Temple University
School of Pharmacy

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2022 RESEARCH RECOGNITION DAY

Abstract Book

Friday, April 22nd

MESSAGE FROM THE DEAN

Since 2007, Temple University School of Pharmacy's Research Recognition Day is an annual tradition that celebrates the research accomplishments of our graduate and professional students and their faculty mentors.

At the Temple University School of Pharmacy, our students have many opportunities to lead innovations in clinical practice as well as in basic and applied sciences while 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. Research Recognition Day offers a sampling of the work we do to foster this endeavor.

This year, we have the honor of hosting Sonak Pastakia, PharmD '04, MPH, PhD, BCPS, FCCP, Professor of Pharmacy Practice at the Purdue University College of Pharmacy and Associate Director of the Center for Health Equity and Innovation. Dr. Pastakia's research focuses on population health, community-based care, implementation science, HIV, non-communicable diseases, and supply chain infrastructure in low- and middle-income countries. He has implemented a variety of programs, such as designing and leading the original pilot for the community-based care model for diabetes and hypertension, a pharmacy distribution system which provides antiretroviral medications to over 205,000 HIV-infected patients receiving care at > 500 satellite clinics throughout western Kenya, a supply chain system for essential medications including cardiovascular disease medications at over 85 sites, and an anticoagulation monitoring program which serves over 4,700 patients.

The School is grateful for the presenting sponsorship from Genentech. Many thanks go to Dan Castiglia, BSPharm '98, MS, Federal Account Manager - Northeast, Genentech, Lieutenant Colonel, US Air Force (ret); presenters, and evaluators, and our event committee, which includes faculty members, Drs. Jason Gallagher, Swati Nagar, Oscar Perez, Mario Rico, Christina Rose, and Tina Tran, and student, Md Abu Sufian.

Thank you for your participation.

Jay Panyam, PhD
Dean & Professor

SCIENCE DEMANDS DIVERSITY

After more than 40 years of tackling the toughest medical challenges, we know that approaching any problem from a single point of view is setting a course for failure.

Success depends upon welcoming diverse approaches, challenging the status quo and exploring hypotheses from all angles. Science demands diversity and so do we.

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AGENDA

12:00 - 12:15 p.m.: Welcome Remarks by Jayanth Panyam, PhD, Dean and Professor, and by Dan Castiglia, BSPharm '98, MS, Lieutenant Colonel, US Air Force (ret), Federal Account Manager - Northeast, Genentech

12:15 - 1:15 p.m.: Keynote Lecture by Sonak Pastakia, PharmD '04, MPH, PhD, BCPS, FCCP - Professor of Pharmacy Practice and Associate Director of the Center for Health Equity and Innovation at the Purdue University College of Pharmacy

"TRUST THE PROCESS: OPPORTUNITY. ENGAGEMENT. DISCOVERY. APPLYING THE TEMPLE EXPERIENCE TO ADVANCING GLOBAL POPULATION HEALTH"

1:15 - 2:15 p.m.: Q&A with Student Research Presenters

2:15 - 3:00 p.m.: Select Oral Presentations

3:00 - 3:15 p.m.: Student Awards

3:15 - 3:45 p.m.: Closing Remarks and Networking Opportunities with Sponsor, Keynote Speaker, Poster Evaluators, and Alumni

RESEARCH DAY EVALUATORS

Shohreh Amini PhD, Professor & Director, Temple University
Allison Andrews PhD, Assistant Professor, Lewis Katz School of Medicine at Temple University
Aneesh Argikar PhD, Associate Director, Syneos Health
Erin Bettine RPh, MBA, Board of Directors Member, Temple University School of Pharmacy Alumni Assoc
Chris Bode PhD, VP, Scientific and Corporate Communications Absorption Systems
Katie Cho PharmD, BCACP, Clinical Assistant Professor, Temple University School of Pharmacy
Kenneth Cleaver PhD, Consultant, Kenneth E. Cleaver Consulting, LLC
Phu Duong PharmD, Senior Director, Virology, Medical Affairs Merck Research Laboratories
Thomas Durig PhD, CTO, Ashland Life Sciences
John Ellingboe PhD, Managing Director, JE Pharma Consulting
Saba Emami PharmD, MS, Associate Director, Merck
Scott Greene RPh, MS, PhD, Director of Experiential Programs, Philadelphia College of Pharmacy/USciences
Alexandra Hanretty PharmD, Clinical Pharmacy Specialist; Infectious Diseases, Copper University Health Care
Madeline King PharmD, Assistant Professor of Clinical Pharmacy, Philadelphia College of Pharmacy
Jan Kitzen PhD, Retired, Retired
Tarek Mansour PhD, CEO, Sabila Biosciences LLC
Oxana Megherea PharmD, Oncology Clinical Pharmacy Specialist, Penn Medicine
Patty Melissen BCACP, AAHIVE, Residency Program Director, Albertsons
Sejal Patel PharmD, Emergency Medicine Clinical Pharmacist, Jefferson Health
Michelle Peahota PharmD, BCPS, BCIDP, Ambulatory Clinical Pharmacist, Infectious Diseases Penn Medicine
Mirza Perez PharmD, Associate Professor, Temple University
Lucia Rose PharmD, Medical Science Director, Paratek
Gregory Shaeffer MBA, RPh, Assistant Professor, University of Maryland Eastern Shore
Eugene Trybulski PhD, Director Med Chem, Retired
Daniel VanDorn PharmD, Lead Scientist for Product Development & Senior Medical Science Liaison, Genomind
Kiyo Yoda PharmD, Pharmacy Clinical Coordinator, Paoli Hospital (MLHS)

GRADUATE POSTER LIST

POSTER ID	TITLE	PRIMARY STUDENT AUTHOR	SUBMITTING FACULTY/ RESEARCH SUPERVISOR:	YOUTUBE LINK
GRADUATE STUDENTS				
G1	In-vitro enzyme kinetics of nicardipine metabolism to dehydronicardipine in rat liver and intestinal microsomes	Tirtha Nandi	Swati Nagar	https://youtu.be/qTuRVSkihvE
G2	Can the glycocalyx impact partitioning of drugs into red blood cells?	Yifan Gong	Swati Nagar	https://www.youtube.com/watch?v=E3a3YZ9HyO0
G3	Novel ureido sulphonamides as potent and isozyme selective cytotoxic agents against several carbonic anhydrase IX expressing carcinomas	Md. Abu Sufian	Marc A. Ilies	https://www.youtube.com/watch?v=jtiENEZUPtE
G4	Variation of physicochemical parameters and stability with composition in a set of liposomal formulation based on natural lipids	Tashnuva Rifat	Marc A. Ilies	https://www.youtube.com/watch?v=KbbjeEiOAL8
G5	Size controlled Turkevich gold nanoparticles	Mathias Sanchez Machado	Marc A. Ilies	https://youtu.be/BH4kxCB89xs
G6	Interaction of liposomes with phospholipases A1 and A2: A comparative study	Shibbir Ahmed Khan	Marc A. Ilies	https://youtu.be/5GxcJ7_YM4c
G7	Lipid membrane polar headgroups cause enhanced partitioning of ionized metoprolol- new insights into the pH-partition hypothesis.	Md Leonard Hridoy	Ken Korzekwa	https://youtu.be/JYB-JhSmxx8
G8	Remodeling this old house with FOLR3	Connor Quinn	Salim Merali	https://youtu.be/zGNYDldpW1Y
G9	Molecular Effect of Difluoromethylornithine on Neuroblastoma Cells	Bryan Zhang Youcef Azzi Nader Afifi	Carlos Barrero	https://youtu.be/39cPOup-uME
G10	Investigation of Diazepam Sequential Metabolism with Hepatocytes via a Microfluidic Device	Zeyuan Wang	Ken Korzekwa	https://youtu.be/YqDEeR_XPt0

PROFESSIONAL POSTER LIST

POSTER ID	TITLE	PRIMARY STUDENT AUTHOR	SUBMITTING FACULTY/ RESEARCH SUPERVISOR:	YOUTUBE LINK
PROFESSIONAL STUDENTS				
P1	What Extent Do Lifestyle Factors Contribute to an Increased Stroke Burden in Pakistanis & Asian Indians Compared to non-Hispanic Whites in the U.S?	Sana Khan Javeria Ali Mahnoor Shahid Karen Wang	Van Hellerslia	https://youtu.be/8kh21YJVknY
P2	Dosing Strategies for de Novo Once-daily Extended-Release Tacrolimus (LCPT) in Kidney Transplant Recipients	Khushbu Patel	Oscar Perez-Leal	https://youtu.be/zmmACIDhT2U
P3	Assessing COVID-19 Vaccination Access, Uptake, and Hesitancy at an Academic Outpatient Clinic in North Philadelphia	Ryan Scanlan	Nima Patel-Shori	https://youtu.be/UIY4RF6SdGQ
P4	Drug Use Evaluation of Continuous Infusion Heparin at Temple University Health Systems	Alicia Nordberg-Payne	Christina Rose	https://youtu.be/9ULSiyuNzYE
P5	Direct Oral Anticoagulant Adherence Patterns	Muhaimin Id'Deen	Talitha Pulvino	https://youtu.be/Fm73-1CQnM0
P6	Cardiovascular and cerebrovascular health status and health disparities of Cambodian-Americans: A rapid scoping review	Julie Hoang	Van Hellerslia	https://youtu.be/uucMAr9Pkaw
P7	Factors associated with initiation of oral antineoplastic therapies in an urban academic medical center: Part 2	Lauren Gebhard	Justina Frimpong	https://www.youtube.com/watch?v=hhMAg6x2eFk&t=197s
P8	Seizure-induced Rhabdomyolysis and Acute Kidney Injury	Kosha Gandhi	Van Hellerslia	https://youtu.be/T0JgztiSKq4
P9	How effective is stroke education in the Vietnamese-American population in improving stroke awareness and readiness to call 911?	Rachel Nguyen	Van Hellerslia	https://youtu.be/LRA6QqWNbEM
P10	COVID-19 pharmacy student perceptions: pharmacists' impact during the COVID-19 pandemic	Bryan Zhang	Frank Breve	https://youtu.be/TbD3H8pyxOY
P11	Evaluation of Tocilizumab for the Treatment of COVID-19 at Temple University Hospital	Sarah Bruzek	Jason Gallagher	https://youtu.be/If0iOlOxeTk
P12	Incidence and Outcomes of Pneumonia in Lung Transplant Patients	Liesel Groninger	Jason Gallagher	https://youtu.be/lpJBku_EBzg

PROFESSIONAL POSTER LIST (CONT.)

