PharmAlliance Graduate E-Symposium

29 September 2020: UNC 7-9 AM|UCL 12-2PM|Monash 9-11 PM
https://uncpharmacy.zoom.us/j/92151933593?pwd=RnZHVHM5aG84R1d5SGgzdEpSNkxWdz09

1 October 2020: UNC 4-6 PM|UCL 9-11 PM|+ 1 day Monash 6-8 AM
https://uncpharmacy.zoom.us/j/96980442372?pwd=N3JpbnVPZzRrSlB0WEpKM3czb3l3Zz09

Note: Presenters have 5 minute time slots: 3-4 minutes for presentation, 1 minute for questions leave some time for transitions. Max of 4 slides. Presenters should send slides to Caroline Sasser by 27 September 2020. This seminar will be hosted via Zoom and presenters will be granted mouse control during the meeting. This meeting will be recorded.

Day 1: 29 September 2020
UNC 7-9 AM|UCL 12-2PM|Monash 9-11 PM
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Moderator	Time – AM (UNC)	Time – PM (UCL)	Time – PM (Monash)	Speaker	Topic
OPEN	7:00-7:05	12:00-12:05	9:00-9:05	Joe Nicolazzo	Welcome and intro
Moderator: Yijun Pan Evaluators: Joe Nicolazzo, Chengxue H. Qin, Caroline Sasser	7:05-7:10	12:05-12:10	9:05-9:10	Stella Aslanoglou	Silicon-Nanotube-Mediated Intracellular Delivery Enables Ex Vivo Gene Editing
	7:10-7:15	12:10-12:15	9:10-9:15	Sarah Clinkscales	Determining the Role of HRP2 in Epigenetic Silencing
	7:15-7:20	12:15-12:20	9:15-9:20	Matthew Challis	Identifying Protein Targets for Novel Antimalarial Compounds Using CETSA Proteomics
	7:20-7:25	12:20-12:25	9:20-9:25	Hajira Bilal	Synergistic Ceftazidime and Tobramycin Combinations for Clinical Hypermutable Pseudomonas Aeruginosa Isolates; An Innovative Dosing Approach to Enhance Bacterial Killing and Mitigate Resistance in a Dynamic Biofilm Model
	7:25-7:30	12:25-12:30	9:25-9:30	Aaron Devanathan	Antiretroviral Penetration and Drug Transporter Concentrations in the Spleens of Three Preclinical Animal Models and Humans
	7:30-7:35	12:30-12:35	9:30-9:35	Erin Scholz	Quantitative Imaging Analysis of ARVs, HIV RNA, and Collagen in NHP Lymph Nodes
	7:35-7:40	12:35-12:40	9:35-9:40	Isabella Young	Ultra-Long-Acting Injectable Multi-Purpose Technology for Prevention of HIV and Unplanned Pregnancy
Moderator: Chengxue Helena Qin	7:40-7:45	12:40-12:45	9:40-9:45	Meihua Luo	Tailoring Porous Silicon Nanoparticles for both Targeted Brain Cancer Killing and Metastasis Prevention

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Evaluators: Steve Brocchini, Sara Garfield, Caroline Sasser	7:45-7:50	12:45-12:50	9:45-9:50	Liisa Niitsoo	Multiplex Nanoparticles for Active Tumour Targeting
	7:50-8:55	12:50-12:55	9:50-9:55	Jiawei Zhou	Spatiotemporal Response Heterogeneity Across Metastatic Lesions in Colorectal Cancer
	8:55-8:00	12:55-1:00	9:55-10:00	Jacob Larson	Peptide and Small Molecule Inhibitor Discovery for a Vulnerable KRAS Mutant
	8:00-8:05	1:00-1:05	10:00-10:05	Ben Bowles	Development and Fabrication of SLA 3D Printed Drug-Eluting Implants for Treatment of Malignant Solid Tumours
	8:05-8:10	1:05-1:10	10:05-10:10	Pegah Maneshi	Validating the Mode of Action of STAT3 DNA Binding Domain Ligands
	8:10-8:15	1:10-1:15	10:10-10:15	Amanda Peterson	Î²-Adrenergic Regulation of Lipopolysaccharide Macrophage Immunometabolism
	8:15-8:20	1:15-1:20	10:15-10:20	Nkiruka Ibeanu	Click Chemistry for the Synthesis of Bispecific Antibody Formats
	8:20-8:25	1:20-1:25	10:20-10:25	Jordan Joiner	Low-Intensity Focused Ultrasound Produces Immune Response in Pancreatic Tumors
Moderator: Sara Garfield Evaluators: Mike Jarsfer, Yijun Pan, Caroline Sasser	8:25-8:30	1:25-1:30	10:25-10:30	Joshua Rennick	mApple as an Intracellular pH Sensor Using Fluorescent Lifetime Imaging (Phlim)
	8:30-8:35	1:30-1:35	10:30-10:35	Harry Smallman	Continuous Flow Processing for API Synthesis and Drug Discovery
	8:35-8:40	1:35-1:40	10:35-10:40	Rumintha Thavarajah	3Dimensional Reactions: A Modern Approach to Chemical Synthesis
	8:40-8:45	1:40-1:45	10:40-10:45	Alaa Alsharif	Prevalence and Incidence of Dementia in People with Diabetes Mellitus in the United Kingdom
	8:45-8:50	1:45-1:50	10:45-10:50	Jiayin Diao	Biased Negative Allosteric Modulators for the Calcium-Sensing Receptor Have Differential Bronchodilator and Bronchoprotective Effects in Mouse Precision Cut Lung Slices
	8:50-8:55	1:50-1:55	10:50-10:55	Ryan Trueman	Bioelectronics for Regenerative Medicine
	8:55-9:00	1:55-2:00	10:55-11:00	Banaz Jalil	Jordanian Pharmacist's Perception of Herbal Supplements
CLOSE				Joe Nicolazzo	Closing

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Day 2: 1 October 2020

UNC 4-6 PM|UCL 9-11 PM|+ 1 day (2 Oct.) Monash 6-8 AM

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Theme	Time – PM (UNC)	Time – PM (UCL)	Time – AM (Monash)	Speaker	Topic
OPEN	4:00-4:05	9:00-9:05	6:00-6:05	Mike Jarstfer	Welcome and intro
Moderator: Chengxue Helena Qin Evaluators: Mike Jarstfer, Niloufar Ansari, Caroline Sasser	4:05-4:10	9:05-9:10	6:05-6:10	Christine Madla	Boosting Drug Bioavailability in Men but Not Women Through the Action of an Excipient
	4:10-4:15	9:10-9:15	6:10-6:15	Solomon Sherif	Studying the Effectiveness of Penetration Enhancers in Delivering Tazarotene Through the Skin by Semi-Quantitative and Quantitative Ex Vivo Confocal Raman Spectroscopy
	4:15-4:20	9:15-9:20	6:15-6:20	Atheer Awad	3D Printed Tablets (Printlets) with Braille and Moon Patterns for Visually Impaired Patients
	4:20-4:25	9:20-9:25	6:20-6:25	Danielle Andrews	Na Salts as Bitter-Blocking Excipients for Children?
	4:25-4:30	9:25-9:30	6:25-6:30	Xiaoyan Xu	What Do Children Think About Tablets Manufactured by Different 3D Printing Technologies?
Moderator: Niloufar Ansari Evaluators: Paulina Ramirez Garcia, Joe Nicolazzo, Caroline Sasser	4:30-4:35	9:30-9:35	6:30-6:35	Hassan Alwafi	Epidemiology and Treatment of Atrial Fibrillation in Patients with Type 2 Diabetes in the UK, 2001-2016
	4:35-4:40	9:35-9:40	6:35-6:40	Zixuan Wang	Association Between Antipsychotic use in Pregnancy and the Risk of Gestational Diabetes: Population-based Cohort Studies from the United Kingdom and Hong Kong
	4:40-4:45	9:40-9:45	6:40-6:45	Rylee Wander	Determining the Substrate Specificity of Heparin/Heparan Sulfate 3-O-sulfotransferase Isoform 5
	4:45-4:50	9:45-9:50	6:45-6:50	Chengsheng Ju	Global Trends In Anti-dementia Medications Consumption in 66 Countries/regions From 2008 To 2018
	4:50-4:55	9:50-9:55	6:50-6:55	Si Hang Lei	WNT and NFAT Signalling Changes in LRRK2 Parkinson's Disease Models
	4:55-5:00	9:55-10:00	6:55-7:00	Marco Sancandi	Exploring the Aetiology and Treatment of Hyposmia in a Rat Model of Pre-Motor Parkinson's Disease
	4:00-5:05	10:00-10:05	7:00-7:05	Cassandra Jay Hatzipantelis	GPR52 Agonism Reverses Schizophrenia-Relevant Spatial Working Memory Deficits in Mice
Moderator: Paulina	5:05-5:10	10:05-10:10	7:05-7:10	Zoe Whiteley	Microfluidic Synthesis of Protein-Loaded Nanogels in a Coaxial Flow

