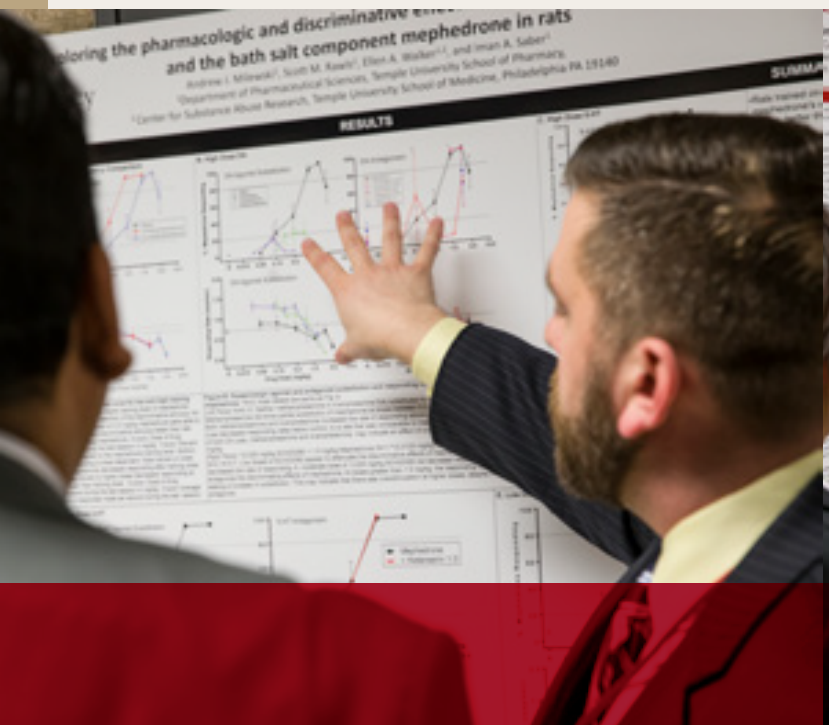
School of Pharmacy

2024

RESEARCH RECOGNITION DAY

Friday, April 12, 2024

School of Pharmacy
3307 N. Broad Street
Philadelphia, PA 19140



MESSAGE FROM THE DEAN

Greetings,

It is my great honor to be a part of Research Recognition Day in 2024, my first year as dean of the Temple University School of Pharmacy.

Since 2007, Research Recognition Day has been an annual tradition that celebrates the research accomplishments of our graduate and professional students and their faculty mentors.

Our students have many opportunities to lead innovations across the spectrum of translational research from basic to clinical to population sciences while they're earning degrees in pharmacy, pharmaceutical sciences, and regulatory affairs and quality assurance. By bringing these disciplines together, we match the reality of the healthcare continuum from drug discovery to care delivery to health stewardship. Some are involved in the scholarship of teaching and learning. For every one of these aspiring researchers, Research Recognition Day offers a sampling of the work we do to foster this endeavor.

This year our Keynote Speaker Omar Galárraga, PhD, Director of the Health Services Research PhD Program at Brown University School of Public Health, will present "Economic-based Interventions and Policies to Improve Health Outcomes". Dr. Galárraga's title and content are so timely for the school, given that the roles of pharmacists and pharmacy researchers are now consistently achieving never-before levels of contributions to public health and outcomes. Even just among our community, we have made headway on the following public health initiatives and more:

- Dr. Van Hellerslia continues to promote stroke identification and treatment awareness among Vietnamese-speaking populations through her grant-funded "Viet-Capacity" education and teambuilding program.
- Dr. Tina Tran co-leads the development of Temple University Health and Wellness at Liberty Square, a community clinic, along with colleagues from the College of Public Health.
- Alumnus Dr. Chichi Ilonzo Momah recently advocated for fair pharmacy benefit management practices on behalf of her Springfield Pharmacy patient community at a livestreamed White House discussion, across the table from celebrity entrepreneur Mark Cuban.

For Research Recognition Day 2024, we are privileged to have received sponsorship support from Dan Castiglia and Soo Ham, both pharmacy class of 1998, and Jan Kitzen, PhD, pharmacy class of 1972. These alumni have shown their commitment to Research Recognition Day through their support and participation for the past several years.

Many thanks go to our sponsors, presenters, and evaluators, and our 2024 event committee which includes faculty members, Drs. Divita Singh, Ken Korzekwa, Tina Tran, Carlos Barrero, Patrick Glassman, and Vasyl Zbyrak and Doctor of Pharmacy student Daniel Ghattas.

Please enjoy our incredibly special event. I look forward to seeing you there.

Sincerely,

S. Suresh Madhavan, MBA, PhD, FAPhA
Dean

THE TEMPLE UNIVERSITY SCHOOL OF PHARMACY GRATEFULLY ACKNOWLEDGES

Dan Castiglia and Soo Ham, Pharmacy Class of 1998
Title Sponsors of 2024 Research Recognition Day

Dan, a loyal champion for research at Temple University, has long been a supporter of Research Recognition Day. Dan and Soo work in the pharmaceutical industry and community pharmacy, respectively, and are married with two children.

SNACK BREAK SPONSOR

Jan M. Kitzen, RPh, BSPharm ‘72,
PhD in Pharmacology (University of Iowa ‘77)

AGENDA

Temple University School of Pharmacy's Research Recognition Day

Friday, April 12, 2024, 11:00 AM-4:00 PM
School of Pharmacy at 3307 N. Broad Street, Philadelphia, PA 19140

11:00 AM – 12:00 PM	**Evaluator Registration and Lunch (TUSP 110)** For student presenters and poster evaluators
12:00 – 12:15 PM	**Welcome Remarks (TUSP 101)** S. Suresh Madhavan, MBA, PhD, FAPhA, Dean Dan Castiglia, BSPharm '98, MS, Lieutenant Colonel, US Air Force (ret), Federal Account Manager - Northeast, Genentech
12:15 – 1:15 PM	**Keynote Lecture (TUSP 101)** Omar Galárraga, PhD, Director of the Health Services Research PhD Program at Brown University School of Public Health *"Economic-based Interventions and Policies to Improve Health Outcomes"*
1:15 – 2:30 PM	**Poster Presentations/Judging (4th floor hallway)**
2:30 - 3:15 PM	**Select Oral Research Presentations (TUSP 101)**
3:15 – 3:45 PM	**Awards Presentation (TUSP 101)**
3:45 PM	**Closing Remarks and Networking Opportunities (TUSP 101)**

KEYNOTE SPEAKER

Omar Galarraga, PhD is the Director of the Health Services Research PhD Program at Brown University School of Public Health; has authored over 130 scientific papers, and serves as associate editor for *Health Economics*. He will discuss the use of health and behavioral economics to inform, design and evaluate interventions and policies to improve health outcomes. Examples will be drawn from past and current research, including NIH-funded R01 projects:

a. Integrated Community-Based Care for HIV/NCD Care and Microfinance in Kenya: A Clustered RCT;

b. Insurance-Based Monetary Incentives to Promote Regular Exercise: an RCT; and

c. Rigorous Non-Experimental Evaluation of Medicaid Policies Affecting Persons Living with HIV in the US.

RESEARCH DAY EVALUATORS

Peter R. Bernstein, PhD, Principal, PharmaB LLC

Chris Bode, VP of Scientific Affairs, Pharmaron (Exton) Lab Services LLC

Dan Castiglia, BSPharm '98, MS, Sr. Federal Account Executive, Genentech (A member of the Roche Group)

Saira Chaudhry, PharmD, MPH, BCIDP, Regional Medical Scientific Director (RMSD)/Merck & Co.

Anne Crissey, MPH, Associate Director, CSL Behring

Phu Duong, PharmD, MBA, BCPS, AAHIVE, Senior Director, Medical Affairs - Merck/Merck Research Laboratories

John Ellingboe, PhD, Director, Mestastop Solutions

John C. Gordon, PhD, Screening Manager for the Moulder Center for Drug Discovery at the Temple University School of Pharmacy

Scott Greene, RPh, MS, PhD, Assistant Dean of Experiential Programs, Philadelphia College of Pharmacy at St. Joseph's University

Marc A. Ilies, Faculty, Professor, Temple University School of Pharmacy

Jan M. Kitzen, PhD, BSPharm '72, RPh, Former laboratory scientist and medical/scientific writer (Wyeth-Ayerst; Wyeth, Rhone-Poulenc Rorer)

Kevin Krick, DMD, Interim Chair, Clinic Director, & Clinical Assistant Professor, Maurice H. Kornberg School of Dentistry

David Lebo, PhD, Temple University School of Pharmacy

Josephine Luong, PharmD, MBA, BCPS, BCCCP, System Director of Clinical Pharmacy Services, Temple Health

Michael Mancano, BSPharm '93, PharmD '87, Vice Dean & Clinical Professor of Pharmacy, Temple University School of Pharmacy

Salim Merali, PhD, Associate Dean for Research, Temple University School of Pharmacy

Tirtha Nandi, PhD '23, Scientist, Clinical Pharmacology, Alnylam Pharmaceuticals

R. Kyle Palmer, PhD, Pharmacology, CSO, Opertech Bio & Adjunct Professor, Temple University School of Pharmacy

Deven Patel, Founder & CEO, InfuCare Rx Nima Patel, PharmD, BCACP, Professor, Temple University School of Pharmacy

Connor Quinn, PhD '22, Postdoctoral Fellow, Merck & Co.

