SCHOOL OF PHARMACY
RESEARCH COLLOQUIUM

Reimagining Pharmacy — **Transforming Lives**

March 30-31

TEXAS A&M UNIVERSITY

Irma Lerma Rangel
School of Pharmacy

INNOVATION **RESPECT** COMMUNITY
LEADERSHIP CARE **COMPETENCE**
INTEGRITY **INNOVATION RESPECT**
COLLABORATION INTEGRITY **CARE**
CARE **COMPETENCE** COMPASSION
INNOVATION LEADERSHIP **CARE**
INNOVATION **RESPECT** COMMUNITY
COLLABORATION INTEGRITY **CARE**
CARE **COMPETENCE** COMPASSION
EXCELLENCE CARE **COMMUNITY**
INTEGRITY **RESPECT** INNOVATION
LEADERSHIP CARE **COMPETENCE**
INNOVATION LEADERSHIP **CARE**
INNOVATION **RESPECT** COMMUNITY
COLLABORATION INTEGRITY **CARE**
CARE **COMPETENCE** COMPASSION

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Research at the Irma Lerma Rangel School of Pharmacy is at the forefront of clinical discovery, focusing on multiple key areas, including specialized pharmaceutical delivery and drug development, while leading diagnostic studies into cures for cancer and other chronic diseases that are prevalent in our world today.

Welcome Message from the Dean

Howdy!

With great pleasure, I welcome you to Aggieland and the Research Colloquium at Texas A&M University Irma Lerma Rangel School of Pharmacy. This event features a dynamic and distinguished group of speakers, all at the forefront of their respective fields, who will share their research work and expertise on a diverse range of topics. I hope this colloquium serves as an open forum for exchanging ideas and insights.

The presentations (podium as well as poster) and discussions at this colloquium will cover a broad range of topics, including cancer research, new drug discoveries, drug design and delivery, pharmacogenomics, precision medicine, and clinical trials, among other research areas. The insights and perspectives shared by our speakers will be of tremendous value to researchers, clinicians, residents, students, and other professionals involved in the field.

We are delighted to bring together renowned researchers, educators, practitioners, pharmacy residents, and graduate students to share their latest research and innovations in pharmacy practice, pharmaceutical sciences, and pharmacy administration. The abstracts presented in this book are testaments to the diversity and depth of topics covered. They should serve as valuable resources for anyone seeking to stay up to date on the latest developments in the field. Undoubtedly, we will all benefit from the presentations and discussions during this event.

From bench to bedside, our team of dedicated researchers are highly committed to advancing pharmaceutical development, drug delivery, and pharmacy education and training to enhance the quality of life in the border region, the state of Texas, and beyond. I urge all of us to use this opportunity to challenge our assumptions, expand our knowledge, and foster new collaborations to advance our understanding of the world.

On behalf of the organizing committee, I would like to express my sincerest appreciation to all our speakers and attendees for their contributions to this event. I hope you will find the information presented here informative, thought-provoking, and inspiring.

Welcome to the Texas A&M *pharmily*!

Gig 'em!

Indra K. Reddy, Ph.D.

Program Schedule

Thursday, March 30

3:00 – 4:00 p.m. | **Registration/Poster Setup**

4:00 – 5:30 p.m. | **Poster Presentations**

5:30 – 7:30 p.m. | **Welcome Reception/Dinner**

Friday, March 31

7:30 – 8:20 a.m. | **Registration/Breakfast**

8:20 – 8:30 a.m. | **Welcome**
Indra K. Reddy, **Ph.D.** Dean, School of Pharmacy and Senior Associate Vice President for Academic Affairs, Texas A&M Health

8:30 – 9:30 a.m. | **Keynote Address**
Pharmacognosy: An Enduring Pharmaceutical Science
Lance McMahon, **Ph.D.** Senior Vice President for Research, Texas Tech University Health Science Center, Lubbock

9:30 – 9:45 a.m. | **Coffee Break**

9:45 – 11:00 a.m. | **Scientific Session I**
Moderator: **Allison Ficht, Ph.D.** Associate Dean of Research, School of Medicine

9:45 – 10:15 a.m. | **Guest Speaker**
Leveraging Thin-film Freezing as a Particle Engineering Platform- Stabilizing and Delivering Antivirals, Antibodies and Vaccines
Robert O. (Bill) Williams III, **Ph.D.** Division Head and Professor of Molecular Pharmaceutics and Drug Delivery, University of Texas, Austin

10:20 – 10:40 a.m.
Zein Nanoparticles for Drug Delivery to Inflammatory Bowel Disease (IBD)
Srinath Palakurthi, Ph.D. Professor, Department of Pharmaceutical Sciences

10:40 – 11:00 a.m.
Nanomedicine for Tumor Targeting and Intracellular Drug Delivery
Lin Zhu, **Ph.D.** Associate Professor, Department of Pharmaceutical Sciences

11:00 – Noon | **Scientific Session II**
Moderator: **Jim Sacchettini**, **Ph.D.** Rodger J. Wolfe-Welch Foundation Chair, Professor of Biochemistry & Biophysics, Chemistry, College of Agriculture & Life Sciences

11:00 – 11:20 a.m.
Positive Allosteric Modulators of the Cannabinoid CB1 Receptor as Novel Non-addictive Pain Relievers
Dai Lu, **Ph.D.** Associate Professor, Department of Pharmaceutical Sciences

11:20 – 11:40 a.m.
Clinical Implementation of Pharmacogenomics and Artificial Intelligence Tools
Sara Rogers, Pharm.D. Clinical Assistant Professor, Department of Pharmacy Practice

11:40 – 12:00 p.m.
E3 = Environment, Epigenetics, and Endocrinology
Mahua Choudhury, Ph.D. Associate Professor, Department of Pharmaceutical Sciences

12:00 – 1:00 p.m. | **Lunch**

1:00 – 2:15 p.m. | **Scientific Session III**
Moderator: **Tiffany Radcliff, Ph.D.** Associate Dean of Research, School of Public Health

1:00 – 1:30 p.m. | **Guest Speaker**
Population-Based Safety Research in Geriatrics
Rajender R. Aparasu, Ph.D. Musty and Sanober Lokhandwala Endowed Professor and Chair, Department of Pharmaceutical Health Outcomes and Policy, University of Houston

1:35 – 1:55 p.m.
Effective but Not Cost-effective: the Price Impact of New Cancer Drugs
Lixian Zhong, Ph.D. Assistant Professor, Department of Pharmaceutical Sciences

1:55 – 2:15 p.m.
Evaluation of Opioid Overdose Education and Naloxone Training Progress Efficacy in Targeted Community Participants
Joy Alonzo, ME, Pharm.D. Assistant Professor, Department of Pharmacy Practice

2:20 – 3:20 p.m. | **Scientific Session IV**
Moderator: **Kelley Wilson, Ph.D.** Associate Dean for Undergraduate Nursing Education

2:20 – 2:35 p.m.
Endoplasmic Reticulum (ER), a Potential Therapeutic Target for Mutant p53 Colorectal Cancer
Ashish Tyagi, Ph.D. Research Assistant Professor, Department of Pharmaceutical Sciences

2:35 – 2:50 p.m. | **Best Grad Student Poster Presentation: In-utero Exposure to e-Hookah Modulates Platelet Reactivity and Increases the Risk of Thrombotic Cardiovascular Disease**
Precious Badejo, Graduate Student, Department of Pharmaceutical Sciences

2:50 – 3:05 p.m. | **Best Post-Doctoral Scholar Poster Presentation: Cadmium-induced NF-kB Regulates Defective Autophagy and Transforms Healthy Prostate Epithelial Cells into Malignancy**
Vaibhav Shukla, Ph.D. Post-Doctoral Research Associate, Department of Pharmaceutical Sciences

3:05 – 3:20 p.m. | **Engineering Human Serum Albumin Nanoparticles for Intracellular Drug Delivery**
Nishat Ara, Graduate Student, Department of Pharmaceutical Sciences

3:20 – 3:30 p.m. | **Closing Remarks**
Chendil Damodaran, Ph.D. Associate Dean for Research & Innovation and Professor of Pharmaceutical Sciences

3:30 – 3:50 p.m. | **Coffee/Refreshment Break**

3:50 p.m. | **Award Ceremony**
Jon Mogford, Ph.D. Chief Operating Officer and Senior Vice President, Texas A&M Health

Speaker Biographies

Keynote Speaker

LANCE McMAHON, Ph.D.

Dr. McMahon is the Senior Vice President for Research and Innovation at Texas Tech University Health Sciences Center, Professor of Pharmaceutical Sciences in the Jerry H. Hodge School of Pharmacy, and Professor of Medical Education in the School of Medicine. He serves on the Department of Defense Chronic Pain Management Programmatic Panel of the Congressionally Directed Medical Research Program, and he has served as regular and ad hoc study section member of the National Institutes of Health Center for Scientific Review. For over two decades, Dr. McMahon has been continuously funded by the National Institutes of Health for a total of $23M to conduct research in behavioral pharmacology and CNS drug discovery and development. Dr. McMahon received his PhD degree from the Department of Psychology at Texas A&M University.

Guest Speakers

RAJENDER APARASU, Ph.D.

Dr. Aparasu is an Endowed Professor and Founding Chair of Pharmaceutical Health Outcomes and Policy at the University of Houston-College of Pharmacy. He is a nationally recognized health outcomes scholar and pharmacy educational leader with over 25 years of experience. His research team aims to provide real-world evidence for practice and policy using available data sources and novel methodological and analytical approaches for causal inference in observational research. He has continuous Federal and non-governmental grants to address the geriatric quality of pharmaceutical care. He edited three textbooks and authored over 160 peer-reviewed publications. In 2012, he was recognized as a Fellow of the American Pharmacists Association (FAPhA) for his exemplary professional achievements and outstanding contributions. As a Fulbright Specialist, he visited Indonesia in 2019. In 2022, the American Association of Colleges of Pharmacy honored him with the Paul R. Dawson Award for Excellence in Patient Care Research.

ROBERT O. (BILL) WILLIAMS III, Ph.D.

Dr. Williams is the Johnson & Johnson Centennial Chair and Professor of Pharmaceutics and the Division Head of Molecular Pharmaceutics and Drug Delivery at the College of Pharmacy, University of Texas at Austin. He earned a B.S. in Biology from Texas A&M University, a B.S. in Pharmacy from the University of Texas at Austin, and Ph.D. in Pharmaceutics from the University of Texas at Austin. Dr. Williams is Fellow of the American Association of Pharmaceutical Scientists, the American Institute of Medical and Biological Engineering and the National Academy of Inventors. He was Inventor of the Year by the University of Texas at Austin in 2017. He received the College of Science Academy of Distinguished Former Students Award from Texas A&M University in 2021. He has co-founded several pharmaceutical companies. Dr. Williams' research interests include drug delivery systems and particle engineering technologies. He has published over 500 peer-reviewed papers, abstracts and book chapters, and co-edited two books in the fields of pharmaceutical technology and drug delivery, including Formulating Poorly Water Soluble Drugs, Third Edition. He is an inventor on over 90 patents and patent applications. He is the Editor-in-Chief of AAPS PharmSciTech since 2014, and on several editorial advisory boards.

Speakers

JOY ALONZO, Pharm.D.

Dr. Alonzo is a Clinical Assistant Professor in the Department of Pharmacy Practice at the Texas A&M School of Pharmacy. She provides leadership on numerous collaborative efforts to design, evaluate, innovate and implement clinical/technological strategies across Texas to address gaps in care associated with access, lack of resources and lack of dissemination of knowledge. Her innovations address needs of underserved and under-represented populations with a specific focus on interventions aimed at substance use disorders and strategies to address Opioid Use Disorder. In her role as Co-Chair of the Texas A&M Opioid Task Force, she has initiated multiple interventions leading to the distribution of reversal agents, and the documented reversal of overdoses. Specific novel interventions include telehealth, Wi-Fi-enabled resources, artificial intelligence, data-analytics and smartphone technologies aimed at addressing underserved populations and unaddressed issues in specialty care such as mental and behavioral disorders. Her key collaborators include: the University of Texas College of Pharmacy and School of Social Work, Texas A&M School of Public Health, Texas A&M School of Medicine, Texas A&M School of Nursing, the Texas A&M Experimental Engineering Station, Texas A&M Rural Community Health Institute, MD Anderson, rural health departments and numerous government, community and commercial entities.

MAHUA CHOUDHURY, Ph.D.

Dr. Choudhury is currently a tenured Associate Professor in the Pharmaceutical Sciences Department. In brief, her research objectives include taking a lead in epigenetic regulations and biomarkers for diseases, and performing studies in cells, animals, and humans. In support of this translational research program, she was able to acquire 35 grants, through which she is training/has trained 14 postdoctoral associates, four PhD students, 39 PharmD students, six research assistants, and 20 undergraduate students. Her lab alumni are well established in either academia or industry including tenure-track Assistant Professors and directors in Bio-industry. Dr. Choudhury's work has been highlighted in national and international media outlets including BBC, and the New York Times. She won the Bill and Melinda Gates Grand Challenge Award twice- a worldwide competition with a success rate of ~3%. Her accomplishments recently earned her the 2021-2022 Mid-Senior Best Research Faculty Award at the Texas A&M School of Pharmacy. These activities led to eight book chapters, 67 publications including three cover pages, and two patents.

Speakers

DAI LU, Ph.D.

Dr. Lu is a tenured Associate Professor of pharmaceutical sciences at the Texas A&M School of Pharmacy. He obtained his Ph.D. from the University of Connecticut, followed by postdoctoral training from Harvard Medical School. Prior to join Texas A&M University, he was a senior chemist and instructor of neurology at Harvard Medical School and Brigham and Women's Hospital. His lab is working in the interface of chemistry and pharmaceutical sciences. His research has focused on the discovery of therapeutics for the treatment of neuropathic pain, cancer, and infectious disease such as COVID-19. At present, The Lu lab is developing several classes of pharmacologically important molecules including allosteric modulators of the cannabinoid receptors, inhibitors of the Abelson kinases (ABLs), and metabolic stable analogs of natural products such as withaferin-A and paclitaxel. Dr. Lu is a major inventor of 11 patented intellectual properties. His research is currently funded by NIH and the X-grant from Texas A&M.

SRINATH PALAKURTHI, Ph.D.

Dr. Palakurthi is a tenured Professor of Pharmaceutical Sciences at Texas A&M School of Pharmacy. He has over 20 years of academic research experience in formulation development and pharmacokinetics. He joined the Texas A&M Health Science Center in 2008. Dr. Palakurthi's current research focuses on targeted combination chemotherapy of ovarian cancer using dendrimers as the drug carriers. He also developed corn protein-based nanoparticles for colon-specific drug delivery for inflammatory bowel disease. He is well-known in generic pharmaceutical industry for his work on establishing *in vitro* drug release tests for topical generic products. His research has been funded by Food and Drug Administration (FDA), National Institutes of Health (NIH), Department of Defense (DoD) and private research foundations. He has authored or co-authored over 50 peer-reviewed publications. Dr. Palakurthi has served as a mentor to 15 post-doctoral fellows, six graduate students and 15 professional and undergraduate students. He is a member of editorial boards of five scientific journals. His research has been funded by NIH, DoD, FDA and the Pharma industry.

SARA ROGERS, Pharm.D.

Dr. Rogers is a Clinical Assistant Professor of Precision Medicine and Ambulatory Care at the Texas A&M School of Pharmacy and Residency Program Director at the Texas A&M Health Family Care Clinic. She serves as President of the American Society of Pharmacovigilance, where her research track record reveals a long-standing goal of informing policy and practice. Rogers co-led the formation of the Pharmacogenomics Access and Reimbursement Coalition and collaboratively developed the Coalition's research agenda to understand the payment and policy landscape for pharmacogenetics testing and its role in disparities in patient access. Rogers serves as an organizational member of the NIH National Human Genomics Research Institute Inter-Society Coordinating Committee and develops educational resources to help practitioners navigate coverage for pharmacogenetics testing. Rogers co-led the formation of the Standardizing Laboratory Practices in Pharmacogenomics (STRIPE) Collaborative Community, a public-private multidisciplinary initiative to develop consensus-based industry standards for pharmacogenetics testing.

ASHISH TYAGI, Ph.D.

Dr. Tyagi is a Research Assistant Professor at Texas A&M School of Pharmacy, and his current research is focused on the discovery of novel small molecules and identifying new therapeutic targets for treatment of metastatic carcinomas. His primary interest lies in modulation of oncogenic signaling and associated pathways to effectively eradicate cancer cell and stem cell populations in metastatic carcinomas. He has managed multiple research projects during his tenure in multinational companies such as TakaraBio and thereafter during his postdoctorate, which resulted in over 30 research publications, 5 book chapters, a patent (PCT/US2021/018119) and manufacturer licensing of two technologies for commercial production. His work on metastatic carcinomas has also been recognized at the national and international level with awards such as the American Association for Cancer Research and Chinese Society of Clinical Oncology (AACR-CSCO) young investigator award, Travel Awards (TiCER: Texas A&M Center for Environmental Health Research), and END2Cancer, Oklahoma.

LIXIAN ZHONG, Ph.D.

Dr. Zhong is an Assistant Professor of Pharmacy with expertise in Pharmacoeconomics and outcomes research. Before joining Texas A&M University, Zhong worked as a health economist in the pharmaceutical industry, generating health economic evidence for new drug launching, reimbursement and market access. Her research interests lie at the intersection of science, medicine and economics, and she evaluates both clinical and economic values for health care interventions. Zhong's current research themes include evaluating the cost and effects of new medications and conducting empirical analysis of retrospective administrative databases or prospectively collected research data to assess real-world outcomes and costs associated with chronic diseases. She has completed several projects evaluating novel oncology medications and received external fundings to evaluate health care outcomes, costs, and clinical resource utilization among different chronic disease populations. She has published over 30 peer-reviewed journal articles. She received her PhD from Duke University, and her postdoctoral training from University of California, San Francisco.