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Ramirez Garcia Evaluator: Niloufar Ansari, Steve Brocchini, Caroline Sasser					Reactor Using a Design of Experiments Approach
	5:10-5:15	10:10-10:15	7:10-7:15	Serena Teo	Unravelling Cytosolic Delivery of Endosomal Escape Peptides with a Quantitative Endosomal Escape Assay (SLEEQ)
	5:15-5:20	10:15-10:20	7:15-7:20	Parham Sahandi Zangabad	Nanoporous Silicon Microparticles for Protected and Prolonged Delivery of Peptides
	5:20-5:25	10:20-10:25	7:20-7:25	Nazia Tabassum	Porous Silicon Nanoneedles for Enhanced Transdermal Drug Delivery
	5:25-5:30	10:25-10:30	7:25-7:30	Nektarios Liaskos	Metabonomic Investigation of Hepatoprotective Effects of Fucus Vesiculosus Extract in a ccl4-induced Hepatotoxicity Animal Model
	5:30-5:35	10:30-10:35	7:30-7:35	Lixiang Zhao	Electrospun Fibres with Two Triggers to Target Colon Disease
	5:35-5:40	10:35-10:40	7:35-7:40	Francesca Gavins	Effect of Food and an Animal's Sex on P-Glycoprotein Expression and Luminal Fluids in the Gastrointestinal Tract of Wistar Rats
	5:40-5:45	10:40-10:45	7:40-7:45	William Murphy	Identification of Amino Acids that Impact Bile Acid Transport in Organic Solute Transporter Alpha/Beta (OSTα/β; SLC51A/B), a Heteromeric Solute Carrier Protein Upregulated in Hepatocytes of Patients with Cholestatic Disorders and Nonalcoholic Steatohepatitis (NASH)
	5:45-5:50	10:45-10:50	7:45-7:50	Thomas Kralj	Characterisation of Cholestatic Drug-Induced Liver Injury Using In Vitro Models
	5:50-5:55	10:50-10:55	7:50-7:55	Heba Abdellah Ali	Novel Platforms for Targeted Colon Delivery
	5:55-6:00	10:55-11:00	7:55-8:00	Chitra Saran	Role of Sodium Taurocholate Co-transporting Polypeptide (NTCP) and Altered Bile Acid Homeostasis in Dasatinib- and Pazopanib-induced Cholestatic Liver Injury
CLOSE				Mike Jarstfer	Close

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Abstracts

Aaron Devanathan, UNC

Adequate antiretroviral (ARV) concentrations in lymphoid tissues are critical for optimal antiretroviral therapy. While the spleen contains 25% of the body's lymphocytes, there are minimal data on ARV penetration in this organ. This study quantified total and protein-unbound splenic ARV concentrations, and determine whether drug transporters, sex, or infection status were modifiers of these concentrations in animal models and humans. Two humanized mice models [hu-HSC-Rag (n=36; 18 HIV+ and 18 HIV-); bone marrow-liver-thymus (n=13; 7 HIV+ and 6 HIV-)] and one nonhuman primate model [NHP; rhesus macaque (n=18; 10 SHIV+ and 8 SHIV-) were dosed to steady-state with ARV combinations. HIV+ human spleens (N=14) from National NeuroAIDS Tissue Consortium were analyzed post-mortem (up to 24h post-dose). ARV concentrations were measured by LC-MS/MS, drug transporter concentrations were measured with LC-MS proteomics, and protein binding in NHP spleens was determined by rapid equilibrium dialysis. Mice generally had the lowest splenic concentrations of the three species. Protein binding in splenic tissue was 6-96%, compared to 76-99% in blood plasma. NHPs had quantifiable Mrp4, Bcrp, and Ent1 concentrations, and humans had quantifiable ENT1 concentrations. None significantly correlated with tissue ARV concentrations. There was also no observable influence of infection status or sex. With these dosing strategies, NHP splenic penetration most closely resembled humans. These data can inform tissue pharmacokinetic scaling to humans to target HIV reservoirs by identifying important species related differences.

Alaa Alsharif

Background: Few studies have shown that an increased risk of dementia is associated with diabetes mellitus. Objective: To estimate the prevalence and incidence of dementia in people with diabetes in primary care in the UK. Methods: We conducted a descriptive study using the UK The Health Improvement Network (THIN) database. People diagnosed with diabetes from 2000 to 2016 were included in the study. Prevalence and incidence rates of dementia were calculated annually, stratified by age and gender. Results: The prevalence of dementia was 0.424% [95%CI (0.420% - 0.427%)] in 2000 and 2.508% [95% CI (2.501% - 2.515%)] in 2016. The highest prevalence was in those aged 85+ from 2.9% [95%CI (2.890% - 2.974%)] in 2000 to 11.3% [95% CI (11.285% - 11.384%)] in 2016. The incidence of dementia increased 3.7 times, from 0.181 cases per 100 persons [95% CI (0.179 - 0.183)] in 2000 to 0.683 cases per 100 persons [95%CI (0.679-0.686)] in 2016, respectively. Women had a higher prevalence and incidence of dementia than men 3.138% [95% CI (3.127% - 3.150%)] vs 2.014% [95% CI (2.006% - 2.022%)] and 0.820 [95% CI (0.814 - 0.826)] vs 0.576 cases per 100 persons [95%CI (0.571-0.580)] in 2016, respectively. Conclusion: There was a trend of increasing prevalence and incidence of dementia in people with diabetes over the period of 2000 to 2016. This study adds to the evidence on dementia prevalence and incidence, particularly in the diabetic population.

Amanda Peterson

Macrophages are part of the frontline response in the innate immune system and are responsive to their environment which determines their function. Their function has been attributed to changes in metabolism where macrophages that have been stimulated by lipopolysaccharide (LPS) are highly glycolytic. Another environmental cue that macrophages are sensitive to are catecholamines that are released from activation of the sympathetic nervous system. There is evidence to suggest that Î²-adrenergic signalling has an anti-inflammatory role in modulating immune responses. The metabolic phenotype of macrophages stimulated by Î²AR signalling has not been defined. Therefore, we undertook an untargeted metabolomics approach to investigate the effects of Î²-agonism on LPS-stimulated macrophage metabolism.
Stimulation of LPS-stimulated macrophages with a Î²AR agonist, isoprenaline, resulted in a decrease of metabolites in glycolysis and pentose phosphate pathway by 20-50% compared with LPS alone. The incorporation of 13C-glucose labelling provided further evidence of LPS-induced flux of glucose from glycolysis towards the pentose phosphate pathway and the addition of isoprenaline decreased key products in the pentose phosphate pathway. Additionally, isoprenaline reduced levels of metabolites in nucleotide biosynthesis pathways from LPS alone.

However, total pools of nucleotides were abundant in both LPS-treated groups (+/- isoprenaline), suggesting active salvage pathways. The secretion of cytokines into cell culture media was also measured and it revealed that isoprenaline decreased pro-inflammatory cytokines. Further studies are evaluating the Î²AR subtypes involved in regulating metabolism and macrophage function.

Atheer Awad

Visual impairment and blindness affects 285 million people worldwide, resulting in a high public health burden. This study reports, for the first time, the use of three-dimensional (3D) printing to create orally disintegrating printlets (ODPs) suited for patients with visual impairment. Printlets were designed with Braille and Moon patterns on their surface, enabling patients to identify medications when taken out of their original packaging. Printlets with different shapes were fabricated to offer additional information, such as the medication indication or its dosing regimen. Despite the presence of the patterns, the printlets retained their original mechanical properties and dissolution characteristics, wherein all the printlets disintegrated within ~5 s, avoiding the need for water and facilitating self-administration of medications. Moreover, the readability of the printlets was verified by a blind person. Overall, this novel and practical approach should reduce medication errors and improve medication adherence in patients with visual impairment.

Banaz Jalil

Herbal supplements pose a global challenge in quality and safety. The lack of regulations and less stringent supply chain, which adulterations with undeclared synthetic substances may occur are considered the major contributor. Pharmacists manage these products, and their role is critical to educate and advise the public and ensure the quality and safety of these products. The study's aim is to explore Jordanian pharmacist's perception of herbal supplements.

The study's link was completed by 401 participants, which was distributed online via Social media. The majority of the participants (n=258) were in the 21-30 years' age range and the 31-40 years' age range (n=94), other age groups (n=49), bachelor's in pharmacy or Diploma (n=379), Master's degree level (n=18) and PhD qualifications (n=1), and PharmD (n=3), graduated from Al-Isra University (n=122), University of Jordan (n=96), Al-Zaytoonah University (n=46), University of Petra (n=23), Al-Ahliya Amman University (n=22), Jordan University of Science and Technology (n=20), other universities (n=72), no further training on herbal medicines received (n=388), and had further training on herbal medicines received (n=13). 98% reported the availability of herbal supplements in their pharmacies; supplements for weight loss (15%), followed by supplements for sexual and sports enhancements (14%) and maintaining general health (12%) were the top categories of products requested by the Jordanians consumers respectively. While supplements for maintaining general health (12%), followed by those used for weight loss, (11%) and skin conditions (9%) were the top categories of products recommended by the Jordanians pharmacists respectively. 96% of Jordanian pharmacists stated their willingness to advise consumers on the safety of herbal supplements. The project provides a unique contribution to the evolving discipline of pharmacy research and education of herbal supplements.

Ben Bowles

The aim of this project is to develop a medical implant that obviates the requirement of systemic dosing by providing a method of local drug release to the target area. Through utilisation of SLA 3D printing, we aim to develop and produce a drug eluting device that provides unidirectional release of patient-specific payloads at pre-determined pharmacokinetic rates. However, before a specific focus could be placed on cancer, three major problems associated with SLA 3D printing pharmaceutics had to be solved. Firstly, SLA 3D printed materials have unsuitable physical properties for medical device applications. Secondly, photopolymer systems based on (meth)acrylate-based monomers/macromers are associated with toxicity and hence have limited use as pharmaceutics. Finally, commercial SLA 3D printers do not support the use of custom photopolymer systems.

Solving each of these problems would provide solid groundwork for the development of SLA 3D printed drug eluting implants for local chemotherapy. To solve the issue of poor mechanical properties, a range of current and novel photopolymers were synthesised, characterised and compared against one another and reference materials. To solve the issue of material toxicity, different post-processing procedures were explored and utilised in attempt to render SLA 3D printed materials as biocompatible. Finally, an RT-FTIR spectroscopy tool was developed to bridge the gap between unprintable and printable photopolymer systems. Furthermore, extensive drug release studies were conducted with aim to characterise effect of different SLA 3D printed materials on drug release kinetics.