Christina Rose, PharmD, Clinical Professor

Mahmut Safak, PhD, Associate Professor, Department of Microbiology, Immunology & Inflammation, Lewis Katz School of Medicine at Temple University

Gregory Shaeffer, BS '74, MBA '88, Assistant Professor, University of Maryland Eastern Shore

Stephanie Sillivan, PhD, Assistant Professor, Department of Neural Sciences, Center for Substance Abuse Research at the Lewis Katz School of Medicine at Temple University

Louis Speizer, PhD, Postdoctoral Fellow in Pharmacology, University of California at San Diego & Managing Partner Griffing Speizer and Partners

Nina Tachikawa, PharmD, BCPS, BC-ADM, BCACP, Director, Medical Outcomes & Analytics, Pfizer, Inc.

Tina Tran, PharmD, Assistant Professor, Temple University School of Pharmacy

Ellen Unterwald, PhD, Professor, Lewis Katz School of Medicine at Temple University

Sara Jane Ward, PhD, Associate Professor, Department of Neural Sciences, Lewis Katz School of Medicine at Temple University

Johnny Zapata, PharmD '19, RPh, Cell Therapy Competitive Intelligence/Bristol Myers Squibb

Vasyl Zbyrak, PharmD '19, Assistant Professor, Temple University School of Pharmacy

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Graduate Platform – Abstract Winner

Kishore Pathivada* and Dr. Patrick Glassman[1]

Pharmacologic Characterization of Engineered Tissue Plasminogen Activator Derivatives

*Pharmacy Student

[1]Department of Pharmaceutical Sciences, School of Pharmacy, Temple University

Purpose: Tissue Plasminogen activator (tPA) and derivatives (Reteplase-rPA, Alteplase-tPA and Tenecteplase- TNKase) are FDA-approved for the treatment of myocardial infarction, acute ischemic stroke, pulmonary embolism, and arterial thrombosis and embolism. Their usage is delimited by their short half-life and severe side effects, namely internal bleeding and aberrant vascular remodeling. Their pharmacokinetics can be enhanced via various half-life extension (HLE) strategies such as polymer conjugation (PEGylation), binding to long-circulating components of blood (albumin, IgG, erythrocytes), and glycoengineering. Albumin binding as a has drawn considerable attention in recent years and many drugs were approved by FDA (Insulin detemir, liraglutide, Albinterferon, rIX-FP). We hypothesize that conjugating tPA derivatives to albumin via SPAAC (Strain-promoted Azide – Alkyne cycloaddition, Click Chemistry) would enhance the half-life of the tPA drugs by increasing the hydrodynamic radius and permitting FcRn recycling of the drug.

Methods: We developed an in vitro clotting assay that we used to evaluate the potency of tPA, rPA, and TNKase in prophylactic and therapeutic settings. Following confirmation of activity, we conjugated tPA to albumin using SPAAC by attaching maleimide-PEG4-DBCO to the unpaired cysteine of tPA and NHS ester-PEG4-azide to lysine residues on albumin. Albumin-azide and tPa-DBCO were reacted overnight at a 5:1 ratio and conjugates were purified prior to testing their potency in vitro.

Results: The results shows that engineered tPA derivatives maintain their potency in both prophylactic (tPA:13.08 nM, rPA:15.17 nM , TNKase:12.42 nM, tPa-albumin:42.56 nM) and therapeutic (tPA:5.48 nM, rPA:12.08 nM,TNKase:8.94 nM , tPa-albumin:11.62 nM).

Conclusions: Our results demonstrate that albumin conjugation is permissive of potent tPA activity. This fosters us to proceed to in vivo studies investigating pharmacokinetics and safety. Additionally, macrophage uptake and FcRn binding studies will be done to investigate their role in tPA-albumin half-life.

PharmD Platform – Abstract Winner

Twisha Patel*, Drs. Swati Nagar[1] and Ken Korzekwa[1]

Effect on Ethinyl Estradiol Concentrations When Co-administered with Ritonavir

*Pharmacy Student

[1]Department of Pharmaceutical Sciences, School of Pharmacy, Temple University

Purpose: Ethinyl estradiol (EE) is present in most preparations of combined oral contraceptives. Ritonavir, a protease inhibitor commonly used as a booster in HIV treatment regimens is also a key component in Paxlovid, which is one of the few treatments approved for COVID-19. Notably, ritonavir is known to be a strong CYP3A4 inhibitor, the enzyme primarily responsible for EE oxidative metabolism. Contrary to expectations, co-administration of EE with ritonavir results in a decrease in EE concentration, likely due to the induction of the glucuronidation pathways and other minor CYP pathways. The purpose of this study was to look at the impact of ritonavir on EE concentrations when co-administered and its clinical implications.

Methods: The initial pharmacokinetic information on ritonavir's and EE's metabolism was collected using PubMed, DrugBank, and Lexicomp. We derived human data of oral administration of ritonavir and EE from the primary literature and digitized it using a Web plot digitizer. Using the data points obtained, we performed a non-compartmental analysis (NCA) using Excel.

Results: Through our NCA analysis we obtained an AUC of 1.122x10-3 ug*h/ml when EE was administered alone, and an AUC of 6.27437x10-4 ug*h/ml when EE was co-administered with ritonavir. Calculation of the AUC change revealed a 44% decrease in AUC when EE was co-administered with ritonavir.

Conclusions: Observing a change greater than 20% in EE concentrations indicates a clinically significant drug-drug interaction. Ritonavir-containing drug regimens may decrease the efficacy of oral birth control leading to unwanted pregnancies. The relevance of this interaction is growing with the increased use of Paxlovid.

Poster 1

Johnny P. Nguyen*, Amber H. Qureshi*, Hanan E. Faddoul*, Anastasia Panayiotou*, Cheyanne Twining*, Fang Chen* and Dr. Carlos Barrero[1,2]

Altered Glucose Metabolism and Alzheimer's Disease: An In Vitro Model

*Pharmacy Student

[1]Department of Pharmaceutical Sciences, School of Pharmacy, Temple University

[2]Moulder Center for Drug Discovery Research, School of Pharmacy, Temple University

Purpose: Alzheimer's disease (AD) is characterized by progressive neurodegeneration associated with amyloid plaque formation and tangle deposition in the cortex and hippocampus of the brain. There is an epidemiological association between healthy subjects with high blood glucose levels, patients with diabetes, and AD severity. Moreover, glucose hypometabolism in the frontal cortex and hypothalamus of the brain is extensively described during AD progression. Nevertheless, the molecular mechanisms linking high blood glucose and the induction of the molecular changes associated with AD are yet to be characterized. A better understanding of the development of Alzheimer's disease physiopathology will facilitate the discovery of novel and early intervention therapies. In this work, using in vitro neuronal models, we evaluated the effects of high glucose levels on the development of AD hallmarks.

Materials & Methods – Amyloid plaque formation in vitro: We tested the Ab42 amyloid plaque formation using SHSY-5Y spheroids cultured in increasing concentrations of glucose (2.5, 5, and 10 mM) for 72h alone or in the presence of 50 uM metformin and 100 uM 2-fluorodeoxyglucose (2FDG). Neuronal glucose flux and energy production:

We used a multiple reaction monitoring (MRM) method to evaluate glucose uptake, glucose metabolism flux, and energy production in human primary neurons (HPNs). HPNs were exposed to increasing glucose concentrations for 48 hours, followed by incubation to 13C6-glucose 5mM and 2-FDG 2.5 mM for 1 hour.

Results: We observed amyloid plaque formation only in response to high glucose concentration (10 mM). Moreover, this amyloid formation was inhibited by metformin and 2FDG. We found altered glucose metabolism flux in neurons exposed to high and low glucose concentrations without changes in glucose uptake. Interestingly, high glucose induces an accelerated consumption rate of glucose and promotes glutamate production. This altered glucose metabolic flux leads to dysregulation of neuronal energy production.

Conclusions: Our results confirm that high glucose levels can promote amyloid plaque formation. More importantly, a pharmaceutical intervention at the glucose metabolism level can ameliorate amyloid plaque formation, as observed with metformin and 2FDG treatment. The drastic changes in the glucose flux suggest a sensitive mechanism of regulation upon high extracellular glucose concentration availability

Poster 2

Clarissa Abella*, Rojin Baniasadi, Peter Crescitelli* and Dr. Carlos Barrero[1]

Alveolar Epithelial Cell Differentiation from Human Progenitor Lung Cells

*Pharmacy Student

[1]Department of Pharmaceutical Sciences, School of Pharmacy, Temple University

Purpose: Human alveolar epithelial in-vitro cell model development is crucial to studying distal lung biology and disease, including chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF).