LIN ZHU, Ph.D.

Dr. Zhu is a tenured Associate Professor in the Department of Pharmaceutical Sciences at the Texas A&M School of Pharmacy. His laboratory is focused on the development of novel drug delivery system and nanomedicine for stimuli-sensitive and targeted delivery of small and/or macro molecules. He has authored or co-authored 50 peer-reviewed articles and book chapters. His research is supported by National Institutes of Health, Department of Defense, American cancer society, TAMU T3, and Texas A&M Health seedling grants. He has received several research awards from American Association of Pharmaceutical Scientists, American Cancer Society and Controlled Release Society.

Moderators

ALLISON FICHT, Ph.D.

Dr. Rice-Ficht is the current Senior Associate Dean for Research and the Director of the Center for Microencapsulation & Drug Delivery. She received her PhD from Vanderbilt University in 1980. She joined Texas A&M's School of Medicine in 1984. Studies in the Rice-Ficht lab are currently focused on the use of unique biomaterials for controlled release of live and subunit vaccines. Her focus is currently directed to the production of vaccines against human Brucellosis and Q fever, but is being applied to the storage and delivery of numerous other vaccines. A study of specific immune mechanisms and potentiation through controlled releases is underway. An additional focus is the study of alpha crystalline structure and function. These unique proteins protect against thermal insult and modulate folding and activity of other proteins.

TIFFANY RADCLIFF, Ph.D.

Dr. Radcliff is a Professor in the Department of Health Policy and Management and the Senior Associate Dean for Research in the Texas A&M School of Public Health. She is currently Chair of the Texas A&M University Research Council and interim Director for the USA Center for Rural Public Health Preparedness. Her research expertise is in health economics and health services research, including analysis of secondary data, mixed methods for program evaluation, and use of novel methodologies to improve measurement of care processes, access, and outcomes for vulnerable populations such as older adults, veterans, and rural residents. Her research is primarily funded through quality enhancement and emergency management initiatives by the U.S. Department of Veterans Affairs. Beyond her administrative and research activities, she teaches a popular graduate course in health economics each Fall, mentors early career faculty and graduate students, and serves on several boards and advisory groups.

JIM SACCHETTINI, Ph.D.

Dr. Sacchettini serves as Director of the Texas A&M Center for Structural Biology. He also serves as the PI and Director of the NIH Program Project - TB Structural Genomics Consortium (TBSGC), that focuses on structure-guided drug discovery of Mycobacterium tuberculosis (Mtb). His lab is also part of the Bill and Melinda Gates Foundation funded TB Drug Accelerator. His lab is part of one of the several Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern formed by NIH. These AViDD centers work on drug discovery efforts for viruses such as coronavirus. He completed his PhD in molecular biology and protein crystallography at Washington University School of Medicine in 1987. He moved to Texas A&M University in 1996 as Professor of Biochemistry and Biophysics, Chemistry, and Wolfe-Welch chair in Science. He has led several multi-investigator efforts in the areas of structural biology and drug discovery. Currently his lab is collaborating with TB Global Alliance, many academic laboratories, and AbbVie, Eisai, Janssen, Evotec, Merck and GlaxoSmithKline.

KELLY WILSON, Ph.D.

As Professor and Associate Dean of Research for the School of Nursing at Texas A&M University, Dr. Kelly Wilson oversees the School of Nursing's research portfolio. As a principal investigator or co-principal investigator, she is a renowned expert in child and adolescent health, sexuality, and reproductive health. Dr. Wilson has secured more than $20 million in external grants to study adolescent and teen pregnancy, sexuality education and more. She has conducted adolescent health focused research, and delivers continuing education and professional development for youth focused researchers and professionals. She has an extensive external funding record, including serving as Co-PI on two OPA funded innovation focused grants (Tier 2a 2015 and 2020),
PI on an ACF funded cPREP adolescent pregnancy prevention grant and as an external evaluator for multiple community-based teen pregnancy prevention grants.

Abstracts

1. The First Step into the World of Translational Research: A Tale from the Undergraduates

Maya Gonsoulin, Anusha Srinivas, Mary-Grace Favre, Liliana Guzman, Patricia Policarpio, Samhita Kosuru, Anastasia Jerman and Mahua Choudhury
Department of Pharmaceutical Sciences

As a fundamental step in a young scientist's career, the research laboratory is the birthplace of multigenerational breakthroughs and a place for exploration. Due to the uniqueness of each experiment, study, and group of individuals, the size, style, and classification vary in laboratories across the world. Despite the steep learning curve of working in a laboratory, it is essential for further application of universal techniques and understanding of the scientific field following graduation. Throughout this project, we explored the foundational aspects of participating in a scientific laboratory and its importance in research, and we will now present what we have learned. First, we will outline several ways to get involved in a research lab as undergraduates and begin networking. Next, we will present the safety procedures necessary for limiting contamination and protecting our researchers and their mice, the model organism used in this lab. After that, we will be explaining methods such as western blots and RNA extraction, which are utilized to understand epigenetic machinery and their impacts on gene expression and metabolic diseases. We will walk Biochemistry and Genetics undergraduate students through how to join a lab, learning essential safety protocols, and understanding scientific principles and techniques that will help them further in their research career.

2. An Interdisciplinary Translational Lab: From A Next Generation Researchers' Standpoint

Anastasia Jerman, Nitya Shree, Mahua Choudhury
Department of Pharmaceutical Sciences

Epigenetics is an emerging frontier of science that involves the study of changes in the regulation of genes without alterations to the genetic sequence itself. These changes are inheritable and can also be modified due to environmental conditions. An altered epigenetic status could be a risk factor for various metabolic diseases, such as type 2 diabetes (T2D), obesity, and non-alcoholic fatty liver disease (NAFLD). The incidence of these diseases is proliferating in our population, likely due to the increased prevalence of a western diet and sedentary lifestyle. Another concern on the rise is pregnancy complications due to environmental effects. Women with dysregulated metabolism are susceptible to developing preeclampsia when pregnant, which is one of the major causes of maternal death worldwide. Evaluating the epigenetic regulation and biomarkers (specifically in noninvasive samples) in these diseases and their associated risk factors is the key to early detection and potential treatment. One of the major focuses of our lab is to evaluate the effect of western diet, endocrine disruptor induced epigenetic modification leading to metabolic dysregulation, and pregnancy complications in vitro, in vivo, and in patients. We are pioneering research in elucidating the roles of miRNAs, lncRNA, HATs, HDACs, and DNA/RNA methylation in various tissues including adipose, liver, bone marrow, placenta, and kidney. Understanding the involvement of epigenetics as the disease progresses would allow us to identify and substantiate biomarkers that can be used to detect disease early. Another beauty to epigenetics is its reversibility, making it an attractive component for the prevention of diseases. We are currently exploring therapeutics, including the use of MSCs, HSCs, and iPSCs, nutraceuticals, and epigenetic therapeutics to correct metabolic dysregulation. Overall, our goal is to thoroughly establish the interconnection of disease and epigenetic modifications in order to improve clinical outcomes and treatment of numerous diseases.

3. Determining the Efficacy of Jak3 Directed Drugs in TNBC -Brain Metastasis *In Vitro* and Cell Culture Model

Irma Garcia, Narendra Kumar and Jayshree Mishra
Department of Pharmaceutical Sciences

Introduction: Triple negative breast cancer is one of the most lethal breast cancer subtypes affecting predominantly minority women and makes up approximately 15-20% of all breast cancers and with 36% metastasizing to the brain. Although some current combination therapies of chemotherapy and immunomodulators can increase survival rates, they have limitations in effectively stopping tumor progression, cancer cell survival, and metastasis into the brain. Overexpression of pathways involved in immune responses such as the Jak3/STAT3 pathway aid in resistance to apoptosis, chemoresistance, immunosuppression, and TNBC cell invasion. Treatments for cancer cell brain metastasis exist and provide promising results; however, drug treatments for brain metastasis of TNBC are limited with present day treatments such as high dosages of methotrexate, etoposide, and cisplatin have only led to an overall 40% maximum of brain tumor reduction. There are existing kinase domain inhibitors. Additionally, many of the immunomodulators used in TNBC treatment cause side effects which can overall weaken patients further in fighting the cancer; whole brain radiation therapy also poses a possible threat in reducing cognitive function. In this study, a new class of Jak3 inhibitor was designed and synthesized and efficacy of these compounds have been tested both in in vitro and in cell culture method.

Methods: Five different Jak3- non kinase domain targeted compounds were selected based on the computational method and efficacy of these compound was tested through in vitro kinase assay, apoptotic assay and MTT assay in cell culture model.

Results: The new class of drugs are targeted towards the non-kinase domain of Jak3 and regulate the activity of the kinase domains of Jak 3. Results from both *in vitro* and in cell culture assays confirms that these new classes of drugs are effective against Triple negative breast cancer metastasis as compared to the kinase domain targeted inhibitor as these are target specific and can cross the blood brain barrier.

Conclusion: Jak/STAT pathway is extensively involved in TNBC invasiveness and metastasis. The new class of Jak3 non kinase domain targeted drugs are found to be effective to TNBC cell brain metastasis in both *in vitro* and cell culture model.

4. Sleep Disorders and Psychostimulants Associated Brain Dysfunction

S. Malaroviyam[1], M. Doke [1], Jay. P. McLaughlin [2] and S. Thangavel [1]
[1]Department of Pharmaceutical Sciences
[2] Department of Pharmacodynamics, College of Pharmacy, University of Florida

Background: Circadian disruption and the psychostimulants (cocaine and methamphetamine: METH) aggravate the inflammatory response and metabolic factors, leading to tissue damage. Cortisol and acute-phase proteins (APPs), such as C-reactive protein (CRP), complement C3 (C3), and serum amyloid A (SAA), are known to associate with damaged circulating mitochondrial DNA (mtDNA) and purine and pyrimidine metabolites. This study aimed to examine the connection between circadian disruption and psychostimulants, focusing on elucidating the inflammatory biomarkers and metabolic signature modifications associated with brain dysfunction.

Methods: Male C57BL/6J mice (10-12 weeks) were subjected to 6 h phase advance every six days for up to eight cycles, generating circadian rhythm and sleep disorder (CRSD) mice. CRSD mice were treated with 11 doses of cocaine (i.p., 15 mg/kg) and METH (i.p., 20 mg/kg) every other day for 22 days. The plasma CRP, C3, SAA, and cortisol levels were measured by enzyme-linked immunosorbent assay (ELISA) and western blot. The cell-free circulating mtDNA content was performed by quantitative real-time polymerase chain reaction (qRT-PCR). The plasma metabolites were analyzed by untargeted metabolomics.

Results: CRSD alone, cocaine alone, and METH alone significantly increased the CRP, C3, and SAA levels and cortisol levels in the plasma compared with the control. Exposure of CRSD mice to cocaine and METH significantly increased CRP, C3, and SAA levels; CRSD mice without exposure did not have any changes in CRP, C3, and SAA levels. Circulating cell-free mtDNA was decreased in CRSD mice with

or without cocaine and METH exposure. The metabolic signature of purine and pyrimidine metabolites are significantly affected by CRSD with cocaine.

Conclusions: Our results suggest that the circadian misalignment and psychostimulant alterations influencing inflammatory markers integrated with metabolic signatures in the plasma may be a good indicator and helpful way to detect psychostimulant addiction related to a sleep disorder.

5. Therapeutic Application of a Small Molecule Inhibitor of Notch1 as Chemosensitizer Against Triple-Negative Breast Cancer

Neha Tyagi[1], Arun Sharma[2] and Chendil Damodaran[1]
[1]Department of Pharmaceutical Sciences,
[2]Department of Pharmacy, Penn State University

Introduction: Despite numerous therapeutic options available for breast cancer (BC), relapse rates among patients remain high, with virtually all women with metastatic BC, particularly metastatic triple-negative breast cancer (TNBC), ultimately dying. We demonstrated earlier that the transcription factor, Notch1, is highly expressed in TNBC, and inhibition of Notch1 by a small molecule, ASR490, had a significant therapeutic impact by curtailing the proliferation of TNBC cells. Hence, we rationalized that its inhibition of Notch1 may enhance the sensitivity of TNBC cells to chemotherapy.

Materials & Methods: To determine the chemosensitization effect of ASR490, we selected Doxorubicin (DOX) as the chemotherapeutic agent and performed several phenotypic and molecular analyses in TNBC (MDA-231) cells.

Results: As established that ASR490 significantly suppressed the growth of TNBC cells, and the IC50 is in nanomolar concentrations (760 nM at 24h). On the other hand, chemotherapeutic agents (Doxorubicin (DOX): IC50-1.2μM), Docetaxel (DTX: IC50-3.6 μM), and 5-fluorouracil:5-FU-IC50-18.6 μM) unresponsive to TNBC. As proof of principle, we selected DOX for our experiments and demonstrated that ASR490 could significantly sensitize ($p < 0.0001$) TNBC cells to DOX. More interestingly, Dox-treatment induced Notch1 activation, which was why complete eradication of TNBC did not occur in the clinic. However, combined with ASR490, it significantly downregulated DOX-induced Notch activation in TNBC cells. On the other hand, Dox alone or combined with ASR490 enhanced DNA damage; hence a complete inhibition of the growth of TNBC was seen. Our ongoing in vivo experiment may confirm and validate our in vitro findings that ASR490 is a potent chemo-sensitizing agent against TNBC cells.

Conclusion: Overall, our results suggest that ASR490 is a potent chemosensitizer, and at very low doses of ASR490 and chemotherapeutic agents significantly suppressed the growth of TNBC cells. Together these results indicate the potential clinical benefit of this novel combination to improve the prognosis of patients with TNBC and alleviate the toxic side effects of chemotherapy.

6. Proteomic Analysis Reveals Potential Therapeutic Targets and Biological Markers for HIV-Associated Neurocognitive Disorders

Sheetal Veera Pandian[1], Mayur Doke and Samikkannu Thangavel[1]
[1]Department of Pharmaceutical Sciences

Background: Neurological complications are frequently observed in individuals living with HIV/AIDS, resulting in HIV-associated neurocognitive disorders (HAND) that cause cognitive and behavioral impairments. HAND remains prevalent, even in patients receiving highly active antiretroviral therapy (HAART), affecting over 30% of the total HIV+ population. The objective of this study was to examine the connection between the frontal and temporal lobes in the brains of HIV-positive (HIV+) individuals, with a focus on elucidating the molecular mechanisms and protein modifications associated with neuropathogenesis. **Methods:** The study utilized label-free liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis to identify differentially expressed proteins between normal and HIV+ brains. Comprehensive proteomic identification and quantification analyses were performed using the data-independent acquisition method.

Result: The study identified 3294 total proteins, with 251 differentially expressed proteins in HIV+ brains. The HIV+ frontal and temporal lobes had 132 and

119 differentially expressed proteins, respectively. The study found protein alterations predominantly in the HIV+ frontal lobe region compared with temporal lobe. GOLPH3, IMPDH2, DYNLL1, RPL11, and GPNMB proteins were significantly altered in HIV+ frontal lobes compared to normal brains. These proteins are associated with metabolic pathways, neurodegenerative disorders, and dementia.

Conclusion: The findings suggest that the identified proteomic-level changes may serve as potential biological markers and therapeutic targets for relieving the symptoms associated with dementia in individuals with HAND. Understanding the protein expression changes may lead to developing targeted therapies for HAND.

7. Medication Use Evaluation of IV Push Levetiracetam

EA Anderson, TD Hintze, JL Jones
CHI St. Joseph Regional Hospital Bryan, Texas

Background: Proposed benefits of switching to IV push levetiracetam include earlier attainment of therapeutic targets and decreased costs by utilizing vials, as opposed to premix medication bags. This study gathered information about safety outcomes, efficacy outcomes, dosing patterns, and cost comparisons between two cohorts of 50 patients before and after the IV Push Levetiracetam was implemented.

Objectives: The objective of this poster is to educate pharmacy practitioners and seminar attendees about IV Push Levetiracetam safety, efficacy, cost, and dosing patterns compared to IVPB Levetiracetam when used in a community teaching hospital. **Method:** Review period was from July 2021 - October 2021, until 50 patients were reached. The same time frame in 2022 was collected to compare 50 patients after IV Push Levetiracetam was implemented. Provider notes, emergency department documentation, and MAR information was used to collect data.

Result: The overall safety and efficacy outcomes between cohorts, IVPB Levetiracetam and IV Push Levetiracetam, had similar results. For the efficacy outcomes, most seizure activity was controlled with 88% in the IV Push cohort and 90% in the IVPB cohort. Dosing patterns were generally in line with the guidelines for each indication, and there were significant cost savings seen with the switch from IVPB to IV Push Levetiracetam.

Conclusion: IV Push Levetiracetam should be preferred on formulary, not the Premix IVPB bags. Follow-up assessment of our prophylaxis dosing patterns, and pulling a larger cohort of status epilepticus patients will allow better dosing analysis and generalization.

8. Evaluation of Caretaker's Knowledge on Over-the-counter Cough and Cold Medication Pediatric Safe Practices in South Texas

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Background: The Rio Grande Valley of Texas has some of the highest poverty rates in the state. Studies have shown that parents from lower socioeconomic backgrounds had lower instances of over-the-counter (OTC) medication use in their children but had more instances of adverse events from OTC medication use due to low health literacy. Studies also show that higher levels of education are positively correlated with medication knowledge.