P13	Outcomes in Kidney Transplant Recipients with Latent Tuberculosis Infection	Janelle Croissette	Nicole Sifontis	https://youtu.be/kbVTN-GSE-w
P14	Community-based participatory research to improve medication adherence in western Kenya	Jennalee Catolos	Tina Tran	https://www.youtube.com/watch?v=Ni55_0BYm3M
P15	Effects of digoxin in Heart Failure (HF) with Reduced Ejection Fraction (EF)	Riya Parikh	Frank Breve	https://youtu.be/59x1y71sDpM
P16	Effects of Serotonin-7 Receptor Agonists and Antagonists on Learning and Memory in Mice	Cecilia Vu	Ellen Walker	https://youtu.be/UygcZrnkPJM
P17	High Content Imaging in Pharmacology	David Nguyen Daniel Ghattas	Carlos Barrero	https://youtu.be/C93UhNgDTvA
P18	Extracellular Histones Associated With Complications in COPD and COVID-19	Sergio Moreno	Carlos Barrero	https://youtu.be/b1Fqd04tE_g
P19	Comparative analysis of non-compartmental, compartmental and physiologically based pharmacokinetic models	Prerna Nahar Deep Patel Siddhant Patel Sriramani Sivapurapu	Swati Nagar Ken Korzekwa	https://www.youtube.com/watch?v=dAmjLGse8N4
P20	In-Vitro Evaluation of Cigarette Smoke & SARS-CoV-2 Spike Protein on Cytokine Expression in Macrophages	Osominomo Garba Fatima Esmail Latifatu Ojo	Carlos Barrero	https://youtu.be/CMhZCnW0uXM
P21	Cannabidiol Effects in Paclitaxel Induced Neuropathic Pain	Arelis Nunez Osominomo Garba Giordanne Melgar	Carlos Barrero	https://www.youtube.com/watch?v=lT_xHpXdGfA
P22	Analysis of Orphan Drugs in the 21st Century by Type of Orphan Drug, Approval Times, and Facilitated Regulatory Pathways	Zach Delisi	David Lebo Larry Liberti	https://youtu.be/nJak55vCrnQ
P23	Identification of Tubulin polymerization inhibitors using a CRISPR-Cas9 edited cell line with endogenous tagging of beta-tubulin	Harutyun Khachatryan	Oscar Perez-Leal	https://www.youtube.com/watch?v=4sm6DmqsDRk

G1

In-vitro enzyme kinetics of nicardipine metabolism to dehydronicardipine in rat liver and intestinal microsomes

Tirtha Nandi*, Ken Korzekwa, Swati Nagar[1]

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BACKGROUND:
Over the last few decades, with the advent of computing power of manmade devices including computers, pharmacokinetic (PK) modeling and simulation has been playing a pivotal role in the tedious process of drug discovery and development. In this process, in vitro metabolic studies are one of the initial assays and their proper analysis provide useful information that can help to anticipate in vivo drug PK.

OBJECTIVE:
Nicardipine (NCD), a dihydropyridine derivative of calcium channel blockers (CCB), is widely used in the treatment of cardiovascular diseases. One of the major metabolites of NCD is dehydronicardipine (DNCD). The aim of the current research was to characterize the in vitro metabolic conversion of NCD to DNCD in Sprague-Dawley (SD) rat liver microsomes (RLM) as well as by rat intestinal microsomes (RIM).

METHODS:
NCD was incubated separately with RLM (0.10 mg/mL) and RIM (0.25 mg/mL) for 5 minutes and 20 minutes respectively. Microsomal protein concentration and incubation time were decided based on time and protein linearity assays as well as previously published reports. Metabolite formation data were obtained from LC-MS/MS analysis. These data were analyzed by fitting single binding Michaelis-Menten model (ESP model) and multiple binding model (ESSP model) to the data using Wolfram Mathematica 12.2.2 student version. Model comparison was conducted based on the corrected Akaike Information Criterion (AICc), mean squared sum of residuals (MSE), and residual plots. Based on the best-fit model, parameter estimation was reported to provide the kinetic profiles (Km, Kcat, and CLint). Equilibrium dialysis was conducted to determine the fraction unbound in microsomes (fum). Finally, unbound Km (Km,u) and unbound intrinsic clearance (CLint,u) were reported.

RESULTS:
NCD incubation with rat microsomes were best explained by the ESS model. Specifically, DNCD formation from NCD by RLM and RIM followed sigmoidal kinetics and biphasic kinetics respectively.

CONCLUSIONS:
ESSP model successfully described NCD metabolism by RIM and RLM although the mechanisms were different. Tissue-specific differences were observed in RLM versus RIM which might explain this difference.

FUNDING:
NIH grants NIGMS 2R01GM114369 and NIGMS 2R01GM104178.

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G2

Can the glycocalyx impact partitioning of drugs into red blood cells?

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BACKGROUND:

Erythrocytes (Red blood cells, or RBCs) as cellular carriers of therapeutic drug molecules have been of interest for many years. The glycocalyx is a glycoprotein and glycolipid covering that surrounds the cell membranes of red blood cells, epithelial, and other cells. The glycocalyx is highly charged with negative charges, which helps RBCs repulse each other and do not become sticky, and also helps them not stick to blood vessels.

PURPOSE:

The purpose of this study is to figure out the role of the glycocalyx in drug partitioning into RBCs.

METHODS:

We performed erythrocyte partitioning experiments to obtain the partition coefficients of drugs in erythrocytes and PBS buffer in the presence of glycocalyx. Then we performed erythrocyte glycocalyx removal experiments and partitioning experiments to get the partition coefficients of the drug in erythrocytes and PBS buffer in the absence of glycocalyx. Hyaluronidase (50 μg/mL), Heparinase (5 U/mL) and Neuraminidase (0.1 U/mL) were used to remove the glycocalyx. Firstly, the RBCs are washed by PBS buffers. Then the washed RBCs are treated with enzymes or PBS. After 2 hours incubation, metoprolol is added to RBCs and incubated at room temperature. We obtained two drug-containing samples, the supernatant and RBCs, by centrifugation. The samples were analyzed with LC/MS-MS. The role of glycocalyx on drug partitioning is determined by comparing the partition coefficients of the two groups. The equation we used is Kp = Cr/Cp, Kp is partition coefficient, Cr is the concentration in RBCs, Cp is the concentration in supernatant.

RESULTS:

At 1 hour incubation time, the Kp value with glycocalyx (Kpg) is 0.979 ± 0.049, Kp value without glycocalyx (Kprg) = 1.020 ± 0.016. At 5 minutes incubation time, the Kpg = 1.133 ± 0.016, Kprg = 0.988 ± 0.135. At 1 minute incubation time, the Kpg = 1.210 ± 0.098, Kprg = 1.183 ± 0.082. At 30 seconds incubation time, the Kpg = 1.058 ± 0.124, Kprg = 1.009 ± 0.252. At 5 seconds incubation time, the Kpg = 1.116 ± 0.107, Kprg = 1.029 ± 0.229. The results were statistically not different among the groups.

CONCLUSION:

Glycocalyx may affect basic drugs partitioning into RBCs. In the future, we will use more types of drugs and find a simple and reliable method to visualize the extent of the removal of glycocalyx.

FUNDING:

NIH grants NIGMS 2R01GM114369 and NIGMS 2R01GM104178

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G3

Novel ureido sulphonamides as potent and isozyme selective cytotoxic agents against several carbonic anhydrase IX expressing carcinomas

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BACKGROUND:
Many solid tumors follow Gompertzian fast growth, outpace angiogenesis and become hypoxic. Persistent hypoxia leads to the activation of hypoxia induced factor (HIF-1), which in turn upregulates an overabundance of proteins, including glucose transporters and carbonic anhydrase IX (CA IX). As a result, glucose uptake significantly increases in these tumor types. Under reduced oxygen supply they heavily exploit anaerobic glycolysis and create a huge intracellular proton burden, making the cytosol acidic. However, the tumor cells get rid of the proton burden with the help of several CA isozymes including CA IX.

SIGNIFICANCE:
CA IX is highly in hypoxic tumors and have a relatively restricted tissue distribution. The expression of CA IX is retained even after the vascularization of tumor mass, making it an excellent target for drug design and development. However, due to the presence of other isozymes, some of which are ubiquitously present throughout the body, design and development of selective CA IX inhibitors is challenging.

OBJECTIVES:
Our objective was to determine the inhibition constant, binding modes, and interactions of a set of novel compounds as selective CA IX inhibitors and to test cytotoxicity of the same set of compounds against several CA IX expressing carcinomas.

METHODS:
The inhibition constants of the compounds were determined by stopped flow CO2 hydrase assay. For molecular docking, compounds 3D structures were calculated and optimized using Gaussian 09 program. X-ray crystal structure of CA IX was retrieved from PDB database and prepared for docking by using PyMOL, and Swiss PDB Viewer. Docking was performed using AutoDock Vina. Non-bonding interactions were visualized in DiscoveryStudio. Cytotoxicity of the compounds were tested by MTT assay.

RESULTS:
In CA inhibition assay, ureido thidiazole sulphonamides showed subnanomolar inhibition potency. In molecular docking, all the ureido sulphonamides docked into the same binding pocket of CA IX and docking results of the compounds nicely correlated with the inhibition constants. Majority of the compounds showed great selectivity for CA IX over CA I, whereas some were selective for CA IX over CA II. In cytotoxicity assay, both under normoxia and hypoxia, the compounds with strong inhibitory constants and high docking scores showed significantly better tumor cell killing efficiency than that of the clinical candidate, SLC-0111.

