority of CVD deaths in Australia occur in people with prediabetes or diabetes, prevalence rates of CVD outcomes are required to forecast the societal burden of CVD in type 2 diabetes. The aim was to project the health and economic outcomes of cardiovascular disease (CVD) among people with type 2 diabetes from Australian public healthcare and societal perspectives over the next decade.

Methods: A dynamic multistate model with yearly cycles was developed to project cardiovascular events among Australians with type 2 diabetes aged 40-89 years from 2022 to 2031. The dynamic model allows for the movement of individuals into and out of the simulations and accounts for changes in mortality and migration as well as incident type 2 diabetes. CVD risk (myocardial infarction [MI] and stroke) in the type 2 diabetes population was estimated using the 2013 pooled cohort equation, and recurrent cardiovascular event rates in the type 2 diabetes with established CVD population were obtained from the global Reduction of Atherothrombosis for Continued Health (REACH) registry. Costs and utilities were derived from published sources. Outcomes included fatal and non-fatal MI and stroke, years of life lived, quality-adjusted life years (QALYs), total healthcare costs, and total productivity losses. The annual discount rate was 5%, applied to outcomes and costs.

Results: Between 2022 and 2031, a total of 83,618 non-fatal MIs (95% uncertainty interval [UI] 83,170-84,053) and 58,774 non-fatal strokes (95% UI 58,458-59,013) were projected. Total years of life lived and QALYs (discounted) were projected to be 9,549,487 (95% UI 9,416,423-9,654,043) and 6,632,897 (95% UI 5,065,606-7,591,679), respectively. Total healthcare costs and total lost productivity costs (discounted) were projected to be 9.59 billion Australian dollars (AU$) (95% UI 1.90-30.45 billion) and AU$9.07 billion (95% UI 663.53 million-33.19 billion), respectively.

Discussion: CVD in people with type 2 diabetes will substantially impact the Australian healthcare system and society over the next decade. Future work to investigate different strategies to optimize the control of risk factors for the prevention and treatment of CVD in type 2 diabetes in Australia is warranted.

Dina Abushanab

Introduction: To date, there have been few analyses of the consequences of cardiovascular disease (CVD) associated with type 2 diabetes (T2D). The majority of these studies have used a closed-cohort model, which follows the same group of people over time and were conducted from Western perspectives, which may over or underestimate the actual impact in the Middle East and North Africa (MENA) region countries such as Qatar, which has a high prevalence of T2D. Therefore, we aimed to predict the future humanistic and economic burden of CVD in T2D in Qatar.

Methods: A dynamic multistate Markov model from a Qatari societal perspective was built to simulate fatal and non-fatal CVD events among people with T2D in Qatar aged 40-90 years. First CVD events (i.e. myocardial infarction (MI) and stroke) were calculated via the 2013 American College of Cardiology-pooled cohort risk equation-Atherosclerotic Cardiovascular Disease, while recurrent CVD events were sourced from the global Reduction of Atherothrombosis for Continued Health registry. Key outcomes were fatal and non-fatal MI and stroke, years of life lived, quality-adjusted life years (QALYs), total direct medical costs, and total indirect costs. Utilities and costs were drawn from published sources. Probabilistic sensitivity analyses were performed to test the robustness around the estimates.

Results: Over 10 years, the burden of non-fatal MI and stroke among people with T2D was estimated to be 123,524 (95% uncertainty interval (UI) (116,923, 130,065)) and 70,466 (95%UI (67,945, 73,476), respectively. CVD deaths were projected to be 15,410 (95%UI 15,217, 15,794). Total years of life lived were 4,834,146 (95%UI 4,781,235, 4,881,695) and QALYs were 3,817,246 (95%UI 3,756,963, 3,870,616). Direct costs account for most of the costs, with a projection of QAR43.59 billion (US$11.94 billion) (95%UI 9.14, 134.20 billion) (US$2.5, 36.77 billion), while the total indirect costs were expected to exceed QAR29.65 billion (US$8.12 billion) (95%UI 2.40, 113 billion) (US$658.08 million, 30.96 billion).