Cassandra Jay Hatzipantelis

The severity of cognitive impairments associated with schizophrenia (CIAS) is the most accurate predictor of patient outcomes and to date there remains no antipsychotic capable of improving CIAS. The orphan G protein-couple receptor, GPR52 has been highlighted as a prospective therapeutic target for the treatment of CIAS due to its unique expression and signalling profile and enrichment in brain regions essential for cognitive functions aberrant in schizophrenia. While GPR52 agonists could theoretically improve CIAS, there is a paucity of literature assessing the pro-cognitive capacity of GPR52 ligands *in vivo*. Using the translationally-relevant mouse touchscreen-based spatial working memory task, TUNL (trial-unique, delayed nonmatching-to-location) we assessed the pro-cognitive efficacy of the GPR52 agonist, 3-BTBZ, in an acute pharmacological mouse model of CIAS (MK801). We found that MK801 significantly impaired working memory performance in TUNL and that 3-BTBZ was able to completely reverse these MK801-induced deficits in working memory. Furthermore, in the absence of MK801, 3-BTBZ significantly improved performance over vehicle at more difficult working memory loads. These data demonstrate not only the schizophrenia-relevant pro-cognitive efficacy of GPR52 agonists in a translational behavioural task, but also that GPR52 agonists can display cognitive enhancing properties in their own right. These data therefore validate GPR52 agonists as a novel and promising therapeutic option for the treatment of working memory deficits in schizophrenia and further implicate a putative physiological role of GPR52 activity in working memory processes.

Chengsheng Ju

We aimed to determine trends and patterns of anti-dementia medication consumption in 66 countries/regions.

Integrated Data Analysis System database to estimate anti-dementia medication consumptions between 2008 and 2018. 66 countries/regions with anti-dementia medication sales data available were analysed, and stratified by country income level (Low/Middle-income countries (LMICs), n=27; High-income countries (HICs), n=37; regions, n=2). The yearly consumption volume was estimated by Defined Daily Dose [(DDD) (WHO DDD, harmonised the size, strength and form of each pack and reflects average dosing)] per 1000 inhabitants per day. Changes in consumption over time were quantified as percentage changes and compound annual growth rates (CAGR) in consumption per person.

Total anti-dementia medication consumption increased from 0.85 to 1.33 DDD per 1000 inhabitants per day between 2008 and 2018 (LMICs: 0.094 to 0.396; HICs: 3.88 to 5.04), which is an increase of CAGR of 4.53% per year. The increase was mainly driven by the LMICs (CAGR=15.42%) in comparison to the HICs (CAGR=2.65%). The overall consumption from 2008 to 2018 increased for all four agents: memantine (CAGR=8.51%), rivastigmine (CAGR=6.91%), donepezil (CAGR=2.72%), and galantamine (CAGR=0.695%). In 2018, the most commonly used anti-dementia medication globally was donepezil contributed to 49.8% of total sales volume, followed by memantine (32.7%), rivastigmine (11.24%) and galantamine (6.36%).

There was an increasing trend in anti-dementia medication consumption globally. The variations in the use of anti-dementia medications between countries/regions reflect international inconsistencies between treatment guidelines and reimbursement policies.

Chitra Saran

Tyrosine kinase inhibitors (TKIs) such as dasatinib, gefitinib, sorafenib, regorafenib and pazopanib increase liver enzymes in 10-65% of patients. Pazopanib and regorafenib have a boxed warning for hepatotoxicity, while sorafenib and gefitinib are labelled with warnings and precautions for liver injury. Although, dasatinib is considered safe, case reports indicate that dasatinib may reactivate hepatitis B; sodium taurocholate co-transporting polypeptide (NTCP) is the hepatocyte entry receptor for the virus. Dasatinib, gefitinib, sorafenib and pazopanib competitively inhibit the bile salt export pump (BSEP). This study examined the roles of bile acid transporters, primarily NTCP and BSEP, and altered bile acid homeostasis in TKI-induced hepatotoxicity. Sandwich-cultured human hepatocytes (SCHH; lots EGO and WID) were pretreated with clinically relevant concentrations of these TKIs for 24hrs. The impact of TKIs on membrane bile acid transporter expression was examined by western blotting. The effect of TKIs on endogenous bile acid species was quantified by liquid chromatography coupled with tandem mass spectrometry. Membrane NTCP protein levels increased by 75-142% (dasatinib), 67-119% (gefitinib), 43-123% (sorafenib), 14-94% (regorafenib) and 28-99% (pazopanib) in both SCHH lots with no significant change in membrane BSEP protein levels. The increase in NTCP expression may contribute to hepatitis B reactivation with dasatinib therapy. Total intracellular bile acid content increased by 15–29% with dasatinib, 32-38% with regorafenib and by 43–53% with pazopanib treatment in both lots. Higher total bile acid content in SCHH is consistent with increased NTCP expression and altered bile acid homeostasis, potentially contributing to TKI-induced hepatotoxicity.

Christine Madla

Active pharmaceutical ingredients are routinely formulated with excipients in the manufacture of drug products. Excipients are considered to be inert components in a formulation, although recent research has contested its inactive behaviour. This study investigated the effect of the excipient polyethylene glycol 400 (PEG 400) on the oral bioavailability and intestinal permeability of cimetidine in male and female human volunteers. Aqueous solutions of cimetidine with PEG 400 at 0%, 0.3%, 0.5%, 0.7% and 1.0% w/v were orally administered to both sexes. Urine samples were then collected and assayed for cimetidine quantification which reflected oral bioavailability. This human study showed that PEG 400 at 0.3%, 0.5% and 0.7% w/v concentrations significantly increased cimetidine bioavailability by 34%, 58% and 41% respectively, although this enhancement was only demonstrated in men and not women ($p < 0.05$). Using chamber transport studies with male human jejunal tissues revealed that cimetidine permeability increased by 26%, 48% and 29% with PEG 400 at 0.3%, 0.5% and 0.7% w/v respectively ($p < 0.05$). No such enhancement was demonstrated in female tissues ($p > 0.05$). To understand the mechanistic action of PEG 400 on cimetidine transport, human jejunal tissues were pre-treated with P-gp inhibitor valspodar. When intestinal P-gp was inhibited, the sex- and dose-dependent effect of PEG 400 with cimetidine was eradicated, thus confirming that PEG 400 has a modulatory, not inhibitory, effect on P-gp. Consequently, PEG 400 is not inert at pharmaceutically relevant concentrations, albeit sex- and dose-dependent via its modulation on human intestinal P-gp.

Danielle Andrews

Bitter-blockers are compounds which act on taste 2 receptors in the oral cavity and interfere with bitter-taste perception. As such, they could offer an improved taste-masking outcome for paediatric liquid formulations when traditional sweeteners are not successful. Initial work reviewing the literature and creating a scoring system for bitter-blockers as potential excipients highlighted three of interest; sodium acetate, sodium gluconate and adenosine 5’monophoshate sodium salt (Na AMP). Subsequent e-tongue work suggested these could be used in

low concentrations to reduce bitter perception of quinine. This work evaluates their bitter masking efficacy in the BATA model using the concentrations found to be beneficial in the e-tongue. The BATA model is a more translatable model of palatability.

12 Crl:CD (SD) male rats (Charles River UK) approximately 12 to 16 weeks of age were exposed to a range of solutions containing quinine at IC50 and IC90 level with and without bitter-blocker in a series of Davis Rig (DiLog Instruments Inc) trials. Sodium acetate was assessed at 3, 10, 30, 100 and 300mM, sodium gluconate at 10, 30, 100, 300 and 1000mM and NaAMP at 1, 3, 10, 30 and 100mM. Rats acted as their own controls.

Sodium acetate and sodium gluconate were not effective at masking the bitterness of quinine and there was no difference in lick rate between quinine alone (0mg/mL bitter-blocker) and any concentration of blocker tested.

NaAMP significantly improved the palatability of IC50 quinine (Q50) at the top three concentrations (10, 30, 100mM). 100mM NaAMP significantly improved the lick rate for IC90 quinine (Q90)

No concentration of any bitter-blocker gave a statistically similar lick rate to water suggesting full taste-masking is not achieved but 100mM NaAMP increased the lick rate by 100% for both concentrations of quinine.

Bitter-blockers could improve taste--masking for children's liquid formulations. Our results suggest the BATA could be used to assess liquid formulations containing Na AMP to assist in the development of paediatric medicines with improved taste qualities and compliance. However, our results also suggest the BATA may not be suitable to assess the use of sodium acetate and sodium gluconate.

Erin Scholz

HIV persistence in tissue reservoirs such as lymph nodes is a major barrier to HIV cure. While antiretrovirals (ARVs) suppress viral replication, antiretroviral therapy (ART) interruption results in rebound viremia that may originate from lymph node tissue. To understand the relationship between places of ARV exposure and viral replication in lymph nodes, we performed mass spectrometry imaging (MSI) of 6 ARVs, RNAscope in situ hybridization of viral RNA, and immunohistochemistry of collagen in mesenteric lymph nodes from 8 uninfected nonhuman primates (NHPs), and 10 NHPs infected with reverse transcriptase-simian/human immunodeficiency virus; all animals were dosed to steady-state with combination ART. MATLAB-based quantitative imaging analysis was used to evaluate spatial and pharmacologic relationships between these targets. Using MSI, 65% of mesenteric lymph node tissue area was covered by cumulative combination ART exposure, and 85% of that coverage was from one ARV alone. Additionally, 67% of total RNA and 61% of cell-associated RNA was exposed to any ARV. Maraviroc had the highest lymph node exposure of all ARVs evaluated, yet only 3.9% of ARV-covered infected cells were exposed to maraviroc concentrations greater than its IC50 concentration, despite total-tissue concentrations of all 6 ARVs meeting IC50 concentrations. Collagen covered ~35% of tissue area, but did not influence ARV distribution heterogeneity. Our findings are consistent with our hypothesis that ARV distribution, in addition to total drug concentration, must be considered when evaluating viral persistence in lymph nodes and other reservoir tissues.