CONCLUSIONS:
We identified selective CA IX inhibitors with sub-nanomolar potency and characterized their cytotoxic profile across several CA IX expressing tumor cell models. In this study, we found more potent compounds than clinical candidate SLC-0111.

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G4

Variation of physicochemical parameters and stability with composition in a set of liposomal formulation based on natural lipids

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BACKGROUND AND PURPOSE

Liposomes are spherical, self-closed structures formed by one or several concentric lipid bilayers with an aqueous phase inside. It has different properties for which it is advantageous; biocompatible, can protect the incorporated drug from external condition and can reduce nonspecific side reaction by delivering the drug into targeted site. The properties of liposome vary with the type and quantity of lipid used, packing parameters of lipids, preparation methods, surface charge. The purpose of the study is to determine the effect of different lipids on the size, zeta potential and stability of liposomes.

MATERIALS AND METHODS

Total eight formulations were made with four different lipids (DPPC, DOPC, DMPC, and POPC); four of them contained cholesterol and others did not. The liposomes were prepared by thin film hydration technique followed by extrusion. The formulations with cholesterol had lipid Cholesterol ratio 1:1. The formulations were characterized by size, PDI, and Zeta potential using zeta sizer nano (Malvern instruments). After 3 days of the preparation, the size and PDI value were again measured to determine the stability.

RESULTS

The size of all liposomes were found with 120 to 160 nm. For the liposome containing DMPC:Chol (1:1) had multimodal peak. But after 3 days, it became unimodal. The liposomes without cholesterol had slight negative zeta potential except the liposome containing DPPC. After 3 days, size of all liposomes had increased. For liposomes containing only DPPC, almost 150nm size had been increased and became extremely heterogenous. Further studies are needed to determine the stability for more extended time and to determine the encapsulation efficiency by incorporating different hydrophobic drug.

CONCLUSION

The size, PDI, and zeta potential of liposomes vary with different types and quantity of lipids. The packing parameters of different lipids has significant effects on the size of liposomes. Cholesterol increases the stability of liposomes.

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G5

Size controlled Turkevich gold nanoparticles

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In the last decades, research in gold nanoparticles (AuNps) has grown due to their interesting properties. Thus, the specific physicochemical properties of Au Nps can be enhanced to induce special optical, plasmon-resonance, and catalytic features for these nanoplatforms. AuNps are widely used nowadays in biological applications such as delivery of enzyme inhibitors, nucleic acids, drugs, and for imaging purposes. In particular, AuNps have been investigated extensively as drug delivery platforms since it is possible to conjugate them with different ligands, linkers, enzymes, and proteins. The Turkevich method, also known as the citrate method, produces regular spherical gold nanoparticles with sizes around 20 nm. This method presents the advantage of producing biocompatible gold nanoparticles that were included in the FDA G.R.A.S. list, which makes them a better option for in vivo translational applications over other highly researched methods to generate Au Nps, such as the Burst method. The aim of this project was to produce tunable gold nanoparticle platforms conjugated with functional ligands as a nanoplatform with improved pharmacokinetics as compared with our standard 20-30 nm AuNps published recently.

Hence, we decided to optimize the Turkevich method to obtain smaller (sub-20 nm and sub-10 nm) gold nanoparticles, while controlling of the size of Au Nps and to conjugate them with different ligands. We studied the effect of different gold/citrate ratios, effect of temperature and pH. We compared direct and inverse Turkevich performance without finding a significant impact. We also compared the standard Turkevich nucleation and growth method with a sequential method developed by us that starts with 5 nm gold seed particles and grows them with different growths rates. We also determine the effect of washing and concentration post-ligand exchange on stability of AuNps. All experiments were followed up by comprehensive characterization of AuNps that included visual aspect (color, turbidity), UV-VIS, DLS, zeta potential, and TEM measurements, which were presented in detail.

In conclusion, we have been able to develop an efficient and reproducible protocol to produce homogeneous round Turkevich gold nanoparticles with controlled sizes ranging from 5 nm to 20 nm, doubled by an extensive quality control follow-up analysis. We investigated the influence of ligand type after ligand exchange on the physicochemical properties and stability of these gold nanoparticles and we defined the most suitable ligands to be used in the future with this sub-20 nm gold nanoplatform.

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G6

Interaction of liposomes with phospholipases A1 and A2: A comparative study

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BACKGROUND AND PURPOSE

Phospholipases A1 and A2 are two major classes of phospholipase enzymes, which hydrolyze phospholipids at sn-1 and sn-2 positions respectively releasing fatty acids and lysophospholipids. These phospholipases are ubiquitously expressed throughout the body and play dynamic roles both in normal physiology and in disease conditions. Both PLA1 and PLA2 can dock on the bilayer of liposomes and destabilize them and release drug. Liposomes-based drug delivery vehicle can be designed as targeted delivery system in disease conditions where PLA1 and PLA2 are overexpressed. The purpose of this study is to determine the ability of PLA1 and PLA2 to hydrolyze/destabilize both PEGylated and non-PEGylated liposomes generated from biocompatible lipids and to study the major factors affecting the destabilization of liposomes in the presence of PLA1 and PLA2.

MATERIALS AND METHODS:

In total six different formulations, three non-PEGylated and three PEGylated liposomes, were prepared using thin film hydration technique followed by extrusion. The non-PEGylated liposomal systems formulated with three different ratios of DSPC:Cholesterol such as 90:10, 75:25, and 50:50 respectively. The PEGylated liposomal systems formulated with DSPC:Cholesterol at 50:50, adding three different ratios of DSPE-PEG2000 as such 0.1%, 1% and 5% (of total lipid content) respectively. The drug loaded liposomal formulations were washed in sephadex column to separate the unloaded drug. The formulations were characterized in terms of size, PDI and zeta potential using Zetasizer Nano (Malvern instruments)

Calcein release from the liposomes under the influence of the phospholipases was monitored using Spectramax M2 spectrophotometer.

RESULT:

PLA1 does affect the stability of the liposomes and release calcein irrespective of its PEGylation. The maximum release of calcein after adding PLA1 is much lower in compared with the total release of calcein after giving Triton X, revealing a slow poration kinetics and enzyme inhibition under the influence of its hydrolyzed products. The amount of calcein released is not proportional to the amount of enzyme applied. PLA2 on the other hand, shows that in non-PEGylated liposomes, the liposomes containing least amount of cholesterol are least active against PLA2 and vice versa. In case of PEGylated liposomes, least PEGylated ones have highest resistance against PLA2 while highly PEGylated liposomes have least resistance. The factors affecting the interaction of PLA2 with PEGylated liposomes need to be further elucidated.

CONCLUSION:

Both PLA1 and PLA2 have impacts on the liposomes irrespective of their PEGylation state with slightly different kinetics. The stability of liposomes increases with the increase of its cholesterol content. PEGylated liposomes are more sensitive towards PLA2.

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G7

Lipid membrane polar headgroups cause enhanced partitioning of ionized metoprolol- new insights into the pH-partition hypothesis.

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BACKGROUND:

Passive permeability of drug molecules through biological membranes is a fundamentally important process that involves the partitioning of molecules into the lipid bilayer membrane and passive permeation across the membrane. More than 60% of the drugs intended for human use contain at least one ionizable group. An analysis by Neuhoff et. al. over an in-house database of 618 registered oral drugs revealed that 40% were amines. Depending on the ionization constant (pKa) of ionizable groups, drug molecules may coexist in various biological fluids both as their charged and uncharged forms to varying extents. According to the widely known pH-partition hypothesis, charged species of organic molecules do not contribute to lipid bilayer permeability and only the uncharged form of ionizable molecules can diffuse through the lipid membranes and therefore, contribute to permeability. However, a growing number of both experimental and molecular dynamics studies indicated deviations from this hypothesis. Permeation of the charged species of ionizable compounds through partitioning into bilayer models has also been reported, though at a much slower rate compared to their neutral form. Our study indicates that a significant portion of the charged fraction possibly becomes uncharged at the membrane polar headgroup region and thereby, can cross the membrane in uncharged form through dynamically changing the protonation state. Therefore, the contribution of the charged species in solution to the total permeability of a molecule at a given pH may have been neglected by the oversimplified pH-partition hypothesis. According to some studies, the charged membrane lipid headgroups might interact with the ionizable groups of molecules by forming a surface ion pair with them and helping it position in the water-accessible headgroup region, followed by its neutralization (change of pKa) by dynamic protonation for permeation across the membrane.

OBJECTIVE:

Our focus is to experimentally determine the impact of the polar headgroup on the membrane partitioning of Metoprolol and its pKa over a range (6-9) of pHs.

METHOD:

A well-validated membrane phospholipid headgroup surrogate, hydrated diacetyl phosphatidylcholine (DAPC) spiked with metoprolol and n-hexane as the surrogate lipophilic tail were put together inside a sealed tube for 15 minutes of inversion for partitioning. Later metoprolol concentration in the n-hexane phase was determined by LC-MS/MS for calculating metoprolol distribution coefficients (D) and respective apparent pKa values at four pH levels.

RESULTS:

The Hydrated DAPC phase caused enhanced metoprolol partitioning into the n-hexane phase resulting in many folds higher distribution coefficients for metoprolol at each of the four pH levels tested when compared to the control (metoprolol solution in only buffer).

CONCLUSION:

Lipid membrane polar head group allows charged species enhanced partitioning into the non-polar phase, resulting in significant changes in the pKa of chargeable molecules. (Funding: NIH & NIGMS grants 2R01GM104178 and 2R01GM114369).