Objectives: To assess the prevalence of OTC cough and cold (OTC-CC) misuse in lower socioeconomic populations, this study will focus on providing an educational seminar on OTC-CC medications. The study objectives are to assess the knowledge of our study population in medication safety best practices, to identify paucity of knowledge regarding these medications in the study population before and after an educational intervention, and to describe the socio-demographic of the study population.

Methods: This is a descriptive survey study conducted in multiple elementary classroom sites in the Rio Grande Valley Region of South Texas from January 2022 to December 2023. For the current results, data was collected from one school district. The encounter includes a pre-survey, a one-hour OTC-CC educational intervention focusing on best practices of OTC-CC medication use in children, and a post-survey. The surveys consist of 20 multiple choice and fill in the blank questions and assess participants' demographic information and OTC-CC medication knowledge. Independent variables will consist of de-

mographic information, and educational intervention outcomes will serve as the dependent variable. To describe the study population, we will use gender, age, ethnicity, income, and education. The study will use SAS analytics software to analyze the variables and report outcomes associated with the objectives.

Results: Data collection is still on-going.

Conclusions: The results of this data collection have not been fully collected, and therefore conclusions cannot be drawn.

9. Optimizing Levothyroxine Dosing for Potential Organ Donors in a Community Teaching Hospital

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Background: In clinical brain death, many organ systems begin to shut down causing a disruption of homeostasis. The anterior pituitary gland loses function causing decreased levels of thyroid hormone, leading to cardiac dysfunction. To aid in increasing the probability of organ procurement as well as reducing vasopressor requirements, intravenous levothyroxine is given in combination with other hormone replacement therapies to maintain adequate perfusion. Currently, the guideline- recommended dose is a 20mcg bolus followed by an infusion of 10mcg/hr.

Objective: To illustrate the potential cost savings of optimizing IV levothyroxine dosing for organ procurement.

Methods: A report of all IV levothyroxine usage between July 1, 2019 and June 30, 2022 was compiled. All patients initiated on levothyroxine drip for organ procurement were included. Collected data included duration, concentration, and total amount of levothyroxine administered; time of brain death declaration, and vasopressor requirements. The calculated total number of bags administered was then compared to the total number of bags that would have been given if dosed at 10 mcg/hr.

Results: If all IV levothyroxine for organ procurement were dosed optimally, an estimated $19,039.52 could have been saved. Additional results are pending.

Conclusion: Optimizing levothyroxine dosing in potential organ donors could serve as a cost-savings initiative to this institution.

10. Medication Use Evaluation of Ketamine Intravenous Infusion in a South Texas Critical Care Unit

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Introduction: Ketamine is a noncompetitive NMDA receptor antagonist that blocks glutamate which produces a state of dissociation to the patient's surrounding environment by direct action on the cortex and limbic system. Per the 2018 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) guidelines, ketamine may be used as an adjunct to opioid therapy when seeking to reduce opioid consumption in patients admitted to the Critical Care Unit (CCU). Furthermore, ketamine may be used to help in weaning patients off sedatives such as dexmedetomidine, propofol, and midazolam. Because of its capability of being both an opioid sparing agent and having sedation capabilities, titration and dosing of ketamine may vary depending on the provider, patient's condition, indication, and the other agents already on board. The purpose of this study is to evaluate dosing appropriateness and utilization of continuous IV infusion of ketamine as compared to our hospital's protocol. Additionally, we want to identify opportunities to optimize ketamine's use in aiding the CCU in managing sedation, agitation, and pain

Methods: A retrospective chart review will be conducted for inpatient adults on ketamine IV infusions from May 2021 to July 2022. The goal is to analyze patients who received IV continuous infusions. The data collected will include patient demographic information, ketamine information (eg, dosing, route, duration of use, etc.), and past medical history. Additionally, pertinent vital signs, sedation and pain scores, and length of intubation will be included for help in determining ketamine safety and effectiveness. Inclusion criteria included 18+ year old patients who were admitted into one of our 3 ICU units (Medical ICU, Neuroscience ICU, and Cardiac CCU), and were on ketamine for longer than 8 hours. Exclusion criteria included

patients who received ketamine less than 8 hours and/or part of the status epilepticus order set. Ketamine dosing appropriateness was defined as whether the starting dose and maximum titrated dose were within our parameters of the DHR ICU sedation protocol, 0.5 mg/kg/hour and 2.5 mg/kg/hour respectively. Medication utilization was evaluated on whether there were reductions in IV continuously infused sedatives and/or opioids. Reduction is defined as any reduction in dosing and/or weaning off a product while on ketamine

Results: Per the study's inclusion and exclusion criteria, 94 patients were analyzed. In terms of dosing appropriateness, 40% of the ketamine orders were not started at the protocol dose of 0.5 mg/kg/hour. 91% of our orders were titrated using the appropriate rate of mg/kg/hr. For reductions noted in sedatives and opioids, 46 patients didn't experience a reduction in sedatives and 72 patients did not see a reduction in opioids. For RASS, 83 out of 94 patients were analyzed. 21 patients were excluded for no documented RASS score. In terms of maintaining RASS, 76 (92%) patients were effectively maintained with the addition of ketamine whereas 7 patients (8%) were not. Looking at the efficacy of maintaining CPOT scores, 36 patients were analyzed. 77 were excluded due to lack of CPOT documentation. 34 (94%) patients were maintained at target CPOT with the addition of ketamine whereas 2 patients (6%) were not.

Conclusion: The most notable areas for improving the use of ketamine will be on the electronic health system. Incorporating informatics to include an indication drop-down (e.g., attempting to reduce opioid usage vs sedative usage) may aid clinical pharmacists and other providers in identifying its use and better optimize administration rates. Education can be provided on documentation and monitoring of RASS and CPOT scores to help ensure the drug is utilized appropriately.

11. Medication Use Evaluation of Alteplase

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Background: Alteplase, a tissue plasminogen activator (tPA), converts plasminogen to plasmin, a proteolytic enzyme that lyses fibrin and fibrinogen. Alteplase is utilized in acute ischemic stroke (AIS). Due to risk of significant hemorrhagic complications, administration is restricted to certain patients who meet eligibility criteria. Due to the high-risk and time sensitive nature of alteplase, protocols for dosing, monitoring, and eligibility are required to mitigate the risk of adverse events. The purpose of the medication use evaluation (MUE) is to examine proper use of alteplase in accordance with the current hospital protocols and evaluate the safety, efficacy, and appropriateness of administration.

Methods: A retrospective chart review will be conducted for all patients who were administered alteplase for AIS from July 2021 to July 2022. The goal is to analyze patients who were administered alteplase. The data collected will include time of symptom onset, exclusion criteria, age, gender, height, weight used for dosing, and dose (bolus and intermittent infusion). Pertinent lab values with times will also be collected such as hemoglobin, platelets, INR, aPTT, blood pressure, and glucose. Time sensitive data that will be collected include preparation time, delivery time, door to needle time, and time from alteplase administration to interventional radiology. Lastly, patient results will be evaluated for a change in NIH stroke scale, if the patient had a true stroke, alteplase not given, hemorrhagic conversions, adverse effects, and death. Collected patient information with be deidentified to ensure patient confidentiality.

Results: Based on the results of the study, all patients that have received alteplase are appropriate tPA candidates per hospital protocol criteria and have received appropriate calculated bolus and infusion doses. Furthermore, all patients were appropriately monitored as there were no concerning lab values that prompted concern for alteplase administration aside from

admitting blood pressure >185/110 mmHg which was appropriately lowered before tPA administration. Ultimately, the average DTN time is 56.6 minutes which meets AHA/ASA's recommended target DTN time but fails to meet The Get With The Guidelines® - Stroke Recognition criteria of having 75% of patients meeting a DTN time of ≤60 minutes with results showing only 62% of patients. Average tPA pharmacy preparation time for emergency pharmacist is lower at 7.5 minutes as compared to 11.8 minutes for main pharmacy. The average DTN time between the two groups were the under the goal DTN of ≤60 minutes. 61% of patients who had EM pharmacists in their initial stroke care team met the DTN goal of ≤60 minutes while main pharmacy reached 65%, however EM pharmacists have 64% of these patients with a DTN time of ≤ 45 minutes vs 54% of main pharmacy.

Conclusion: The findings of the study show a decrease in tPA pharmacy preparation time and shorter DTN times with EM pharmacists. Delays for tPA administration may have influence DTN times for both arms. Overall, the results continues to support and add evidence that the involvement of EM pharmacists in the initial stroke care team reduces the time between tPA treatment to the patient.

12. Mechanistic Role of Jak3 in Obesity-associated Cognitive Impairments

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Introduction: A compromise in intestinal mucosal functions is associated with several chronic inflammatory diseases. Previously, we reported that obese humans have a reduced expression of intestinal Janus kinase-3 (Jak3), a non-receptor tyrosine kinase, and a deficiency of Jak3 in mice led to predisposition to obesity-associated metabolic syndrome. Since meta-analyses show cognitive impairment as a co-morbidity of obesity, the present study demonstrates the mechanistic role of Jak3 in obesity associated cognitive impairment. Our data show that high-fat diet (HFD) suppresses Jak3 expression both in intestinal mucosa and in the brain of wild-type mice.

Methods: Recapitulating these conditions using global (Jak3-KO) and intestinal epithelial cell-specific conditional (IEC-Jak3-KO) mice and using cognitive testing, western analysis, flow cytometry, immunofluorescence microscopy and 16s rRNA sequencing, we demonstrate that HFD-induced Jak3 deficiency is responsible for cognitive impairments in mice, and these are, in part, specifically due to intestinal epithelial deficiency of Jak3.

Results: We reveal that Jak3 deficiency leads to gut dysbiosis, compromised TREM-2-functions-mediated activation of microglial cells, increased TLR-4 expression and HIF1-α-mediated inflammation in the brain. Together, these lead to compromised microglial-functions-mediated increased deposition of β-amyloid (Aβ) and hyperphosphorylated Tau (pTau), which are responsible for cognitive impairments. We also identified changes in the brain's neuron and astrocyte composition, which is a symptom commonly found in neurodegenerative diseases. Collectively, these data illustrate how the drivers of obesity promote cognitive impairment and demonstrate the underlying mechanism where HFD-mediated impact on IEC-Jak3 deficiency is responsible for Jak3 deficiency in the brain, reduced microglial TREM2 expression, microglial activation and compromised clearance of Aβ and pTau as the mechanism during obesity-associated cognitive impairments.

Conclusion: We demonstrate the mechanism of obesity-associated cognitive impairments but also characterize the tissue-specific role of Jak3 in such conditions through mucosal tolerance, gut–brain axis and regulation of microglial, neurons and astrocytes.

13. Role of Janus Kinase 3 in Predisposition to Obesity-associated Metabolic Syndrome

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Introduction: Obesity, a worldwide epidemic, is a major risk factor for the development of metabolic syndrome (MetS) including diabetes and associated health complications. Recent studies indicate that chronic low-grade inflammation (CLGI) plays a key role in metabolic deterioration in the obese population. Previously, we reported that Jak3 was essential for mucosal differentiation and enhanced colonic

barrier functions and its loss in mice resulted in basal CLGI and predisposition to DSS induced colitis. Since CLGI is associated with diabetes, obesity, and metabolic syndrome, present studies determined the role of Jak3 in development of such conditions.

Methods: Mice, wild type and Jak3-KO, were assessed for weight, fasting blood glucose, glucose tolerance, insulin tolerance test, weight of epidydamal fat-pad and liver, and liver histological examinations.

Results: Our data show that loss of Jak3 resulted in increased body weight, basal systemic CLGI, compromised glycemic homeostasis, hyperinsulinemia, and early symptoms of liver steatosis. Lack of Jak3 also resulted in exaggerated symptoms of metabolic syndrome by western high-fat diet. Mechanistically, Jak3 was essential for reduced expression and activation of Toll-like receptors (TLRs) in murine intestinal mucosa and human intestinal epithelial cells where Jak3 interacted with and activated p85, the regulatory subunit of the PI3K, through tyrosine phosphorylation of adapter protein insulin receptor substrate (IRS1). These interactions resulted in activation of PI3K-Akt axis, which was essential for reduced TLR expression and TLR associated NFB activation.

Conclusion: Collectively, these results demonstrate the essential role of Jak3 in promoting mucosal tolerance through suppressed expression and limiting activation of TLRs thereby preventing intestinal and systemic CLGI and associated obesity and MetS.

14. Medication Use Evaluation of Alteplase Compared to Tenecteplase in Acute Ischemic Stroke

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Background: Stroke is the second leading cause of death worldwide, and the leading cause of disability. There are about 800,000 new strokes every year in the United States and the incidence is expected to increase. Strokes can be categorized as ischemic or hemorrhagic with the goal of therapy to reduce ongoing neurologic injury. Fibrinolytic therapy is used for the dissolution of thrombi when clinically appropriate. Studies have shown tenectplase is non-inferior to alteplase in the management of acute ischemic stroke and provides several advantages over alteplase.

Objective: The objective of this study was to evaluate the current use of alteplase compared to tenecteplase in acute ischemic stroke from a safety, effectiveness, and cost standpoint.

Method: A retrospective chart review was conducted for adult patients who received alteplase from July 1st, 2021 to December 31st, 2021 and tenecteplase from July 1st, 2022 to December 31st, 2022 to evaluate the transition and implementation of alteplase to tenectplase. The primary outcome was the incidence of hemorrhagic conversion. Secondary outcomes include the number of significant adverse events, effectiveness of therapy based on NIH and Modified Rankin Scale, and cost.

Result: For alteplase, 38 patients were reviewed during the specified period. Of the 38 patients, 17 were removed from the evaluation for not meeting the criteria. The remaining 21 patients were included in the final analysis. Baseline characteristics are listed below. Two patients had a hemorrhagic conversion with alteplase use. For tenecteplase, 30 patients were reviewed during the specified period. Four of the 30 patients were removed from the evaluation for not meeting the criteria. The remaining 26 patients were included in the final analysis. Baseline characteristics are listed below. One patient had a hemorrhagic conversion with tenecteplase use

Conclusion: Tenecteplase, a genetically engineered thrombolytic medication used off-label for acute ischemic stroke, presents a few advantages over the current standard of therapy, such as preparation, administration, and cost. Regarding safety and efficacy, tenecteplase can be considered non-inferior, given the incidence of hemorrhagic conversion and other notable adverse effects. From a cost perspective, tenecteplase is distinctly cheaper and cost-effective, given the same effectiveness.

15. Assessing Patients' Comfortability Discussing Mental Health Since the Beginning of the COVID-19 Pandemic in the Community Pharmacy Setting

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Introduction: Prior studies found that providing mental health services and resources in the community pharmacy improves medication adherence and strengthens patient-pharmacist relationship. The aim of this study is to assess patient's comfortability discussing their mental health with their community pharmacist and identify barriers to providing mental health resources in the community pharmacy setting.

Methods: This is a prospective, survey-based study approved by the Texas A&M Investigational Review Board. Data collection using Qualtrics will be from February 2023-March 2023. Patients ≥ 18 years old and who can speak and read in English will be provided a voluntary survey link or QR code. The survey questions will be used to assess patient demographics, patient comfortability discussing mental health with their pharmacist, and opinions about expanding access to mental health resources. The data will be aggregated into summaries using descriptive statistics and will be analyzed using SAS software.

Results: Data collection is ongoing. From our initial data representation, around 57% of the survey takers trust that their pharmacist could help them in an immediate mental health situation (such as self-harm or harm to others), but only 28% would like to spend more time discussing their mental health with their pharmacist. Over 70% of our participants have experienced mental health challenge during the COVID-19 pandemic, but only 42% have accessed mental health resources in-person or online and only 7% reached out to their pharmacy for mental health resources. Around 43% of our participants were not interested in accessing mental health resources in the pharmacy and 28% were unaware of the mental health services their pharmacy provides.

Conclusions: Based on the interim data, patients are mostly unaware or uninterested in accessing mental health resources at the pharmacy. Researchers hope to identify barriers to patient perception and increase awareness of mental health resources at the pharmacy.

16. Comparative Analysis of Molecular Dynamics Simulations Software for Rational Drug Discovery

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Molecular dynamics (MD) simulation is a very integral part of molecular modeling and computational designs for studying the transient evolution of atoms in molecular systems. With the use of classical force fields such as CHARMM, GROMOS, AMBER, and OPLS, a predictive analysis of the movements and energies associated with individual atoms in molecular systems can be studied within a biologically relevant time scale (nanoseconds). In drug design, MD simulations are very vital in understanding protein-ligand interactions and in target validation.

The goal of our study is to compare commonly used MD packages (Amber, NAMD, Desmond, and GROMACS) and demonstrate how the chosen force field influences their performance and accuracy in validating protein-ligand interaction. From the literature, comparison between the four MD software packages typically uses different forcefields, giving room for a flawed comparison. Using a predetermined force field and free energy calculation algorithms for each of the packages, a specified statistical metric system has been used for a valid comparison, comparing the different energy terms (such as Van der Waals, non-bond, bond, electrostatic, and potential energies) within the various software packages.

In conclusion, an effective comparison of the predictive performance of the four MD packages is more realistic if a particular forcefield is chosen across the different software packages.

17. Engineering Human Serum Albumin Nanoparticles for Intracellular Drug Delivery

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Introduction: Human serum albumin (HSA) is a promising nanocarrier for drug delivery due to its biocompatibility, biodegradability, safety, and low immunogenicity. Phenylboronic acid (PBA) has emerged with exceptional capability as a small molecule ligand to bind with cis-diols and poly(hydroxyls) of cell surface glycoprotein (glycan) to mimic lectin as well as bind to the extracellular matrix components, such as sialic acid, saccharides, mannose, galactose, and fucose residues. This study aims to design and engineer HSA with PBA for intracellular drug delivery to improve drug efficacy.