Discussion: This study highlights that the considerable rising health and economic burden of CVD in T2D in the Qatari setting will impact not only the healthcare system but also the society overall. Prevention strategies are likely to lead to a reduction in societal burden. Thus, policy makers and clinicians are encouraged to engage in preventive strategies to limit the burden of CVD among T2D people in Qatar. Additionally, prevention efforts to reduce the overall burden should also engage stakeholders outside the health sector who ultimately bear the indirect cost of CVD in T2D.

Miriam Leung

Background: Suboptimal antiresorptive use may be associated with higher risk of second hip fractures. We investigated trajectories of oral bisphosphonate use following first hip fractures and factors associated with different trajectories.

Methods: We conducted a retrospective study of all patients aged ≥50 years dispensed two or more bisphosphonate prescriptions following first hip fracture in Victoria, Australia from 2012-2017. Twelve-month trajectories of bisphosphonates use were categorized using group-based trajectory modelling. Factors associated with different trajectories compared to the high adherence trajectory were assessed using multivariate multinomial logistic regression.

Results: We identified four patterns of oral bisphosphonate use in 1,811 patients: persistent adherence (66%); delayed initiation (17%); early discontinuation (9%), and late discontinuation (9%). Pre-admission bisphosphonate use was associated with a lower risk of delayed initiation in both sexes (relative risk [RR] 0.28, 95% confidence interval [CI] 0.21-0.39). Female patients who were older (≥85 years old versus 50-64 years old, 0.39, 95% CI 0.21-0.72) had a lower risk of delayed initiation. Males with anxiety (RR 9.80, 95% CI 2.24-42.9) and females with previous falls had increased risk of early discontinuation (RR 1.80, 95% CI 1.16-2.78).

Discussion: Two-thirds of patients demonstrate good adherence to oral bisphosphonates over 12 months following hip fracture. Efforts to further increase post-discharge use of antiresorptives should address possible persistent uncertainty around delaying treatment initiation. Intervention to increase persistence in bisphosphonates use should also tailored for different sexes as different factors were found to affect their bisphosphonates use.

Lay summary: Bisphosphonates reduce the risk of developing future hip fractures. We investigated patterns of bisphosphonate use and associated factors in 1,811 people aged 50 years and older who were hospitalised with a first hip fracture in Victoria, Australia from 2012-2017. More than 60% of patients had good treatment adherence over twelve months. However, one in six of the patients experienced a delay in bisphosphonate initiation and another one-six of the patients discontinued treatment within twelve months after discharge. Different factors were associated with bisphosphonates use across different sexes.

Lexy Ehlert

Introduction: Prescription medication costs in the United States continue to climb. Price hikes, or episodes of large and sudden price increases, are a contributing factor. While price hikes negatively impact patients, the consequence to manufacturers is unclear. We hypothesized that medication price hikes would result in increased stock price and Google searches in the year following a price hike.

Methods: We used Yahoo Finance and Google Trends data to evaluate changes in stock price and search volume respectively. We analyzed 12 instances of medication price hiking and compared outcomes to controls, the S&P 500, and the healthcare sector of the S&P 500 using difference-in-differences methodologies.

Results: Relative to controls, cases experienced an increase in stock price, but not Google searches. We also note that most price hike case companies were experiencing a decrease in stock price prior to initiating the price hike.

Discussion: Manufacturer motivations for price hiking need to be incorporated into any policy addressing price hiking.

100-word lay summary: Medications are getting more expensive in the US, and one reason is because of price hikes. In this study, we looked at data from Yahoo Finance and Google Trends to see how price hikes affect stock prices and Google searches. We found 12 cases where drug prices went up and compared them to 12 similar companies that did not raise their prices. We found that the companies that hiked prices saw their stock prices rise, but there was no difference in Google searches. To tackle price hikes, policies need to understand why manufacturers do it in the first place.