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G8

Remodeling this old house with FOLR3

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Nonalcoholic steatohepatitis is an advanced form of nonalcoholic fatty liver disease characterized by steatosis, inflammation, and liver fibrosis and is commonly associated with other metabolic comorbidities. Previous studies have shown that fibrosis is the main determinant of mortality in NASH patients. It is imperative to better understand liver fibrogenesis to discover rational therapeutic targets. To address this knowledge gap, we compared and profiled the liver proteome from healthy, steatosis, type II diabetes, and NASH subjects to specifically identify unique extracellular matrix (ECM) profile and elevated folate receptor gamma (FOLR3) in NASH. Further proteomic analysis of patient liver samples with varying degrees of fibrosis showed FOLR3 abundance increased with increasing stages of fibrosis. To understand the effect of FOLR3 on fibrogenesis we performed in vitro studies using human hepatic stellate cells treated with FOLR3 and TGF1 . Proteomic analysis of cell culture media showed remarkable increases in ECM proteins in cells treated with the combination of FOLR3 and TGF1 , including increases in TGF1 and several regulators of TFG signaling. These results demonstrate FOLR3 treatment can over activate TFG signaling resulting in remodeling of the extracellular matrix.

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G9

Molecular Effect of Difluoromethylornithine on Neuroblastoma Cells

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Difluoromethylornithine (DFMO) has been recently demonstrated as a potential drug in neuroblastoma treatment as well as having a role in inhibiting the replication and the viral action of different types of viruses. This function relies on the fact that DFMO is an irreversible inhibitor of ornithine decarboxylase (ODC) which is the primary enzyme in the biosynthesis pathway of polyamines. Neuroblastoma is a sympathetic nervous system tumor and the most common non-CNS pediatric solid tumor primarily presenting in children under 6 years of age. The long term prognosis for patients with high risk neuroblastoma (HRNB) remains poor despite aggressive multimodal therapy. Elevated ODC expression and high polyamine content have been shown in NB and other tumors, and suppression of polyamine levels by DFMO reduces tumor proliferation in vitro and in xenograft models. The aim of this study is to identify the role DFMO plays in neuroblastoma, beside inhibiting polyamines, using a quantitative proteomics and metabolomics approach. The study showed that DFMO affects, either upregulation or down regulation of different cellular proteins by examining two different doses on neuroblastoma cells, a low dose of 2 mM and higher dose of 20 mM.

By means of bioinformatics program ingenuity pathway analysis (IPA) we were able to characterize different pathways that are related to neuroblastoma other than the polyamine pathway. 210 out of the 1100 identified proteins were significantly altered upon DFMO treatments (42 proteins up-regulated and 168 down-regulated). These differentially expressed proteins were selected and clustered by biological functions, pathways and upstream regulator analysis, by using IPA. The study suggests potential pathways and proteins that can be targets in drug development in tumor diseases like neuroblastoma.

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G10

Investigation of Diazepam Sequential Metabolism with Hepatocytes via a Microfluidic Device

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OBJECTIVES AND HYPOTHESIS:

The purpose of this study is to investigate the sequential metabolism of diazepam (DZP) in a dynamic system. In rat liver, DZP can be metabolized into primary metabolite temazepam (TZP), nordiazepam (NDP), p-hydroxydiazepam (PHD), and secondary metabolite oxazepam (OXP) and temazepam glucuronide (T-G). It is reported that a lag time of DZP metabolite formation can be observed in rat liver single-pass perfusion and PK study. We are using a microfluidic device to represent liver sinusoid and to investigate the contribution of metabolism and drug transport in the disposition of diazepam and its metabolite along the sinusoid. Ordinary differential equation (well-stirred model) and partial differential equation (PDE) models are being developed to characterize the disposition of DZP and its metabolites. We hypothesize that characterization of sequential metabolism in a dynamic system compared to a static system (microsomal incubation or static hepatocyte incubation) can provide a more accurate prediction of in vivo sequential metabolism.

METHODS:

The perfusion study was conducted with rat hepatocytes. Rat hepatocytes were seeded in collagen I coated microscopy slides to form a monolayer, followed by three-day enzyme induction. An ibidi® µ-sticky slide was mounted on the microscopy slide to create a microfluidic device. Hepatocyte culture medium containing 5 µM DZP was perfused through the device and subsequently perfused by DZP-free culture medium. The concentration of diazepam and its metabolites in the perfusate was measured by LC/MS/MS. Mathematical modeling was applied to predict the concentration-time (C-t) profile of the perfusion study via Mathematica version 12.3 (software). The model parameters include metabolic intrinsic clearance (CLint,met) and passive diffusion clearance (CLdiff), partitioning into membranes, hepatocyte volume, and device volume. Other relevant model parameters were collected by literature search.

RESULTS:

At 10 µL/min flow rate, three primary metabolites all show similar lag time (pre device dead volume plus device volume) to that of DZP. OXP shows a longer lag time compared to T-G. The lag time of T-G is similar to that of primary metabolites. However, a significant decline of TZP and NDP formation at a steady-state is observed, but not PHD. One possible rationale is constant enzyme loss for CYP3A (responsible for TZP, NDP formation), but not CYP2D (responsible for PHD formation). For the DZP-free perfusion phase, a similar lag time was observed for DZP and its metabolites. A well-stirred model and a PDE model to characterize the dimension and spatial information are being optimized.

CONCLUSIONS:

Generally, this microfluidic device can characterize the sequential metabolism of diazepam. The C-t profiles of DZP and its metabolites are similar to that of the liver single-pass perfusion study. Due to the existence of transporters, the lag time of T-G is similar to that of primary metabolites. As a future study, the distribution of DZP and its metabolites along the device will be measured by MALDI imaging. The information of spatial distribution is expected to further help optimize and validate the mathematical models.

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P1

What Extent Do Lifestyle Factors Contribute to an Increased Stroke Burden in Pakistanis & Asian Indians Compared to non-Hispanic Whites in the U.S?

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BACKGROUND:

Stroke is one of the more prevalent disease states across the world that causes an increased burden on the economic and health systems, especially in the United States. Stroke is the 5th leading cause of mortality, which is becoming more dominant in certain ethnic groups in the US. As a preventable disease, it is pertinent in finding various factors and reasons that might contribute to the growing incidence of stroke, especially in the South Asian American population with its increased risk of stroke mortality. The lack of data and thorough research in this growing population in the US on stroke risks highlights the gap of knowledge and the decreased initiative in managing public health. We aim to examine the health disparities and to highlight the key lifestyle factors and its extent in impacting the risk of stroke in Pakistanis and Asian Indians in the US. We want to look closer at the different factors that may be looked into when working in preventative medicine in this specific population.

OBJECTIVE:

Our objective is to conduct a rapid scoping review to answer our research question: "What Extent Do Lifestyle Factors Contribute to an Increased Stroke Burden in Pakistanis & Asian Indians Compared to non-Hispanic Whites in the U.S?" The scoping review will help us map the difference in these lifestyle factors in comparison to non-Hispanic Whites and how the differences might possibly be correlated with the increased stroke burden risk in the Pakistanis and Asian Indian American population.

METHODS:

A rapid scoping review was conducted utilizing a PRISMA-ScR checklist with the following:

Inclusion criteria includes: 18+ years old, Asian Indian Americans, Pakistani Americans, English and native language speaking, stroke (transient and ischemic), non-Hispanic whites. Our exclusion criteria includes: South Asians Americans from Bangladesh, Bhutan, Nepal, Sri Lanka, Afghanistan and Maldives; Hispanic whites and other races, studies done outside of the US, and studies that include aggregated data for the entire South Asian population.

OUR SEARCH STRATEGY:

We utilized PICO search strategy to organize our search terms before using them to perform a search in the databases. We used 2 databases to perform our preliminary search, Pubmed and Embase. Our search returned a total of 25 Pubmed results and 44 Embase results.

STUDY SELECTION:

The scoping review is still in its early stages and we have yet to evaluate our literature results. We plan to follow the inclusion criteria strictly and only include studies in our final results that meet the criteria. Studies will be screened in 2 phases, first we will be evaluating the title and abstract and if the studies do not meet the inclusion criteria then they will be excluded. In the second screening phase, we will be thoroughly evaluating the full literature of the studies that had a clear inclusion criteria listed in the abstract and the studies that are inconclusive and require further evaluation.

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P2

Dosing Strategies for de Novo Once-daily Extended-Release Tacrolimus (LCPT) in Kidney Transplant Recipients

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BACKGROUND:

Tacrolimus extended release (Envarsus®) is an immunosuppressant that can be used to prevent kidney transplant rejection. Tacrolimus has a narrow therapeutic index and a high pharmacokinetic variability due to genetic variations of the CYP3A5 metabolic enzyme.

OBJECTIVES:

To use Envarsus® as de-novo therapy to prevent kidney transplant rejection. To determine the required daily dose of Envarsus® to achieve therapeutic trough concentrations. To identify the time to achievement of therapeutic trough concentrations. To identify if there were CYP3A5 phenotypes which can be correlated retrospectively to the clinical response to the treatment.

METHODS:

We conducted a prospective, single-center, Phase 4 IRB-approved trial in which charts for the kidney transplant patients were assessed from November 2018 till July 2021 (ClinicalTrials.gov, NCT03713645). We enrolled 36 patients (56% male) with an average age of 51.61 ± 13.65 years. Envarsus® was dosed at 0.13 mg/kg based on patients' actual body weight and doses were titrated to maintain a goal trough level of 8-10 ng/mL. Tacrolimus plasma concentration was measured daily while admitted and 3 times per week in the outpatient clinic setting. Patients were followed up to 30 days post-transplant. The patient's buccal swab was collected and stored for DNA extraction. Real-time PCR genotyping of CYP3A5 was performed at the end of the study and data analysis was conducted to determine the allele composition of each patient.

RESULTS:

We found the following CYP3A5 phenotypes in the studied patients: 42% were poor metabolizers (PM), 36% were intermediate metabolizers (IM), and 17% were extensive metabolizers (EM). The number of days needed to reach the goal trough concentration was 5 ± 3.84 (PM), 7.85 ± 4.71 (IM), and 13.67 ± 7.37 (EM). The goal trough level of tacrolimus was found to be 10.71 ± 2.1 (PM), 9.1 ± 1.6 (IM), and 7.9 ± 1.3 (EM). We found that the average dose (mg/kg) to reach the goal trough level was 0.13 ± 0.04 (PM), 0.15 ± 0.05 (IM), and 0.18 ± 0.06 (EM).