Methods: The HSA-PBA conjugate was synthesized by covalently attaching PBA to HSA via a carbodiimide-mediated coupling reaction. The conjugation was identified by thin layer chromatography (TLC) and sodium dodecyl sulfate- polyacrylamide gel electrophoresis (SDS-PAGE). The physicochemical properties of the HSA-PBA conjugate, including particle size, polydispersity index (PDI) and zeta potential, were characterized. To investigate the internalization of the conjugate in cancer cells, the engineered HSA was labeled with fluorescein isothiocyanate, and the cellular uptake was determined by the flow cytometry and fluorescence microscopy. The cytotoxicity of the conjugate was assessed by the CellTiter-Blue® cell viability assay.

Results: The particle size of the engineered conjugates were in the nano range after modification. The particle size of the HSA-PBA conjugate was 151.64±30.00 nm with the polydispersity index (PDI) of 0.25 and the zeta potential of the HSA-PBA conjugate was 14.99±2.14 mV. The engineered conjugate HSA-PBA was taken up more efficiently and showed no significant difference in cytotoxicity compared with the unmodified HSA nanoparticles.

Conclusions: The excellent physicochemical properties, safety and promising in vitro data suggested that the HSA-PBA conjugate might hold great potential as a nanocarrier for intracellular drug delivery.

18. *In-utero* Exposure to e-Hookah Modulates Platelet Reactivity and Increases the Risk of Thrombotic Cardiovascular Disease

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Introduction: Cardiovascular disease (CVD) is well documented as the leading cause of death worldwide, with smoking being the most preventable cause. Indeed, most smokers die from thrombotic-based diseases, in which platelets play a major role. To this end, because of the proven harm of smoking, other novel tobacco products- including e-hookah- have been gaining popularity, especially amongst women of child-bearing age. This increase in usage is, in part, because of 'false safety claims'. While much is known regarding the thrombotic CVD health effects of smoking during pregnancy, virtually nothing known regarding e-hookah, which we investigated herein.

Methods: We employed a whole-body exposure model of e-hookah and exposed female mice one-week before mating and throughout the *in-utero* period, with experiments performed on the offspring once they have reached 10-12 weeks of age. Exposures took place seven times a week, according to the well-known Beirut protocol, whereas control mice were exposed to clean air. The Beirut exposure protocol- which has been employed in many studies as it mimics real-life scenarios- involves the delivery of 171 puffs of 530 ml volume of the e-liquid at 2.6s puff duration and 17s puff interval.

Results: Our results showed that in-utero e-hookah exposed mice had shortened bleeding and occlusion times when compared to the controls, which indicates a prothrombotic phenotype. Investigation of the mechanism underlying this phenotype showed that e-hookah exposed platelets had enhanced agonist-triggered aggregation. Also, flow cytometry analysis of surface proteins showed that integrin IIb-IIIa and P-selectin activation was also enhanced in the e-hookah exposed platelets, indicating hyperactivity.

Conclusion: Based on these results, we document, for the first time, that e-hookah does exert negative health

effects in the context of thrombosis-based CVD, in part, via promoting platelet hyperreactivity. Hence, e-hookah should not be considered a safe alternative to traditional cigarette smoking, especially in pregnancy.

19. MMP2-sensitive Carbon Nanotubes: Potential Nanocarriers for Tumor-targeted Drug Delivery

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Introduction: Discrete multiwalled carbon nanotubes (dMWCNTs) have been shown to deliver cargos such as small molecules, peptides, nucleic acids, etc. The purpose of this study is to engineer the dMWCNTs and develop a novel MMP2-sensitive CNT-based nanocarrier for tumor-targeted drug delivery.

Methods: The MMP2-sensitive copolymer, poly(ethylene glycol)-peptide (pp)-phosphoethanolamine (PEG-pp-PE) was used to modify the dMWCNTs. The modified dMWCNTs (dMWCNT/PEG-pp-PE) were characterized for their particle size and zeta potential. They were labeled with rhodamine-PE for studying the cellular uptake in cancer cells. Doxorubicin (DOX) was loaded into the dMWCNT/PEG-pp-PE nanoparticles and the drug release was investigated by a dialysis method. The cytotoxicity of the DOX-loaded dMWCNTs were evaluated.

Results: Modification of the dMWCNTs by PEG-pp-PE significantly decreased dMWCNTs' particle size, probably due to the improved self-assembly (folding) and nanoparticle stability. The DOX-loaded dMWCNT/PEG-pp-PE nanoparticles had a particle size of 125±30 nm. The DOX encapsulation efficiency in dMWCNT/PEG-pp-PE nanoparticles was around 75%. The DOX-loaded dMWCNT/PEG-pp-PE nanoparticles showed the prolonged drug release under the simulated "sink" condition. The cellular uptake of dMWCNT/PEG-pp-PE nanoparticles with the MMP2 pre-incubation was almost double than that without MMP2 pre-incubation. Finally, the DOX loaded dMWCNT/PEG-pp-PE nanoparticles showed higher toxicity in cancer cells than the unmodified dMWCNTs.

Conclusions: The excellent physicochemical properties, stability, MMP2 sensitivity, drug loading and release, and *in vitro* data suggest that the MMP2-sensitive dMWCNTs might be a promising nanocarrier for tumor-targeted drug delivery.

20. Computer-Aided Design, Synthesis, and Biological Screening of Novel Quinazolines as Selective Anti-Her2 and Angiogenesis Kinase-Targeted Breast Cancer Therapy

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Background: Breast cancer (BC) is one of the leading causes of cancer deaths among women, with an estimated 43,250 deaths reported in 2022. Angiogenesis, on the other hand, has piqued the interest of researchers as a critical target for treating various cancers. Quinazoline scaffolds, such as tucatinib, have a wide range of therapeutic applications, including potent targeting for HER2+ and the angiogenesis kinases pathways.

Approach: Inspired by the facts, we developed innovative structural optimization aided by computational design for potential selective anti-HER2+ agents beside anti-angiogenesis oncogenes. Proceeding to synthesize a quinazoline moiety that fits within the ATP binding site of the kinase domain, the hydrophobic group at position 4 extends into the back pocket for HER2 inhibition. It solubilizes the group at position six fits into the solvent-accessible region. The best candidates were then subjected to biological screening against HER2+BC and anti- angiogenesis cell lines (BT-474, HePG2respectively) and kinase profiling against 20 kinase.

Results: We performed a prospective molecular docking study on our novel entities, enabling the flexibility of the key residues (M801 and D863) before and after. Compared with the co-crystallized ligand, a small library (240 candidates) was docked into the target kinase (PDB: 3PP0). The best candidate exhibited two hydrogen bonds with these amino acid keys.

Unprecedented flexible scaffolds were synthesized to target the HER2 kinase to reveal high selectivity towards the aggressive HER2+BC. Our reported compounds revealed potent antiproliferative activities (IC50: 89nM & 64nM) against (BT-474 & HePG2, respectively). They also exhibited selective inhibition against HER2 & c-kit kinase (-79% to - 82%). This promotes us to conduct another computational study on angiogenesis kinase to optimize our hits.

Conclusion: We have successfully designed and synthesized the top computationally selected candidates with the highest scores of 4-quinazoline derivatives. Then structurally elucidated and biologically screened.

21. Epigenetic Regulation in Diabesity and Nonalcoholic Fatty Liver Disease: The Intricate Inherited Pathway

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The concomitancy of Diabesity and nonalcoholic fatty liver disease (NAFLD) brings forth a debilitating burden. NAFLD affects 35% of all adults in North America and well over 58% of obese adults. The global prevalence of NAFLD is projected to reach 56% by 2040. Furthermore, NAFLD globally afflicts approximately 53% of obese children and adolescents under the age of 21. Genetics and lifestyle have been the main factors considered for this rise; however, epigenetics describes that there is more to the story. By altering the organization of chromatin, epigenetics links how the environment can impact gene expression in a reversible and heritable manner. In our recent transgenerational study, we revealed the effects of a maternal high-fructose high fat diet (HF-HFD) on three subsequent generations. For three weeks prior to and throughout pregnancy, dams were fed either CD or HF-HFD totaling six weeks of treatment. All male breeders were only fed CD. The partitioned male and female litter then received either CD or HF-HFD for 20 weeks. Fascinatingly, several long noncoding RNAs (lncRNAs) were downregulated in the livers of all F1, F2, and F3 groups where the mother or offspring was fed HF-HFD compared to the CD fed groups. Two of these lncRNAs had never before been discovered in any metabolic diseases. Our lab was the first to discover one of these novel metabolically related lncRNA's role in obesity. Its downregulation was associated with metabolic perturbations including increased body weight, liver weight, and elevated fasting blood glucose levels. Alongside decreased lncRNA expression, histone modification regulators responsible for removing histone acetylation known as histone deacetylases, including sirtuins, were also significantly altered. We will now examine the role of this lncRNA in directing epigenetic mechanisms such as histone modifications in the contexts of Diabesity and NAFLD.

22. Physicochemical Characterization for Intramammary Infusion Products of Animals

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Introduction: Intramammary infusion veterinary products were introduced into clinical practice after FDA approval in 1975. The marketing exclusivity and patents of many of these products have expired which means generic products should be available to the American public. However, this is not the case for these products. This is due to difficulty in proving bioequivalence of locally acting generics with the reference products. For example, intramammary infusion products are locally acting products and minimally absorbed in the systemic circulation. It is difficult to measure blood concentration of the drug, typically done for systemically absorbed drugs. Pharmacodynamic and clinical approaches for bioequivalence comparison require testing on a large number of animals which is practically and ethically not feasible.2-4 However, there is a knowledge gap in understanding product quality and its correlation with clinical performance. This study will address these knowledge gaps and develop in-vitro quality matrix for intramammary infusion products. This will help FDA in formulating the policy and review of intramammary infusion products, which in turn results in availability of affordable drug products to the American public. Outcome of the study will be disseminated in the public domains with FDA participation so that industries and academics can use it with full confidence. It will also help develop regulatory pathways for long held drug products whose patents and exclusivity have expired.

Method: Two marketed veterinary intramammary products (Spectramast® LC and Spectramast DC®) were selected as representative products for this project. A full Characterization was performed for both of them, including particle size analyses, rheological properties investigations, Near Infra-Red (NIR) analysis, thermodynamic analysis, sedimentation rate experiments, and X-ray diffraction characterizations. Drug content was analyzed via a newly developed, validated High Performance Liquid Chromatography analysis (HPLC) to detect the main active ingredient (Ceftiofur HCl). The HPLC method was fully evaluated for three successive days. Moreover, Drug release was tested via pharmacopeial dissolution test. Design of experiment was adopted to formulate similar in-house formulations to investigate the interplay of materials attributes (active and inactive), manufacturing method and process variables on the product critical quality attributes.

Results: The average particle size for both marketed products and in-house formulations were around 12 micrometers across all products and in-house formulations. The rheological analyses showed that both marketed products and in-house formulations showed pseudo-plastic properties, suspension shear thinning system. The sedimentation rate was Characterization and comparable across the products. The HPLC method is reproducible and sensitive to detect Ceftiofur HCl across the three successive days.

Conclusion: The knowledge gained from this research can be used by the FDA reviewers in critically reviewing the submission of intramammary products. Intramammary infusion products are locally acting, and very complex formulations which require broad knowledge, and great effort to understand these products.

23. Microdialysis as a Biorelevant IVRT Technique for Complex Ophthalmic Products

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Introduction: Ophthalmic emulsions are considered as complex products due to the manufacturing process involved. Following topical administration of eye drops, dilution with the tears and rapid clearance from the eye necessitate appropriate methods that allow monitoring the drug release from the formulations as early as one minute up to several minutes. Traditional IVRT techniques have limitations in simulating in vivo conditions for testing drug release from topical ophthalmic formulations, but microdialysis is sensitive enough to detect drug release as early as one minute after topical administration. The technique was validated by studying drug release from different formulations of varying strengths and preparation methods and was found to be a powerful tool with high reproducibility and discriminatory ability for ophthalmic emulsions.

Methods: Drug release was investigated by microdialysis for different concentrations of DFBA (Difluprednate) ophthalmic emulsion formulations, including 0.05% (Rererence standard, F1 & F2=In house), 0.025% (F3), and 0.1% (F4) and a micellar formulation made using surfactant but no oil. Formulations were analyzed using microdialysis with HPLC-UV after preparation using high-pressure homogenization and microfluidization. Globule size distribution was measured with ZetaPals, and the Wilcoxon Rank Sum/Mann-Whitney rank test was used to compare between the formulations.

Results: F1 exhibited a similar drug release profile as Reference standard, while F2 showed a significantly different profile due to the variation in globular size distribution. Microdialysis was used to differentiate drug release from different strengths of the formulation, and the statistical analysis using Wilcoxon Rank Sum/Mann-Whitney rank test confirmed the sameness of DFBA 0.05% ophthalmic emulsions. The globular size distribution of the emulsion formulations was found to correlate with the drug release, with smaller globular size emulsion showing better release than the one with larger globular size.

Conclusion: Microdialysis is a biorelevant IVRT technique that can differentiate the formulations of different strengths and physicochemical characteristics and is a valuable tool for developing generic ophthalmic products in both industry and academia.

24. *In Vitro* and *In Vivo* Testing of 3D Printed Amorphous Lopinavir Printlets: Improved Bioavailability of a Poorly Soluble Drug

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Solubility and dissolution are the major hurdle in oral absorption of solid dosage forms. Many drugs fail to reach clinical stage due to this reason even though the molecules have favorable safety and efficacy profiles. Various approaches reported in the literature for solubility and dissolution enhancement, however, they may not result in an increase in dissolution of extremely insoluble drugs. Selecting amorphous form of the drug is another approach which results in increase of *in vitro* and *in vivo* dissolution rate and, oral bioavailability of poorly soluble drugs. However, amorphous form is not as stable compared to crystalline and requires stabilization by adding polymer to form amorphous solid dispersion (ASD). BCS class II and IV drugs are commercially available as ASDs. Hot-melt extrusion and spray drying are the most used manufacturing methods, and both are cumbersome processes. Lopinavir (LPV) is used in the treatment of HIV-1 and exhibits low oral bioavailability (~25%) due to extensive metabolism and poor dissolution.

Aim of this paper was to investigate effects of formulation parameters on physicochemical and pharmacokinetic (PK) behavior of amorphous printlets of lopinavir (LPV) manufactured by SLS. Formulation variables investigated were disintegrants (magnesium aluminum silicate 5-10%, microcrystalline cellulose 10-20%) and polymer (Kollicoat® IR 42-57%) while keeping printing parameters constant. Differential scanning calorimetry, X-ray powder diffraction and Fourier transformed infrared conformed transformation of crystalline drug into amorphous form. Direct correlation between disintegrant concentration and dissolution was found. Dissolved drug was 71.1±5.7 to 99.3±2.7% in 120 min. Comparative PK study in rabbits showed significant differences in rate and extent of absorption between printlets and compressed tablets. Tmax, Cmax and AUC were 4-folds faster, and 2.5 and 1.7 folds higher in the printlets compared to the compressed tablets, respectively. In conclusion, SLS printing method can be used in printing amorphous delivery system in a single continuous process.

25. Investigating a Suitable *In vitro* Release and Permeation Testing Method for Rectal Suppositories

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Introduction: Bioequivalence of the generic rectal suppositories are usually established by expensive and time-consuming clinical trials designed to obtain the PK endpoints. The development of an IVRT method for rectal suppositories that could establish bioequivalence of the formulations solely based on the formulation sameness, physiochemical characters, strength may help to enhance the approval process and patient access to the generic formulations. Currently there are no compendial assays for testing drug release from rectal suppositories. As a part of our continuous effort to develop IVRT assays and enhance access to the generic formulations, in the present investigation we have compared the release and permeation profiles of the mesalamine fat base suppositories.

Methods: In the present study, three different rectal suppository formulations of mesalamine (CANASA, Generic, and In-house) were studied for in vitro bioequivalence. Four different IVRT techniques such as Dialysis, Horizontal Ussing Chamber, Vertical Franz cell, and USP apparatus 4. IVPT studies were performed using Horizontal Ussing chamber and Vertical Franz cell methods. Q1/Q2 equivalent products (CANASA, Generic) and a half-strength product were studied to understand the reproducibility, bio relevance, and discriminatory ability of the IVRT and IVPT methods.

Results: The suitability of each method for comparison and QC of similar or different formulation was evaluated using the percent cumulative drug release (IVRT) and cumulative amount permeated (IVPT) over the period of four hours. Cumulative percent drug release of RLD, Generic, and In-house formulations using USP 4 were found to be 49.21±8.87%, 48.58±7.49%, 44.43±2.18% respectively ($n=6$; $p<0.01$). Flux (cm-2s-1) of RLD, Generic, and In-house formulations obtained from IVPT using Ussing cham-

ber were 77.165 ± 7.601, 55.93 ± 16.327, and 25.503 ± 11.374 respectively (n=3; p<0.01). Wilcoxon Rank Sum/Mann-Whitney rank test confirmed the sameness of RLD and generic rectal suppositories.

Conclusion: This study suggests that among the tested methods, the USP 4 method and Horizontal Ussing chamber methods were found to be suitable IVRT and IVPT techniques, respectfully, for rectal suppositories.