Francesca Gavins

Limited information between the sexes and the effect of food consumption on the gastrointestinal (GI) physiology is understood. This study aimed to investigate the potential sex differences and effect of food intake on the intestinal luminal fluid and the efflux membrane transporter P-glycoprotein (P-gp) along the intestinal tract of male and female Wistar rats. To characterise the intestinal luminal fluids, pH, surface tension, buffer capacity and osmolality were measured. Absolute P-gp expression along the intestinal tract was quantified via liquid chromatography-tandem mass spectrometry (LC-MS/MS). In general, the characteristics of the luminal fluids were similar in male and female rats along the GI tract. In fasted male rats, the absolute P-gp expression gradually

increased from the duodenum to ileum but decreased in the colon. A significant sex difference ($p < 0.05$) was identified in the jejunum where P-gp expression in males was 83% higher than in females. Similarly, ileal P-gp expression in male rats was approximately 58% higher than that of their female counterparts. Conversely, following food intake, a significant sex difference ($p < 0.05$) in P-gp expression was found but in a contrasting trend. Fed female rats expressed much higher P-gp levels than male rats with an increase of 77% and 34% in the jejunum and ileum, respectively. A deeper understanding of the effects of sex and food intake on the absorption of P-gp substrates can lead to an improved translation from pre-clinical animal studies into human pharmacokinetic studies.

Hajira Bilal

Pseudomonas aeruginosa chronically infects patients with cystic fibrosis and is associated with increased morbidity and mortality. Ceftazidime and tobramycin are considered first-line treatments. However, hypermutability and biofilm formation results in treatment failure due to selection of resistant mutants. We systematically investigated the pharmacodynamic effects of intravenous versus inhalation dosage regimens of tobramycin with and without intravenous ceftazidime.

Two clinical hypermutable P. aeruginosa isolates CW30 (MICCAZ 0.5 mg/L, MICTOB 2 mg/L) and CW8 (MICCAZ 2 mg/L, MICTOB 8 mg/L) were investigated for 120 h in the dynamic in vitro CDC biofilm reactor. Clinically relevant treatments were: continuous infusion ceftazidime 9 g/day (33% lung penetration); intravenous tobramycin 10mg/kg Q24h (50% lung penetration); and tobramycin 300 mg Q12h as inhalation, and their combinations. Total and less-susceptible planktonic and biofilm bacterial counts were carried out over 120 h. Ceftazidime and Tobramycin were quantified by LC-MS/MS.

All treatments in monotherapy were ineffective for both isolates, with a regrowth of planktonic (â‰¥4.7log10 CFU/mL) and biofilm (>6.6log10 CFU/cm2) bacteria, and amplification of less-susceptible planktonic and biofilm bacteria by 120 h. Both combination treatments demonstrated synergistic bacterial killing, not only for planktonic but also biofilm bacteria; however, greatest bacterial killing against both modes of bacterial growth was observed with the combination simulating tobramycin inhalation. In addition, the combination regimens resulted in a very substantial suppression of resistance of planktonic and biofilm bacteria to each of the antibiotics for both isolates.

Thus, ceftazidime combinations with intravenous or, especially, inhaled tobramycin hold promise to treat challenging infections caused by hypermutable P. aeruginosa strains and warrant clinical investigation.

Harry Smallman

Recently, continuous flow reactors as an enabling technology in chemical synthesis have grown in popularity and utility. In particular, continuous flow processing is well suited to the generation and use of reactive intermediates owing to the ability to scale up reactions, contain hazards and heat solvents past their atmospheric temperature boiling points.
Ketenes are a family of reactive intermediates that demonstrated interesting reactivity and uses in the synthesis of many drug targets and natural products. My current research focuses on the chemistry of acyl ketenes, generated from diazo dicarbonyl compounds, under continuous flow conditions. Preliminary results and progress towards reaction condition optimisation will be discussed, as well as future work and outlook to access interesting molecular scaffolds towards drug discovery and analogue synthesis.

Hassan Alwafi

Patients with Type 2 diabetes mellitus (T2DM) have an increased risk of atrial fibrillation (AF). The current study aimed to investigate the prevalence and treatment of AF in patients with T2DM, assess the impact of direct oral

anticoagulants (DOACs) introduction on oral anticoagulant (OACs) prescribing rates, and factors associated with OAC initiations in patients with T2DM and AF.

The Health Improvement Network (THIN) database (2001-2016), was used to examine the annual prevalence and treatment of AF in T2DM. The impact of DOACs introduction on OAC prescribing rates were investigated using interrupted time series analysis (ITS). Factors associated with OAC initiations were also identified using multivariate logistic regression.

The prevalence of AF increased from 2.7 (95% confidence intervals (CI) 2.5-2.8) in 2001 to 5.0 (4.9-5.1) in 2016 per 100 persons. OACs prescribing within 30-days of AF diagnosis increased from 21.5% in 2001 to 56.8% in 2016. ITS analysis showed that OAC prescribing increased after DOAC introduction (P<0.001), however, no immediate change was observed (P=0.29). T2DM patients with AF, aged 60-79, male gender and BMI ï‚³ 25 were more likely to receive OAC, adjusted OR 1.3 (1.2-1.5) for aged 60-79, 1.3 (1.2-1.4) for male gender and 2.0 (1.9-2.2) for BMI â‰¥ 25, respectively.

This study highlighted an increase in prevalence of AF in patients with T2DM during the study period. Further studies are warranted to investigate factors contributing to the underuse of OAC in patients with T2DM and AF.

Heba Abdellah Ali

Colon specific drug delivery systems (CDDS) are highly desirable approaches for the treatment of colon diseases such as inflammatory bowel disease, irritable bowel syndrome, and colorectal cancer. CDDS are also beneficial for the systemic delivery of labile biomolecules such as peptides, proteins. pH-dependent systems are one of CDDS that have no practical applications so far. Their efficiency is attenuated by the similarity in pH between the small intestine and the colon that often leading to the prior release of the drug into the small intestine. Hence, our lab largely focuses on developing novel pH-dependent systems with versatile drug release kinetics and improved site-specificity to meet the growing therapeutic need.

The payload (fluorophore or drug) will be attached to pH-sensitive handle then the resultant prodrug will be covalently attached to porous silicon nanoparticles via click chemistry. The site-specificity will be achieved via changing the chemistry of the linker with the rise in pH along the GIT. Fluorescence-based assays are being used to study the stability of the synthesized linkers at conditions that mimic the pH along the GIT.

Preliminary results showed that compound; MIPS-0049901 successfully protects the payload at pH conditions that are similar to the stomach (pH 1.2) and the duodenum (pH 5.0). Also, it preserves 60% of the payload from being released early in the small intestine. Additionally, a sustained release of the payload was achieved in the colon; > 90% of payload released over 38 h.

We are the pioneers to utilize smart linker chemistry in colon delivery formulations, and our efforts present MIPS-0049901 as a promising candidate for future optimization.

Isabella Young

Globally 37.9 million people are living with HIV and half of all pregnancies are unplanned. There is an urgent need for the control and prevention of these sexual and reproductive health indications since current preventative daily oral dosing regimens are ineffective due to low patient compliance. Thus, we propose to develop a polymer-based, ultra-long-acting, injectable in-situ forming implant (ISFI) as a multipurpose technology (MPT) for the prevention of HIV and unplanned pregnancy.

ISFIs are formulated in a 1:2 (w/w) poly(lactic-co-glycolic acid) (PLGA) and N-methyl-2-pyrrolidone (NMP) solution.

ISFIs were loaded with antiretroviral, Dolutegravir (DTG), and one of two contraceptives, Etonogestrel (ENG) or Medroxyprogesterone acetate (MPA). The drug-loaded ISFI formulation (30 ÂµL) was injected into 200 mL of PBS where a phase inversion occurs to generate a solid depot and evaluated for in vitro release kinetics at 37ÂºC under sink conditions. Sample aliquots of release media are collected at preset time intervals until 100% cumulative release was reached and analyzed using high performance liquid chromatography.

Previous data has shown that drug release can be tuned with the ISFI technology, DTG-ISFIs could successfully maintain target drug plasma concentrations in vivo, and can successfully co-formulate multiple drugs in a single ISFI formulation. In vitro release studies showed that DTG/DMPA ISFI formulations achieved target in vitro release rates and duration. Further optimization is required to enhance the release rate of DTG/ENG-ISFIs. Overall, this first-in-line injectable MPT can address and close a major gap in the field of HIV PrEP and unplanned pregnancies.