Stem cells and induced pluripotent stem cells (iPSCs) are valuable in researching disease pathophysiology. These cells can be dedifferentiated to become any type of cell. Alveolar type 2 (AT2) cells were previously shown to proliferate and were hypothesized to differentiate into AT2 and AT1 cells. Recent work, through genetic lineage tracing experiments and 3D cultures, showed evidence that AT2 cells are stem cells. In this work, we obtained human progenitor lung cells (HPLCs) derived from the long-term culture of human alveolar epithelial cells (HPAEpiC) and developed an AT2 and AT1 differentiation protocol.

Methods: HPAEpiCs were cultured for a long time in alveolar epithelia cell media (2-3 weeks) to obtain HPLCs. HPLCs were cultured in differentiation media adapted from stem cell lung alveolar epithelial cell differentiation containing growth factor and small molecules for six days. Additional treatments with nuclear receptor activation and maturation factors were also evaluated. Differentiation culture conditions were optimized to enhance alveolar epithelial cell phenotypic characteristics. Cell morphology and alveolar epithelial markers (Pro-SPC for AT2 and aquaporin for AT1) were evaluated by high-content imaging analysis using confocal microscopy.

Results: The obtained HPLCs were smaller, elongated, and had a higher replication rate than the original HPAEpiC. We were able to induce HPLC differentiation into AT1 and AT2 alveolar epithelial cells in two steps using a stem cell differentiation cocktail followed by maturation stimulation with 25 nM dexamethasone, 1uM vitamin D, 10 nM TGFβ-1 and mTOR pathway activation. The alveolar epithelial phenotypic characteristics were promoted in an air-liquid interface used in collagen-coated plates to simulate lung conditions. AT1 aquaporin+ cells exhibit a distinct morphology, featuring a centrally positioned nucleus with filamentous extensions. In contrast, AT2 cells present a large, cuboidal structure and were Pro-SPC+.

Conclusions: We were able HPLCs from lung human primary cells and expand them for long periods of time. We have also developed methodologies that allowed us to produce AT1 and AT2 cells that exhibited the desired morphology and demonstrated functional characteristics indicative of their role in lung physiology.

Funded by: Flight Attendant Medical Research Institute (FAMRI) YFAC142023.

Poster 4

Vidhi Desai*, Colin Joseph Foraker*, Vilson Koka* and Dr. David Lebo[1]

Analysis of Orphan Drugs from 2016 to 2020 of Efficacy, Type, and Type of Facilitated Review Pathway on the Size of the Approval Clinical Trial.

*Pharmacy Student

[1]Department of Pharmaceutical Sciences, School of Pharmacy, Temple University

Purpose: The purpose of this study was to analyze the type of orphan indication, the efficacy of the drug and the type of Facilitated Review Pathway (FRP) on the size of the Approval Clinical Trial.

Methods: Drugs approved by the FDA from 2016 to 2020 were reviewed, focusing on the indication development type, the efficacy results, and whether the drug was designated as Fast Track by the FDA.

Results: Between 2016 and 2020, 107 orphan drug designations were approved. 30 of the 137 drugs were approved as an expansion indication(s) following their initial approval. The trial size for Approval was from 11 to 1472 subjects. An increase in Efficacy did not lower the size of the trial. For drugs with an original orphan indication, the mean size of trial was 169 participants and the median size of the trial was 125. For drugs with an expansion orphan indication, the mean size of the trial was 63 and the median size of the trial was 48.

Conclusions: Between 2016 and 2020, 22% of the drugs were approved for expansion orphan indications. The size of the Approval Clinical Trial for drugs with an original orphan indication were 2.7 times larger than the drugs with an expansion orphan indication. The Expansion of an Approved drug did significantly decrease the size of the clinical trial. This is probably because the safety of the drug was already established in the original indication. The FDA FRP designation of Fast Track did not reduce the size of the trail. Drugs with a high percent efficacy did not have a significantly lower number of subjects in the Approval Trial.

Poster 5

Sarah John*, Yirgalem Gizachew* and Dr. Nicole M. Sifontis[1]

Clinical Conundrum: Case Report of Thrombocytopenia Upon Initiation of Chronic Hemodialysis

*Pharmacy Student

[1]Department of Pharmaceutical Practice, School of Pharmacy, Temple University

Thrombocytopenia is often observed in hemodialysis patients due to a myriad of factors including heparin use, platelet adhesion and complement activation based on the dialysis membrane itself. Polysulfone dialysis membranes are considered biocompatible with low affinity to activate complement, however, these membranes can still reduce platelet count through platelet activation. We report the case of a woman who developed thrombocytopenia (59% decrease in platelet count from baseline) within the first four days of initiating chronic hemodialysis. Given that the patient had received 22 days of subcutaneous heparin for DVT prophylaxis during her hospital stay up to that point, heparin induced thrombocytopenia (HIT) was part of the differential. However, dialyzer membrane associated thrombocytopenia (DMAT) could not be ruled out. Her calculated T score of 4 suggested an intermediate probability of HIT, therefore prophylactic heparin was discontinued, and the patient was started on anticoagulation with argatroban. Confirmatory serotonin release assay returned 9 days later ruling out HIT, however, the patient had already received 6 days of argatroban and transitioned to apixaban. This report highlights the clinical assessment necessary to evaluate thrombocytopenia in a hemodialysis population. Although not widely recognized by clinicians due to incomplete understanding of its pathophysiology, appreciation for DMAT can change management in these patients. In some instances, it may negate the use, laboratory monitoring, and cost associated with direct thrombin inhibitors.

Poster 7

Mariah Mendez*, Emnet Kefeni* and Dr. Patrick Glassman[1]

Comparative Pharmacokinetics of Anti-CGRP Monoclonal Antibodies for the Preventative Treatment of Migraines in Adults

*Pharmacy Student

[1]Department of Pharmaceutical Sciences, School of Pharmacy, Temple University

Purpose: The objective of this study was to examine the pharmacokinetic properties of FDA-approved anti-CGRP monoclonal antibodies, galcanezumab and fremanezumab, in migraine prophylaxis. This analysis was performed to determine factors influencing drug exposure assessed/as seen through variable doses and variability in patient response by reviewing absorption, distribution, metabolism, and elimination (ADME) profiles.

Methods:Concentration vs. time profiles were extracted from publications using WebPlotDigitizer. Properties were extracted from FDA package inserts and pharmacokinetic data was obtained from published literature. To analyze pharmacokinetic data, non-compartmental analysis was performed to determine parameters such as AUC, t1/2, CL, and Vss. A one-compartment model with first order absorption was selected to estimate parameters related to distribution of clinically used dosing regimens of the antibodies studied.

Results: The pharmacokinetic model well-characterized observed data and parameters were estimated with good confidence (CV% < 5%) across both antibodies. Fremanezumab model results projected increased serum trough concentrations and elevated serum levels following administration compared to galcanezumab, indicating differential exposure between the two antibodies. Galcanezumab model results show there was an extended period of absorption with a median time to peak concentration around 10 days following single-dose administration. In addition, concentration-exposure time of galcanezumab was more prolonged than fremanezumab, allowing galcanezumab to be dosed less frequently while still obtaining similar clinical benefit for migraine prevention.

Conclusions: Overall, a comprehensive understanding of the pharmacokinetics of anti-CGRP monoclonal antibodies is crucial for optimizing their use in migraine prophylaxis and results show variations in ADME profiles, which may alter therapy. By explaining the connection between drug disposition and clinical response, this analysis aims to inform healthcare providers and researchers in the pursuit of personalized and effective migraine management strategies. Future studies should be performed to further analyze inter-subject variability.

Poster 8

Mohamed Elkaeid*, Daniel Ghattas*, Nadeen Elbergdar† and Dr. Van Hellerslia[1]

Developing a Culturally Tailored Stroke Education Toolkit for Arab American Communities: IMPACT Arabs

*Pharmacy Student

†Lewis Katz School of Medicine at Temple University

[1]Department of Pharmaceutical Practice, School of Pharmacy, Temple University

Purpose: The Arabic community is a growing minority in the United States. A 2022 American Community Survey conducted by the US Census Bureau estimated that there are 2.3 million Arab Americans. However, other sources suggest that these estimates are greatly undercounted and that there are 3.7 million Arab Americans. According to the 2022 US census data, 42.5% of Arabs are foreign-born, and 59.8% speak a language other than English, with 19.6% of them reporting less than proficient English skills. These statistics highlight the vulnerability of the Arab American community to healthcare disparities, arising from factors like lack of culturally tailored outreach, language barriers, and barriers to accessing healthcare, such as lack of insurance and health literacy, as well as cultural health beliefs.

Research indicates that foreign-born individuals from minority backgrounds have lower levels of stroke awareness compared to the general population. Moreover, culturally tailored and community-based stroke education has shown its effectiveness in enhancing short-term knowledge, stroke recognition, and the willingness to contact emergency services, particularly among various racial and ethnic minority groups.

This research aims to build a culturally sensitive stroke education toolbox for Arab American communities, and measure its effectiveness in improving the recognition of stroke symptoms and the behavioral intent to call 911.