26. Discovery of Potent Abelson Kinase Inhibitors from the Scaffold of Pyrano[2,3-D] Pyrimidin-7-One

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Background: The pyrido[2,3-d]pyrimidin-7-one is a so-called privileged heterocyclic scaffold scaffold for the discovery of protein kinase inhibitors. Drug- or drug-candidates derived from this scaffold include the CDK4/6 inhibitor Palbociclib from Pfizer, the p-38 MAP kinase Dilmapimod from GlaxoSmithKline, and experimental drug PD173955 from Parke-Davis. In comparison with the pyrido[2,3-d]pyrimidin-7-one scaffold (I), we invented the scaffold pyrano[2,3-d] pyrimidin-7-one (II), which is structurally analogous to pyrido[2,3-d]pyrimidin-7-one. This novel scaffold has not been extensively studied in synthetic chemistry and pharmacology. The compound PD173955 is a potent ABL kinases inhibitor from the scaffold pyrido[2,3-d]pyrimidin-7-one (I) by Parke-Davis. The Abelson (ABL) family of protein kinases comprise ABL1 and ABL2, which link diverse extracellular stimuli to signaling pathways that control cell growth, survival, invasion, adhesion and migration. To discover novel ABL inhibitors, we investigated the scaffold pyrano[2,3-d]pyrimidin-7-one (II).

Method: The synthesis of pyrido[2,3-d]pyrimidine-7-one (I) typically requires expensive starting materials that contains a pyrimidine ring and involves a lengthy synthesis and burdensome workup to build the pyridopyrimidinone core. We used inexpensive and readily obtained starting material methyl coumalate and 2-methylisothiouroniumsulfate synthesized the pyrido[2,3-d]pyrimidin-7-one scaffold (I) in two steps. The compound LDK 1504 generated from this scaffold is a close analog of PD173955. The preparation of this class of compounds was achieved through a facile synthesis of 2-(methylthio)-7H-pyrano[2,3-d]pyrimidin-7-one followed by Suzuki coupling reaction and derivatization of the C-2 position of the pyrimidine ring.

Result: In the enzymatic assays, compound LDK1504 was demonstrated with a binding affinity (Kd =3.3 nM) comparable to PD173955 (Kd = 0.58 nM) for ABL1 kinase. It can inhibit the ABL1 kinase with an IC50 of 18.7 nM. Further optimization of LDK1504 led to the identification of an inhibitor LDK1512 (Kd = 0.38 nM; IC50 = 1.27 nM) against ABL1.

Conclusion: Pyrano[2,3-d]pyrimidin-7-one (II) is a viable scaffold for potent ABL1 inhibitors.

27. Inequalities of Race and Region for in-Hospital Death Among Patients with 2019 Novel Coronavirus Disease (COVID-19): Evidence from National Inpatient Sample (NIS) of 2020

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Introduction: Based on the racial and regional inequalities regarding COVID-19, more research is required to deconstruct how the pandemic impacted different populations. This study aims to explore differences in COVID-19 in-hospital mortality rates by patient and hospital factors.

Methods: The 2020 United States National Inpatient Sample (NIS) collected the study's data. All samples were obtained by the International Classification of Disease, 10th version (ICD-10) codes, and sampling weights were used for all statistical analyses (total n=200,531, national estimate = 1,002,655). Patient factors include differences in mortality by anthropometric information, and hospital factors include differences in mortality by rurality level, region, and census division. Multivariate logistic regression analysis was used to examine the association between COVID-19 and some characteristics (*e.g.*, age, region, and race), and subgroup analysis was conducted by race.

Results: 88.9% did not have an in-hospital death (n=178,369), and 11.1% died inhospital (n=22,162). Patients over 70 years old were 10 times more likely to have an in-hospital death than patients younger than

40 years old (p<0.001). Males were 37% more likely to have an in-hospital death than females (p<0.001). Hispanic were 25% more likely to have in-hospital deaths than white (p<0.001). The highest significantly increased mortality odds were in the Middle Atlantic and Pacific. In the sub-analysis, Hispanics over 50 years old were more likely to die in-hospital than white (p<0.001). Also, patients with dementia or diabetes were 47% and 69%, respectively, more likely to have an in-hospital death than those not.

Conclusion: Health disparities in the COVID-19 pandemic occurred across races and regions and must be addressed to prevent future deaths. Age and comorbidities like dementia and diabetes have increased disease severity and mortality risk. Hispanic patients were at increased odds of mortality because of age and economics.

28. Investigation of the Impact of Thirdhand E-Cigarette Exposure on Platelet Function

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The use of e-cigarettes (ECs) has been on the rise, achieving unprecedented levels due to the misconception of their safety. Thus, there have been efforts to characterize the effects of direct EC exposure on cardiovascular disease (CVD), which is the leading cause of death worldwide. To this end, we previously showed that direct EC exposure increases the risk of thrombotic CVD, via modulating platelet function. Interestingly, there is evidence that ECs are a source of thirdhand exposure (THEC) to toxicants "within" their vapor that deposit on surfaces, *e.g.*, upholstery and carpet. However, nothing is known regarding THEC impact on thrombotic CVD, which we sought to characterize herein. We devised a mouse THEC exposure protocol that resembles real life scenarios in which common household materials are exposed to EC vapor or clean air, before being placed in cages for mice to live within for a four month period. We first validated our model by showing that the levels of the nicotine marker, cotinine, are elevated in the THEC mice, but undetectable in the clean air group. Next, our *in vivo* characterization demonstrated that THEC exposed mice exhibited a prothrombotic phenotype reflected by their shortened tail bleeding and occlusion times; measured by the tail bleeding and $FeCl_3$ thrombosis models, respectively. Importantly, we found no difference in the platelet counts between the THEC and clean air mice. As for the underlying mechanism, separate experiments revealed enhanced platelet aggregation and dense granule secretion in response to agonist stimulation.

Moreover, flow cytometry showed enhanced alpha granule/P-selectin secretion, integrin/GPIIb- IIIa activation and phosphatidylserine exposure. Interestingly, we also found platelet spreading to be enhanced, suggesting that THEC also modulates platelet outside-in signaling. Taken together, these studies support the notion that THEC is detrimental to cardiovascular health, which should increase awareness of its "forgotten/ignored" danger to innocent non-EC users.

29. Caspase-11 and NLRP3 Mediate Klebsiella Pulmonary Infection through Regulating Pulmonary Bacterial Burden

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Gram-negative bacterium *Klebsiella pneumoniae* is the third most commonly isolated microorganism in blood cultures from sepsis patients and can cause serious epidemics and endemic nosocomial infections. Despite intensive investigation, the pathogenesis and mechanism of *K. pneumoniae*-induced sepsis remains elusive. Here using an intraperitoneal injection sepsis model, we found that *K. pneumoniae* is more lethal to mice than Pseudomonas aeruginosa or Salmonella typhimurium, while the latter caused more severe disseminated intravascular coagulation (DIC) and systemic inflammation. In contrast, *K. pneumonia* induced more severe lung injury than *P. aeruginosa* or *S. typhimurium,* as indicated by decreased oxygen saturation levels (SpO_2). The bacterial load in key organs of *K. pneumoniae*-infected mice, especially in the lung, was higher than that in *S. typhimurium* treated mice under similar experimental conditions. Lung tissue pro-inflammatory cytokine levels were also higher in *K. pneumoniae* infection. *K. pneumoniae* was found to accumulate preferentially in the lung, causing a high level of IL-6 in lung tissues. In the absence of caspase-11 or NLRP3, the pulmonary bacte-

rial burden reduced, the SpO_2 levels recovered, and the pulmonary IL-6 level decreased compared to the WT counterparts. Accordingly, caspase-11 or NLRP3 deficient mice were less susceptible to *K. pneumonia* infection. Our data suggest that the acute respiratory failure along with the release of cytokine IL-6 due to high pulmonary bacterial burden is the main cause leading to the death following *K. pneumoniae* infection, which is mediated by caspase-11 and NLRP3.

30. Alterations in the Platelets Transcriptome Underlie Prenatal THS-Exposure Associated Thrombogenicity

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Cigarette smoking is the most preventable risk factor for thrombogenesis-associated disease. To this end, we have previously shown that even when the exposure is indirect, namely thirdhand (THS) in nature, and occurs under prenatal settings, the offspring mice exhibit a higher tendency to develop occlusive thrombosis, through enhancement of several platelet activation functional responses/markers. However, the mechanism underlying prenatal THS-associated prothrombotic phenotype is unknown. In this study, we demonstrated an altered platelet gene expression profile in the prenatal THS exposed mice that is linked to platelet functional responses. Moreover, RNA seq analysis for both mRNA and small RNA revealed distinct changes in both gene expression and microRNA profiles of their circulating platelets. Indeed, 517 coding genes showed significantly altered expression between the two exposure groups, which were accompanied with a concurrent alteration in platelet microRNA profile. In fact, 18 microRNA were found to be differentially expressed between the two groups. Using the same population platelets for generating both mRNA and small RNA libraries for sequencing guaranteed the temporal and spatial co-localization of mRNA and miRNA that's required for the integrative microRNA-miRNA analysis proposed for identification of gene regulatory networks involving miRNA-mRNA pairs. This integrated analysis highlighted 14 of our differentially expressed miRNAs that potentially target 120 of the 517 differentially expressed coding genes in our sequencing dataset. Additionally, the significantly altered coding genes that are potentially targeted by miRNAs that are already altered in the same dataset were functionally enriched into signaling pathways associated with platelet biology, including platelet activation, platelet signaling and aggregation, platelet degranulation, integrin-mediated cell adhesion and cellular response to chemical stimulus. Collectively, we establish that prenatal exposure to THS significantly modifies the platelet transcriptome, prompting elevated functional activation responses that may contribute to THS related thrombogenicity.

31. The role of Metal-responsive Transcription Factor-1 (MTF-1) in Cadmium-Induced Prostate Carcinogenesis

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Background: Cadmium (Cd) is a human carcinogen, and chronic exposure to Cd is a risk factor for transforming non-malignant benign prostate hyperplasia (BPH) into prostate cancer. The incidence of BPH occurs in men starting at 40 years of age, and it progresses by 10% per decade. Earlier, we reported that chronic exposure to Cd activates Zic family member-2 (ZIC2) transcription factor and results in the transformation of BPH cells. However, how Cd activates ZIC2 expression has yet to be delineated; hence, the study aims to dissect the mechanism by which this transcription factor is activated during the transformation of BPH cells.

Methods: The transformation of BPH1 cells was done by exposing Cd (10μM) for 12 months. To understand the mechanism by which Cd induces ZIC2, we performed the phenotypic and molecular analysis in BPH1 cells.

Results: We performed several knock-in and knockout studies to obtain mechanistic insights into how Cd activates ZIC2 signaling in BPH1 cells. We found that the induction of metal response element-binding transcription factor-1 (MTF-1) was responsible for ZIC2 activation in Cd-exposed BPH1 cells. While silencing of MTF-1 expression inhibited ZIC2 expression and its stem cell function in transformed BPH1 cells. We also confirmed that knocking out ZIC2 expression did not alter MTF-1 expression in BPH1 or Cd-exposed BPH1 cells suggesting MTF1 lies upstream of ZIC2

signaling. To confirm these results, we overexpressed MTF-1 in normal BPH1 cells and saw an induction of ZIC2, as well as other stem cell markers, such as ALDH1A1 and CD44. Similarly, MTF-1 overexpressed cells exhibit a malignant phenotype by forming organoids in the culture and induced pro-survival signaling, which mimics malignant prostate cancer. Finally, we identified MTF-1 binding sites in the ZIC2 promoter, and sequentially deleting MTF-1 binding sites in the ZIC2 promoter diminished ZIC2 activation in transformed cells. Currently, we determine whether the knockdown of MTF-1 in BPH1-transformed cells forms a tumor in xenograft models.

Conclusion: Altogether, our results suggest that MTF1 plays an oncogenic role and is responsible for ZIC2 mediated transformation of Cd-induced prostate cancer.

32. MiRNA-17 Therapeutics for Preeclampsia

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Preeclampsia (PE) is the leading cause of maternal, fetal, and neonatal mortality. Most of the existing biomarkers focus on late gestation or lack sufficient sensitivity or specificity for earlier detection. A successful intervention will require better understanding of disease progression and development of accurate, early biomarkers that appear before clinical symptoms. In a case-control study of healthy and PE women's first trimester blood, we identified several epigenetic biomarkers including DNA methylation, histone modification, and microRNA. To decipher the explicit mechanism of how microRNA regulates PE pathogenesis, we chose to characterize the function of miR-17-5p in placental development. First, we investigated the effect of miR-17-5p on cell invasion through 3D matrix assays. We discovered that a miR-17-5p mimic significantly inhibits human umbilical vein endothelial cells (HUVECs) migration, while a miR-17-5p inhibitor promotes it. We further overexpressed miR-17-5p in the trophoblast layer of blastocysts (E2.5) via lentivirus infection and evaluated the placenta at E16.5. Consistently, we observed severe defects in angiogenesis and other PE-related complications, including placental hemorrhage. To elucidate potential targets of miR-17-5p, we performed RNA-seq analysis in miR-17-5p mimic-transfected and single-cell sequencing analysis in invading and noninvading HUVECs. The results of both analysis were combined to narrow down a list of common genes that are potentially associated with cell invasion, cytoskeletal destabilization, and angiogenesis. We subsequently validated the gene expressions in full-term placenta from PE patients and miR-17-5p overexpressed mouse placenta. In conclusion, miR-17-5p is a predictive marker of PE, and it regulates PE pathogenesis through targeting epigenetic regulations which are essential in placenta development. Future efforts targeting miR-17 inhibition during early pregnancy can provide therapeutic potential for treating PE.

33. Differential Expression of Long Non-coding RNA DLEU2 in Siblings Influence Hepatic Insulin Signaling and Lipogenesis Program in a Murine Transgenerational Study

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Altered parental metabolic state is associated with prevalence of metabolic syndrome in subsequent generation and among siblings. While several elements contribute to this diseased state, epigenetic transmission modulated via non-coding RNAs may be attributed as one of the underlying factors. We recently identified a long non-coding RNA, DLEU2 (deleted in leukemia), whose hepatic expression is downregulated in offspring when the F0 mothers are fed on obesogenic diet during pregnancy and lactation. Herein, we hypothesize that in utero dietary stress in F0 pregnant mothers may impact the hepatic function of siblings in F2 and F2'generation via DLEU2. Female C57Bl/6 mice (F0 mother) were maintained on either chow-diet (CD) or high-fat high-fructose diet (HF-HFD) during pregnancy and lactation. Pups (F1) obtained from above groups were bred. Resulting pups

(F2) from first breeding and siblings (F2') obtained from second breeding were maintained on CD or HF-HFD for 20 weeks. Differential expression of pathways regulating hepatic lipogenesis and insulin signaling were correlated with DLEU2 levels in F2/F2' siblings and further investigated for DLEU2-dependent mechanistic link using AML-12 cells. Enlarged liver weights were observed under both CD and HFHFD groups of F2' siblings originating from the F0-HFHFD mother but not in the F2 mice. DLEU2 levels negatively correlated with liver weights and was only downregulated in F2' mice from the F0-HFHFD group. Decrease in mRNA transcripts related to insulin signaling and increase in lipogenesis markers directed towards hepatic dysfunction in F2' siblings but not in the F2 mice. Similar changes were observed in AML-12 cells upon silencing DLEU2 confirming that the altered hepatic function observed in F2' siblings are DLEU2-dependent. Our transgenerational sibling study suggests that perturbations rising from in utero dietary stress can alter hepatic DLEU2 expression and potentially lead to hepatic dysfunction by affecting insulin and lipogenesis pathways in a sibling-specific manner.

34. Hyaluronic Acid Targeted Multi-Walled Carbon Nanotubes for Efficient Colon Cancer Targeting

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Introduction: The purpose of the present research was to evaluate *in vitro* and *in vivo* potential of gemcitabine (GEM) loaded hyaluronic acid (HA) conjugated multi-walled carbon nanotubes (GEM/HAPEG-MWCNTs) for effective colon cancer targeting.

Methods: HA was conjugated onto the surface of aminated or PEGylated MWCNTs which were evaluated for size, surface morphology, entrapment efficiency (~ 90%), in vitro drug release, in vitro cytotoxicity, and in vivo performance in Sprague Dawley rats.

Results: *In vitro* release showed that the release rate of GEM in acidic conditions (pH 5.3) was faster than in physiological conditions (PBS, pH 7.4) followed by a sustained release pattern. The developed GEM/HA-PEG-MWCNTs indicated significantly less hemolytic toxicity (7.73± 0.4%) paralleled to free GEM (18.71±0.44%) and showed higher cytotoxicity against HT-29 colon cancer cell line. The antitumor study assured that GEM/HAPEG-MWCNTs significantly reduced tumor volume as compared to free GEM and increased survival rate without noticeable loss in body weight. *In vivo* studies showed an improvement in pharmacokinetics in terms of remarkable escalation in mean residence time, half-life, AUC, AUMC, and median survival time in tumor-bearing mice treated with GEM/HA-MWCNTs and GEM/HA-PEG-MWCNTs as compared to free GEM ($p<0.001$).

Conclusion: The outcomes proved engineered MWCNTs as a safe and effective nanomedicine in colon cancer targeting.

35. Novel Anti-VEGFR2 Potentiates Sorafenib's Antiangiogenic Effects on Hepatocellular Carcinoma: Implications for Clinical Translation

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Background: VEGFR2 plays a crucial role in the development and progression of hepatocellular carcinoma (HCC). Inhibitors of VEGFR2, such as sorafenib and lenvatinib, have been developed as targeted therapies; however, prognostic outcomes are still poor. We have developed 20 novel pyrrolotriazines, where compounds HA31 and HA32 revealed promising VEGFR2 inhibition (IC50: 0.72-1.3 nM) compared to sorafenib (IC50: 68 nM). Our compounds significantly blocked basal and VEGF-induced tube formation.