Jacob Larson

Aberrant KRAS signaling is one of the primary drivers of oncogenesis, with mutations in KRAS implicated in prevalent pancreatic, lung, and colon cancers. Oncogenic mutations keep KRAS in the active state, such as by preventing GTP hydrolysis or rapidly exchanging in GTP. Based on KRAS's picomolar affinity for these nucleotides, it is nearly impossible to produce competitive inhibitors. Yet, there is a need to develop anti-KRAS therapies as few effective treatments for KRAS-driven cancer exist. This project focuses on finding small molecule chemical probes and binding peptides against KRAS A146T, a "fast cycling" mutant, most often found in colorectal cancer (CRC). A146T has reduced affinity for nucleotides compared to other isoforms, thus we hypothesize that we will discover peptides or small molecules that inhibit this vulnerable KRAS mutant.
Our approach involves novel TR-FRET and phage display screens that allow rapid and efficient exploration of a large, diverse chemical space to identify molecules that inhibit KRAS A146T. Our TR-FRET-based high-throughput screen (HTS) will discover small molecules that bind KRAS A146T's nucleotide site. Preliminary hits will be validated using orthogonal assays, dose-response curves, and ITC binding assays. In parallel, we will synthesize a phage display library based on the KRAS-binding macrocyclic peptide KRpep2d to uncover novel peptides that bind A146T. We will rationally design peptides based on preliminary hits to optimize size, permeability, and affinity, and top peptide binding will be validated by phage ELISA, ITC, and TR-FRET assays. Following identification and validation of small molecules and peptides, we will further characterize their potential use as chemical probes with methods such as X-Ray crystallography, cell permeability and selectivity assays, and growth inhibition and apoptosis assays on A146T-driven CRC cells.

Jiawei Zhou

The sum of target lesions is often used to evaluate patient objective response to interventions, without considering the response heterogeneity across metastatic lesions. This study argues that the response heterogeneity across metastases is informative to drug efficacy and patient survival.

We analyzed the longitudinal size data in 11,404 metastatic lesions from 2,802 colorectal cancer patients and examined their spatiotemporal heterogeneity in response to the first-line therapies. The response heterogeneity across lesions was computed by the Gower distance of five variables describing the tumor response patterns: response, stable, and relapse phase, tumor nadir and last size before trial ends.

Our results showed that the response dynamics of all metastatic lesions broadly differ across anatomical locations and therapies. About 60% of patients had at least one lesion responding contrarily from the total tumor size. High inter-lesion heterogeneity is closely associated with worse patient overall survival (HR=1.14, $p < 0.001$) and progression-free survival (HR=1.19, $p < 0.001$). Targeted therapies (bevacizumab or panitumumab), combined with the chemotherapy backbone, reduced the inter-lesion heterogeneity ($p<0.05$) and elicited a more favorable effect on liver lesions ($p < 0.001$), compared to chemotherapy alone. Moreover, the favorable responses in liver

metastases were more relevant to extended patient overall survival ($p < 0.001$) than the lesions in the lungs and lymph nodes.

In conclusion, the high spatiotemporal heterogeneity across metastatic lesions is closely associated with treatment efficacy and patient overall survival, which have strong implications to our current method in drug evaluation and patient prognosis.

Jiayin Diao

The calcium-sensing receptor (CaSR) detects changes in extracellular calcium (Ca2+o) to maintain Ca2+o homeostasis. The CaSR is upregulated in asthma, and CaSR negative allosteric modulators (NAMs) reduce inflammation, remodelling, and airway hyperresponsiveness in a mouse model of chronic allergic airways disease (1). Whether CaSR NAMs, which engender biased modulation (2), have different bronchodilator and/or bronchoprotective effects is unknown.

To assess CaSR NAM (NPS2143, Pfizer cmpd 1, BMS cmpd 1) bias in CaSR-HEK293 cells and compare NAMs with the Î²2-adrenoceptor agonist salbutamol for airway relaxation.
Methods. Intracellular calcium (Ca2+i) mobilisation and IP1 accumulation assays in CaSR-HEK293 cells were used to quantify the affinity and cooperativity of CaSR NAMs. Precision cut lung slices from male C57Bl/6 mice were prepared to visualise changes in airway area after contraction stimulated by 300 nM methacholine (MCh) followed by NAM or salbutamol (bronchodilation assays) or after overnight pre-incubation with 1 Î¼M NAMs (bronchoprotection assays).

CaSR NAMs engendered differential and biased modulation of Ca2+i mobilisation and IP1 accumulation. CaSR NAMs relaxed pre-contracted airways in a biphasic manner, with the highest potency first phase of their response being 1000-fold higher potency than salbutamol. Salbutamol and NAMs caused variable maximal bronchodilation (salbutamol 50Â±7%, NPS2143 32±8%, Pfizer cmpd 1 70±16%, BMS cmpd 1 48±16%, n=4-6). Overnight incubation with NPS2143 and Pfizer cmpd 1, but not BMS cmpd 1 prevented contraction.

CaSR NAMs show differential effects on MCh-induced airway contraction, with Pfizer cmpd 1 exhibiting greater bronchodilator efficacy and potency than salbutamol. Confirmation of benefit compared to salbutamol in asthmatic airways would further support the CaSR as a novel therapeutic target for the treatment of asthma.
(1) Yarova et al (2015) Sci Transl Med. 7:284
(2) Davey et al (2012) Endocrinology. 153:1232

Jordan Joiner

Pancreatic cancer has a dismal 5-year survival rate as a consequence of late diagnosis and therapy resistance. Attempts to invigorate anti-tumor immune responses using checkpoint blockade have been unsuccessful, highlighting the need to understand barriers that impede immunotherapy. Low-intensity focused ultrasound has emerged as a potential immunomodulatory treatment modality in several cancer types. One of the main consequences of ultrasound application at the tumor site is a transient increase in vascular permeability and availability of antigens that may boost delivery of therapeutics and augment anti-tumor immune responses.

To understand how FUS treatment modulates anti-tumor immunity and vascular parameters, we have used murine syngeneic models of pancreatic cancer. We treated 30 female C57Bl/6J mice with subcutaneous KPC tumors using low-intensity focused ultrasound and the following parameters were used: 100 Hz PRF, 1 MHz frequency, 0.5 MPa, 10% duty cycle, 0.13 W/cm2, and 2 seconds/spot for a total treatment time of 8-10 minutes with an IV infusion of decafluorobutane microbubbles (MBs) with a DSPC-PEG2k lipid shell (7 x 107 MBs total). Animals were sacrificed at

2 days (n=8) and 14 days (n=8) post-treatment to evaluate tumor growth and immune cell filtration in the tumor and lymph node. Part of the tumor tissue was analyzed for histology and the rest for flow cytometry.

Joshua Rennick

Changes in pH are critical for the modulation of scores of intracellular processes, and measuring these changes offers insight into numerous biological functions. Here we demonstrate that the fluorescent protein dsRed variant, mApple, can be used as an intracellular pH sensor by following changes in the fluorescent lifetime. Using fast fluorescent lifetime imaging we can measure subcellular pH by localising mApple to several intracellular compartments including the cytosol, endosome lumen and lysosome lumen. Using a phasor plot, a colour scale can be applied to confocal fluorescent images to represent different lifetimes and therefore different pH values. To demonstrate the utility of this system we followed the pH of endosomal compartments when NIH-3T3 cells are treated with polyethylenimine, an endosomal escape agent proposed to work via the proton sponge effect. We did not observe a change in the pH of endosomal compartments after treatment with polyethylenimine despite significant differences with bafilomycin A1 (acidification inhibitor) treatment, which underscores the ability of the sensor to distinguish pH fluctuations of many processes. This sensor could be applied to many other applications such as detection of endosomal disruption, protease activity and cellular stress based on these facile pH measurements.

Liisa Niitsoo

Tumour cells present a variety of surface markers that could be targeted using a variety of high affinity ligands for safer and more specific treatment, as the markers are either not expressed, or expressed to a much lower degree, in healthy cells. Nanoparticles (NPs) provide multifunctional ligand platforms as well as diagnostic and therapeutic opportunities for the treatment of a variety of conditions, many advantages over unencapsulated drugs. However, realisation of actively targeted NPs has been challenging in the clinic. GCPQ is an amphiphilic chitosan derived polymer that self-assembles into highly stable NPs capable of encapsulating poorly water soluble hydrophobic drugs. In biological fluids, these NPs appear to be stable and sustain long circulation, as well as avoid the liver and spleen. Hence, these NPs could be an interesting platform to address some of the challenges for active NP targeting in cancer. The current aims are to explore active and potentially multiplexed targeting to solid tumours using folate receptor targeting modified GCPQ NPs. Multifunctionality of GCPQ can be achieved either by conjugation of multiple functional moieties at defined stoichiometries, or via assembly of a combination of mono-functional polymers with distinct properties. These strategies could tune the avidity and affinity of a given targeted particle as well as explore combination targeting using a mixture of ligands, resulting in stable and targetable particles with improved binding.

Lixiang Zhao

Maize starch is a bacteria trigger, Eudragit S100 is a PH trigger.
Both of them aiming for targetting colonic disease.

Due to the solution for each trigger is different, applied co-axial techniques to formulate the products.

Maize starch with the model drug (Metronidazole) dissolved in formic acid as a core solution; Eudragit S100 in ethanol as a shell solution

Marco Sancandi

The symptomatology of Parkinson's disease consists of motor and non-motor symptoms (NMSs). The latter has been linked to a loss of neurotransmitters other than dopamine and it has been shown to be modulated by treatments that do not act directly on the dopaminergic system, such as the glucagon-like peptide-1 receptor

agonist exendin-4 (EX-4). Nevertheless, the aetiology of NMs, alongside with their potential treatments, has yet to be fully investigated. Recently, using injections of the neurotoxins N--N-ethyl-2-bromobenzylamine (DSP-4) and 6-hydroxydopamine (6-OHDA), a rat model of pre-motor PD, that displayed NMSs in the absence of motor symptoms was developed. In this study, taking advantage of this model, the effect of partial noradrenergic and dopaminergic denervation in several brain regions within the olfactory pathway was investigated using immunohistochemical and electrophysiological techniques. Surprisingly, the combined denervation led to a reduction in the expression of interneuronal calcium binding proteins in the prefrontal cortex, whilst the expression in the olfactory bulbs was found to be increased, alongside with dopaminergic expression. Electrophysiologically, neurones recorded intracellularly in layer II-III of the piriform cortex from the model exhibited abnormal prolonged epileptiform-like depolarizing postsynaptic potentials on local electrical stimulation of lateral olfactory tract (LOT) afferent fibers. Both structural and electrophysiological changes were partially prevented following treatment with EX-4. This rat model of pre-motor PD offers a useful means for research into early diagnosis as well as early intervention of PD, possibly resulting in a delay of disease progression together with improved patient's quality life.