John Jackson

Introduction: Performance-linked remuneration for dispensing in which payment to pharmacies may be adjusted based on a measure of the outcome of the service, has been introduced by some funders in the US. However, in most countries, pharmacists' dispending is still remunerated on a set fee-for-service (FFS) basis. The objective of this work was to assess in an Australian context, the application of FFS and performance-linked payment to dispensing, and determine funding principles that may enhance quality of outcomes.

Methods: Within an adaptation framework, the study used thematic analysis of interviews with Australian community pharmacy stakeholders to evaluate the existing FFS dispensing payment model, determine the fit of four key elements of a US performance-linked payment model, and evaluate the level of acceptance of a simple performance-linked model. We induced quality-focused dispensing payment principles from the data.

Results: FFS funding is not ideal for either patients or the profession as it encourages pharmacists to dispense quickly rather than commit time and expertise in accordance with each patient's requirements. However, the lack of specificity and correlation between pharmacists' services and patient outcomes is an impediment to using performance-linked payment in Australia.
Discussion: Quality-focused principles should be incorporated into the fee-for-service dispensing model, including separation of payment for commercial aspects of dispensing from professional aspects, the introduction of a schedule of time-based professional payments linked to patient and medication risk factors, and payment of professional fees to the individual pharmacist performing the service.

Lay summary: Payment to pharmacies for dispensing prescriptions should foster improvements in patient care while being equitable to the pharmacy. The existing fee-for-service payment model in Australia was compared with a model from the US in which payments to pharmacies are adjusted, ostensibly based on a measure of the quality of care provided. Neither the current Australian model nor the US performance-linked model proved ideal. Quality-focused concepts that we argue should be

incorporated into payment for dispensing include separating payment for commercial activities from professional activities, and for professional fees to be based on medication risk and patient complexity.

Nouf Alsalem

Background: Effective medication reconciliation reduces medication errors and adverse drug events (ADEs) and support safe medication use. Patient held medication records (PHMR) can be used to reduce information loss across different health care settings. The aim of this review is to investigate the effectiveness of PHMRs in reducing medication discrepancies (MDs) at care transition, and drug related problems (DRPs) during and after health care utilization.

Methods: A systematic search was conducted using Medline, Embase, PubMed, Cochrane via Ovid and CINAHL for the period 1990-2022. Qualitative, quantitative and mixed-methods studies examining the impact of PHMR in isolation or in combination with other interventions were included; studies had to report the impact of PHMR interventions on identifying and resolving MD at any point of care transition and/or DRPs during or after health care utilization. Findings were extracted to produce a narrative synthesis. Quality appraisal was undertaken using the Mixed Methods Appraisal Tool.

Results: A total of 28 studies were included. Studies reported data on outcomes related to MDs (n = 12), DRPs (n = 9), or both (n = 7). Most studies (n=19) investigated paper PHMRs, eight studied electronic PHMRs and one explored both. The use of PHMRs was combined with other interventions including MedRec, patient interview, and other medication management activities (14/28). In a few studies, patients used electronic PHMRs to complete MedRec remotely and independently without the necessity of a face-to-face interview (4/28). For MD-related outcomes, a mostly positive impact was found across studies including facilitating patients' and providers' detection of different types of MDs and/or increasing the rate of medication list updates and medication reconciliation and improving the accuracy of patients' medication lists (15/19). For DRP-related outcomes, a mostly favourable results in identifying and resolving DRPs (e.g., drug-drug interaction, adherence) were found (9/13) with no significant difference was shown in the rate of ADEs (3/3).

Conclusion: PHMRs can be seen as effective patient empowerment tools for reducing MDs at care transition and DRPs. Interventions are required to raise awareness of the potential value of these tools and efforts are needed to facilitate their widespread integration in clinical care.

Nouf Alaboud

Background: Electronic prescribing (EP) systems have been widely adopted in different healthcare settings in the last few years. However, few studies have evaluated the end-users' opinions and satisfaction with the various design features of EP systems which is essential to identify their needs and expectations to develop effective EP systems in future.