CONCLUSION:

We found Envarsus® pharmacokinetic variability due to differences in the CYP3A5 phenotypes. CYP3A5 genotype testing prior to starting Envarsus® may have a clinical benefit in kidney transplant patients in terms of selecting the correct dose for reaching the goal trough level in a shorter amount of time.

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P3

Assessing COVID-19 Vaccination Access, Uptake, and Hesitancy at an Academic Outpatient Clinic in North Philadelphia

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In this mixed-methods research project, we will be gathering information from patients at Temple Health General Internal Medicine Outpatient Clinic (TIMA) regarding their vaccination status and the factors that impacted their decision. The study objective is to evaluate characteristics predicting successful COVID-19 vaccine initiation and to identify barriers and facilitators to vaccine access, uptake, and hesitancy. We also aim to estimate the proportion of patients at TIMA who initiated COVID-19 vaccination.

For the quantitative aspect of the study, we will be estimating the proportion of patients that initiated vaccination at TIMA and describe their demographic, social, and health/clinical characteristics from patient charts. Data from the TIMA clinic has shown to be similar to the national vaccination rates as of May 2021 (62%) and slightly above the PA average as of May 2021 (57.6%). For the qualitative aspect of the study, which is still in progress, we will gather our data by performing two types of interviews. In-depth-interviews (IDI) will be conducted with unvaccinated individuals in a one-on-one setting. Focus group discussions (FGD) will be conducted with vaccinated individuals in a group setting. The maximum number of participants for a single focus group discussion will be ten. Audio recording will be utilized for both interview types to help document participant responses. In focus group discussions, field notes will be taken by members of the research team to document observations such as patient reactions to questions and body language while responding. These participant observation notes will aid our understanding of a participant's thoughts and feelings of the various topics discussed.

Participants can participate in the study if they are at least 18 years old and had at least one clinical visit (physical or virtual) at Temple Health General Internal Medicine Outpatient Clinic between January 1, 2020 and August 31, 2021. Patients who are not active at Temple Health General Internal Medicine Outpatient Clinic, defined as not having had any clinical visits documented since January 1, 2020 are excluded. Each interview will begin with participants thoughts and feelings of COVID-19 and the vaccine. The interview will open with participant thoughts on how the COVID-19 pandemic has impacted each individual's life and general knowledge about the COVID-19 vaccine. Concerns about getting the COVID-19 infection is also a point of discussion in this section. For vaccinated individuals participating in the focus group discussions, we will then discuss what motivated the participants to choose to get the vaccine and if they were hesitant with their decision. For unvaccinated individuals, we will discuss their motivation for their decision along with any possibilities that could change their mind in the future. With vaccine mandates in place, we will also explore if being unvaccinated has impacted any of the participants lives. Social influences will be explored regarding who the participant discussed vaccination with to help form their decision. This could be influence from family members, friends, or their current healthcare provider. For practical issues, topics such as accessibility, harmful experiences from past vaccinations, transportation, and missing work to schedule a vaccine appointment will be discussed. We hope to use clinic driven data to implement specific interventions to increase vaccination rates and decrease health inequity.

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P4

Drug Use Evaluation of Continuous Infusion Heparin at Temple University Health Systems

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BACKGROUND:

Heparin is a widely used anticoagulant medication that requires close monitoring and adjustments to ensure optimal patient outcomes and prevention of adverse safety events. We assessed the appropriateness of heparin dosing and monitoring at Temple University Health Systems (TUHS) based on the TUHS guidelines and nomogram.

OBJECTIVE/METHODS:

This was a retrospective chart review of patients who received continuous infusion heparin for ≥ 24 hours at TUHS from October 2020 to December 2020. Initial dosing regimens, dose adjustments, and aPTT values were collected from electronic medical records. Patients were included if they were admitted to TUHS, had an order for continuous infusion heparin, and were treated for ≥ 24 hours. Patients were excluded if they received heparin for a period <24 hours, had diagnostic history of antiphospholipid syndrome or cirrhosis, were on concomitant mechanical regulatory support, were dosed based on continuous renal replacement therapy, were treated with subcutaneous (SC) or intravenous (IV) bolus heparin only, had received thrombolytics within the studied admission, and/or had a lower institutional aPTT goal according to TUHS's nomogram. The primary outcomes were appropriateness of initial dosing, including infusions and boluses, subsequent dose adjustments based on aPTT results within a 72-hour period following initiation of therapy, and timing of aPTT monitoring. Appropriateness of dosing and timing were defined as following TUHS protocol ±50 units and/or ±1 hour, respectively. The secondary outcome assessed the mean institutional time to first therapeutic aPTT and the mean institutional time to first aPTT collection.

RESULTS:

Out of the 143 patients, 51 were included and 92 were excluded. Out of the 25 patients who received a bolus dose, 17 (68%) followed the nomogram. Twenty-nine (58.6%) received an appropriate initial infusion dose. Only 52/122 (41.6%) dose adjustments followed the nomogram and only 102/299 aPTT values (34.6%) were collected at an appropriate time. For secondary outcomes, the mean time to achieve a therapeutic aPTT was 19.4 hours and the average time of collection between aPTTs was 10.4 hours.

CONCLUSION:

Our data showed that TUHS clinical team members did not consistently follow TUHS's nomogram for heparin dosing adjustments and aPTT monitoring. Clinical staff should be re-educated on TUHS's heparin guidelines to ensure successful patient outcomes.

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P5

Direct Oral Anticoagulant Adherence Patterns

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BACKGROUND:
Over the last decade, direct oral anticoagulants (DOACs) have replaced warfarin for the treatment of atrial fibrillation and venous thromboembolism due to ease of use, advantages with adverse effects, and other reasons. Patients taking warfarin need regular laboratory monitoring and consultation with healthcare providers. There is concern that without these frequent touchpoints, patients taking DOACs may have unknown adherence which could limit the benefits of the drugs. Gaining an understanding of local DOAC adherence patterns can help inform decisions about prescribing and patient education in the future.

METHODS:
This retrospective chart review of Temple Internal Medicine Associate patients examined the days over the time allotted by the prescription that new prescriptions were reordered for patients receiving DOAC prescriptions. Patients 18 years and older prescribed apixaban, rivaroxaban, dabigatran, or edoxaban for atrial fibrillation or venous thromboembolism between March 2015-March 2020 were included.

RESULTS:
Data was collected for 27 patients with an average age of 67.4 years. The patients were 63% female, 85.2% African American, and 81.5% of the patients were prescribed apixaban. Prescription reorder history revealed an average of 14.4 days (3.1%) not covered by a prescription. Most instances of prescriptions not being renewed on time occurred in patients prescribed a 30-day supply of medication.

CONCLUSION:
Nonadherence, as detected by this method, was low in the population studied.

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P6

Cardiovascular and cerebrovascular health status and health disparities of Cambodian-Americans: A rapid scoping review

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BACKGROUND:

Use of aggregated data from Asian race masks important heterogeneity in socioeconomic status, language proficiency, and health literacy among Asian subgroups. Looking at the economic status that contributes to the health disparities of Cambodian Americans, overall 12% of Asian American fall under the poverty line, however Cambodian Americans contribute to 26% of the percentage of Asian Americans overall. Although this type of data exists in California, there was a general trend seen in other states such as Massachusetts, Minnesota, Texas, and Washington. Due to the lack of published national Cambodian-American health data, little is known about the cardiovascular or cerebrovascular health status and health disparities that affects Cambodians; although there is an estimation of 339,000 of the Cambodian population in the United States as of 2019.

OBJECTIVE:

The objective of this rapid scoping review is to examine and map the cardiovascular or cerebrovascular (context) health status and health disparities (concept) of Cambodian Americans (population).

"What is known about the cardiovascular or cerebrovascular health status and health disparities of Cambodian-Americans?"

METHOD:

Our protocol was drafted using the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) Protocols. This rapid scoping review will be reported in accordance with the PRISMA extension for Scoping Reviews (PRISMA-ScR).

STUDY SELECTION:

Inclusion: Time Period: 1975 - Present; Language: English; Population: Cambodian Americans; Study Focus: Cardiovascular or cerebrovascular health status and health disparities

EXCLUSION:

Data that is aggregated within all ethnicities in Asian American

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P7

Factors associated with initiation of oral antineoplastic therapies in an urban academic medical center: Part 2

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PURPOSE:

The objective of this is to identify barriers within our patient population affecting time to initiation of oral antineoplastic therapy to improve health outcomes. Recent research has shown that patients with government funded insurances, such as Medicare, will utilize oral oncolytic medications in a specific patient population with certain cancers, such as chronic myeloid leukemia (Doshi, et al, 2021). Patients with commercial insurance may have barriers obtaining their medication, but low-income patients having issues with communication to their providers (Murphy et al, 2019). Also, specialty pharmacies internally affiliated to healthcare institutions provide better access to and management of medications, as opposed to external specialty pharmacies (Academia et al, 2021).

PATIENTS AND METHODS:

Adult patients (>18YO) with a diagnosis of cancer, treated by physicians at an urban academic medical center were retrospectively studied. Patients were included if they were prescribed an oral antineoplastic agent from March 2021 to October 2021. The primary endpoint was to determine the proportion of patients with the following potential barriers leading to delays in initiation: stage of cancer at initiation, costs/financial burden, language barrier, pharmacy processing delays, insurance denial, delays in contacting patient/caregiver, delays in delivery, in-network pharmacy required, and prescription initially sent to non-specialty pharmacy. Secondary endpoints included assessing the time involved in the initial processing of the oral antineoplastic prescription (date prescription generated to the date prescription filled.) Descriptive statistics were used to analyze the endpoints.

RESULTS:

A total of 64 patients were reviewed. The majority of these patients were African American and about 63 years of age, with the following primary malignancies: breast, prostate, colorectal, lung, renal cell carcinoma, pancreatic, brain, hepatobiliary, thyroid, gastric. The common barriers identified in more than 10% of patients were: issues with prescription insurance (36.9%), in-network pharmacy required (15.9%), delays in contacting patient/caregiver (14.0%), followed by delays in delivery (12.0%). Average time to fill was 7.58 days (range: 0-49 days; standard deviation: 10.15).