Matthew Challis

Current antimalarial treatments are failing due to the emergence of resistance to current frontline antimalarials and there is an urgent need for the development of new antimalarial compounds, with novel mechanisms of action (MoA). The aminobenzimidazoles (ABIs) are a novel class of antimalarial that have excellent potency against the blood stage of Plasmodium falciparum however, the mechanism of action of these compounds remains unknown, limiting the scope for further development.

An emerging technique for identifying protein targets is the Cellular Thermal Shift Assay (CETSA). CETSA Takes advantage of the thermal stabilisation that occurs when a protein is bound by a compound, allowing the protein targets of novel compounds to be identified from a complex proteome. A lysate of P. falciparum trophozoites was incubated with increasing concentrations of our compound of interest, before being subjected to heat treatment, denaturing susceptible proteins. The denatured proteins were subsequently removed and the remaining soluble proteins were prepared for proteomics analysis via Mass Spectrometry, utilising a data independent acquisition (DIA) workflow.

This method was validated using the common antimalarial pyrimethamine, which successfully stabilised its known target dihydrofolate reductase-thymidylate synthase (DHFR-TS), highlighting the potential for CETSA proteomics to be an effective target identification method. When subsequently performed on a representative ABI compound, a shortlist of significantly thermally stabilised proteins were identified from two independent experiments. Other untargeted techniques, including in vitro resistance generation and chemo-proteomic pulldown approaches will be used to further investigate the MoA of the ABIs.

Meihua Luo

The bottlenecks of glioblastoma multiforme (GBM) treatment are the permeability of the blood-brain barrier (BBB), the low bioavailability of drugs at the tumour site, and the invasiveness of the cancer cells. This work evaluates transferrin-functionalised porous silicon nanoparticles (Tf@pSiNPs) as a glioma-targeted drug delivery system. Tf@pSiNPs are tailored to exhibit a selective and enhanced cellular internalisation and to deliver chemotherapy drugs through the in vitro BBB for glioma cell killing. We observed that Tf@pSiNPs can also inhibit glioma cell migration and invasion, even in the absence of drug loading. These attributes highlight the potential of Tf@pSiNPs as targeted anticancer drug carriers and migration inhibitors for GBM treatment.

Nazia Tabassum

The transdermal route is attractive for minimal invasive administration of small and large molecular bio-actives. Among transdermal techniques (e.g. iontophoresis, electroporation, jet injectors, ablation, powder injection, etc), micro/nanoneedles are particularly promising because of their straightforward, cost-effective, and safe

administration. However, precise control over degradation rate of micro/nanoneedles within the skin remains a great challenge. Here, we introduce porous silicon nanoneedles (pSiNNs) for pain-free transdermal drug delivery (TDD) of biomolecules with controlled degradation rate. The pSiNNs are fabricated with photolithography followed by deep reactive ion etching. Then, a porous surface of a certain thickness is developed by electrochemical anodisation in over an optimised time. pSiNNs morphology, pore size, and porous layer thickness were characterized by scanning electron microscopy. Ex vivo penetration experiment was performed on pig and mouse skin to determine the TDD into the skin. The pSiNNs with 40-50 µm length, tip diameter below 1 µm were successfully fabricated. The biodegradability and their mechanical properties found that nanoneedle biodegradability and mechanical strength could be tuned by changing porous layer thickness. In addition, small as well as macromolecular molecules could be uniformly loaded into porous layer of pSiNN arrays with adjustable drug loading capacity, and up to 250% increase compared to solid nanoneedles. Ex vivo pig and mouse skin penetration experiment demonstrated that pSiNN can significantly increase TDD. In summary, we have fabricated pSiNNs with tunable porosity, biodegradability, and mechanical strength for transdermal delivery. This platform can potentially deliver various biotherapeutics through skin and thereby contributes to innovations in pharmaceutical sciences.

Nektarios Liaskos

Drug-induced hepatotoxicity (liver injury, DILI) is a leading cause of acute liver failure and a major contributor to the attrition of drug candidates during late stage clinical trials and the withdrawal of drugs from the market. Treatment options for DILI are limited and preclinical methods of screening for hepatotoxicity in novel drugs is inaccurate. In this study a hepatic injury model was created using carbon tetrachloride (CCl_4), a well-known hepatotoxicant, which is metabolized in the liver by cytochrome P450-2E1 to form free radicals that induce topical oxidative stress. Fucus Vesiculosus, a brown alga, contains a high concentration of phlorotannins, which are thought to be effective antioxidants and therefore have hepatoprotective potential. This study was designed to identify metabolite changes in serum, urine and liver following CCl_4-administration in male Hanover Wistar rats and to determine if phlorotannins extracted from F. vesiculosus could protect against hepatotoxicity. Three groups of animals were used, each consisting of five rats: Group one (control) was treated with vegetable oil, group two received a single dosed with 1.2 ml/kg CCl_4 on the seventh day; the third group was pre-treated with 25 mg/kg phlorotannin for seven consecutive days before receiving a 1.2 ml/kg single dose of CCl_4. Serum, urine and liver samples were analysed by NMR and multivariate statistical analysis. Metabolites were identified using the Human Metabolome Database (HMDB) and further validated by spiking with the respective standard. CCl_4-treated animals showed increased levels of endogenous antioxidants, taurine and glutathione, and increased products of lipid peroxidation, including cholesterol and arachidonic acid. Supplementation with phlorotannins resulted in increased free amino acids, taurine and hypotaurine, choline and phosphocholine, dimethylglycine, β-hydroxybutyrate, cholesterol and arachidonic acid levels as compared to CCl_4-treated animals. In addition, reduced glutathione (GSH) and lactic acid were present upon phlorotannin supplementation. Further analysis revealed that two of the animals treated with phlorotannin showed possible hepatoprotection, as the levels of taurine, creatinine, formate and hippurate in these animals were similar to controls. The exposure levels of phlorotannins can be modulated in future dose-response studies. Further work will identify and map all metabolite peaks which could reveal additional information about the effects of the phlorotannins.

Nkiruka Ibeanu

Site-specific PEGylation has emerged as a method for the synthesis of multifunctional antibodies such as Fab-PEG-Fabs (FpFs) which can be exploited to provide half-life extension capabilities to antibodies and antibody motifs which exhibit typically short half-lives following intraocular administration. FpFs synthesised by site-specific PEGylation using bifunctional PEG reagents have been described as more stable than the protein on which the FpFs were based. However, final protein yield can be low, and purification is a challenge.

Click chemistry reactions are fast, simple and versatile processes which can be employed to produce modified proteins that are easily purified with high yield and may offer a modular approach for FpF synthesis compared to the use of bifunctional conjugation reagents.

The conjugation of antibody fragments (Fabs) to *bis*-alkylating PEG click reagents for the generation of FpFs was conducted using azide-alkyne cycloaddition conjugation (with *bis*-sulfone PEG-dibenzocyclooctyne and *bis*-sulfone PEG-azide) and click conjugation reactions between a PEGylated strained alkene and tetrazine (*bis*-sulfone PEG-trans-cyclooctene and *bis*-sulfone PEG-tetrazine). Results showed that both strategies yielded the desired FpFs with significantly higher reaction yield than observed with the use of a heterobifunctional reagent. In addition, the use of PEG-tetrazine and PEG-trans-cyclooctene reagents as starting materials for protein conjugation gave reactions which proceeded with quicker kinetics and greater efficacy than cycloaddition reactions. Click chemistry therefore presents a unique method for preparing FpFs and indeed other bispecific antibody formats which can be applied for half-life extension purposes.

Parham Sahandi Zangabad

Therapeutic peptides, suffer from short plasma half-life, limited oral bioavailability, rapid clearance, and low chemical stability in vivo, as well as poor patient compliance. Here we designed a nanoporous silicon-microparticle (npSiMP) formulation for protected and sustained release of Exendin-4 (a therapeutic for treatment of type 2 diabetes) via subcutaneous administration.
npSiMPs were fabricated via electrochemical etching where their particle size, pore size, and surface chemistry were tailored. npSiMPs with different pore sizes (i.e., 8 nm, 16 nm, and 45 nm) and surface chemistries (i.e., thermal hydrocarbonisation (THC; hydrophobic), thermal oxidation (TO; hydrophilic), silanisation (3-aminopropytriethoxy silane; positive charge), and thermal hydrosilylation (THS; 10-undecenoic acid; negative charge) were fabricated. Highest loading capacity (360±20µg/mg particle) and sustained release kinetics (over 60 h) were achieved when npSiMPs' pore size and surface chemistry were optimised to be 8 ±2.5 nm and, APTES silanised and thermal oxidised. Performing cAMP bioassay, we confirmed the functional activity of the released peptide as the EC50 (11pM) was determined to be similar in comparison to the standard peptide. Conducting a proteolytic activity test also showed that the payload was protected from the effects of proteolytic enzymes. Eventually, to measure the release kinetics of Exendin-4 loaded in npSiMPs in a mimicked environment to in-vivo skin subcutaneous, a model based on agarose gel integrated in a transwell plate was designed. APTES-TO pSiMP formulation using this model showed a prolonged release kinetics over 2 weeks, which showed the potential of this formulation as a prolonged delivery system via subcutaneous administration.