Methods: Phase 1 of the research involves two primary steps. The first step involves conducting literature searches and collecting data from representative members, and the second step focuses on integrating these findings into the original interventions and translating materials. Phase 2 will focus on testing the toolbox within the cultural group for appropriateness.

Results: To be reported

Poster 10

Matthew Richardson*, Drs. Swati Nagar[1] and Ken Korzekwa[1]

Drug-Drug Interaction Between Atorvastatin and Cyclosporine Mediated by Cytochrome P450 and OATP1B1

*Pharmacy Student

[1]Department of Pharmaceutical Sciences, School of Pharmacy, Temple University

Purpose: To evaluate literature on the pharmacokinetics of a drug-drug interaction and the potential consequences if not identified in patients co-medicated with atorvastatin and cyclosporine.

Methods:A literature review was conducted to obtain pharmacokinetic and physiochemical data for atorvastatin and cyclosporine. DrugBank, Lexicomp, Pubmed, and the 2020 FDA guidance on in vitro DDI interactions were used to aid in the research. In-vitro studies were analyzed in human liver microsomes to assess enzyme and transporter inhibition. In vivo clinical studies and reports were researched to assess clinical impact of the drug-drug interaction. IC50 data using human liver microsomes, and clinical AUC data were used to characterize the extent of drug interaction.

Results: Atorvastatin's metabolism, primarily by CYP3A4, is inhibited by cyclosporine. This results in an increase in HMG-CoA inhibition potentially leading to serious adverse effects associated with statin therapy.

Conclusion: Our findings indicated a drug-drug interaction between atorvastatin and cyclosporine that is primarily mediated by CYP3A4, secondary to the uptake transporter OAT1B1. The potential for serious harm indicates a need for discontinuation of therapy, or a dose reduction.

Poster 11

Esrat Jahan*, Kelley Maberry*, Drs. Ken Korzekwa[1] and Swati Nagar[1]

Drug-drug Interaction of Metoprolol with Fluoxetine and Omeprazole with Clopidogrel Mediated by Cytochrome P450 Enzymes

*Pharmacy Student

[1]Department of Pharmaceutical Sciences, School of Pharmacy, Temple University

Purpose: To evaluate the two pharmacokinetic drug-drug interactions (DDIs), in-vitro data was assessed along with in-vivo data to compare and analyze the relevance of the DDIs in clinical practice.

Methods:Research was conducted to obtain the pharmacokinetic and physiochemical properties of the drugs in question using Drug Bank, Access Pharmacy, Lexicomp, and the 2020 FDA Guidance on in vitro DDI Enzyme and Transporter Studies. In vitro studies in human liver microsomes were analyzed to understand the extent of CYP450 inhibition assessed by IC50 experiments. In vivo clinical studies were used to understand the clinical impact of this drug-drug interaction, assessed by the changes in AUC values.

Results: Clopidogrel-Omeprazole: Most PPIs inhibited the formation of 2-oxo-clopidogrel with IC50 values ranging from 20-32 μM and inhibited the formation of H4 with IC50 values ranging from 6-20 μM. The AUC and Cmax was statistically significantly reduced (p-value < 0.001) in clopidogrel given simultaneously with omeprazole group vs clopidogrel alone group.

Metoprolol-Fluoxetine: Fluoxetine's major metabolic pathway is mediated through CYP2D6 forming fluoxetine's metabolite, norfluoxetine. The high affinity fluoxetine and norfluoxetine demonstrate poses a pharmacokinetic drug-drug interaction with metoprolol, a substrate metabolized through CYP2D6. In vitro studies using liver microsomes will be used to assess IC50 values and in-vivo studies will be used to assess the AUC values. Resulting IC50 and AUC values will be presented.

Conclusion: Our findings indicate a metabolic DDI between clopidogrel and omeprazole that is mediated by CYP2C19. However, the interaction is not class effect and PPIs with less CYP2C19 inhibitory capacity (such as pantoprazole) would be better PPI of choice for patients on clopidogrel. While the use of metoprolol and fluoxetine demonstrated in-vitro effects, co-administration in clinical studies did not demonstrate a clinically significant concern. Rather, pharmacists should use caution and counsel patients on the signs and symptoms of bradycardia.

Poster 13

Ernest Appiah*, Ahja Brown*, Mahima Chaluvadi*, Drs. Swati Nagar[1] and Ken Korzekwa[1]

Evaluating the Pharmacokinetic Mechanisms of CYP450 Drug Interactions: A Comparison Between Different Drug Pairs

*Pharmacy Student

[1]Department of Pharmaceutical Practice, School of Pharmacy, Temple University

Purpose: To evaluate the pharmacokinetic profile between different drug pairs, comparing their interactions when used in combination via various CYP450 enzymes including CYP2C19, CYP2D6 and CYP3A4.

Methods:Data and literature were obtained for review from Drugbank, Lexicomp and Pubmed. Data were digitized via WebPlotDigitizer to determine the primary pharmacokinetic parameters for each drug. The distribution and elimination information of each drug pair was then analyzed via noncompartmental analysis (NCA) in excel to assess their drug interaction and mechanism of action with respect to being exposed to various CYP450 enzymes.

Results: When analyzing duloxetine and desipramine, duloxetine was found to increase the maximum plasma concentration and decrease the clearance of desipramine, since desipramine is metabolized by CYP2D6 and duloxetine is both a substrate and an inhibitor of CYP2D6. Further NCA analysis determined a decrease in clearance of citalopram along with an increase in the maximum drug concentration when given with omeprazole, indicating the inhibition of CYP2C19 metabolism by omeprazole. Apixaban is a substrate of CYP3A4 while itraconazole is a strong CYP3A4 inhibitor. Apixaban and itraconazole were analyzed together to determine the interactions that exist between them. Apixaban drug concentration and AUC was significantly increased when used in combination with itraconazole which is the perpetuator. The CL/F of apixaban was reduced to about 80% by itraconazole.

Conclusions: Upon using NCA analysis to determine the pharmacokinetic interactions that exists between different drug pairs, it can be concluded that the metabolism and clearance of the different drugs may be significantly influenced when exposed to various CYP450 enzymes and these intricate interactions may affect the absorption, metabolism, and elimination of these drugs pairs.

Poster 14

Elizabeth George* and Dr. Craig B. Whitman[1]

Evaluation of Disease State Topics Taught in a Doctor of Pharmacy Curriculum Using the ACCP Toolkit: A Descriptive Report

*Pharmacy Student

[1]Department of Pharmaceutical Practice, School of Pharmacy, Temple University

Purpose: To evaluate the inclusion of topics from the 2019 American College of Clinical Pharmacy (ACCP) Pharmacotherapy Didactic Toolkit in the Doctor of Pharmacy (PharmD) curriculum at Temple University School of Pharmacy (TUSP).

Methods:Disease state topics listed in the Toolkit were compared to the content covered in required and elective therapeutics courses in the PharmD program using course syllabi. Topics covered were categorized as Tier 1, Tier 2, or Tier 3 based on the Toolkit. The number of topics and amount of class time in hours per topic were also collected. Descriptive statistics were used to analyze the data.

Results: A total of 130 therapeutic topics were identified in the curriculum. 49.3% were classified as Tier 1 topics, 49.3% as Tier 2 topics, and 1.54% as Tier 3 topics. 6.4% of Tier 1 topics, 10.5% of Tier 2 topics, and 93.3% of Tier 3 topics were not included in the curriculum. 348.5 hours of therapeutic topics are included in the PharmD curriculum. 59.34% of the hours were Tier 1 topics, 39.45% Tier 2 topics, and 1.15% Tier 3 topics. An average of 3.12 hours was spent on Tier 1 topics, 2.07 hours on Tier 2 topics, and 2.00 hours on tier 3 topics.

Conclusion: The therapeutics curriculum at TUSP was assessed using the ACCP Didactic Curriculum Toolkit. Almost all Tier 1 and Tier 2 topics are included in our curriculum. Most of the Tier 3 topics are not included in the curriculum. Additionally, the majority of hours spent in the curriculum are dedicated to Tier 1 topics. Based on the ACCP recommendations, our curriculum appears to be in line with the appropriate inclusion of topics based on their Tier and how much time is spent on each.

Poster 16

Jessika Patel*, Francesca Graziano*, Yash Solanki*, Grace Ni*, Drs. Christina Rose[1] and Jason Gallagher[1]

Evaluation of the Use of Phenylephrine in Patients with Shock

*Pharmacy Student

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Purpose: Phenylephrine is a vasopressor that is approved for the treatment of severe hypotension or shock that persists during and after adequate fluid volume replacement. We assessed the use of phenylephrine in the treatment of shock at Temple University Hospital (TUH).

Methods:This was a retrospective chart review of patients ≥ 18 years old who received at least one dose of IV phenylephrine for an indication of shock at TUH or Jeanes Hospital from January 2020 to December 2022. Data regarding the classification of shock, all vasopressors used for the shock, and the dosing of phenylephrine was collected. The primary outcome was if phenylephrine was used appropriately for shock. The secondary outcomes were shock resolution and patient death during admission.