CONCLUSION:

Issues with prescription insurance, delays in contacting the patient/caregiver, and restrictions on pharmacy allowed to fill the prescription were amongst the common barriers identified that represent areas that we can target for improvement moving forward. Notably, prior to this review, our historical data demonstrated issues with prescription insurance (36.9%) being the most common barrier with an average time to fill of 13.67 days (range: 1-64 days; standard deviation: 11.31). These findings show a consistent pattern that insurance companies and health care providers can address to provide better patient care.

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P8

Seizure-induced Rhabdomyolysis and Acute Kidney Injury

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Current literature on seizure-induced rhabdomyolysis is limited to isolated case reports. This report combines the previously published case reports to create a narrative summary of the causative factors, creatine kinase trend, and factors enabling safe hospital discharge. This report will help physicians interpret when CK normalization occurs in hospitalized patients. Prolonged convulsive seizures can cause muscle injury often resulting in rhabdomyolysis. This results in systemic release of muscle contents into the blood which raises the serum Creatine Kinase (CK) and myoglobin levels. Myoglobin is a direct nephrotoxic agent and thus a major complication of this condition is Acute Kidney Injury (AKI). CK elevation is the most reliable and sensitive indicator of muscle injury. Normal CK enzyme levels are 45–260 U/L[3] and CK levels peak in 1-3 days. Usually CK levels above 1000 U/L indicate rhabdomyolysis and above 5000 U/L increase the risk of rhabdomyolysis-induced AKI.

Five individual case reports were identified through literature search on medical databases such as PubMed and google scholar. The inclusion criteria was that the patient should be an adult, should be admitted in hospital due to seizure episode(s) and must have a complication such as rhabdomyolysis and/or acute kidney injury. The exclusion criteria was drug-induced seizures. The result of the case reports was that all patients survived, and discharged on an average of two weeks. The peak CK levels ranged from 4489 U/L to 93809 U/L. There was a positive correlation between CK levels and AKI. CK levels were measured and monitored during hospital stay and thus the increasing trend indicated rhabdomyolysis and suspected AKI. The patients were managed with fluids, alkaline diuresis alongside anti-seizure medications (ASM). Early monitoring of CK levels and laboratory values that indicate renal function is of high clinical significance and this can help prevent AKI. CK levels started to decrease as optimum hydration and supportive care was provided and normalized by day 7 on average. The patients were kept longer due to other co-morbidities.

To conclude, a high index of suspicion of rhabdomyolysis is necessary for early diagnosis and prevention of AKI. It is also safe to discharge patients after day 7 as the CK downtrend begins and consistently approaches normal limits, provided the patient is on appropriate anti-seizure medications to prevent recurrent episodes and instructed to keep hydrated.

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P9

How effective is stroke education in the Vietnamese-American population in improving stroke awareness and readiness to call 911?

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BACKGROUND:

Recognizing stroke symptoms and acting quickly, such as calling 911 or getting emergency medical services can reduce resulting consequences, such as disability or mortality. Asian Americans are known to have more severe outcomes in regards to stroke, and among them, Vietnamese Americans have the second highest stroke mortality rate. Some explanations for the higher and more severe stroke incidence in the Vietnamese American population include having a lower overall education level, limited English proficiency, and low health literacy levels. The purpose of this study is to determine if stroke education will enhance Vietnamese American health outcomes in regards to preventing disability and death due to strokes by improving stroke responsiveness and the willingness to call 911.

OBJECTIVE:

The objective of this rapid scoping review is to evaluate "the effectiveness of stroke education in the Vietnamese American population and its correlation to improving stroke awareness and readiness to call 911." This rapid scoping review will help determine the level of knowledge that the Vietnamese American population currently possess on how to recognize and respond to a stroke.

METHOD:

With the help of the librarians, a rapid scoping review following PICO search guidelines was initiated. The formulated PICO search terms were then run through PubMed and Embase to obtain a targeted list of articles. Mendeley and Rayyan will be utilized in order to find and isolate relevant literature to answer the research question. Mendeley will be used to eliminate duplicate results and the results will then be imported to Rayyan. Relevant articles will be established using predetermined inclusion and exclusion criteria.

RESULTS:

A preliminary literature evaluation of stroke knowledge and outcomes in the Vietnamese American population was conducted to identify keywords and relevant concepts for the study. Rapid scoping review search strategies such as PICO and PRISMA-R and literature review applications such as Mendeley and Rayyan were reviewed. The search terms utilized for PubMed and Embase and the research question were refined. A completed search strategy will be performed in the future to yield relevant literature that addresses the research question.

CONCLUSION:

This literature search is an ongoing process. The screening of the articles still has to be conducted using Mendeley for deduplication and Rayyan for literature review. Because there is little stroke education available for the Vietnamese American population, this study helps to highlight the importance of this essential intervention given the increased mortality in Vietnamese Americans from stroke.

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P10

COVID-19 pharmacy student perceptions: pharmacists' impact during the COVID-19 pandemic

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Pharmacists around the world are playing an active role in educating the public about COVID-19. First-year pharmacy students taking a healthcare course at Temple University in Philadelphia were asked to write papers based on the nature of a pharmacist's contributions during the pandemic. 90% of the essays outlined the importance of community pharmacists, as they are the most accessible healthcare professional, providing immediate social interaction and drug expertise. They help minimize the need for hospital visits, limiting their time in public, therefore reducing their risk of becoming infected. For the pharmacies that have a drive-thru window, over-the-counter medications and other necessities can be sold to decrease the likelihood of transmission. Many students also proposed the opportunity for more leniency in prescribing power. Unless pharmacists are within a collaborative practice agreement, they cannot prescribe even maintenance medication. Due to the pandemic, it has become increasingly hard to reach the doctor or see them in person, as most offices have switched to telehealth. Clinical pharmacists operating out of hospitals have the opportunity to oversee proposed treatment options or experimental drugs, such as remdesivir. Retail pharmacies are emerging as key resources in this pandemic, and it is important that students see this as a vibrant and important form of pharmacy practice.

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P11

Evaluation of Tocilizumab for the Treatment of COVID-19 at Temple University Hospital

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BACKGROUND:

Tocilizumab is an interleukin-6 (IL-6) receptor antagonist approved for the treatment of various types of arthritis. Recently, tocilizumab has been used to attenuate the overactive immune response seen in many patients with COVID-19, as a positive correlation between elevated IL-6 and severity of disease in patients with COVID-19 has been observed. However, little is known about the appropriate use of tocilizumab in COVID-19.

OBJECTIVE:

The primary objective of our drug use evaluation (DUE) was to determine how tocilizumab in COVID-19 was being used for the treatment of COVID-19 at Temple University Hospital (TUH). A secondary objective of this evaluation was to document patient outcomes after tocilizumab treatment, including clinical deterioration and end of hospital stay outcomes.

METHODS:

A retrospective chart review of patients ≥ 18 years of age who received ≥ one dose of tocilizumab for the treatment of COVID-19 at TUH between March 2020 and December 2020 was conducted. Patient data was analyzed and collected in the Temple University Health System via the electronic health record for entry into REDCap.

RESULTS:

Most patients who received tocilizumab were classified as having Stage 3 or 4 COVID-19 according to TUH protocol (69.8%). The average hospital day of administration of tocilizumab was on day 6 (SD ± 6.41), with the majority patients receiving 1-3 doses. Most patients were receiving oxygen supplementation (94.3%), had elevated CRP (96.2%) and IL-6 (93.3%) levels, and were on concomitant therapies upon administration of tocilizumab. Of the 22 patients that experienced clinical deterioration, 11 patients required new mechanical ventilation and 17 patients required intensification of oxygen supplementation. A majority of patients (73.6%) were discharged to rehab and non-rehab.

CONCLUSION:

The results demonstrate that tocilizumab was used in a vast array of patients at TUH with varying degrees of illness between March 2020 and December 2020. Most patients who received tocilizumab were considered to have severe or very severe disease according to TUH protocol. Tocilizumab was primarily used in patients with elevated levels of inflammatory markers that required oxygen supplementation. Only 28 patients met the criteria of the RECOVERY trial, which was the largest trial providing the strongest evidence supporting the use of tocilizumab in COVID-19 at the time of our DUE. All patients were also receiving at least one additional investigational COVID-19 therapy, with all but one patient receiving corticosteroids. Our analysis demonstrates a lack of consensus regarding the treatment of the novel coronavirus throughout the pandemic.

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P12

Incidence and Outcomes of Pneumonia in Lung Transplant Patients

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BACKGROUND

Lung transplant patients (LTPs) experience considerable infection-related morbidity and mortality, including from pneumonia. Our institution performs the highest volume of lung transplants in the US, providing an opportunity to describe the scope and impact of pneumonia in LTPs.

METHODS

We conducted a retrospective cohort study of all patients who received a lung transplant at our institution in 2019. Patient records were reviewed from the pre- transplant period to 1-year after transplant for data pertinent to comorbidities, transplantation characteristics and complications, donor organ cultures, immunosuppression, prophylactic and therapeutic antibiotic regimens, pathogens, and outcomes. Cases of pneumonia were reviewed by two physicians independently using standard criteria. The primary outcome was 1-year survival and secondary outcome was clinical success.

RESULTS

146 patients received lung transplants in 2019 and were included. Patient characteristics are in Table 1. Characteristics of pneumonia are in Table 2.

Patients with pneumonia had significantly lower 1-year survival rates than those without (25/34, 73.5% vs 107/112, 95.5%; p=0.0007). Number of readmissions were higher in patients who had pneumonia (mean 3.73 + 2.42 vs 1.09 +1.34, p<0.0001). More patients who developed pneumonia had a bronchial stent placed (8/34, 23.5% vs. 4/112, 3.6%, p=0.001). Positive cultures from donor lungs were common but less common in patients who developed pneumonia (22/34, 64.7% vs 94/114, 82.5%, p=0.0489).