Methods: The most effective anti-VEGFR2 inhibitor HA31 was evaluated using in-vitro assays in comparison with sorafenib (SOR). For in-vivo evaluation, 40 SCID/Beige mice were divided into 4-groups (n=10), where 6 from each group were injected subcutaneously with 2.1x106 HepG2WT cells and another 4

with 2x106 HepG2Luc cells for live imaging. The drug treatment was initiated following two weeks of injection (tumor size ~200 mm2). The tumor volume was measured weekly and calculated via ellipsoid formula (V = 1/2 (Length x Width2). The live imaging was conducted using IVIS system following 10 minutes of luciferin I.P. injection (75 mg/kg).

Results: Compound HA31 significantly decreased the expression of VEGFR2 ($p < 0.001$) compared to sorafenib. In-vivo assays revealed that both SOR and HA31 significantly inhibited growth of HepG2WT HCC tumor xenografts (SOR = 72.5%, HA31 = 69.2%; $p < 0.01$); however, the combinational therapy group was most effective, suppressing tumor growth to more than a half compared to the negative control (SOR+HA31 = 41.8%, $p < 0.01$) and both the SOR and HA31 treatment alone. Significantly, there was no noticeable weight reduction (toxicity) observed. The in-vivo imaging from HepG2Luc groups reflected the same pattern, and no metastasis was observed.

Conclusion: HA31 has the potential to be a highly effective therapeutic agent alone, or in combination with sorafenib, to synergistically enhance its anti-angiogenic effects. These findings provide a compelling rationale for conducting clinical studies on HCC patients.

36. A QbD Approach for Evaluating the Effect of Formulation and Printing Variables on Critical Quality Attributes of Printlets rinted by Selective Laser Sintering

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Purpose: 3D printing is one of the promising techniques for printing personalized medications. Selective laser sintering (SLS), is one of the printing methods, has not been explored significantly in pharmaceuticals field. The aim of this work was to study the effect of formulation and process variables on the properties of 3D printed printlets using design of experiment methodology. Clindamycin palmitate hydrochloride (CPH) was used as a model drug.

Methods: The process and formulation parameters were selected based on results of preliminary work. CPH, Kollidon VA 64 polymer, laser absorbent were mixed with different concentration of lactose monohydrate (LMH, 5-10%) and microcrystalline cellulose (MCC, 5-10%), and printed at laser scanning speed of 200-300 mm/s. The tablets were characterized for physicochemical properties (FTIR, DSC and XRD), drug distribution (NIR-chemical imaging) and surface morphology (scanning electron microscopy, SEM) and porosity (X-ray micro-CT scanning). Hardness, disintegration time (DT), dissolution were tested for performance evaluation.

Results: Hardness, DT and dissolution of the printlets ranged from 7-18N, < 5 minutes, and >80% in 30 min, respectively. The laser scanning speed and MCC concentration showed statistically significant ($p<0.05$) effects on hardness, DT and dissolution of the printlets. No change in FTIR spectra were observed that indicated no chemical interactions between the components of the formulation before or after printing. XRD and DSC indicated a decrease in crystallinity of the LMH in the printlets due to melting during the printing process. NIR- chemical images showed uniform distribution of the drug. SEM and X-ray micro-CT scanning showed an increase in porosity from 24% to 31% by increasing laser scanning speed from 200 to 300 mm/s.

Conclusion: SLS method provide another method of printing dosage forms. The process and formulation variables have significant effect on the quality attributes of printlets. The printlets of target quality attributes can be printed by understanding the variables.

37. Synthesis of Aza-Baccatin III for Semi-Synthesis of Aqueous Soluble Analogs of Paclitaxel

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Background: Paclitaxel, an antimicrotubule agent exhibits remarkable antineoplastic effects in a variety of human cancers including advanced ovarian and breast cancer, small-cell and non-small cell lung cancer, head and neck cancers, and in metastatic melanoma. However, the drug molecule has extremely poor aqueous solubility (4 μg/mL), which hampered its clinical application. Paclitaxel was proved by FDA and marketed as Taxol, which is formulated as a concentrated solution containing 6 mg of paclitaxel per milliliter of Cremo-

phor EL (polyoxyethylated castor oil) and dehydrated alcohol (50% v/v). The formulation agent Cremophor EL has been linked to several side effects including vasodilatation, dyspnea, hypotension, and serious hypersensitivity in humans. In addition, Cremophor EL, a surfactant, is known to leach phthalate plasticizers such as di(2-ethylhexyl)phthalate (DEHP) from the polyvinylchloride bags and intravenous administration tubing. These liabilities have led to higher costs and unwanted side effects when the drug is applied in clinical settings.

Method: To increase the solubility of paclitaxel, tremendous efforts have been made to synthesize prodrugs of paclitaxel by introducing solubilizing moieties such as succinate, sulfonic acid, amino acids, and phosphates at the 2'-hydroxyl or at the 7-hydroxyl position. To develop new paclitaxel analogs aiming at enhancing solubility of this class of drugs, we designed and synthesized a group of aza-baccatin III for semi-synthesis of aza-paclitaxel with the goal of increasing the solubility and maintaining anticancer effects of this class of compounds. In 1995, K. C. Nicoloau reported a seven-step synthetic route from 10-DAB to the key intermediate aza-bacctin III, which involved the nucleophilic opening of 1,2-cyclic carbonate with pyridinyl lithium. Considering the functional group incompatibility during in situ generation of substituted pyridinyl lithium with n-BuLi even under -78oC, we designed and developed a six-step strategy from 10-DAB to a series of aza-baccatins. **Results:** In this route, the DCC-DMAP mediated ester coupling was utilized to synthesize the key nicotinate from the pan-triethylsilylated precursor. Finally selective protecting of the C-7 hydroxy group led to the aza-baccatin III in overall 15% yield.

Conclusion: The developed aza-baccatins can be easily scale up and will be utilized in the synthesis of paclitaxel analogs with significantly improved aqueous solubility.

38. High Fat-High Fructose Diet Elicits Brown Adipocyte Dysfunction by Blocking miRNA Biogenesis Machinery via miR-103

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Department of Pharmaceutical Sciences

**Equal contribution*

Obesity is a global public health concern, with its prevalence on the rise in many countries worldwide. The Western diet is a prominent contributing factor to metabolic dysregulation, which precedes the obesity epidemic. Recent evidence emphasizes the essential role of adipose tissue, including brown adipose tissue (BAT), in regulating whole-body metabolism. BAT is unique in its ability to dissipate energy as heat and maintain thermogenesis. However, the explicit mechanism through which BAT regulates energy balance is still unknown. Here, we hypothesized that miRNA biogenesis machinery may play a significant role in the regulation of BAT function under the influence of Western diets. Mice were fed on Low fat diet (LFD) and High fat-high fructose diet (HFHFD) for 4, 12, and 20 weeks. We observed a significant increase in BAT weight and beiging as well as elevated miR-103-3p expression, with long-term HFHFD feeding. Interestingly, miR-103-3p has a seed sequence within Dicer, a miRNA biogenesis machinery biomarkers. Dicer and TRBP2 showed significant upregulation at 4 weeks with a concomitant decrease in transcriptional and translational level at 12 and 20 weeks of HFHFD. We further showed a significant decrease in thermogenesis via UCP1 and PGC1α with a significant increase in Bax / Bcl-2 ratio, an apoptosis marker, with 12 weeks of HFHFD feeding. To confirm the mechanistic connection, we performed an in vitro miR-103 knockdown in T37i brown adipocyte cells. Our findings revealed that miR-103 knockdown leads to an increased Dicer and TRBP2 gene expression, however only Dicer protein showed a significant increase. Based on this we concluded that, high fat-high fructose diet may elicit brown adipocyte dysfunction by inhibiting Dicer via miR-103. Further investigation into the role of miRNA or miRNA biogenesis machinery in BAT dysfunction can pave way for the development of novel therapeutics strategies to address metabolic complications linked to obesity.

39. Chronic Arsenic Exposure Epigenetically Regulates the Transformation of Healthy Bladder Epithelial Cells to Malignancy

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Background: Arsenic (As) in drinking water and polluted environment has been linked with an increased risk of Bladder Cancer (BC). Recent studies suggested that epigenetic changes, particularly in microRNA (miRNA) regulation, play a significant role in As-induced bladder carcinogenesis. Hence, to understand the landscape of epigenetic events in As-induced bladder carcinogenesis, we selected telomerase reverse transcriptase immortalized normal bladder epithelial cell line (TRT-HU1) and physiological concentration of As for our preclinical experiments.

Methods: Arsenic (250nM) was exposed to TRT-HU1 cells for a year, and once we confirmed the malignant transformation in in vivo models, we selected 6- and 12-month As-exposed cells for small RNA seq analysis. The significantly altered miRNAs were selected and validated by qRT-PCR. Further, we analyze the significantly downregulated miRNAs function by *in vitro* models conducting phenotypic (sphere formation, proliferation, migration, and invasion) and molecular analysis in transforming and As-transformed bladder epithelial cells.

Results: Differential small RNA expression analysis revealed that a total of 87 miRNAs in 6 months and 97 miRNAs in 12 months (log2FC>1 and log2FC<-1, padj <0.05) were changed in As-exposed cells compared to vehicle-treated TRT-HU1 cells with the same time point. Further, we selected the significantly downregulated three miRNAs (miR-181, miR-361, and miR-629) compared to vehicle-treated cells and validated by Real-time PCR analysis. The pathway analysis predicted the downregulation of miR-181, miR-361, and miR-629 expressions responsible for enriching stem cell activation during the transformation. To confirm these results, we ectopically overexpressed these three miRNAs individually in transformed cells that inhibited the transfected cell's growth by downregulating the expression of stem cell activators ALDHA1A1 and OCT4. Further, in miRNA-transfected cells, we have seen the inhibition of invasion and migration and downregulation of metastatic markers signifying the role of these three miRNAs as As-induced bladder carcinogenesis.

Conclusion: Our studies suggest that As-exposure epigenetically regulates miRNA function, which results in healthy bladder epithelial cells to malignant transformation. Our ongoing *in vivo* results may validate our *in vitro* findings.

40. Cadmium-induced NF-kB Regulates Defective Autophagy and Transforms Healthy Prostate Epithelial Cells into Malignancy

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Department of Pharmaceutical Sciences

Background: Activation of Nuclear factor Kappa-B (NF-kB) is responsible for the induction of inflammation, a prime reason for cancer pathogenesis. Earlier, we demonstrated that chronic cadmium (cd) exposure transforms healthy prostate epithelial cells into malignant prostate cancer. We observed the induction of NF-kB activation and an autophagy-regulating gene, Plac-8 (Placenta specific 8), during the transformation of prostate epithelial cells. Hence, the goal of the study is to understand the molecular interplay between NF-kB and Plac8 and in what way this interaction facilitates the transformation in Cd-exposed prostate cells.

Method: To examine the molecular interaction between NF-kB and Plac8, we performed overexpression and silencing studies in normal prostate epithelial cells (RWPE-1) and transformed cells (CTPE). In addition, we performed phenotypic and molecular analysis, including promoter-based studies, western blot, and in vivo analysis to determine the interaction between Plac8 and NF-kB in Cd-exposed prostate epithelial cells.

Results: Chronic exposure of Cd (10uM) transformed healthy prostate epithelial cells (RWPE-1) into malignant on both cell culture and mice models. In addition, NF-kB activation and Plac-8 gradually increased during the transformation. Further, our results confirmed that Cd- exposure shuttles NF-kB to the nucleus, and a gradual increase in nuclear accumulation of NF-kB was seen during the transformation. Silencing NF-kB activation either by genetic

approaches or pharmacological inhibitors downregulated Plac8 expression and its survival function of transformed cells. We found NF-kB binding sites in the PLAC8 promoter, and mutating those binding sites inhibited Plac8 activation in Cd-exposed prostate cells. These results suggested that NF-kB lies upstream of Plac8 and may regulate Plac8 expression and function in Cd-exposed cells. Finally, we confirmed that silencing either NF-kB or PLAC8 inhibited autophagy and survival signaling in transformed cells, which resulted in the abrogation of tumor growth in either silenced p65 or PLAC8 xenograft models.

Conclusion: Our results suggest that NF-kB regulates Plac8 function, a critical determinant for transforming Cd-exposed prostate epithelial cells. Plac8 could be a novel molecular biomarker to detect Cd-exposure and a possible indicator for the development of prostate cancer.

41. Targeting Epigenetic Machinery, a Promising Therapeutic Approach for Muscle-invasive Bladder Cancer

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Background: Muscle-invasive Bladder Cancer (MIBC) accounts for approximately 20% of all urothelial bladder carcinomas (UBC) at diagnosis. Patients with non-muscle invasive Bladder Cancer (NMIBC) at the time of diagnosis also progress to MIBC over time, which remains a challenge to treat with current treatment regimens. Though it has been established that epigenetic mechanisms contribute to MIBC progression, the underlying mechanisms are yet to be delineated. Here, we identified that the methylation status of RNA Binding Protein, CPEB1 (Cytoplasmic Polyadenylation Element Binding Protein1), regulates the MIBC cell growth.

Methods: To investigate the methylation status of CPEB1, we performed a meta-analysis with Shiny Methylation Analysis Resource Tool (SMART). Further, functional role of CPEB1, we performed the phenotypic and molecular analysis in MIBC cells.

Results: Using the publicly available clinical database, we identified a CGI (CpG Island) methylator phenotype in the subset of bladder cancer samples. More importantly, CPEB1 was hypermethylated across all bladder cancer samples compared to the normal tissue. As a result, CPEB1 expression was significantly downregulated ($P<0.0001$) in BC patients. We performed IHC and RT-PCR analysis to validate our results, confirming CPEB1 downregulated in our MIBC patient cohort specimens. To restore the CPEB1 function, we treated MIBC cells with hypomethylating agent 5-aza-2'-deoxycytidine (5-AZ), which upregulated CPEB1 expression and inhibited MIBC cell growth. Further, CPEB1 overexpression in MIBC cells mimicked the 5-AZ effect on growth inhibition by inducing apoptosis in MIBC cells. We also identified that restoration of CPEB-1 activates its downstream activators (ex: p27/Kip1) thereby abrogating the growth of MIBC cells.

Conclusion: Our data suggest that epigenetic silencing of CPEB1 is a critical determinant of MIBC progression and restoring CPEB1 function can impede the growth of MIBC. We are currently screening a library of over 20,000 small molecules which potentially restore the CPEB1 function and inhibit the growth of MIBC.

42. Saving Babies in the Heart of Texas: An Interdisciplinary Translational Approach

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Birth defects are the leading cause of infant mortality across the nation. In Texas between 2011 and 2017, over 5000 babies born with birth defects died before their first birthday; tragically, the rate of death of African American or Hispanic babies was higher than Caucasian babies. Studies have examined the relationship between infant mortality, race/ethnicity, and social stressors, but none have integrated a biological pathway, specifically, non-coding RNA such as microRNA. We aim to fill this gap by investigating the mortality among Texan infants with three selected birth defects to correlate them against social stressors as well as the demographics of the mother and the baby. Our proposed study encompasses a holistic society-to-genes

approach to assess the influence of microRNA by collecting saliva samples from babies born with the selected birth defects and their mothers. We will measure the longitudinal microRNA expression pattern and compare them with social stressors to produce an epigenetic score. In a pilot epidemiological analysis from the birth defect dataset in Texas, we have observed a significant association 1) between proximity to the border and infant death among minority subjects and 2) between the type of birth defect and infant death regardless of geography. We created interview questions and a survey instrument to assess stress levels and quality of life in participant communities. Moreover, we are currently conducting a pilot study to compare two commercially available saliva collection kits for babies to evaluate which is more effective. This will help us to successfully conduct our primary study for vulnerable babies born with birth defects by achieving significant quality and quantity of microRNA. In short, our project will fill the pressing, unmet public health needs to develop appropriate screenings and educational tools that facilitate this multi-pronged approach to reduce mortality among babies born with birth defects.

43. IKK-specific Inhibitors Block Platelet Activation Mediated by GPVI in an IKKβ-independent Manner

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Introduction: NF-κB and its regulator IKK are important in gene expression. Despite lacking genomic DNA, platelets possess both NF-κB and IKK. Researchers have reported that NF-κB is activated when platelets are stimulated, which triggered research for a non-genomic function for NF-κB/IKK. Although many investigators have observed that IKK activity is vital for the activation of platelets, others have reported contradictory results, leaving its role inconclusive. This prompted us to investigate the role of IKK in platelets.

Methods: We used mouse platelets to test different IKK inhibitors and the IKK conditional knockout. Platelets were activated by collagen, convulxin, collagen-related peptide (CRP), ADP or thrombin in the presence or absence of the inhibitors. Secretion, aggregation and calcium mobilization were determined by flow cytometry, whereas the phosphorylation of specific proteins by Western Blot.

Results: Our results showed that the IKK inhibitors did inhibit platelet aggregation, secretion and integrin activation by CRP and convulxin, but not by other agonists, suggesting that IKK is important for GPVI signaling. However, much to our surprise, platelets derived from the IKK conditional knockout didn't exhibit differences relative to the wild type. Thus, when we investigated the mechanism of inhibition, we found that the effects of IKK inhibitors on platelets are independent of the IKK protein through a yet unknown mechanism.

Conclusion: It appears that IKK has no apparent role in platelet activation, as the capacity of the aforementioned inhibitors to modulate platelet activation through GPVI stimulation was unrelated to IKK. Researchers should utilize these IKK inhibitors, since they appear to have significant off-target effects. However, our results don't rule out a potential role of IKK in other platelet functions (e.g., immune response), nor do they discard a possible role of IKKα.