Objective: To assess a newly implemented paediatric sepsis screening tool as a clinical decision support system (CDSS) within the EP system from the end-user's perspective regarding tool usability, staff awareness and satisfaction.

Methods: A cross-sectional survey-based study from October 2022 to April 2023 of doctors and nurses

working in paediatric areas at an academic hospital in England. The tool usability and staff satisfaction were assessed using a 5-point Likert scale of the system usability scale (SUS). The survey was distributed online and as paper-based copies with five different sections.

Results: Responses were received from 36 individuals (22 doctors and 14 nurses), with a response rate of 39% for doctors and 52% for nurses. 67% were female, 53% were aged 31-40, and 81% used the EP system for 1-5 years. 43% of nurses liked using colour codes and visual clues, 82% of doctors liked using auto-calculators, and 50% of the doctors and nurses disliked the pop-up alerts. Although there was higher awareness of the tool amongst nurses (86%) compared to doctors (45%), usage was low in both groups, with only four doctors and eight nurses used it before, of whom only two doctors and six nurses received a training session on how to use it. The usability of the paediatric sepsis tool was low (mean= 2.5) from doctors' perspective and high (mean=3.9) from nurses' perspective. Doctors were less satisfied (mean=2.6) than nurses (mean=3.8) with the paediatric sepsis tool, and 50% of the doctors and nurses agreed they needed more training on using the tool.

Conclusion: The lack of staff awareness of EP system functionalities and training on using them affects the utilisation and staff satisfaction with these systems. More investigations are needed to understand the main reason behind the low usability of CDSS by the end-users.

Brigid McInerney

Introduction: International guidelines recommend psychotropic adverse drug event (ADE) monitoring for people living with dementia and in long-term care facilities (LTCFs). There are no published comparisons of psychotropic ADE monitoring tools for this purpose. The objective of this review was to evaluate psychotropic ADE monitoring tools intended for use in LTCFs.

Methods: Medline, CINAHL, Embase and PsycInfo databases were searched from inception to August 2022 for studies reporting the development, validation, or use of psychotropic ADE monitoring tools. Quality was assessed against the criteria: test-retest reliability, inter-rater reliability, content validity and construct validity.

Results: Of the 2522 retrieved records, eight articles describing six psychotropic ADE monitoring tools were included. Tools monitored antipsychotic (n=6), benzodiazepine (n=4) and antidepressant (n=4) ADEs. Tools were designed for use by nurses (n=4), general practitioners (n=1), and multidisciplinary teams (n=1). Two tools reported taking 10-60 minutes to apply. Five tools described escalation of suspected ADEs. Test-retest reliability and construct validity was not reported for any tools. Inter-rater reliability was reported for two tools. Four tools were deemed to have adequate content validity.

Discussion: Psychotropic ADE monitoring tools were primarily designed for use by nursing staff. ADEs were escalated to other members of the multidisciplinary team, with infrequent involvement of residents/relatives. The complexity of existing tools may preclude their use in routine practice. A suitable LTCF psychotropic ADE monitoring tool should feasibly integrate into routine clinical care. Further research using rigorous scientific methodology is required to assess the applicability of existing and future psychotropic ADE monitoring tools.

100-word lay summary: We found six published tools that help detect side effects that are due to psychotropic medications such as antipsychotics, antidepressants or sleeping pills in people living in nursing homes. Tools monitored 4-95 side effects. Some tools were time consuming to use, which may not be feasible as part of standard care. A tool that considers specific side effects that are important to nursing home residents and can be used as part of routine care is required. Identifying side effects can help residents and their care staff discuss the benefits and harms of their psychotropic medication.

Shin Liau

Objective: To investigate longitudinal changes in symptomatic and preventive medication use among community-dwelling people with and without Alzheimer's disease (AD) five years pre- and post-AD diagnosis.