CONCLUSIONS

Pneumonia occurred within the first year of transplant in 23.3% of LTPs and was associated with lower survival. Positive donor cultures did not predict subsequent pneumonia.

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P13

Outcomes in Kidney Transplant Recipients with Latent Tuberculosis Infection

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INTRODUCTION:

Tuberculosis (TB) is caused by the pathogen, Mycobacterium tuberculosis (M.tb), and continues to be one of the top 10 causes of death worldwide. Development of active TB from latent TB infection (LTBI) occurs in 10% of people infected with LTBI, and increases when additional risk factors are present such as immunosuppressive agents commonly used in renal transplantation. Solid organ transplant recipients have an increased risk of contracting TB with a high mortality rate, however, the prevalence and incident remain unclear.

OBJECTIVE:

To determine the outcomes in kidney transplant recipients with latent TB.

STUDY DESIGN:

Single-centered, IRB-approved observational cohort study of patients with latent TB who received a kidney transplant between January 1st 2016 to December 31st 2019 at Temple University Hospital.

METHODS:

Data was collected through chart review of the electronic health record for 174 kidney transplant patients included between 2016 and 2019. Data analysis was completed using intention to treat descriptive statistics .

RESULTS:

Twelve patients met inclusion criteria and were included in the analysis with an average age of 59 (+/-SD 8.9), 92% were male, 41% were african american, 42% were hispanic, 8% caucasian and 8% asian. Mean cPRA% was 21% (SD +/- 30.6%). 92% of the recipients received thymoglobulin as induction therapy with the average total dose of 5mg/kg and +/-SD of 1.10. Basiliximab induction was utilized in one patient. Maintenance therapy consisted of TAC/ MMF +- corticosteroids. Tacrolimus was the calcineurin inhibitor of choice in all patients. Eight (67%) of the recipients received TB prophylaxis consisting of isoniazid monotherapy, n=6, and rifampin monotherapy, n=2. None of the patients had reactivated TB nor acute rejection within 12 months of transplant. Only 2 patients, (18.2%) experienced antibody mediated acute rejection within 24 months. Both of these patients did not have documented TB prophylaxis prior to transplant. The average time of acute rejection was at 543(SD +/-234) days post transplant. None of the patients experienced graft loss or death during the study period.

CONCLUSION:

Our data suggest that the presence of latent TB is highly unlikely to influence mortality in kidney transplant patients. Lack of proper prophylaxis treatment could have influenced graft loss in some patients. Further investigation is needed to make a more definitive observation in this patient population.

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P14

Community-based participatory research to improve medication adherence in western Kenya

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BACKGROUND:
Non-adherence to antihypertensive medications is a major cause of uncontrolled hypertension worldwide, leading to cardiovascular morbidity and mortality. In low-resource settings worldwide, up to 60 percent of hypertensive patients report non-adherence to their medications for hypertension. Ensuring consistent medication possession is crucial in addressing non-adherence. Community-based medication delivery is a strategy that may improve medication possession, adherence, and blood pressure (BP) reduction. However, despite many evidence-based interventions to manage hypertension, substantial implementation gaps of these interventions persist. Community-based participatory research (CBPR) can address the research-implementation gap by bringing together researchers and community members to address diseases that disproportionately affect populations experiencing health disparities.

OBJECTIVE:
We aim to identify common CBPR frameworks that have been successfully employed in low-resource settings, specifically in sub-Saharan Africa where there is a high burden of cardiovascular morbidity and mortality. Additionally, we aim to showcase the success of CBPR through a real-life example to demonstrate the utilization of CBPR in the implementation of a community-based medication delivery intervention, with the goal of improving medication adherence and reducing blood pressure in hypertensive patients living in rural western Kenya.

METHODS:
We searched Pubmed, African Journals Online, and Google Scholar using the following keywords: 'community based participatory research or CBPR, Kenya OR Africa OR Sub-Saharan Africa.' We included only articles that described health- or community-related interventions between January 2010 and December 2021. We excluded articles that were not in English nor utilized a CBPR approach and framework.

RESULTS:
A total of 188 articles were identified and screened for eligibility. Of those, 120 articles were excluded. The remaining 68 articles were fully reviewed and 6 articles had CPBR models described in detail. Six CBPR frameworks including the Donabedian model, the Emanuel framework, the Social Ecological model, the Grounded Theory model, PRECEDE-PROCEED, and OSCAR were identified. One of these frameworks, the PRECEDE-PROCEED model, was used to guide the development and implementation of a community-based medication delivery intervention to improve adherence to hypertension medications within our own program in Western Kenya. Through meaningful community engagement, this pilot program resulted in improvement in medication adherence and blood pressure reduction.

CONCLUSION:
CBPR has been shown to provide meaningful evidence and implement sustainable and community-responsive changes. Through an extensive literature search, we identified proven frameworks that can be adapted and replicated in low-resource settings around the world to improve clinical outcomes, specifically in vulnerable populations.

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P15

Effects of digoxin in Heart Failure (HF) with Reduced Ejection Fraction (EF)

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In this review, we evaluated the literature on the benefits and deleterious effects of digoxin in heart failure (HF) with reduced ejection fraction (EF). Although digoxin was once considered an effective treatment for HF, the current supporting evidence is conflicting. Before the conventional use of modern HF therapies, digoxin was widely used for symptomatic relief on these patients. Further randomized trials are required to reach a definite conclusion about its efficacy and safety in patients experiencing HF with a reduced EF (HFrEF).

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P16

Effects of Serotonin-7 Receptor Agonists and Antagonists on Learning and Memory in Mice

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PURPOSE:

Recent evidence suggest the involvement of 5-HT7 receptors in specific aspects of hippocampal dependent contextual learning and memory processing. Suggestions show that 5-HT7 receptor antagonists and agonists prevent memory impairment and facilitates learning in situations involving high cognitive demand. The objective of this study is to assess the effects of 5-HT7 receptor agonists and antagonists on learning and memory in mice in a simple assay of recognition memory and compare the effects to a well known amnesic, the muscarinic antagonist, scopolamine. In order to assess the effects of the agonists and antagonists, mice were administered with either saline, scopolamine, SB-269970, or LP-211 immediately after the exposure of two similar objects.

METHODS:

The Novel Object Recognition Test (NORT) was used where 20 male Swiss-Webster mice went through a protocol of two 5 minute sessions, consisting of the initial familiarization session with two similar objects and the introduction of a novel object in the second. In the first session, two familiar objects were placed in the testing area and live-recording was taken when the mice got within 3 centimeters of the object. After 5 minutes, the mice were taken out of the testing area and placed back in their home cage for one hour to allow time for memory and learning. Then, the mice were placed back in the same testing area and one object was replaced. The same recording parameters were the same as the first session.

RESULTS:

A total of 18 mice were tested and observed, with 2 excluded during analysis. Scopolamine failed to produce memory impairment in two mice and increased locomotor activity at a dose of 1.0 mg/kg of an average of 85 second exploration with novel to 11.6 second to familiar. 5-HT7 receptor antagonist SB-269970 did not impair or improve recognition memory, i.e., the results were comparable to saline. Results of LP-211 were varied due to the lack of activity of the mice in Trial 1 and 2 leading to the exclusion of the data from the results.

CONCLUSIONS:

More subjects and doses of scopolamine, SB-269970, and LP-211 will be tested in the next set of tests since only one dose was studied for each. Although initial testing of LP-211 appeared to dramatically improve recognition memory, only four mice were tested and two mice failed to explore objects in the training trials (i.e., <5 seconds per object).

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P17

High Content Imaging in Pharmacology

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High content imaging (HCI) is an important imaging tool to maximize data capture. Utilizing a combined methodology of automated microscopy and quantitative imaging analysis. HCI is an important tool for addressing biological questions within the research sector and the pharmaceutical industry. HCI plays a vital role in visualizing key subjects of concern, such as small molecules, and provides live imaging to understand important mechanisms within the cell of interest, including mechanisms of action, target identification.

The use of HCI combined with computational algorithms and machine learning can greatly reduce the time required to analyze cells of interest, and is an important tool towards both time efficiency and cost. Combining the two technologies, research and development costs can be greatly reduced especially in toxicology. Utilizing in vitro techniques, HCI can also reduce the amount of animal models required for toxicology.

High content imaging plays a vital role in the drug discovery process as well as functional genomics, including target identification, secondary of confirmation, mechanism of action studies, as well as its importance in in vitro toxicology.

As technology continues to advance, high-content imaging in the drug development process will allow for:

Decreased costs in the high R&D development process (less animal models required because of in vitro)

Target-specific identification, allowing for discovery of vital mechanisms and drug repurposing

Grouped together with automated algorithms and computational models will allow for fast and efficient analysis of critical clinical data

In this study, we will be discussing various applications of high-content imaging for studying personalized tumors in oncologic profiles, its role in the drug discovery process, and its significance in live-data capture.

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P18

Extracellular Histones Associated With Complications in COPD and COVID-19

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Extracellular histones are associated with the aggregation of platelets that are known to cause pulmonary damage in chronic obstructive pulmonary disease COPD and coronavirus disease 19 (COVID-19). The pathogenic effects of platelets are seen with histones causing complications such as micro-thrombi formation, pulmonary cell toxicity, and lung inflammation. Release of extracellular histones are a product of the natural occurring innate immune system. Neutrophils release neutrophil extracellular traps (NETs) which are composed of chromatin and granule proteins that bind and kill microorganisms. By using experiments that have tested for in vitro platelet aggregation and granular secretion, comparisons were able to be made on how similar extracellular histone 3.3 (H3.3) was to platelet activator PAR-4 agonist AYPGKF. The use of in vivo platelets were activated by intratracheal administration of aerosolized recombinant H3.3 (rH3.3) to demonstrate the induced change that lungs go through during high levels of rH3.3. These changes lead to decreased alveolar tissue and increased air space which made passage of gas exchange laborious. COVID-19 severity in patients has also been tied to the number of circulating histones in patients' plasma. During the first few stages of COVID-19, NETs are released through apoptosis to combat the infection. As time goes on increased NETs, increase the levels circulating histones which are very toxic to patients. Targeting early platelet aggregation from extracellular histones is a therapy being currently used to combat the lethality of the disease. Preliminary results provide an insight to better treatment for COVID-19 patients with the use of known medicines for their anti-inflammatory therapies.