Results: The first 52 eligible patients were included in this analysis. 27% of the patients analyzed received phenylephrine as the first vasopressor inappropriately, while the rest of the patients received it appropriately as additive therapy to another vasopressor. 50% of the patients treated with phenylephrine received this treatment for septic shock and 21.2% of patients received it for cardiogenic shock. 4 patients required a switch from another vasopressor to phenylephrine.

Conclusion: The use of phenylephrine was not consistent throughout the treatment of shock at TUH. Phenylephrine as a first-choice vasopressor is not recommended per the Surviving Sepsis guidelines, especially in cardiogenic shock. While further research is required, based on the results, it is recommended to include education to providers regarding the appropriate usage of phenylephrine in the various types of shock.

Poster 17

Fatima Saleem*, Taslima Sultana* and Dr. Patrick Glassman[1]

IL-6R Blockers for the Treatment of Rheumatoid Arthritis-Tocilizumab and Sarilumab

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Purpose: This study investigates the clinical utility of antibodies targeting the interleukin-6 receptor (IL-6R) in rheumatoid arthritis and focuses on understanding the pharmacokinetic (PK) differences and dosing variations between two specific antibodies:

tocilizumab and sarilumab. Rheumatoid arthritis is a chronic autoimmune disease characterized by joint inflammation and tissue damage, for which IL-6R blockade has emerged as a therapeutic strategy. By elucidating the pharmacokinetic properties of tocilizumab and sarilumab in the context of rheumatoid arthritis treatment, this study aims to provide insights into optimizing dosing strategies and enhancing clinical outcomes for patients with this debilitating condition.

Methods:A comprehensive literature search was conducted to gather PK data related to tocilizumab and sarilumab. Subsequently, the obtained data were digitized using WebPlotDigitizer and analyzed using non-compartmental analysis techniques. The PK parameters of interest, including area under the curve (AUC), maximum concentration (Cmax), clearance (CL), volume of distribution (Vd), and half-life (t1/2), were calculated. Additionally, a pharmacokinetic model is being developed to describe the digitized data.

Results: Pharmacokinetic data were successfully collected and analyzed for tocilizumab and sarilumab. The calculated PK parameters provide valuable insights into the distinct pharmacokinetic profiles of these two IL-6R antibodies. Moreover, ongoing efforts are directed towards developing a pharmacokinetic model capable of describing the digitized data.

Conclusions: Although specific conclusions are pending the completion of the analysis, this study lays the groundwork for understanding the rationale behind the differential dosing regimens of tocilizumab and sarilumab. The insights gained from our results have the potential to inform clinical practice regarding the optimal dosing strategies for IL-6R antibody therapy in various clinical settings.

Poster 19

Amrit Pabla*, Drs. Swati Nagar[1] and Ken Korzekwa[1]

Inhibition of the Metabolism of DPD by an Antiviral Sorivudine on Anticancer Agent 5-Fluorouracil: A Pharmacokinetic Analysis

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Purpose: To evaluate drug interactions between the antiviral sorivudine and antineoplastic 5-fluorouracil in colorectal cancerpatients.

Methods:The pharmacokinetic profile changes upon a single intravenous bolus or short infusion dose of anticancer agent 5-fluorouracil (5FU) was analyzed with and without the coadministration of an antiviral agent sorivudine. To determine whether there was a significant interaction potential between the two drugs, data collected from multiple in-vitro and in-vivo studies was used to perform non-compartmental analysis (NCA), and results were compared. Sources of data were obtained using PubMed, DrugBank, and The Human Protien Atlas. Human data from the literature were collected for the IV dosing and digitized using Web plot digitizer. NCA was conducted with Excel. The pharmacogenomics of DPD were also considered.

Results: Utilizing the trapezoidal rule, NCA was conducted of 5-fluorouracil with and without the coadministration of sorivudine. The area under the curve (AUC) and clearance (CL) of 5-fluorouracil alone with an intravenous bolus dose of 370mg/m2 was 7.58 ng·h/mL and 49 mg/L/m2, respectively. With the coadministration of sorvudine, the predicted AUC and CL of 5-fluorouracil is 37 ng·h/mL and 10 mg/L/m2, respectively. The predicted AUC with coadministration of sorvudine over the AUC of 5FU alone is 4.9 ng·h/mL. Polymorphisms within the gene encoding for DPD were observed within literature.

Conclusion: For there to be a significant interaction between two drugs where one is inhibiting the metabolism of the other, an AUC ratio of 1.2 should be observed based off FDA clinical DDI guidance. Based on the results, a significant DDI was observed. Inhibition of DPD causes 5FU levels to increase causing significant toxicity or even death. Polymorphisms within DYPD gene can predispose patients to an increased risk of toxicity.

Poster 20

Mohamed Elkaeid*, Joshua Sebastian*, Akhil Thomas* and Dr. Patrick Glassman[1]

The Differences in Pharmacokinetic Properties of Anti-Tumor Necrosis Factor Agents Indicated for the Treatment of Crohn's Disease

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Purpose: This study aimed to comprehensively review and compare the pharmacokinetic properties of anti-tumor necrosis factor (TNF) agents used for the treatment of Crohn's disease, namely Humira, Remicade, and Cimzia. Specifically, the objective was to evaluate the absorption, distribution, metabolism, and elimination profiles of these agents to provide insights into their clinical dosing regimens and plasma concentrations.

Methods:The methods of this research include extracting data from FDA-posted clinical pharmacology and biopharmaceutics reviews and published manuscript of TNF blockers for Crohn's disease treatment, utilizing WebPlotDigitizer to extract quantitative data, performing a comprehensive non-compartmental analysis (NCA) to identify key pharmacokinetic parameters, and creating a mathematical model to validate the clinical dosing regimen at steady-state concentrations.

Results: The NCA findings revealed that Humira exhibits a half-life ranging from 216.2 to 525.4 hours, while Remicade ranges from 198.2 to 329.5 hours, with Cimzia having a mean half-life of 288.48 hours. The final model structure data for Monoclonal antibodies indicates that Humira follows a 2-compartment model with first-order absorption, Remicade follows a 2-compartment model, and Cimzia follows a 1-compartment model with first-order absorption.

Conclusions: Humira showed a 2-compartment model with first-order absorption as the extrapolated data follows the pharmacokinetic model very well. Remicade showed the same 2-compartment model, but it wasn't feasible to fit a model with non-linear PK terms with good confidence in parameter estimates since additional data at low concentrations is needed. Cimzia demonstrated a 1-compartment model with first-order absorption, however, the PK data was not available in the literature hence we used published NCA parameters and model parameter estimates to allow us to compare its PK properties to other molecules. The mathematical model enables the prediction of alternative dosing regimens and enhances better understanding of the need for different regimens for each antibody.

Poster 22

Carissa Hickey*, Yash Solanki* and Dr. Jason Gallagher[1]

The Temple University Hospital Cohort of the Ceftazidime-Avibactam Versus Ceftolozane-Tazobactam for Multidrug-resistant Pseudomonas Aeruginosa Infections in the United States (CACTUS) Study

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Purpose: Pseudomonas aeruginosa (PsA) is often responsible for multi-drug resistant (MDR) nosocomial infections. Ceftazidime-avibactam (AvyCaz) and ceftolozane-tazobactam (Zerbaxa) are newer cephalosporin/beta-lactamase inhibitor combination antibiotics with proven efficacy against PsA. There are limited data available comparing the clinical efficacy of these two similar agents. The primary investigators designed the larger multicenter study to compare the overall clinical success of these antibiotics. The local investigation sought to evaluate patients at Temple University Hospital (TUH) with known MDR-PsA pneumonia and/or bacteremia to be included in the larger study.

Methods:The local study was a retrospective chart review of patients admitted to TUH who received AvyCaz or Zerbaxa for known MDR-PsA pneumonia and/or bacteremia. Adult patients were included if they were admitted between 2016 and 2022 and received either agent for at least 48 hours within 7 days of index culture. Eligible patients were paired based on infection type, illness severity, intensive care status, and time to treatment to comply with the matched-cohort design of the study. Only matched patients were submitted to the primary investigators for analysis.

Results: After careful analysis of over 200 records, eight patients met the inclusion criteria. Due to the matching requirements of the study, only two patients were included in the larger analysis. Both patients were treated for bacteremia with severe sepsis, received treatment within 72 hours of positive culture, and were admitted to an intensive care unit at the time of treatment initiation.

Conclusion: The local study found a lack of eligible matching participants, a setback observed in other participating centers of the CACTUS study. The larger investigation reported an interim analysis of no clinical difference in outcomes between agents and associated this with an underpowered study. The larger study plans to continue enrollment and perform further analyses.

Poster 23

Ritika Malik* and Dr. Patrick Glassman[1]

Unveiling Pharmacokinetic Variations in HER2-Targeting Antibodies: Insights into Breast Cancer Therapeutics

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Purpose: HER2 (Human Epidermal Growth Factor Receptor 2) plays a pivotal role in breast cancer, guiding the development of targeted therapies. This study focuses on the pharmacokinetic properties of 3 FDA-approved HER2-targeting antibodies: Trastuzumab (Herceptin), Pertuzumab (Perjeta), and Margetuximab (Margenza) in HER2-positive breast cancer patients.