Methods: Retrospective matched cohort study comprising 58,496 people with AD and 58,496 matched comparators without AD in Finland from 2005-2010. Prevalence of symptomatic and preventive medication use were evaluated every six months from five years before to five years after AD diagnosis and further stratified by age and sex.

Results: Compared to people without AD, people with AD had the highest increase in prevalence of both symptomatic and preventive medications from five years before until the time of diagnosis. This increase was most pronounced in the oldest age group (>/=85 years) in comparison to younger age groups. After AD diagnosis, symptomatic medication use in people with AD stabilised, while preventive medication use decreased over the next five years. In contrast, people without AD had a continuous increase for both medication categories throughout the 10-year period. The prevalence of symptomatic medication classes including paracetamol, antipsychotics, proton pump inhibitors, opioids, and antibiotics increased over time in people with AD. The prevalence of preventive medication classes including antidepressants, calcium supplements, beta-blockers, and statins increased up until the time of diagnosis in people with AD but declined thereafter.

Conclusions: AD diagnosis is the key timepoint for change in symptomatic and preventive medication use. Prevalence of both medication categories increased up until the time of diagnosis among people with AD, upon which the use of symptomatic medications plateaued over the next five years, while preventive medications gradually declined. The time of AD diagnosis prompts for regular medication reviews to re-evaluate the appropriateness of each nominated treatment and better align regimens to individual priorities of care.

Dana Alsugeir

Background: Menopausal (perimenopausal and postmenopausal) women are at higher risk of osteoporotic fractures. Menopausal women may experience common mental health problems (CMHP) which require the prescribing of selective serotonin re-uptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants. Prescribing of SSRI/SNRI antidepressants may pose an additive risk of osteoporotic fractures.

Objectives: To investigate the association between prescribing of SSRI/SNRI antidepressants and risk of osteoporotic fractures in menopausal women with CMHPs.

Methods: In this cohort study, primary care records of menopausal women were retrieved from the IMRD-UK database, previously known as THIN. We defined menopausal women as women with a record of menopause or aged ≥50 years. Our study cohort comprised menopausal women with a CMHP (i.e. depression or generalized anxiety disorder). Osteoporotic fractures were defined as first incident fracture. Relative risk of osteoporotic fractures was estimated by comparing women prescribed SSRI/SNRI antidepressants to those unexposed using a Cox proportional hazards model to estimate hazard ratios (HR) with 95% CI.

Results: We identified 459,431 menopausal women with CMHPs, with 44,582 osteoporotic fractures within a median follow-up of 5.44 years. The risk of osteoporotic fractures was higher in women prescribed SSRI/SNRI antidepressants with an IR of 16.05 (95%CI 15.87-16.23) per 1000 PYAR compared with an IR of 12.43 (95%CI 12.23-12.64) per 1000 PYAR in non-users. We found strong evidence of an association between the use of SSRI/SNRI and risk of osteoporotic fractures (adjusted HR=1.30, 95%CI 1.27-1.32).

Conclusions: In a population of menopausal women with CMHPs, prescribing of SSRI/SNRI antidepressants was associated with a higher risk of osteoporotic fractures.

Lay summary: Women going through menopause commonly experience depression and anxiety. They are often prescribed antidepressants to manage their symptoms. Also, menopausal women after menopause are vulnerable to fractures. This study examined whether use of antidepressants increases risk of fractures in menopausal women. Women's medical records were extracted from a large database in the UK. Risk of fractures was compared between women with depression and anxiety using antidepressants and women with these conditions but not using antidepressants. It was found that the use of antidepressant medicines was associated with a 30% increased risk of fractures in menopausal women.

Monica Jung

Introduction: Tapering opioids may improve pain, function and quality of life. However, abrupt discontinuation may pose new risks such as uncontrolled pain, suicidal attempts and overdose. The aim of this study was to identify differing opioid tapering trajectories among patients prescribed long-term, stable dose of opioid analgesics, and examine patient-level characteristics associated with different trajectories.