Pegah Maneshi

Identified as an oncogene STAT3 is a transcription factor shown to be overexpressed in 70% of cancers. STAT3s' involvement in cancer cell transformation and down-regulation of apoptosis has enhanced the appeal for the development of inhibitors to target its cancer inducing activities. However, these attempts have been unsuccessful either due to toxicity or low specificity. This study aims to understand the mechanism of action of STAT3 inhibitors of the DNA binding domain (DBD) through crystallographic analysis and provide the methodology to adapt and improve these inhibitors. STAT3 purified protein was used in the high-throughput screening fluorescence polarisation (FP) assay to identify potential STAT3:DNA binding domain inhibitors. Once identified, x-ray crystallography was used to further investigate the mode of action of these inhibitors. IC50 values obtained from FP assay data identified four compounds as potential ligands of the STAT3:DNA binding domain; Niclosamide, compound A, compound B and compound C. We then successfully co-crystallised STAT3:DNA and STAT3:DNA:Niclosamide. Co-crystallisation attempts were unsuccessful for ligands A, B and C; therefore, ligand soaking was adopted. Analysis of the electron density maps provided after diffraction at a high-throughput synchrotron facility showed evidence confirming the presence of Niclosamide at a 2.6È¦ resolution. Electron

density maps from ligand soaking experiments showed potential binding of compounds A and B to the DBD, however, a higher resolution is required for further confirmation. X-ray crystallography provides visual evidence of the site of interaction between the protein and the ligand, with this information being utilised to modify and further develop STAT3 ligands.

Rumintha Thavarajah

Additive manufacturing (AM) is more commonly known as three-dimensional (3D) printing. It is a process by which desired 3D objects can be created from a digital design with precise geometry. Stereolithography Apparatus (SLA) is one 3D printing technique, which offers high definition printing and involves an additive fabrication process.

Within the Hilton group, we are interested in using this technology in combination with chemical syntheses to optimise well known reactions. This led to the development of a novel 3D printed stirrer device that is being investigated. During a chemical reaction, the device is spun at high speeds, which allow the reactants to be rotated at a great velocity with a high flow of solvent covering over the surface of the stirrer device.

The ability to incorporate catalysts (e.g: Lewis acid catalysts) into the stirrer device has optimised both reaction efficiency and simplicity. The main scope of the project is to incorporate more than one catalyst into the stirrer device to demonstrate and explore the feasibility of more challenging reactions. In the initial phase, the devices have been used to catalyse the reaction of diamines/thiazoles with aldehydes to make benzimidazoles and benzothiazoles.

The efficient stirring of the stirrer devices allows for a greater interaction of the reactants in comparison to the traditional synthetic route involving the powdered catalyst and conventional stirrer. The use of such devices omits the need of weighing out powdered catalysts and the work up procedure, thus saving time. In the next phase of our research we have successfully impregnated dual metal catalysts to examine Sonogashira coupling reactions. The reusability of these stirrer devices in more than one reaction and the surface morphology have been investigated.

Ryan Trueman

Small physiologically relevant electric fields are paramount to effective cellular organisation and differentiation in the developing organism. Electrical stimulation has been shown to exhibit pro-regenerative phenotypic changes within a variety of different cell types in vitro. It is possible to simulate these small electrical fields in vivo using biocompatible semiconductors, which have the potential to provide varying doses of electrical stimulation. For these electronics to be intimately interfaced with host tissue, a tissue engineering approach can be adopted. We are attempting to synthesise novel materials in the form of peptide-based, conductive hydrogels that can be used for regenerative medicine, in this case, of the Peripheral Nervous System (PNS). Once the materials are created, an electrical stimulation dose-response relationship will be investigated for the different cells of the PNS in an attempt to harness and enhance the natural capability for regeneration of an injured Peripheral Nerve.

Rylee Wander

3-O-sulfation is one of the rarest, yet most significant modifications found on heparin/heparan sulfate as it is essential for both heparin's anticoagulant activity and the ability of heparan sulfate to serve as a receptor for herpes simplex virus 1 (HSV-1) entry to establish infection. The enzymes that install this modification, the 3-O-sulfotransferases, exist in seven unique isoforms which differ in both tissue expression and substrate specificity. While the specificities of isoforms one and three have been well-characterized, much remains unknown about the remaining isoforms. In my work, I utilize structurally-defined oligosaccharides to investigate the specificity and activity regulation of 3-O-sulfotransferase isoform 5 (3OST-5). My results confirm the ability of 3OST-5 to sulfate

both glucuronic acid- and 2-O-sulfated iduronic acid-linked glucosamines as well as the role of enzyme “gate” residues in directing specificity. Additionally, I report new findings which suggest a role for product inhibition in the activity regulation of 3OST-5. These findings contribute to the growing pool of knowledge concerning the activity of these biosynthetic enzymes, allowing for the design of more effective chemoenzymatic routes in order to achieve a diverse array of oligosaccharide products. Furthermore, my results concerning product inhibition provide insight into how the activity of these enzymes may be regulated in vivo.

Sarah Clinkscales

The human genome catalogues a tremendously large array of genetic information. Extensive cooperation between macromolecules is required to precisely express pertinent information in response to developmental and physiological stimuli. Epigenetic proteins facilitate gene regulation at the chromatin level, allowing for decisive changes in gene expression without altering the genetic code. However, the specific molecular mechanisms of interaction between epigenetic complexes, particularly those with overlapping functions, are poorly understood. Both the heterochromatin protein 1 (HP1) pathway and the human silencing hub (HUSH) complex facilitate trimethylated histone H3 lysine 9 (H3K9me3)-mediated gene repression, yet are currently studied as separate entities. We identified UNC2524 in a high-throughput chemical screen as an inhibitor of the HP1 heterochromatin gene repression pathway. Affinity purification followed by quantitative mass spectrometry, revealed that M-phase phosphoprotein 8 (MPP8), the H3K9me3-binding component of the HUSH complex, and hepatoma-derived growth factor-related protein 2 (HRP2) are putative molecular targets of our HP1 pathway inhibitor. Further investigation confirmed that HRP2 interacts with both HP1 and the HUSH complex and co-localizes with each complex at silenced genetic loci. Additionally, epigenetic modulation of HRP2 expression results in correlative changes in the expression of each major silencing complex, coupled with changes of localization to chromatin. These data suggest that HRP2 is a novel chromatin modulator and may contribute to the coordination of H3K9me3 deposition to effectively organize heterochromatin domains.

Serena Teo

To date, endosomal escape of biomolecules remains a major challenge in intracellular drug delivery. Current understanding of endosomal escape mechanisms remains limited due to significant number of conflicting reports, which are compounded by low sensitivity and indirect assays. To address these limitations, we developed a highly sensitive Split Luciferase Endosomal Escape Quantification (SLEEQ) assay to quantify endosomal escape efficiency. Luminescent signal is generated when a short peptide fragment (HiBiT) attached to the delivered cargo binds to a truncated NanoLuciferase protein (LgBiT) expressed in the cytosol of the target cell. We applied SLEEQ to evaluate the endosomal escape efficiencies of a range of widely studied putative endosomal escape peptides (EEPs) fused to green fluorescent protein (GFP) as a model cargo. We established that endosomal escape of GFP is a highly inefficient process (~2%). Cationic EEPs increased cytosolic delivery of GFP, while negatively charged EEPs did not increase cytosolic delivery. Although cationic EEPs improved cytosolic delivery, we demonstrated that the enhanced delivery was a result of increased non-specific cell membrane association, rather than increased endosomal escape. The endosomal escape efficiency of cationic EEPs are lower than unmodified GFP. These results challenge our understanding of how EEPs promote cytosolic delivery, and demonstrates how SLEEQ is a powerful tool has the potential to quantify endosomal escape of a range of biological therapies.

Si Hang Lei

LRRK2 mutation is the major cause for sporadic and inherited PD, but the exact mechanism on how mutated LRRK2 cause PD still remains unclear. There is accumulate evidences showing LRRK2 interacts with WNT signalling pathways. It was previously reported by Harvey’s group that G2019S mutation leads to a reduction of WNT signalling activity. WNT signalling is important for synaptic formation as well as neuronal maintenance. This project, we used wild type (WT), LRRK2 knock-out (KO) and G2019S knock-in (KI) mouse models. We identified the

brain regions with WNT and NFAT signalling activities by applying the biosensor system via lentiviral construct transduction into the brain at P0 and investigate signalling activation by immunohistochemistry at 6 months old. We investigated genomic and protein expression changes under basal condition via real-time PCR and western blot, respectively. Primary neuronal cultures were used to study signalling activities under basal and stimulated condition. Our preliminary data showed there is WNT signalling pathway activation in different brain regions. But the WNT pathways components gene and protein expression is differed in different brain regions, as well as sex and genotypes. We also observed that neurons without glial cells showed a significant reduction of WNT and NFAT activities. It is still at an early stage to judge whether LRRK2 interacts specifically with certain component of interest and affect WNT signalling activities. But this set of data gives us an idea on LRRK2 mutation alters genomic and protein expressions and the effect is different between male and female.

Solomon Sherif

Tazarotene is the first of a new generation of receptor-selective retinoids. Its actions are focused on and target two specific retinoic acid receptors (RARs), RAR-Î² and RAR-Î³ improving its therapeutic index compared to non-selective retinoids. However, in-vivo studies of topically administered tazarotene gel have highlighted its limited ability to penetrate across human skin. Crystallization of APIs on and in the skin is proposed to be one of the factors limiting the amount of API which may be delivered to the skin. Non-invasive techniques such as confocal raman spectroscopy (CRS) can provide detailed information about the penetration of actives and excipients though the skin without disturbing the system under investigation. The main objectives of our most recent work were to track tazarotene in the skin and examine the affects penetration enhancers have on its deposition. Conventional Franz diffusion cell studies were conducted using porcine skin to determine the penetration of tazarotene from the commercially available ZoracTM gel and simple solvent systems after a 6-hour finite dose application. Raman measurements were then performed on the porcine skin using the model 3510 Skin Composition Analyzer (River Diagnostics) to track both tazarotene and the excipients driving its penetration into the skin. Compared with the commercially available ZoracTM gel, tazarotene in all solvent systems examined could be detected in greater proportion deeper into the skin. The findings have provided further support for the use of confocal raman spectroscopy to monitor drug delivery into the skin.