Methods:A literature search was performed to find pharmacokinetic data for HER2-targeting antibodies in peer-reviewed publications and FDA Clinical Pharmacology and Biopharmaceutics Reviews and concentration vs. time profiles were digitized using WebPlotDigitizer. Non-compartmental analysis (NCA) and mathematical modeling were employed to evaluate the pharmacokinetic properties of the aforementioned drugs. A pharmacokinetic model was then created to project drug exposures at FDA-approved dosing regimens.

Results: The NCA findings revealed that Margenza exhibits a half-life ranging from 2.78 to 5.31 days, while Pertuzumab ranges from 0.428 to 0.976 days, and Trastuzumab has a mean half-life of 2.78 days. The developed pharmacokinetic model was able to well-characterize the digitized data.

Conclusions: Clear differences in pharmacokinetics were observed between Herceptin, Perjeta, and Margenza. The mathematical model will be used to better understand the need for different dosing regimens for each drug, as well as to project alternative dosing regimens. The observed pharmacokinetic differences support the hypothesis that dosing variations may be driven by underlying differences in pharmacokinetics among these monoclonal antibodies.

Poster 25

Katie Quigg*, Oyinlola Adeola Shofolawe-Bakare*, Sergio Moreno* and Dr. Nicole Sifontis[1]

Use of Photovoice to Educate Student Pharmacists on Structural Factors that Impact Health Outcomes

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Purpose: Photovoice is a qualitative research method where people through images can capture, represent and communicate their experiences and perspectives about issues that are important to them with the final goal of raising awareness and triggering social change. Photovoice is a research method not only with the potential to unmute patient voices, but also to enhance community engagement and raise awareness of social injustices linked to the development, access and use of medicines.

Objective: The aim of this teaching innovation was to provide student pharmacists an educational structure for deeper reflection on social determinants impacting health outcomes and inspire them to engage in a systems-based approach to solve complex problems.

Methods:Ten third year pharmacy students enrolled in a Public Health Elective. Each Student asked to capture a photograph in their community to reflect one of 5 social determinants of health. Student were asked to answer each of the following prompts: "What was your overall reflection of the project? Comment on the impact or emotions elicited by this project. Comment on what you learnt about yourself during this experience?" Through the inductive process, thematic analysis of the reflective statements was performed.

Results: The analysis of the assigned determinants highlighted the Neighborhood and Built Environment as the predominant category, encompassing 70% of the photos examined. In response to the initial prompt, students shared comprehensive reflections, with pertinent quotes extracted to evaluate the project's effectiveness. Prompt two evoked themes centered around the emotional responses elicited by the project, predominantly leaning towards positive sentiments, notably a profound sense of reward. Prompt three unveiled insightful reflections on personal growth, including heightened situational awareness, a more profound comprehension of privileges, and a heightened sense of responsibility towards community engagement and contribution.

Conclusion: This photovoice assignment served as a platform for students to articulate their viewpoints by delving into the structural determinants influencing health disparities, thereby focusing on factors that affect health outcomes. Through this project, awareness regarding the presence of social programs aimed at addressing these disparities were highlighted. The students' reflections centered on recognizing their own privilege and expressed a strong commitment to advocating for change.

Poster 26

Alexandra Lichvar*, Arina Lazutina*, Jennifer Jeune*, Kerim Cakir*, Brandon Shepherd*, Mariah Nguyen†, and Dr. Ellen A. Walker[1]

Xylazinee Prevents the Rewarding Effect of Fentanyl When Used in Combination in Conditioned Place Preference in Mice

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Introduction:

Xylazine is a potent alpha-2 adrenoreceptor agonist commonly found as an adulterant in the illicit drug supply of Philadelphia. Little is known about the drug in human subjects as the FDA has only approved veterinary use of this sedative. Methods:In this study, we evaluated the conditioned rewarding effects of xylazine alone and in combination with fentanyl by using a biased, three-chamber conditioned place preference procedure in Swiss Webster mice. Before beginning training, a baseline preference was obtained for each mouse as a comparator. Mice then trained for 25 minutes, once a day for ten days and alternated between saline training or active drug. On drug training days, mice received injections of xylazine, fentanyl, a combination of the two, or yohimbine; an alpha-2 antagonist. On the 12th day, mice were given free access to the 3 chambers and postconditioning preference was measured. Results: A dose of 0.3 mg/kg fentanyl produced significant conditioned place preference in mice when injected alone. Xylazine and yohimbine, however, failed to produce conditioned place preference significantly different from saline. When administered by itself, xylazine tends to trend towards aversion rather than reward. When used in combination, the effect of xylazine on the rewarding effect of fentanyl is dose dependent.

Conclusion: Based on the results of our research, we propose that xylazine does not produce conditioned place preference. Furthermore, the administration of xylazine in combination with fentanyl reduces the rewarding effects seen with fentanyl alone. The specific interaction between fentanyl and xylazine seems to be dependent on both dose and the ratio of the combination. Further research is needed to articulate the exact mechanism by which xylazine and fentanyl interact with each other.

(Supported by Peter F. McManus Charitable Trust).

Poster 28

Kerim Cakir* and Dr. Ellen A. Walker[1]

α2-Adrenoreceptor-agonist, Xylazine, Reveals Different Receptor Pharmacology, and Withdrawal Effects Compared to μ Opioid Receptor Agonist Fentanyl

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Purpose: A shift in the national illicit opioid market has seen the addition of α2-adrenoreceptor-agonist, xylazine, as an adulterant, specifically with the μ opioid receptor agonist fentanyl. While the two have been used concomitantly, little is known about the pharmacology behind the combination and the potential effects, leading to gaps in clinical knowledge and potential treatment options. We sought to understand the receptor pharmacology of this combination in Swiss-Webster mice by using an antinociception analysis, assessing their sensitivity on a 52.5°C hot-plate, and how the treatment with different combinations of antagonists and agonists alters the observed baseline sensitivity. Naltrexone produced antagonism of various doses of fentanyl, observed as decreases in antinociception in mice. However, naltrexone did not produce significant antinociception when combined with xylazine, suggesting that it does not have pharmacological effects at opioid receptors (MOR, KOR, and DOR). Yohimbine produced dose-dependent antagonism when co-administered with xylazine but increased antinociception when administered with fentanyl. Idazoxan, more selective for α2-adrenoreceptors than yohimbine, produced greater antagonism than yohimbine, suggesting that yohimbine may have additional pharmacological effects that may add to analgesia when given with xylazine and/or fentanyl. Precipitated withdrawal was observed in Swiss-Webster mice by injecting mice with large doses of either fentanyl or xylazine for two hours and then administering a high dose of antagonist (naloxone or idazoxan) to force acute withdrawal. More global physical withdrawal symptoms were seen in mice undergoing fentanyl withdrawal compared to mice undergoing xylazine withdrawal. Mice in acute xylazine withdrawal demonstrated signs of anxiety in addition to scratching which became more pronounced as the days of acute withdrawal increased to 3 days. The pharmacological and pharmacodynamic effects seen by fentanyl and xylazine differ when given separately and together, indicating there may be different underlying pathways which may alter antinociception and withdrawal.

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Poster 3

Lisa Petersohn* and Dr. Marc A. Ilies[1]

Applying Molecular Modeling to Gain Insights Towards the Design of Isozyme-selective Carbonic Anhydrase Inhibitors

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Purpose: Carbonic anhydrase (CA) is a ubiquitous enzyme responsible for catalyzing the reversible reaction of carbon dioxide and water to bicarbonate and a proton. This enzyme is essential for the homeostasis of different tissues and organs. Overexpression of certain CA isozymes is observed in many diseases including Alzheimer's disease, glaucoma, obesity, epilepsy and cancer.

Twelve catalytically active isoforms have been identified in humans. Substantial efforts have been made in developing isozyme-specific inhibitors, yet unsatisfactory progress has been made due to the lack of understanding of essential structural differences between the active sites.

In this work, the active site structures of disease-associated CA subtypes were examined using bioinformatic methods, paired with in silico docking of existing inhibitor structures.

Methods:We used well-cited and validated open-source programs: visualization of 3D protein structures was achieved with Discovery Studio, the preparation of structures for docking was done in Autodock Tools, and the docking of protein-ligand complexes was achieved using Autodock4.

The goal of the study was to resolve structural differences between CA subtypes both in overarching structural elements as well as on the amino acid level. Several different inhibitor complexes that have achieved relative subtype specificity were docked and their binding modes examined.

Conclusions: What can be concluded from this study is that significant parts of the active site is conserved between isozymes. The selectivity of inhibitors can be modulated to a certain extent by varying the warhead type and by means of substitution.