Methods: We identified 3,731 patients prescribed long-term opioids between January 2016 and September 2019 using Australian primary care data. Group-based trajectory modelling and multinomial logistic regression analysis were conducted to determine taper trajectories and examine demographic and clinical factors associated with the different trajectories.

Results: Six distinct opioid taper trajectories were identified: three successful discontinuation and three non-completed taper trajectories. Trajectories with differing rates of taper were identified: gradual and

faster taper. A successful discontinuation trajectory from high opioids dose was not identified. For patients prescribed medium opioid doses, compared to those that didn't complete taper, those that successfully completed taper were more likely to have higher geographically-derived socio-economic status (relative risk [RR], 1.067; 95% CI,: 1.001-1.137) and less likely to have sleep disorders (RR, 0.661; 95% CI, 0.463-0.945). Patients who didn't complete taper were more likely to be prescribed strong opioids, regardless of whether they were tapered from lower (RR, 1.441; 95% CI, 1.137-1.828) or higher (RR, 1.344; 95% CI, 1.027-1.760) doses.

Conclusion: Those prescribed strong opioids and high doses appear less likely to complete taper and warrant additional support and monitoring during taper.

Lay summary: Tapering opioids can help to improve pain and function. Our study aimed to understand how opioids are being tapered in primary care settings, and whether there are any differences between patients that are able to successfully taper compared to those that don't. Our study showed that patients tapering from long-term opioids followed one of six distinct taper trajectories. Patients in the gradual taper group tended to have higher socio-economic index and reduced risk of having sleep disorders. Prescription of strong opioids was associated with non-completed taper. These trajectory models may help to identifying at-risk populations requiring additional support during taper.

Ashley Trojniak

Kappa Opioid Receptor (KOR) agonism offers a unique opportunity to treat pain and itch without the possibility of addiction. Previous studies have shown that desired effects, such as analgesia and pruritus, can be untangled from undesirable effects such as dysphoria, via the development of G-protein biased agonists. Our group has previously developed triazole 1.1 as a lead molecule. Current work focuses on replacement of the sulfur containing side-chain with a carbon-containing side chain in order to further develop the SAR of the scaffold. In particular, we aim to identify metabolically labile sites with the goal of developing a more potent, biased, and metabolically stable KOR agonist. These novel 3,4,5-trisubstituted triazoles are more potent and bias than triazole 1.1 and offer a new tool to study biased agonism at the KOR.

Yunan Peng

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons. Recent research has focused increasingly on genetic factors such as mutations in the LRRK2 gene as potential underlying causes of PD. Cell signalling pathways such as the canonical Wnt/β-catenin pathway, also have gained increasing interest in late-onset neurodegenerative diseases. Previous studies conducted by our lab have shown that LRRK2, acting as a scaffolding protein, interacts with both canonical and non-canonical Wnt signalling pathways. My study is focused on investigating the relationship between Wnt/β-catenin signalling pathways and LRRK2 in PD LRRK2 G2019S knock-in and LRRK2 knockout mouse model lung tissue, primary lung endothelial cell culture, and immortalized immune cells. Preliminary data suggests genotype- and sex-specific differences in Wnt signalling protein expression levels in lung tissues, as well as gene expression changes in lung endothelial cells under basal conditions and after Wnt signalling stimulation.