Stella Aslanoglou

Engineered nanobio cellular interfaces driven by vertical nanostructured materials are set to spur transformative progress in modulating cellular processes and interrogations. In particular, the intracellular delivery “a core concept in fundamental and translational biomedical research” holds great promise for developing novel cell therapies based on gene modification. This study demonstrates the development of a mechanotransfection platform comprising vertically aligned silicon nanotube (VA-SiNT) arrays for ex vivo gene editing. The internal hollow structure of SiNTs allows effective loading of various biomolecule cargoes; and SiNTs mediate delivery of those cargoes into GPE86 mouse embryonic fibroblasts without compromising their viability. Focused ion beam scanning electron microscopy (FIB-SEM) and confocal microscopy results demonstrate localized membrane invaginations and accumulation of caveolin-1 at the cell’s NT interface, suggesting the presence of endocytic pits. Small-molecule inhibition of endocytosis suggests that active endocytic process plays a role in the intracellular delivery of cargo from SiNTs. SiNT-mediated siRNA intracellular delivery shows the capacity to reduce expression levels of F-actin binding protein (Triobp) and alter the cellular morphology of GPE86. Finally, the successful delivery of Cas9 ribonucleoprotein (RNP) to specifically target mouse Hprt gene is achieved. This NT-enhanced molecular delivery platform has strong potential to support gene editing technologies.

Thomas Kralj

Drug-induced liver injury (DILI) affects 1 to 1.5 million people globally each year and cholestatic liver injury, a liver injury phenotype caused by changes to bile acid homeostasis, occurs in up to half of all DILI cases as either the sole

phenotype or as a comorbidity. In vitro modelling of DILI can provide valuable insight to the biochemical changes and toxicological pathways that result in DILI. In vitro DILI models utilising HepaRG and HuH-7 cells and primary human hepatocytes were used to identify cholestatic potential of several clinically used drugs that have been associated with some form of liver injury using C-DILIâ„¢ and B-CLEARÂ® assays. LC-MS-based metabolomics was also applied to characterise the impact of these drugs on the bile acid profiles of the in vitro models. Diclofenac, ethinyl estradiol, ritonavir, and troglitazone were identified to be drugs that induced cholestatic liver injury using the C-DILIâ„¢ and B-CLEARÂ® assays. Targeted metabolomics analysis showed these drugs caused a significant depletion to the intracellular pool of several primary bile acids, indicating drug-induced perturbations to bile acid homeostasis. These results show that impact to hepatocellular bile acids shows similar trends across a diverse selection of DILI-associated compounds indicating that there may be similar toxicological pathways through which these drugs induce cholestasis.

William Murphy

OSTα/β is a bidirectional, heteromeric, bile acid transporter localized on the basolateral membrane of hepatic, intestinal and renal epithelial cells that is upregulated in disease states characterized by elevated bile acid levels (e.g., cholestatic disorders, NASH). This study was designed to identify amino acids in OSTα/β that are important for bile acid transport.

Site-directed mutagenesis and the Flp-In™ 293 system were used to incorporate potential pore-lining mutations into the OSTα subunit. Ten distinct cell lines were generated, each co-expressing OSTβ and one OSTα mutant, including Q269K and S228K. RNA levels, and the protein expression and cellular localization of mutant and wild-type (WT) OSTα/β were evaluated. Accumulation studies (n=3 in triplicate) using OSTα/β bile acid probe substrates, [3H]-taurocholate (TCA) and [14C]-glycocholate (GCA), were conducted at 10min with and without a subsequent 5min efflux phase. Statistically significant differences in TCA and GCA transport between mutant and WT OSTα/β were determined using one-way ANOVA with Dunnett's multiple comparisons test.

TCA and/or GCA cellular accumulation was significantly altered in several mutants compared to WT OSTα/β cells. Accumulation of TCA and GCA increased by 21% and 35%, respectively, in Q269K, and by 11% and 12%, respectively, in S228K mutant cells. The % efflux of TCA and GCA was reduced by 23% and 35%, respectively, in Q269K, while the % efflux of GCA was reduced by 16% in S228K mutant cells.

This research identified several hydrophilic/polar OSTα residues in predicted transmembrane domains that have substantial effects on OSTα/β transport and expression. These data will advance our understanding of the function of OSTα/β, a clinically relevant transporter.

Xiaoyan Xu

3D printing (3DP) in the pharmaceutical field is a disruptive technology that allows the preparation of personalised medicines at the point of dispensing. The paediatric population presents a variety of pharmaceutical formulation challenges such as dose flexibility, patient compliance, taste masking and the fear or difficulty to swallow tablets, all factors that could be overcome using the adaptable nature of 3DP. User acceptability studies of 3D printed formulations have been previously carried out in adults; however, feedback from children themselves is essential in establishing the quality target product profile towards the development of age-appropriate medicines. The aim of this study was to investigate the preference of children for different 3D printed tablets (Printlets™) as a surrogate for perceived acceptability. Four different 3DP technologies; digital light processing (DLP), selective laser sintering (SLS), semi-solid extrusion (SSE) and fused deposition modelling (FDM) were used to prepare placebo printlets with similar physical attributes including size and shape. A single-site, two-part survey was completed with participants aged 4 – 11 years to determine their preference and opinions based on visual inspection of the printlets. A total of 368 participants completed an individual open questionnaire to select visually the best and

worst printlet, and 310 participants completed further non-compulsory open questions to elaborate on their choices. Overall, the DLP printlets were the most visually appealing to the children, with both the FDM and SSE printlets receiving the lowest scores. However, after being informed that the SSE printlets were chewable, the majority of participants changed their selection and favoured this printlet, despite their original choice, in line with children's preference towards chewable dosage forms. Participant age and sex displayed no significant differences in printlet selection. Printlet descriptions were grouped into four distinct categories; appearance, perceived taste, texture and familiarity, and were found to be equally important when creating a quality target product profile for paediatric 3D printed formulations. This study is the first to investigate children's perceptions of printlets, and the findings aim to provide guidance for further development of paediatric-appropriate medicines using different 3DP technologies.

Zixuan Wang

Aims: To investigate whether exposure to antipsychotic medications during pregnancy is associated with gestational diabetes mellitus (GDM) in United Kingdom (UK) and Hong Kong (HK) population cohorts.
Methods: Two population-based cohort studies were conducted using data from the UK The Health Improvement Network (THIN) and HK Clinical Data Analysis and Reporting System (CDARS). Nondiabetic women who received any type of antipsychotic medicine before their first pregnancy were included in our cohorts. The exposed group comprised women who continued using antipsychotics from the start of pregnancy to delivery (continuers), while the comparison group included women who were prescribed antipsychotics before the start of pregnancy but stopped during pregnancy (discontinuers). GDM was identified using GDM diagnosis and/or clinicians reported GDM. Odds ratios (ORs) with a 95% confidence interval (CI) were calculated to assess the association between antipsychotic use during pregnancy and GDM. Propensity Score fine-stratification weighting was used to adjust for potential confounding factors.
Results: 3,114 women with registered first pregnancies (2,351 in THIN and 763 in CDARS) were included. 5.49% (2.55% in THIN and 14.55% in CDARS) were diagnosed with GDM. The adjusted OR of GDM in continuers was 0.73 (95% CI: 0.43-1.25) in THIN and 1.16 (95% CI: 0.78-1.73) in CDARS compared with discontinuers.
Conclusions: Our results do not suggest an increased risk of GDM in women who continued using antipsychotics during pregnancy compared to women who stopped. Based on these results, women should not stop their regular antipsychotics prescriptions in pregnancy due to the fear of GDM.

Zoe Whiteley

In this work we present a novel approach to the continuous manufacture of protein-loaded chitosan nanogels using microfluidics whereby we demonstrate high control and uniformity of the product characteristics. Specifically, a coaxial flow reactor (CFR) was employed to control the synthesis of the nanogels, comprising an inner microcapillary and a larger outer glass tube. The CFR successfully facilitated the ionic gelation process via chitosan and lysozyme flowing through the inner microcapillary, while cross-linkers sodium tripolyphosphate (TPP) and 1-ethyl-2-(3-dimethylaminopropyl)-carbodiimide (EDC) flowed through the larger outer tube.

In conjunction with the CFR, a four-factor three-level face-centered central composite design (CCD) was used to ascertain the relationship between various factors involved in nanogel production and their responses. Specifically, four factors including chitosan concentration, TPP concentration, flow ratio and lysozyme concentration were investigated for their effects on three responses (size, polydispersity index (PDI) and encapsulation efficiency (%EE)). A desirability function was applied to identify the optimum parameters to formulate nanogels in the CFR with ideal characteristics. Nanogels prepared using the optimal parameters were successfully in the nanoparticle range at 84 ± 4 nm, showing a high encapsulation efficiency of 94.6 ± 2.9 % and a high monodispersity of 0.26 ± 0.01. The lysis activity of the protein lysozyme was significantly enhanced in the nanogels at 157.6 % in comparison to lysozyme alone. Overall, the study has demonstrated that the CFR is a viable method for the fabrication of functional nanogels containing bioactive molecules.