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P19

Comparative analysis of non-compartmental, compartmental and physiologically based pharmacokinetic models

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BACKGROUND:
Predicting pharmacokinetics of highly protein bound drugs is difficult to accomplish using traditional methods. Using prior data, the parameters of compartmental and noncompartmental analysis can be determined by assembling concentration-time profiles.

OBJECTIVE:
To test whether the pharmacokinetics of highly protein bound drugs could be analyzed more accurately with physiologically based pharmacokinetic models (PBPK) than with compartmental models.

METHODS:
The drugs studied were amlodipine, atorvastatin, glyburide and pitavastatin. These drugs are highly plasma protein bound and to model their pharmacokinetics, both compartmental and noncompartmental analysis (NCA) were performed by gathering intravenous data from both literature and internet databases such as drug bank, chemspider, vcclab, chemaxon, and lexicomp. IV data was used to perform the compartmental analysis and NCA using a plot digitizer and mathematica. With the assistance of instructors, PBPK models were developed to observe and analyze the accuracy of pharmacokinetic parameters and concentration-time profiles using mathematica.

RESULTS:
Human IV data was utilized in assembling datasets for each drug. The NCA of each drug was performed successfully with the application of the trapezoidal rule. The AUC and CL for each drug is as follows: Amlodipine AUC: 20.82 mg.min/L, Cl: 0.48 L/min; Atorvastatin AUC: 307.7 mg.min/L, CL: 0.13 L/min; Glyburide AUC: 22.2 mg.min/L, CL: 0.09 L/min; Pitavastatin AUC: 5.4 mg.min/L, CL: 0.37 L/min. The 2-compartment model accurately represented pitavastatin, glyburide, amlodipine and a 3-compartment model was used for atorvastatin. Estimates between compartmental and NCA were similar.

CONCLUSIONS:
Non-compartmental as well as compartmental analysis with the use of Mathematica were able to accurately predict the pharmacokinetic parameters of highly protein-bound drugs. Regarding PBPK modeling, the PermQ modeling technique was most representative of the data that was gathered in predicting pharmacokinetic parameters.In comparison to standard PBPK approaches which assume distribution to be perfusion-rate limited, the PermQ model uses permeability-rate limited distribution. This appears to capture more appropriately the concentration-time profiles of the drugs tested in this work. Acknowledgement: Graduate students Yifan Gong and Md. Hridoy.

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P20

In-Vitro Evaluation of Cigarette Smoke & SARS-CoV-2 Spike Protein on Cytokine Expression in Macrophages

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Cigarette smoking increases the likelihood of developing severe coronavirus disease 2019 (COVID-19). Current data shows that severity of SARS-CoV-2 infection is not dependent on the amount of viral load but dependent on the response of the immune system.Severe COVID-19 is associated with increased inflammation mediators, characterized by cell death, leukocyte infiltration, and excessive cytokine production, known as a "cytokine storm". An effective immune system response against the SARS-CoV-2 can control the virus and prevent severe COVID-19 in asymptomatic and mild disease subjects.

This proposal aims to identify the effect of smoking on developing severe COVID-19 at the molecular level in parenchymal innate immune lung cells, specifically its effect on alveolar macrophages. To test the association between cigarette smoking and the release of cytokines from a severe COVID infection and macrophages, macrophages were stained using Perkin Elmer to identify specific cytokines released. Additionally, we utilized the Operetta CLS High Control Analysis System. Through Operetta, we were able to identify and analyze various parameters of stained cells like nuclei, cytoplasm, calculate the intensity propensity of the stained cells and define the nuclei and nuclei population.

To further strengthen our findings, we utilized findings from several studies and literature as reference. The results show that there is an increase in lung cell's cytokine production and secretion upon exposure to cigarette smoking. The induced specific immune mediators are IL-6, IL-1 , and TNF . The proposed mechanism is that exposure to cigarette smoking causes SARS-CoV-2l spike protein to bind to the surface of A549 and induces protein changes on innate signaling protein activation. The additive proinflammatory response from smoking, on COVID-19

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P21

Cannabidiol Effects in Paclitaxel Induced Neuropathic Pain

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Paclitaxel-induced peripheral neuropathy (PIPN) can limit oncologic treatment in a growing number of patients leading to discontinuing therapy in several cancer treatment types, including breast and ovarian cancer. The pathophysiological mechanisms of PIPN have been extensively characterized in vitro and in animal models although to date there is no effective therapy that can control the neuropathy of this condition. Cannabinoids have been used for medicinal purposes for thousands of years, and current research supports the use of at least one component of medical cannabis, cannabidiol (CBD) for PIPN. The overall goal is to determine a reliable and reproducible in vitro screening model for paclitaxel-induced neuropathic pain. The methods evaluate different cellular characteristics of pain model including physiological signaling of pain such as calcium flux and neurotransmitter release, morphological and structural changes including mitochondrial distribution and dendrite length, and de novo production of proinflammatory markers. We characterized our in vitro cell model with F11 cells which are hybrid cells combining neuroblastoma cell of mice and embryonic rat dorsal-root ganglion sensory neurons and characterized the expression of cannabinoid receptor CB1, CB2 and CGBR55 on these cells. As we measured the functional response of the cells, we were able to detect the activation of intracellular calcium flux when the sensory neurons received stimulus of a combination of chemicals such as histamine, leukotrienes, and prostaglandins, but this response was impaired by the pretreatment with cannabidiol. On the other hand, when we tested the effects of paclitaxel in a drug response curve, we could determine that as the concentration of paclitaxel increased the calcium signaling decreased confirming that paclitaxel is highly neurotoxic. At the completion of this project, we confirmed that cannabidiol can partially restore the paclitaxel induced neuronal damage. We aspire to further develop novel management therapies for PIPN that can be tested in further models of inflammatory and neuropathic pains.

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P22

Analysis of Orphan Drugs in the 21st Century by Type of Orphan Drug, Approval Times, and Facilitated Regulatory Pathways

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INTRODUCTION:

Since 2000, numerous orphan drugs have been approved by FDA to treat diseases linked to genetic mutations. FDA approval also frequently included at least one type expedited review: Fast Track, Accelerated Approval, Breakthrough Therapy Designation, or Priority Review. This poster reviews development and approval timelines for orphan drugs intended to treat a disease state linked to a genetic mutation.

METHODS:

Data for 30 orphan disease drugs approved by FDA since 2000 were reviewed to (1) assess timelines for drugs approved to treat a rare disease with a genetic basis and (2) understand the impact of expedited programs on the approval timeline. All data is procured from what is publicly available, including FDA review and approval packages and FDA or Sponsor press releases.

RESULTS:

For the selected drugs, there are distinct trends in development and approval efficiency. Over the 13-year period in which INDs were opened, Phase 1 clinical trials become more targeted to mutation-specific disease states (50% of trials 2005-2012; 63% 2013-2018). Over the 10-year period of NDA/BLA submissions (2011-2020), the average approval shortens from 232 ± 104 days (2011-2015) to 204 ± 58 days (2016-2020). These and other trends will be presented in the poster.

DISCUSSION:

The project assesses clinical development strategies and FDA approval of orphan drugs to treat diseases due to a genetic mutation. The disease state intended for treatment at the outset of the clinical program is compared to the progress of clinical trials and specifically the pivotal clinical trials and the indication in the (originally) approved label.

CONCLUSION:

Since 2000, FDA has approved 31 drugs to treat orphan diseases associated with a genetic mutation. The more recent the development program, the faster the overall development and approval timelines, associated primarily with the orphan drug designation as well as with FDA's expedited programs.

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P23

Identification of Tubulin polymerization inhibitors using a CRISPR-Cas9 edited cell line with endogenous tagging of beta-tubulin

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Tubulin is an essential protein for cell division. The inhibition of tubulin polymerization has been used as an excellent approach to inhibit the growth of cancer cells. Traditionally, the identification of tubulin polymerization inhibitors involved using pure tubulin for in vitro assays or procedures that use cells that require cell fixing and anti-tubulin antibody staining. We wanted to explore using a cell line with green fluorescent protein endogenous tagging of tubulin via CRISPR-Cas9 genome editing as a cell model to identify tubulin polymerization inhibitors without using cell fixing or exogenous staining. The advanced cell line was created using HeLa cells, modified to contain three endogenous tagged genes, each containing an individual fluorescent protein. The three fluorescent proteins, mTagBFP2, mClover3, and mRuby3, were tagged to the genes encoding Histone 1, beta-tubulin, and P62. In this modified cell line, image segmentation for single-cell analysis is done using the Histone 1 label to identify the cell nucleus and the beta-tubulin label for cytoplasm detection around each identified nucleus. Subsequently, the cytoplasm's image texture characteristics can be measured to determine potential changes in the pattern of microtubules. We treated the cells with known tubulin polymerization inhibitors, Colchicine and Vincristine, and confirmed via high-content imaging (HCI) analysis the presence of phenotypic changes that indicate tubulin polymerization inhibition. We tested the functionality of the CRISPR-modified cell line to discover tubulin polymerization inhibitors by screening a library of 454 kinase inhibitors by using HCI. We identified three compounds, ON-1910, HMN-214 and KX2-391, that alter tubulin polymerization by comparing to effects seen with known tubulin polymerization inhibitors, Colchicine and Vincristine. To further validate this, we did live-cell tracking and visualized the cells over 3 hours, and detected tubulin polymerization inhibition in real-time. The compound ON-1910 was reported previously to have tubulin polymerization inhibition capabilities, while the FDA recently approved KX2-391 to treat actinic keratosis by inhibiting tubulin polymerization. These results validate our approach and suggest that we can use this modified cell line to screen larger compound libraries containing diverse chemical families to identify novel tubulin polymerization inhibitors.

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