Poster 6

Tashnuva Rifat* and Dr. Marc A. Ilies[1]

Determination of the Potency of Different Inhibitors of Blood Esterases Using an Optimized 96 Well Plate-based Assay

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Purpose: Different esterases present in blood hydrolyze a plethora of esters with different lipophilicity. Some have a preference for more hydrophilic substrates, while others prefer lipophilic substrates. We have shown that the activity of these esterase can be evaluated either by the hydrolysis of 4 nitrophenyl acetate (4NPA) for esterases preferring hydrophilic substrate (e.g. carbonic anhydrase) or 4 nitrophenyl palmitate (4NPP) for esterase preferring lipophilic substrate (e.g. classical lipase, lipoprotein lipase). Based on these reactions, we also developed a 96 well plate-based assay for carbonic anhydrase enzyme and classical lipase enzyme and we validated the assay by determining their kinetic parameters of these esterases. Using this optimized plate assay, we were able to assess the potency of different inhibitors against these two enzymes, both reversible and irreversible.

Methods: The assays involving the hydrolysis of 4NPA for bovine carbonic anhydrase (bCAII) and 4NPP for Lipase Pseudomonas cepacia (LPC) were developed in a 96 well plate format and the Vmax and Km values for both esterases were determined using classical Michaelis-Menten kinetics. Stock solution of different inhibitors of these enzymes were made in dmso and their potency was determined following serial dilutions of the dmso stock, using the above-mentioned assay.

Results: The Vmax and km value for bCAII were 4.1 μM/min and 1.37mM and Vmax and km value for LPC were 7.04μM/min and 0.777mM respectively. The IC50 and Ki value of several CA and LPC values were determined and were found to be in good agreement with published values. Several known amphiphilic esterase inhibitors were assessed on LPC for the first time.

Conclusion: The potency of different inhibitors was successfully determined using our optimized 96 well plate based assay for both carbonic anhydrase and lipase blood esterases.

Poster 9

Yifan Gong*, Drs. Swati Nagar[1] and Ken Korzekwa[1]

Developing a New Rat PBPK Model to Improve Prediction of Concentration-time Profiles

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Purpose: To improve human plasma concentration-time predictions of drugs, our lab has recently developed the human PermQ model. During the model development, it was found the concentrations of many drugs were greatly over-predicted at very early time points after IV bolus or infusion, particularly for hydrophobic bases with a high blood-to-plasma ratio. The addition of a shallow compartment improved the prediction of early timepoint concentrations. This needs further evaluation, and data collection in rats is facile. The purpose of the present study is to develop a rat PermQ model to evaluate mechanisms of distribution kinetics of hydrophobic bases.

Methods:This model is a permeability- and perfusion-limited PBPK model and was developed using the human PermQ framework briefly described as follows. Drug can reversibly distribute between capillaries and interstitial fluid by fenestra or discontinuities in capillaries, or by transcellular diffusion through endothelial cells. Passive membrane permeability and transporter mediated are considered. Drugs also can partition into intracellular phospholipids and neutral lipids except into aqueous volumes. A shallow distribution compartment was added particularly for basic drugs. C-t profiles were modeled for 3 basic drugs using the same experimental inputs for three different models:

Rodgers and Rowland (RR), a perfusion-limited membrane-based model (Kp,mem), and rat PermQ. All models were built and evaluated using Mathematica version 12.3 (Wolfram Research Inc.).

Results: For metoprolol, the exposure overlap coefficients (EOC) values for RR, Kp,mem and rat PermQ are 0.833, 0.820 and 0.966, respectively. For atenolol, the EOC values for RR, Kp,mem and rat PermQ are 0.681, 0.675 and 0.868, respectively. For carvedilol, the EOC values for RR, Kp,mem and rat PermQ are 0.770, 0.779 and 0.947, respectively.

Conclusion: Rat PermQ model improved the prediction of rat C-t profiles for basic drugs. Mechanisms of basic drug distribution will be evaluated next.

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Poster 12

Kapish Karan*, Quyen Schwing*, Thomas Dürig* and Dr. Reza Fassihi[1]

Exploring The Interplay of Process Parameters and Novel Binder Properties in Extrusion-Enabled Melt Granulation

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Abstract: The production of immediate-release granules is an attractive option as it removes the need for a time-consuming and energy-intensive drying process. This simplifies the manufacturing process, reduces the need for expensive drying equipment, and could increase productivity. Melt granulation using a binding agent has been found to increase the strength of tablets compared to traditional granulation. Despite the potential benefits, there are concerns about in-process drug degradation of thermolabile drugs, which have hindered the widespread use of twin screw melt granulation (TSMG). To address these challenges, a new tablet binder called klucel™ Fusion hydroxypropyl cellulose (HPC) has been developed. This binder allows for low extrusion process temperatures (50°C- 80°C) and low shear levels at a low binder level of 5%.

Purpose: The performance and comparison of a novel Fusion HPC binder and commercially available HPC EXF (ultra fine tablet binder) and Polyethylene glycol (PEG) 8000 with TSMG process using Gabapentin as an example of a highly thermolabile drug.

Results: This new melt granulation binder showed significantly lower melt viscosity, lower storage modules, and higher Tan (δ) than commercial HPC, indicating enhanced thermoplasticity and processability compared to the commercial HPC grade between 50-180°C. Klucel™ Fusion HPC performed exceptionally well across a wide range of processing conditions, yielding stronger granules than HPC EXF and PEG 8000 in TSMG using Gabapentin. In addition, the formulation with the klucel™ Fusion HPC showed the lowest degradant level relative to other binders. Klucel™ Fusion granulations produced under all conditions delivered the strongest tablets with acceptable friability. The formulation processed with PEG 8000 at high temperature had the highest impurity level and yielded the softest tablets. Immediate-release dissolution behavior was not impacted.

Conclusion: The klucel™ Fusion HPC exhibited better processability and stability of Gabapentin than the commercial HPC EXF grade and PEG 8000 due to its low melting temperature and complex viscosity. To move beyond traditional batch processing (e.g., wet and fluid bed granulation) to continuous processing technology via melt granulation, the klucel™ Fusion HPC is a promising choice as a binder due to the ease of processing and protection of moisture-sensitive and thermolabile drugs.

Poster 15

Nader Afifi*, Dennis J. Colussi*, Magda L. Florez*, Drs. Oscar Perez-Leal and Carlos A. Barrero

Integration of Gene Editing and High Content Imaging for Developing In Vitro Phenotypic Disease Models for Studying Neurological Diseases

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Purpose: Understanding neurodegenerative disorders at the neuronal level is key for drug discovery. In-vitro cell models that resemble disease phenotypic changes are crucial to determining the efficacy of novel drug candidates. The main aim of this work is to generate a gene-tagged cell model that facilitates the study of neurological diseases and can be used to create in vitro models for drug discovery.

Methods:SH-SY5Y neuroblastoma cell line was used to induce FAST-HDR (homology-directed repair) and CRISPR-Cas9 gene editing system tagging the endogenous protein tubulin 3 (TUBB3). Each backbone plasmid allows adding both 5′ and 3′ recombination arms in a single enzymatic reaction, hence decreasing the time and the multi-step processes in the traditional methods. Single guide RNA (sgRNA) was designed using 'benchling' software, and the DNA constructs were transformed and expanded in E. coli. FAST-HDR and CRISPR-Cas9-TUBB3 were electroporated in SH-SY5Y cells, and positive transformed cells were selected for colony formation. The SH-SY5Y-TUBB3 cells continuously grow in vitro and are used for several applications, including reporter gene expression, differentiation into mature neurons, and spheroid formation. Morphological phenotypic characteristics of the differentiated neurons and the neuroblastoma cells were evaluated using high-content image analysis.

Results: Using the FAST-HDR and CRISPR-Cas9 system we were able to insert a TUBB3 tagged protein that can mark the cytoskeleton of the cells. Gene editing was verified by DNA sequencing, and SH-SY5Y-TUBB3 cells were successfully edited, selected, and visualized by fluorescence microscopy. SH-SY5Y-TUBB3 cells were successfully used for neuronal differentiation and 2D and 3D cultures. This SH-SY5Y-TUBB3 cell was further used as a reporter cell for the expression of a Huntington's disease model.

Conclusion: We were able to generate SH-SY5Y-TUBB3 genetically edited cell line that can be used as a neuronal model to study different neurological disorders. More importantly, this SH-SY5Y-TUBB3 cell line can be used in a high-throughput for phenotypic drug screenings.

Funded by: Office of Vice-president for Research at Temple University OVPR and the Pharmacy School.

Poster 18

Mathias Sanchez Machado* and Dr. Marc A. Ilies[1]

Interplay Between the Stabilization of AuNPs by Thiolated Ligands and Their Colloidal Destabilization by Different Chemical Entities in the Design of Novel Drug Delivery Systems

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Introduction: In recent years, gold nanoparticles (AuNPs) have emerged as promising candidates for drug delivery systems due to their biocompatibility and unique physicochemical properties.

Purpose: This study aimed to explore the intricate balance between stabilization of AuNPs by thiolated ligands and ligand detachment from the surface of AuNPs, with colloidal destabilization, upon treatment with different chemical agents, for the generation of efficient drug delivery systems.