Showmika Tabassum Supti

Alzheimer's disease (AD) is characterised by hallmark features such as amyloid-beta (AÎ²) accumulation, neurofibrillary tangles formed by hyperphosphorylated tau, brain atrophy and sustained neuroinflammation. Apart from these hallmarks, a reduction in docosahexaenoic acid (DHA) has also been observed in the brain of people with AD. The de novo synthesis of DHA in the brain is limited. Hence plasma-derived DHA has to be transported across the blood-brain barrier (BBB) to maintain healthy brain DHA levels. There is plenty of evidence demonstrating the effects of iron on the pathology of AD but limited understanding of its impact on the BBB. The data from the present study are the first to demonstrate that increasing intracellular iron levels using ferric ammonium citrate (FAC) led to a 22% downregulation of fatty acid transporter protein (FATP1) at the protein level (via western blot) but not the mRNA level on human cerebral microvascular endothelial (hCMEC/D3) cells. Furthermore, upon performing functional studies, it was observed that FAC had no impact on the uptake of 3H-oleic acid (3H-OA) and 14C- DHA, but FAC significantly impacted the efflux of 3H-OA and 14C- DHA from the hCMEC/D3 cells at various time points. While further studies are required to elucidate the molecular mechanisms underlying the FAC-induced downregulation of FATP1, these studies provide insight into the role of iron in regulating FATP1 at the BBB, which may have implications on the transport of fatty acids to and from the brain.

Lay summary: Alzheimer's disease is a brain disorder that causes the slow deterioration of normal brain structure and function. There is plenty of evidence demonstrating the effects of iron on the physiological processes associated with AD but limited understanding of its impact on the blood-brain barrier. The data from the present study are the first to demonstrate that increasing intracellular iron levels led to a lower expression of fatty acid transporter protein in human brain endothelial cells and a lower outflow of fatty acids from human brain endothelial cells.

Kai Kikuchi

Amyloids are macromolecular aggregates that form when proteins assemble in a manner that generates a cross-Î² structure. 1 Toxic amyloids are famously implicated in a wide range of diseases, most notably Alzheimer's and Parkinson's diseases, however less well known are functional amyloids that play important roles in normal biological functions. Despite two decades of research on functional amyloids, it remains unclear how cells can produce both toxic and functional amyloids under physiological conditions. To better improve our understanding of amyloids, it is important to understand the microenvironments (e.g., polarity, viscosity) presented on their surface, and how these affect solubility and stability of amyloid assemblies and govern their interactions with lipid membranes and other hydrophobic surfaces in the cell.

The challenges associated with studying amyloid are many. Structurally, amyloids and their pre-fibrillar oligomers can be heterogeneous in structure and size. In addition, traditional techniques such as fluorescence microscopy, electron microscopy, PET and SPECT do not give information about micro-environments. Fluorescence lifetimes are incredibly sensitive to the environment (e.g., polarity, viscosity) surrounding the fluorophore. Fluorescence lifetime microscopy (FLIM) can be used in conjunction with environment-sensitive probes in order to gain information about minute differences in micro-environments in amyloid assemblies that cannot be visualised with other techniques
In this presentation, I will discuss the design and testing of a library of naphthalimide-based fluorescent

sensors that show both polarity and viscosity dependent fluorescence emission properties. I will also discuss their use in FLIM of amyloids, allowing us to distinguish different forms, as well as allowing mapping of micro-environments present within amyloid. We also extend this methodology to 3DFLIM, enabling 3-dimensional analysis of amyloid micro-environments.

Huan Yee Koh

PhySICOchemical graph neural network (PSICO) is an interpretable deep learning model that predicts protein-ligand interaction properties purely from sequence data (i.e., ligand SMILES and protein sequence). Without high-resolution 3D protein structures or co-crystallised protein-ligand complexes, it is able to match and outperform state-of-the-art 3D and complex computation methods with the same amount of training data, while being unaffected by resolution quality of input data. Through comprehensive test on 12 drug discovery settings, we find PSICO to generalise effectively across diverse scenarios. We also examine the inner workings of PSICO via its interpretable mechanism, and observe that PSICO learns patterns of interaction mechanisms adhering to physicochemical principles. As a proof-of-concept, we then employ PSICO in virtually screening a diverse library with 28,000 compounds for potential A1 Receptor protein (A1R) agonists. Encouragingly, by experimentally validating the agonism of these compounds against A1R, we find that PSICO effectively ranks the top hit compound at the top 99 percentile. Overall, PSICO is an effective, generalisable and interpretable model for protein-ligand interaction prediction task that requires only sequence data. PSICO will be available for public usage.