44. A Systematic Survey of Reversibly Covalent Dipeptidyl Inhibitors of the SARSCoV- 2 Main Protease

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Introduction: SARS-CoV-2 is the coronavirus pathogen of the current COVID-19 pandemic. It relies on its main protease (M Pro) for replication and pathogenesis. M Pro is a validated target that has been demonstrated by PAXLOVID TM approved for emergency use in treating COVID-19 patients. Due to concerns (e.g. drug combination, COVID-19 rebound, drug resistance) related to existing small-molecule SARS-CoV-2 antivirals, the development of next-generation antivirals with improved pharmacokinetic (PK) properties and antiviral potency is still urgent.

Methods: M Pro is a cysteine protease that uses

four binding pockets S1, S2, S4, and S1' in the active site to engage P1, P2, P4 and P1' residues in a protein substrate for binding. Since P3 is not necessary for an inhibitor to engage M Pro for binding, multiple potent dipeptidyl inhibitors have been reported by using their P1 and P2 residues and N-terminal group to bind S1, S2, and S4 pockets in M Pro and a covalent warhead to engage C145 of M Pro . However, a systematic study of dipeptidyl M Pro inhibitors on how different chemical identities in P1 and P2 residues, N-terminal groups, and warheads influence M Pro inhibition, structural aspects in binding M Pro , cellular and antiviral potency, and metabolic stability has not been reported. We synthesized and systematically surveyed various dipeptidyl M Pro inhibitors and their potential use as SARS-CoV-2 antivirals.

Results: We synthesized about 30 reversibly covalent dipeptidyl MPro inhibitors and characterized them on in vitro enzymatic inhibition potency, structures of their complexes with MPro, cellular MPro inhibition potency, antiviral potency, cytotoxicity, and in vitro metabolic stability. Our results showed that MPro S2 pocket is flexible in accommodating large P2 residues in dipeptidyl MPro inhibitors. Inhibitors MPI60 and MPI61 with two large P2 spiro residues had the highest antiviral potency with an EC50 value of 0.37 μM, and also displayed the most favorable characteristics.

Conclusion: Our findings strongly suggest MPro has a flexible S2 pocket that accommodates dipeptidyl inhibitors with a large P2 residue and dipeptidyl inhibitors with a large P2 spiro residue offer optimal characteristics as a novel group of MPro inhibitors with high antiviral potency. MPI60 and MPI61, our leading compounds with high antiviral potency and metabolic stability, hold promising further preclinical investigations.

45. Dual-responsive ZnO Nanomedicine for Tumor-targeted Drug Delivery

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Introduction: Multidrug resistance (MDR) and low tumor specificity are two challenges in cancer treatment. Development of effective and safe nanomedicine for targeted drug delivery and cancer treatment is a growing research area. Here, we develop a novel dual-responsive zinc oxide nanoparticle (ZnO NP) based nanomedicine for targeted drug delivery and treatment of MDR cancer.

Methods: The developed nanomedicine, containing ZnO NPs, phospholipid (DPPG), and enzyme-sensitive polymer (PEG-pp-PE), could respond to the tumoral matrix metalloproteinase 2 (MMP2) and intracellular acidic pH. Using the model drug doxorubicin (DOX) and fluorescent probe, the physicochemical properties, MMP2 and pH dual sensitivity, *in vitro* and *in vivo* performance of the nanomedicine were studied.

Results: Results: The *in vitro* results showed that, the ZnO/DPPG/PEG-pp-PE/DOX nanomedicine had MMP2 dependant cellular uptake and enhanced anticancer activity in the MDR cancer cells and their 3D spheroids. The *in vivo* studies in the MDR tumor model, showed the nanomedicine enhanced the biocompatibility, tumor specificity, and anticancer activity of DOX and ZnO NPs without significant toxicity compared to free DOX, ZnO/DOX, and nonsensitive ZnO NPs.

Conclusions: Our results suggest that the dual-responsive ZnO nanomedicine is a promising delivery system for targeted drug delivery and sensitization of MDR cancer, with global implications for cancer treatment.

46. Inflammasome Activation Mediates Coagulopathy and Inflammation in Salmonella Systemic Infection

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Inflammasome activation is a critical defense mechanism against bacterial infection. Previous studies suggest that inflammasome activation protects against Salmonella oral infection. Here we identify inflammasome activation as an important contributor to the pathogenesis of Salmonella systemic infection. We show that in a systemic infection model by i.p. injection of Salmonella, deficiency of caspase-1 or gasdermin-D prolonged survival time, reduced plasma concentrations of the proinflammatory cytokines IL-1β, IL-6 and TNFα, and protected against coagulopathy. In ad-

dition, the prolongation of prothrombin time and the increase in plasma thrombin-antithrombin complex concentrations were diminished in the caspase-1 or gasdermin-D deficient mice challenged with Salmonella, suggesting that activation of the NAIP/NLRC4 inflammasome by flagellin and/or the components of the SPI1 type 3 secretion system (T3SS) plays a major role in Salmonella-induced coagulopathy. Further, the Salmonella mutant deficient in flagellin and SPI1 could still trigger coagulopathy through the caspase-11/NLRP3 pathway. Our results provide evidence for an important role of the inflammasomes and pyroptosis in the pathogenesis of Salmonella systemic infection.

47. Extracellular Histones Trigger Disseminated Intravascular Coagulation by Lytic Cell Death

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Histones are cationic nuclear proteins that are essential for the structure and functions of eukaryotic chromatin. However, extracellular histones trigger inflammatory responses and contribute to death in sepsis by unknown mechanisms. We recently reported that inflammasome activation and pyroptosis trigger coagulation activation through a tissue-factor (TF)-dependent mechanism. We used a combination of various deficient mice to elucidate the molecular mechanism of histone-induced coagulation. We showed that histones trigger coagulation activation in vivo, as evidenced by coagulation parameters and fibrin deposition in tissues. However, histone-induced coagulopathy was neither dependent on intracellular inflammasome pathways involving caspase 1/11 and gasdermin D (GSDMD), nor on cell surface receptor TLR2- and TLR4-mediated host immune response, as the deficiency of these genes in mice did not protect against histone-induced coagulopathy. The incubation of histones with macrophages induced lytic cell death and phosphatidylserine (PS) exposure, which is required for TF activity, a key initiator of coagulation. The neutralization of TF diminished the histone-induced coagulation. Our findings revealed lytic cell death as a novel mechanism of histone-induced coagulation activation and thrombosis.

48. Inflammasome Activation Promotes Venous Thrombosis Through Pyroptosis

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Crosstalk between coagulation and innate immunity contributes to the progression of many diseases, including infection and cardiovascular disease. Venous thromboembolism (VTE), including pulmonary embolism and deep vein thrombosis (DVT), is among the most common causes of cardiovascular death. Here, we show that inflammasome activation and subsequent pyroptosis play an important role in the development of venous thrombosis. Using a flow restriction-induced mouse venous thrombosis model in the inferior vena cava (IVC), we show that deficiency of caspase-1, but not caspase-11, protected against flow restriction-induced thrombosis. Interleukin-1β expression increased in the IVC following ligation, indicating that inflammasome is activated during injury. Deficiency of gasdermin D (GSDMD), an essential mediator of pyroptosis, protected against restriction-induced venous thrombosis. After induction of venous thrombosis, fibrin was deposited in the veins of wild-type mice, as detected using immunoblotting with a monoclonal antibody that specifically recognizes mouse fibrin, but not in the caspase-1-deficient or GSDMD-deficient mice. Depletion of macrophages by gadolinium chloride or deficiency of tissue factor also protected against venous thrombosis. Our data reveal that tissue factor released from pyroptotic monocytes and macrophages following inflammasome activation triggers thrombosis.

49. Texas A&M Opioid Overdose Education & Naloxone Administration (OENA) Training as a Public Health Initiative

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Introduction: Opioid overdose is a significant public health concern worldwide, with a high incidence of mortality. The administration of naloxone by laypersons is a promising intervention to reduce overdose mortality. Harm reduction strategies aimed at opioid use disorder, such as training on the use of naloxone, are essential in reducing mortality rates.

This prospective study aimed to assess the impact of training provided to the community on the use of nasal naloxone to reverse opioid overdoses and reduce mortality. Additionally, the study evaluated the trainees' knowledge, efficacy, and attitude toward harm reduction strategies aimed at opioid use disorder.

Methods: The study was conducted in a community setting in which harm reduction training, including information on recognizing opioid overdose, administering naloxone, and providing rescue breathing, was delivered to community members. The impact of the training was assessed by comparing pre- and post-training surveys completed by the trainees. The surveys assessed knowledge, efficacy, and attitude toward harm reduction strategies aimed at opioid use disorder. Additionally, data on naloxone distribution, use, and overdose mortality in a defined geographic area that provided this data via first responder de-identified events was collected over a 12-month period.

Results: A total of 300 community members completed the training, including 50% police and first responders, 40% healthcare professionals to include school nurses, and 10% interested community laypersons with access to high-risk populations. The training was found to significantly increase knowledge ($p<0.001$), efficacy ($p<0.001$), and attitude toward harm reduction strategies aimed at opioid use disorder ($p<0.001$) among trainees. Over the 12-month period, a total of 350 doses of naloxone were distributed, with 41 doses used to reverse opioid overdoses. There was a significant reduction in opioid overdose mortality in the community during the study period compared to the previous year ($p<0.05$).

Conclusion: The study demonstrates that training provided to the community on the use of nasal naloxone is effective in increasing knowledge, efficacy, and attitude toward harm reduction strategies aimed at opioid use disorder. The inclusion of harm reduction training in the community and interprofessional healthcare education curricula is essential to reduce opioid overdose mortality. Further research is needed to determine the long-term impact of harm reduction strategies aimed at opioid use disorder on reducing mortality.

50. E^3 =Environment, Epigenetics, and Endocrinology

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Epigenetic changes modify the way genetic information is expressed without directly changing the genetic code stored in DNA. Although some epigenetic changes are part of normal development and aging, environmental factors may cause epigenetic changes that lead to health problems. Epigenetic changes likely play an important role in development and are thought to be involved in a wide range of diseases and disorders, including autoimmune and neurodevelopmental disorders, cardiovascular disease, and cancer. Epigenetic changes in the cells or extracellular fluid underlie the development of human diseases can predict the diseases ahead of any symptoms. These changes include DNA methylation changes throughout the genome, post-translational chromatin modifications, and several non-coding RNA alterations. Identification of these alterations for use as predictive and prognostic biomarkers has been a highly sought-after goal. Recent advances in the field have not only greatly expanded our knowledge of the epigenetic changes in diseases but also demonstrated their significant clinical utility as biomarkers. These biomarkers have proved to be useful for identifying patients who might be on high risk of developing diseases. On the other hand, biomarkers augment the success rate of drug development and thereby accelerate the availability of new therapeutics. The Choudhury laboratory has taken a lead in seeking new early epigenetic biomarkers, clarifying the associated molecular mechanisms, and performing translational studies in cells, animal models, and human patients. These research programs have provided multiple undergraduate, graduate, professional, and postdoctoral training who are now well established in either academia or industry and also established national and international presence.

51. Effect of In-use Stability Condition on Dissolution and Nitrosamine Impurity of FDA Approved Metformin Products

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Purpose: Metformin is the most widely used medication globally for the treatment of type-2 diabetes and prediabetes. As a first-line oral antidiabetic agent it reduces the serum glucose level in several ways, notably through non-pancreatic mechanisms without increasing insulin secretion. Furthermore, it is the only oral medication approved for diabetes treatment in children and has also been used to treat obesity in children and adolescents. Recently, there are concern regarding safety of clinically available metformin products due to presence of carcinogenic impurity, NDMA that led to recall of many commercial products. NDMA level in the products found to be above acceptable daily intake (ADI) >96 ng/day. The objective of the present study was to quantify NDMA in commercial metformin products and perform dissolution during patient in-use condition.

Methods: A simple, specific, and sensitive LC-MS method was developed and validated for NDMA quantification in metformin formulations. A gradient elution method was developed using 0.02 % formic acid in water and acetonitrile as mobile phases flowing at 0.4 mL/min with m/z at 75.06. Four immediate-release (M1-M4) and six extended-rerelease (M5-M10) metformin products were evaluated in the stability testing. All products were repacked in pharmacy vials and stored at 30 oC/75% RH for 12 weeks. Individual tablets (n=3) were crushed and powder samples were taken into polypropylene tubes. Ten mL of 1 N HCl was added to polypropylene tubes containing metformin samples and vortexed for 5 min. An organic solvent (dichloromethane or ether) was added to the resultant mixture and vortexed for 2 more min. All the tubes were kept in the shaking water bath for up to 48 h at 25 oC. Organic solvent/layer was collected from each tube and filtered through 0.2 µm nylon filter and the samples were injected into LC-MS for analysis. The dissolutions of 500 mg IR and ER tablets were performed with USP basket and paddle methods respectively in 1000 mL phosphate buffer pH 6.8 at 100±1 rpm and 37±0.5 °C.

Results: LOD, LOQ, and linearity range of the method were 1.72, 5.2 and 10-100 ng/mL (R=0.993), respectively. The method has high accuracy and precision as indicated by recovery values of 97.0-110.3% and RSD values of 1.6-4.7%. The method was found to robust with no significant effect on linearity, accuracy, and precision by deliberate changes on the method and instrument parameters. Five products (M2, M3, M5, M7 and M10) had NDMA level above ADI limit (96 ng/day) before in-use stability exposure. NDMA levels detected in IR products M2 (1164±52.9 ng/tablet), M3 (3776±351.9 ng/tablet) were 12 and 39 folds of ADI, respectively. Similarly, ER products M5 (191±94.1 ng/tablet), M7 (1473±47.3 ng/tablet) and M10 (423±55.8 ng/tablet) showed NDMA levels 1.9, 15.3 and 4.4 folds of ADI, respectively. The impurity increased significantly ($p<0.05$) after 12 week stability exposure to 2.72, 2.47, 2.23 and 2.78 folds of initial values in M2, M3, M7 and M10.

Conclusion: In summary, the developed method was successfully validated as per regulatory guidelines and met specificity, linearity, accuracy and precision criteria. The method can quantify NDMA ≥31.25-312.50 % (10-100 ng/ml) of ADI in the commercial products with extraction efficiency of >94.0%. In-use stability assessment of the commercial products showed wide variation in NDMA content before and after exposure to stability condition. An increase in rate of NDMA content formation was not similar in all the product. Products M1 and M4 were stable against NDMA generation. An increase in the impurity after exposure to temperature and humidity indicated fastening of nitrosating chemical reaction. Nitrosating agent may be coming from drug, excipient(s) and/or process. No significant change in dissolution profiles were observed after stability exposure and met USP dissolution criteria. It can be concluded that NDMA is not likely to have any significant effect on clinical performance of the product.

52. Maximum Dosage of Intravenous Diltiazem for the Treatment of Acute Atrial Fibrillation with Rapid Ventricular Rate: A Systematic Review

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Background: Atrial fibrillation (afib) with rapid ventricular rate (RVR) is a common arrhythmia that is often managed with diltiazem. Initially, diltiazem is given as a weight-based dose of 0.25 mg/kg over 2 minutes, however, guidelines do not specify a maximum dosage, raising concerns in some patient populations.

Objective: The aim of this review was to determine if a maximum dose of IV diltiazem for acute afib with RVR can be safely recommended.

Method: A comprehensive literature search was conducted to identify articles studying the use of diltiazem for the treatment of acute afib with RVR. Articles were included if they utilized a diltiazem IV push for acute management of atrial fibrillation with RVR, rates of hypotension, and a rate of efficacy for rate control. Articles were excluded if they were not peer reviewed, abstracts, or training materials.

Results: A total of 15 articles were included in this review. Studies that utilized weight-based dosing compared to standard dosing were more likely to achieve rate control. Secondary outcomes also showed superiority of weight-based dosing. Studies examining dosing in obese patients saw no significant difference in outcomes between groups weighing less than 100 kg versus greater than 100 kg.

Conclusion: We recommend weight-based diltiazem dosing to be 0.25 mg/kg for weights up to 100kg as the initial bolus with a maximum dose of 25mg.There is a potential for future research analyzing differences in using ideal body weight versus actual body weight dosing for diltiazem, and in extremes of body weight.

53. Providers in Rural Texas Prescribe Opioid and Benzodiazepine Medication Combination at a Higher Rate

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Introduction: Although many drugs are implicated in overdose deaths, opioids and concomitant sedatives have contributed to overdose in both rural and urban communities. Individuals in rural areas are up to fivefold more likely to experience adverse outcomes related to opioids. The primary objective of this study was to evaluate concomitant use of opioid and benzodiazepine prescriptions in Texas, compare metropolitan and rural differences, and use this data to inform clinicians and to help develop harm reduction strategies.

Methods: Prescribing data were extracted from the Texas Prescription Drug Monitoring Program (PDMP) public use data file, the statewide monitoring program administered by the Texas State Board of Pharmacy (TSBP). An overlapping drug combination prescription day was defined as any day in which a patient had at least one of the overlapping drug types (*e.g.*, opioid + benzodiazepine, opioid + benzodiazepine + carisoprodol).

Results: In Texas 47.4% of the counties with the highest number of overlapping days (per patient) bordered other states. Providers who practice in rural areas prescribe opioid and benzodiazepine medications with 8.2 more overlapping days per quarter.

Discussion: Taking both opioid and benzodiazepine prescriptions is associated with increased overdose risk. Opioid prescription data provides a distinct view into the opioid epidemic that allows all states and counties to view the trends of opioid utilization. There are only a few studies using Prescription Drug Monitoring Program (PDMP) data to compare urban and rural trends.

Conclusions: Rural patients had more benzodiazepine & opioid days overlap than urban patients. The prevalence is higher among older adults and providers who practice in rural areas (average 8.2 more days per quarter). Our findings in Texas indicate a trend downward in overlap for both rural and urban areas over the last year of measurement. However, rural areas are still significantly higher.