Method: Utilizing the Turkevich-Frens reaction, we refined the synthesis of small (<20 nm) and ultrasmall (<10 nm) AuNPs while maintaining precise control over particle size and shape. We decorated these nanoparticles with various thiol-containing ligands and elucidated the pivotal role of ligand type in AuNP stabilization.

Results: Our investigations unveiled that PEGylation, involving the conjugation of polyethylene glycol (PEG) chains to AuNPs, effectively stabilizes the nanoparticles for extended periods, surpassing six months, crucial for sustained drug delivery. However, our latest findings underscored the destabilizing impact of glutathione and 2-mercaptoethanol, emphasizing the delicate balance between colloidal stabilization/destabilization in AuNP-based drug delivery systems. In addition, we found out that SH-TEG serves as a protective stabilizer when decoration with short-chain ligands is required. Through meticulous analysis of the time and concentration-dependent stability profiles of PEGylated AuNPs, we delineated their suitability for diverse drug delivery strategies.

Conclusion: These findings underscore the significance of considering ligand properties, nanoparticle stability, and environmental factors in designing optimized drug delivery platforms with improved efficacy and biocompatibility.

Poster 21

Shibbir A. Khan and Dr. Marc A. Ilies[1]

Phospholipase A2-mediated Degradation of Amphiphilic POPC-based Self-assemblies

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Introduction: Phospholipase A2 (PLA2) constitute a superfamily of enzymes among the large class of phospholipases that hydrolyze phospholipid substrates at sn-2 position releasing a fatty acid and a lysophopholipids. Unlike other hydrolases, these groups of enzymes dock on lipid/water interface and cleave the fatty acid chain of individual lipids within the phospholipid bilayer assemblies. The enzymatic hydrolysis rate for this enzyme depends on the amount of substrate present and also on accessibility of the substrate to the active site of the enzyme. Thus, different self assemblies containing phospholipids such as liposomes and micelles could show different rates of hydrolysis for the enzyme.

Purpose: To develop a PLA2 assay method using natural substrate (POPC) and to make a comparative analysis of PLA2 enzyme kinetics using different POPC self-assemblies such as liposomes, micelles.

Method: An indicatory dye based assay was developed which tracked the PLA2 activity by detecting the change in the absorbance. This was translated into different PLA2 kinetic parameters.

Results: PLA2 was able to process micellar based self-assemblies more than compared to liposomal based assemblies.

Conclusion: PLA2 kinetic parameters could be affected based on the self-assembly systems of the substrate.

Poster 24

Mohammed Yousuf*, Drs. Ken Korzekwa[1] and Swati Nagar[1]

Predicting Impact of Pgp Transporter in Drug Distribution and Disposition from In Vitro Drug Transport Assay Through Modeling and Simulation Approaches

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Purpose: Transporters have a significant role in drug permeation, distribution, and disposition. We can evaluate the transporter activity of potential drug candidates prior to preclinical and clinical studies. Our research aims to determine the transporter efflux clearance from in vitro drug permeation across MDCK cell monolayers.

Methods:The MDCK cells are cultured as a monolayer on the insert filter of the transwell device. Upon plating, the Pgp transporters are expressed on the apical side of the cells. Using the net clearance concept, we developed equations for measuring the efflux clearance (CLeff) and clearance into the membrane (CLi) from the apparent permeability from the apical side to the basolateral side and the basolateral side to the apical side. Drug transport assays provide the time course of drug concentrations in the donor and receiver chambers after dosing in the apical or basolateral chamber with or without a Pgp inhibitor. The time course data are used to optimize model parameters. The fraction unbound in microsome (fum) is used to parameterize the membrane partition coefficient (Kp, mem). The fum values are measured by equilibrium dialysis.

Results: The measured fum value for Loperamide is 0.38 at 1mg/ml microsomal protein concentration after 6 hours of incubation in an equilibrium dialysis device. The non-steady state transport model is parameterized with the concentration-time data.

Conclusions: The primary parameters, the efflux clearance and clearance into the membrane, can be added to PBPK models to see the Pgp impact of any drug candidate early in drug discovery. This approach will help predict the distribution and disposition profile of Pgp substrate molecules.

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Poster 27

Xinyue (Cindy) You*, Drs. Swati Nagar[1] and Ken Korzekwa[1]

Propranolol Glucuronide: A Potential Substrate for CYP2C8

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Purpose: Glucuronidation is an important elimination pathway for propranolol. There are two potential 4-hydroxypropranolol glucuronides, aliphatic-linked and aromatic-linked. The purpose of our study is to test the ability of CYP2C8 to hydroxylate propranolol glucuronide.

Methods:An LC-MS-MS method was developed for propranolol, propranolol glucuronide and aromatic-linked 4-hydroxypropranolol glucuronide with propranolol d7 as the internal standard. Standard curves were generated at 0.033-1.33μM for propranolol and aromatic-linked 4-hydroxypropranolol glucuronide, and 0.067-1.33μM for propranolol glucuronide. Stock solutions were in DMSO at 1mM with PBS. Acetonitrile (with 0.2μM internal standard) was added to the final samples. Samples were analyzed on an Agilent 1100 series HPLC coupled to an ABSciex triple quadrupole linear ion trap 4000 MS with electrospray ionization. Analytes were separated on an Agilent, 5μm C18, 150 × 4.6 mm column with a C18 guard column (4 × 2.0 mm). The method was validated by linearity, LLOQ, selectivity, intra- and inter-day precision and accuracy.

Propranolol glucuronide (4μM) was incubated with 50pmol/ml CYP2C8 in 0.1M potassium phosphate buffer (pH 7.4) at 37°C. NADPH regeneration system (consisting of 1.3mM NADPH+, 3.3 mM glucose-6-phosphate, 3.3mM MgCl2, 0.4U/ml glucose-6-phosphate dehydrogenase) initiated the reaction. At 15–120 min, reactions were terminated with acetonitrile (with propranolol d7). Negative controls were without NADPH. Diclofenac Acyl-β-D-glucuronide was the positive control.

Results: The optimized mobile phase was aqueous solution with 0.1% formic acid (FA) (A) and ACN with 0.1% FA (B) at the flow rate of 0.8ml/min with gradient elution. The method showed good selectivity with linear calibration curves. QC samples showed good intra-and inter-day precision and accuracy. Results for the CYP2C8 incubations will be presented.

Conclusions: An LC-MS-MS assay for propranolol, propranolol glucuronide and aromatic-linked 4-hydroxypropranolol glucuronide was developed and validated. Future studies will determine whether propranolol glucuronide is a substrate for CYP2C8.

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Poster 29

Bayan A. Alshahrouri*, Drs. Reza Fassihi[1] and Benjamin Blass[1]

Use of Thermo-Responsive Biodegradable Triblock Copolymers in the Development of a Sustained Release In-situ Gel Forming Delivery Formulation for Intravitreal Injection

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Abstract: Eye, the body's most sensitive sensory organ, possess a sophisticated anatomical structure that is crucial in the visual system. Age-related Macular Degeneration (AMD) is one of the primary causes of vision loss among older adults (mostly 20 million individuals in the United States). Several anti-vascular endothelial growth factor (anti-VEGF) for intravitreal injection are available and may enhance vision. In patients who exhibit incomplete response to anti-VEGF therapy, Dexamethasone (DXM) appears to improve retinal fluid resorption. Additionally, DXM is shown to treat Macular edema when blood vessel in the eye is clogged. The most suitable method of administration depends on which area of the eye is target for the remedy. Intravitreal injection of drugs close to the target region with sustained delivery (SD) over period of few days or weeks may enhance therapy and improve patient compliance.

Purpose: Formulation development and optimization for delivery of DXM using thermo-responsive biodegradable triblock copolymers for intravitreal (IVT) administration to achieve SD with reduced side effects associated with biodegradation.

Methods:The copolymer solution was prepared and assessed via 1HNMR, Gel Permeation Chromatography (GPC), and Dynamic Oscillatory Rheology. DXM+β-cyclodextrin solution using PLGA–PEG–PLGA copolymer was prepared. From this solution 50 µL of 4 mg DXM/ml containing 30%w/w polymer was added to a glass vial and upon phase transition to a gel 15 ml of PBS (pH 7.4) +1% Tween-80 was added to maintain sink conditions at 37 °C and subjected to release study at 20 rpm horizontal movement.

Results and Discussion:

The 1H-NMR spectrum confirmed the chemical structure of PLGA–PEG–PLGA. GPC determined the copolymer's polydispersity (approximately 1.30) with a symmetric peak and narrow molecular weight distribution. The sol–gel transition of the triblock copolymer from liquid phase to a gel confirmed at approximately 37 °C. The DEX-loaded liquid formulation underwent phase transition into a gel at body temperature. Dynamic Oscillatory Rheological properties as a function of temperature and oscillation to determine storage modulus (G`) and loss modulus (G``) was done and sol-gel transition temperature was detected around 32°C, through observation of G`` and G` curves intersection. In vitro release experiments demonstrated sustained release of DXM over 15 days.

Conclusion: The results reveal that SD-formulation developed could serve as a promising thermo-responsive platform for long-acting ocular delivery of DXM. This approach is encouraging and lends itself to further research in AMD.