Ameya Chaudhari

Small extracellular vesicles (sEVs), or exosomes, are involved in many homeostatic and pathological processes. Over the years they have gained significant attention as potential drug delivery vehicles due to their unique properties. However, despite thousands of studies on sEVs as drug delivery vesicles, most studies report non-specific accumulation of sEVs in the liver post-administration, which impedes their therapeutic use due to high off-target effects. While there have been efforts towards developing strategies to improve organ targeting of sEVs, the efforts have two critical limitations. 1) Current strategies of in vivo sEV tracking are not high throughput, often relying on bulk low-efficiency labeling, and 2) they utilize complex and costly methods like antibodies or peptides to target organs. Here, we have developed a novel strategy to overcome these limitations of sEVs as drug-delivery vesicles. The strategy involves labeling sEVs with DNA barcodes for high-throughput screening while surface decorating the sEVs with small molecules to promote organotropism. We propose to use small molecules for passive targeting, as they are highly effective in altering cell targeting, highly modular, and economical. This approach allows us to screen hundreds of surface modifications in a more cost-effective and timely manner than current strategies using peptide or antibody surface decoration. The sEVs are loaded with unique nucleic acid barcodes capable of being quantified with Next Generation Sequencing (NGS), thus allowing us to examine the sEV organ targeting and cargo uptake efficiency at a single particle level. Overall, this strategy allows for a high-throughput screening method to identify surface modifications that promote extra-hepatic delivery of sEVs.

Effrosyni Alexandrou

The cellular functions of nucleic acids rely not only on their sequence but also on their structure. Beyond the most widely known double helix, DNA can adopt other classes of secondary structural motifs, including the cytosine-rich four-stranded helical i-motifs. Such non-canonical DNA conformations are formed in vivo, but to date, structural information on i-motifs is very limited. Our aim is to reveal more structural detail about i-motif DNA structures using biophysical methods. Here we describe our initial studies with sequences from the human insulin gene-linked polymorphic region and the regulatory region of nitric oxide synthase from Paracoccus Denitrificans.

Narges Mahdavian

Introduction: Hirschsprung disease (HD) is a life-threatening disorder caused by the absence of enteric neurons in the distal colon. Treatment requires surgical removal of the aganglionic bowel. Over 50% of patients experience postsurgical symptoms including chronic constipation, enterocolitis, and fecal incontinence, suggesting the remaining ganglionated bowel may have additional anomalies. We hypothesise that non-neuronal cells with a role in motility may be impacted in HD. This study aims to determine the distribution and function of cells involved in motility in HD versus healthy colon and to correlate this to neuromuscular function.

Methods: Colon samples were collected from 13 HD and 8 control patients. Muscle tension was measured in segments along the length of resected bowel. The effects of electrical and pharmacological stimulation of neurons were assessed. Immunofluorescence imaging was used to quantify the innervation and distribution of neurons, interstitial cells of Cajal (ICC) and PDGFRÎ±+ cells throughout the external muscle.

Results: We have identified that smooth muscle contractions, cell distributions, and innervation differed along the resected HD colon and with healthy control bowel. There was a significant reduction in neurons and PDGFRÎ±+ cells between ganglionated HD bowel and healthy controls. Neurons, ICC, and PDGFRÎ±+ cells were variably expressed throughout different regions of the HD colon.

Discussion: There is a difference in cell expression and associated function between the ganglionic region of the HD bowel and healthy control bowel. This may indicate why most patients still experience post-surgical dysmotility. Future analyses will reveal changes along the full resected HD colon and quantify the proportion of excitatory and inhibitory innervation. These findings will broaden the scope for understanding HD pathophysiology.

Lay Summary: Hirschsprung Disease (HD) is caused by the absence of nerve cells in regions of the colon. This causes severe bowel issues and must treated with surgical removal of the affected region. We explore how other cells essential for the movement of bowel contents are altered in HD, and how this affects bowel function. We report that gut contractions and the distribution of key cell types in HD are not comparable to healthy control. These findings enhance our understanding of HD.