54. Positive Allosteric Modulators of the Cannabinoid CB1 Receptor, an Alternative Armamentarium for Pain Relief

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Chronic pain affects nearly 50 million people in the United States. The misuse and addiction of prescription and non-prescription opioids including morphine and synthetic opioids such as oxycodone and fentanyl is a serious national crisis that affects public health as well as social and economic welfare. Pain medications that lack addictive liability is an unmet medical need worldwide. The cannabinoids isolated from plant cannabis are known for pain-relief effects. They exert analgesic effects mainly though activation of the brain type cannabinoid receptors (*i.e.*, the cannabinoid CB1 receptors) by binding to the receptor orthosteric sites where the endogenous ligands bind. Plant-derived and synthetic cannabinoids that bind to the orthosteric site have been found to induce psychological and physiological side effects. In contrast, allosteric modulators, which bind to sites that are topologically different from the orthosteric binding site of a receptor provide novel pharmacology distinct from the pharmacology of orthosteric ligands. Allosteric modulators of CB1 receptors have been identified and demonstrated with less CNS side effects and robust pain suppressing activity in preclinical inflammatory and neuropathic pain models. The findings offered new opportunity for developing pain medications that have no CNS liability and function via new mechanism of action. The representative CB1 positive allosteric modulators (PAM) including ZCZ011 and GAT211 are derived from 2-phenyl-3-alkyl indole scaffold. However, these compounds are racemates and possess an aliphatic nitro group, both of which are attritions for drug discovery and development. To overcome these challenges, we optimized the 2-phenyl-indole scaffold and developed the second generation of CB1 PAMs (Fig.3). The novel hit exhibit strong analgesic activity and lack of CNS side effects that typically found in CB1 orthosteric agonists and some of the first generation CB1 PAMs. Optimization of this novel class of compounds towards IND enabling studies is ongoing in our lab and will be discussed.

55. Using a Common Data Model to Describe Healthcare and Medication Utilization in a Diverse Patient Sample with Systemic Sclerosis in a Large Integrated Health System

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Background: Systemic sclerosis (SSc) is a rare autoimmune disease requiring multidisciplinary care. Utilization studies for rare diseases often rely on claims data with limited detail. Using the virtual data warehouse (VDW) that includes electronic health record and claims data, SSc healthcare utilization was described in an integrated health system.

Methods: Most recent 12-month demographic, encounter, and service data for SSc patients with ≥1.5 years of enrollment between 2005-2019 were extracted. Encounters were stratified by type; further organized by CPT-4 (Category I), HCPCS, and ICD-9/10 PCS codes; tabulated and described. Unique medications were identified using generic product identifier (GPI) codes and described by general therapeutic categories, GPI medication groupings, and select individual medications most relevant to SSc. Daily outpatient medication burden was estimated as follows: [total supply for all medications dispensed during the observation period]/365 days.

Results: Of the 191 patients with SSc, 90% were female; either Black (36%), White (28%), Hispanic (13%), or Asian (11%); and had a mean age of 59.4y (±14.3y). SSC diagnosis variants included systemic sclerosis (27%), systemic sclerosis unspecified (39%), and CREST syndrome (28%) with 16% having ≥1 diagnosis variant. Medians for Charlson Comorbidity Index, unique medications, and daily medication burden were 4, 10, and 3.3, respectively. Of the 5,347 encounters, 58% were ambulatory, 15% lab only, 13% virtual care, 9% radiology, and 4% emergency/acute inpatient stays. Most CPT-4-defined procedures (n=17,792) involved laboratory/pathology (58%), medicine (15%), and evaluation/management (14%) service groupings. Cardiovascular, gastrointestinal, anti-infective, endocrine/metabolic, and topical medications were dispensed in 79%, 63%, 61%, 55%, and 54% of SSc patients, respectively.

Conclusion: SSc patient healthcare utilization mainly occurred in ambulatory settings and involved substantial laboratory, medical, and evaluation/management procedures. Medication use was consistent with SSc. Future work will translate observed utilization into costs using a peer-reviewed Standardized Relative Resource Cost Algorithm that applies available fee schedules.

56. Zein Nanoparticles for Drug Delivery to Inflammatory Bowel Disease (IBD)

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Cyclosporine A (CsA) is one of the most effective therapies for the acute, severe steroid refractory ulcerative colitis. Whilst therapy with CsA was shown to reduce the probability to avoid colectomy, systemic side effects limit its long-term use. In this context, slow and sustained colon-specific delivery of CsA may be ideal. To this end, we developed stable, CsA-loaded nanoparticles using a natural protein from corn, zein. Physicochemical characterization such as size, polydispersity, zeta potential, and in vitro drug release were tested in simulated gastric fluid (SGF, pH1.5), simulated intestinal fluid (SIF, pH6.5) and phosphate buffered saline (pH7,4). In vivo efficacy of the NP was tested in DSS-induced colitis mouse model. CsA levels in the colon were ~7 fold higher in the mice treated with zein NP as compared to the marketed formulation, Neoral. Similarly, colon:serum ratio of drug concentration was also significantly higher with zein NP than Neoral ($p<0.01$). Further, improved weight loss, and colon length, colon:body weight, and decreased rectal bleeding, and liver:body weight, increased anti-inflammatory cytokine levels accompanied with decreased pro-inflammatory cytokines was observed in colon tissues compared with Neoral ($p<0.01$). In conclusion, a stable CsA-loaded zein NP formulation with high drug loading and pH-sensitive drug release profile showed improved efficacy in DSS-induced colitis mice as compared to the marketed Neoral.

57. Recommendations for Pharmacogenetic Testing in General Medicine Clinical Practice Guidelines in the USA

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Background: Pharmacogenomics looks at how an individual's DNA affects the way they respond to drugs. Pharmacists play an important role in implementing pharmacogenomics, including promoting the optimal use and timing of pharmacogenomic tests; interpreting pharmacogenomic test results; and educating healthcare professionals, patients, and the public about the field of pharmacogenomics. Guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) provide consensus recommendations for using PGx information in treatment decisions. While testing guidance from PGx consortia are helpful, most practicing clinicians are unaware of these guidelines and rely on clinical practice guidelines (CPGs) published within their clinical specialty to guide which tests they order.

Objectives: The primary objective is to review general medicine CPGs and identify if pharmacogenetic testing is recommended for gene-drug pairs with potential clinical utility.

Methods: CPGs from US-based clinical organizations were reviewed for information regarding PGx testing for 5 gene-drug (or drug class) pairs that were categorized as general medicine medications. An effort was made to be inclusive of major known guidelines from USA-based clinical practice organizations, including those listed in Lexicomp for each drug of interest. Results: Pharmacogenetic information was identified in 7 CPGs for 4 drug-gene pairs. Conclusions: This review demonstrates inconsistency in PGx testing guidance, including a lack of any recommendation in many CPGs. Further work is needed to clearly define clinical utility for PGx and provide guidance on appropriate study designs to generate the evidence to support clinical utility.

58. Clinical Implementation of Pharmacogenomics and Artificial Intelligence Tools

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Introduction: Chronic disease management often requires use of complex regimens that lead to challenges on the patient, provider, and health-system levels. Rising costs and healthcare utilization associated with polypharmacy have been well documented, yet, effective tools to address these challenges remain elusive. In a previous report, we described informatic and bioanalytic methodologies that integrate patient reported outcomes and electronic health record data with pharmacogenomic analysis and clinical pharmacokinetic profiles to strengthen drug-gene associations and inform comprehensive medication management.

Methods: Implementation of the Interprofessional Pharmacogenomics (IPGx) model: (1) Patients are referred to the to the Texas A&M Health Family Care Clinic IPGx service. (2) Relevant medical history is collected and input into the Clinical Semantic Network for analysis. (3) Pharmacogenomic and pharmacokinetic profiling is performed. (4) A medication management report is returned to the referring physician. Total # of medications, total # of gene variants identified, # drug levels in toxic range and # of actionable genotypes were tracked.

Results: Pilot data were collected between 12/15/21 to 3/31/22 from 24 patients (White/Caucasian: 83%; Black/African American: 17%, Hispanic/Latino 4%) referred to the IPGx clinic for polypharmacy management. Thirteen received pharmacogenetics testing and clinical pharmacokinetics, and eight received comprehensive medication management (CMM). Patients who underwent CMM were on an average of 17 medications (range of 12 to 25 medications). An average of nine clinically relevant variants per patient were identified upon genotyping. Most of these patients (75%) were found to have a clinically actionable genotype associated with a medication they were taking. Two patients were found to have toxic levels of at least one prescribed medication.

Conclusion: A reproducible approach to obtain real-world data to inform patient care and regulatory decision-making is needed. This approach will overcome the current paucity of population-level genomics information needed to improve patient outcomes within the expanding personalized precision medicine landscape.

59. Review of Weight Based Metoprolol for Acute Atrial Fibrillation with Rapid Ventricular Rate

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Background: A flat dose of IV metoprolol or weight-based dosing of IV diltiazem are most commonly used for rate control for AFIB with RVR, but pharmacokinetic differences, differing dosing strategies, and evidence from a few studies have led clinicians to favor diltiazem.

Objective: The objective of this article was to review the evidence for using weight-based metoprolol in the treatment of AFIB with RVR.

Methods: The literature review was conducted based on the principles from the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Articles that met inclusion criteria for the review were original, published in the English language, utilized a weight-based dosing strategy for the treatment of AFIB with RVR, and compared intravenous metoprolol to diltiazem.

Results: Review of the literature yielded two studies that met the inclusion criteria. The first study, published in 2005 by Demarcan and colleagues, was a prospective trial that included 40 patients that showed no statistical difference in the number of people who reached treatment success. A second prospective study published in 2015 by Fromm and colleagues included 54 patients. Diltiazem versus metoprolol had significantly higher rates of reaching the primary outcome ($p<0.001$).

Conclusion: Some of the published literature on the acute treatment of AFIB with RVR suggests dil-

tiazem may be the preferred agent, though it is important to recognize the overall paucity of literature and limitations of the published studies. Using weight-based metoprolol over the current flat dosing strategy may prove beneficial and more research is needed to provide better guidance.

60. Endoplasmic Reticulum (ER), a Potential Therapeutic Target for Mutant p53 Colorectal Cancer

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Background: Patients with metastatic colorectal cancer (mCRC) do not respond well to current therapeutic regimens. Consequently, the disease remains incurable upon metastasis. Over 57% of metastatic CRC (mCRC) patients exhibit p53 (a tumor suppressor gene) mutations associated with tumor progression and chemoresistance. Hence, new agents for improving mCRC therapy, particularly to treat p53 mutant (Mutp53) CRC, are required to curtail the disease.

Methods: To investigate the effect of ASR-458, a drug-like molecule, on Mutp53 cell lines (R273H-mutated p53: SW620 and SW480), we performed MTT assays, FACS analysis, siRNA knockdown, western blotting, calnexin staining, immunofluorescence, and Xenograft studies.

Results: In our bioinformatic analysis of an extensive TCGA database of 2818 CRC patients, 64% (1804 out of 2818) of mCRC patients exhibited Mutp53 rather than wild-type p53, which subsequently correlated with worse progression-free survival (PFS) compared to wild-type p53 CRC patients. Subsequently, we identified a nontoxic and plasma-achievable small molecule, ASR458, which sensitizes Mutp53 CRC cells in nM concentrations (SW620: 250nM and SW480: 410nM at 72h) while being nontoxic to healthy colon epithelial cells (84% Cell viability at 52-fold higher concentration). Most therapeutic agents targeting Mutp53 CRC work by restoring wild type p53 function or activating its downstream effector molecules (p21), thereby causing growth inhibition. Instead, ASR458 activated Unfolded Protein Response (UPR) pathway via the induction of phosphorylated Eukaryotic Initiation Factor 2 alpha (peIF2α). The elevated levels of peIF2α resulted in increased translation of Activating Transcription Factor 4 (ATF4), a crucial regulator of endoplasmic reticulum (ER) stress and critical to induction of autophagy. As anticipated, ASR458 treatment increased expression of key autophagy regulators such as ATG5 and LC3B in Mutp53 CRC cells, and silencing ATF4 expression abrogated autophagy, which affected ASR458 efficacy in terms of decline in ASR458 mediated cell death in p53Mut CRC cells.

Conclusion: Our results suggest that the novel small molecule ASR458 may activate ER stress-mediated autophagic cell death in p53mut CRC cells. Performing PK/PD studies will confirm the translation potential of ASR458 as a therapy for p53mut CRC.

61. Pharmacy Advances Clinical Trials (PACT) Network to Achieve Diversity in COVID-19 Clinical Trials: A Strategic Framework

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Introduction: The COVID-19 pandemic has been one of the worst pandemics, with the most extensive socioeconomic disruptions in the United States and globally in the last century. The pandemic disproportionately affected underrepresented minorities (URMs). As of January 2023, death rate ratios compared to White, Non-Hispanic persons were as follows: American Indian and Alaska Native (AIAN), 2.0x, Hispanic or Latino (H/L) 1.7x, Black or African American (AA), 1.6x. Texas A&M University (TAMU) has partnered with the American Association of Colleges of Pharmacy (AACP) to develop the 'Pharmacy Advances Clinical Trials' (PACT) Network to Achieve Diversity in COVID-19 Clinical Trials. This analysis focuses on leveraging Artificial Intelligence (AI), Machine Learning (ML), Geospatial Intel-

ligence (GEOINT), and Clintrials.gov data to enable environmental scans in target communities to optimize URM participation in COVID-19 clinical trials.

Methods: AI, ML, and GEOINT were used to survey the US population and census maps to identify URM residents by zip code. This data was then overlayed with the US Clinicaltrials.gov data using an AI/ML algorithm to develop a database of COVID-19 clinical trials in the US and their proximity to URMs, enrollment into ongoing and completed clinical trials by race and ethnicity. Additionally, a commercial Red Lion database of 176,000 community pharmacies in the US was added to query URMs' proximity to community pharmacies.

Results: The results demonstrated that while 97% of URMs reside within 5 miles of pharmacies, 97% reside approximately 150 miles from COVID-19 clinical trial sites. Participation in COVID-19 clinical trials was as follows: 8% AA, 8% H/L, 8% Other (including AIAN), and 61% CA.

Conclusions: Although URMs reside near clinical trial sites, their enrollment can be improved. Equity in clinical trials is essential for equal access and accrual in clinical trials. Underrepresentation of minority patients in clinical trials compromises the generalizability of trial results. This may lead to miscalculations of disease-free survival rates and erroneous estimates of treatment efficacy, and, as a result, may further exacerbate health disparities. Pharmacies could be leveraged for URM participation in clinical trials.

62. Effective but Not Cost-effective: The Price Impact of New Cancer Drugs

Lixian Zhong
Department of Pharmaceutical Sciences

Introduction: Breast cancer is the most common cancer in women in the United States. High-cost novel cancer drugs such as ribociclib have gained approval to treat women with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced or metastatic breast cancer. The significant clinical benefit comes with a high drug price. Given the ever-rising healthcare expenditure nationwide, it is critical to evaluate cost-effectiveness of novel interventions to ensure efficient allocation of healthcare resources.

Methods: Partitioned survival analysis models were constructed alongside pivotal randomized clinical trials of ribociclib, one for pre/peri menopausal and one for post-menopausal women. The analysis considered three health states (progression-free, progressed disease, and death) and estimated life years (LYs), quality-adjusted life-years (QALYs), and total costs. The safety and efficacy of the treatment were obtained from clinical trials, and costs were estimated based on resource utilization.

Results: The results show that the addition of ribociclib is not considered cost-effective for postmenopausal women or pre/perimenopausal women at a willingness-to-pay threshold of $150,000/QALY. In the base case, ribociclib plus fulvestrant was associated with an incremental costeffectiveness ratio of $425,951/QALY, while ribociclib plus endocrine therapy had an ICER of $282,996/QALY. The cost of ribociclib had the greatest impact on the model, constituting 84% of the total cost for ribociclib plus fulvestrant.

Conclusion: The findings send a strong price signal to the manufacturer and can be used to facilitate payers with price negotiation in making coverage decisions. One-way and probabilistic sensitivity analyses were conducted to test the model robustness, and several scenario analyses were also investigated. Overall, the cost-effectiveness of high-cost cancer drugs such as ribociclib remains a complex issue, and careful consideration of the costs and benefits must be made to ensure that patients receive the most effective treatment without imposing undue financial burden.

63. Nanomedicine for Tumor Targeting and Intracellular Drug Delivery

Lin Zhu
Department of Pharmaceutical Sciences

Introduction: Low tumor specificity and insufficient drug efficacy are two major issues of many anticancer drugs. In this talk, we introduce a novel "core-shell" polymeric nanoparticle-based strategy for effective tumor targeting and intracellular drug delivery.

Methods: Using the fluorescent dyes or vitamin E succinate as the cargo, the drug delivery and targeting capabilities of the prepared polymeric nanoparticles were evaluated in the cell lines, tumor cell spheroids, and tumor-bearing mice.

Results: We demonstrated that the polymeric nanoparticles could efficiently carry and deliver hydrophobic anticancer drugs to cancer cells. More important, the internalized nanoparticles were found to mainly accumulate in cells' mitochondria. With the improved delivery efficiency and targetability, the drug's anticancer activity was improved.

Conclusion: The proposed nanoparticle might have great potential to a simple and reliable tool for intracellular drug delivery and tumor targeting.

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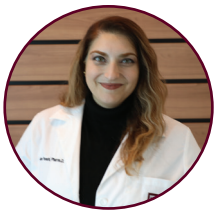

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