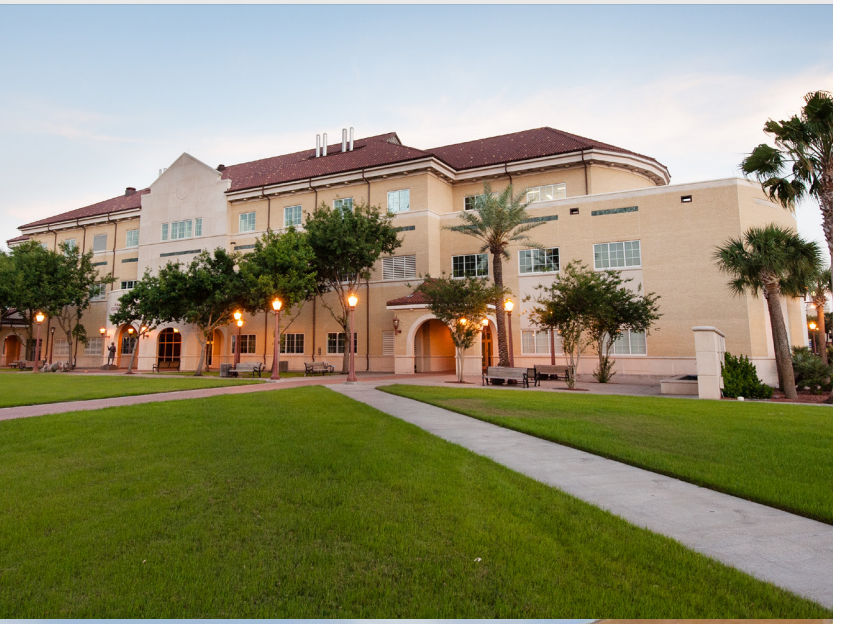
The Second

COLLEGE OF PHARMACY RESEARCH COLLOQUIUM

MARCH 27-28, 2025

HILDEBRAND EQUINE COMPLEX | COLLEGE STATION, TX



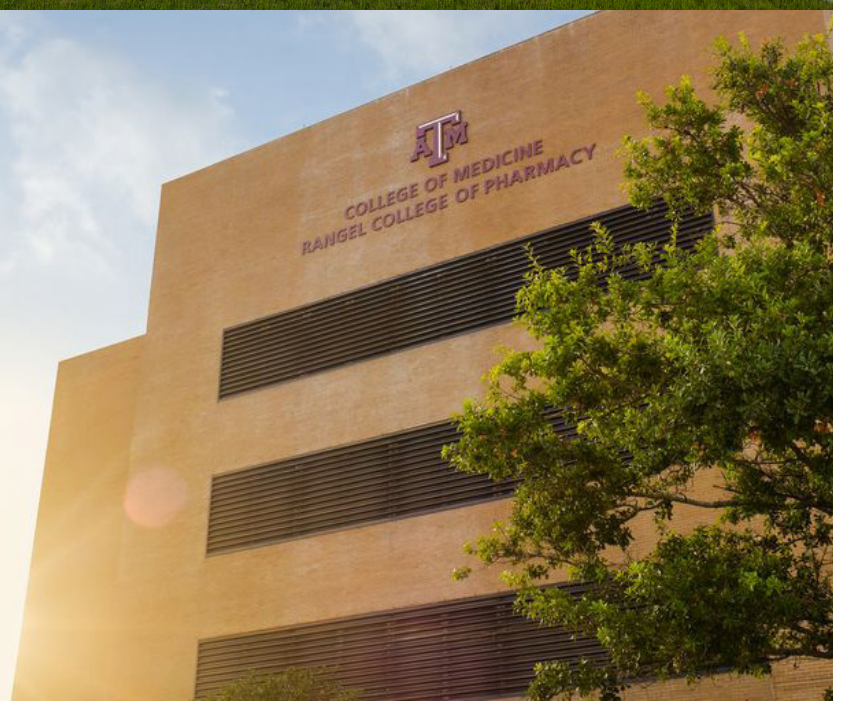
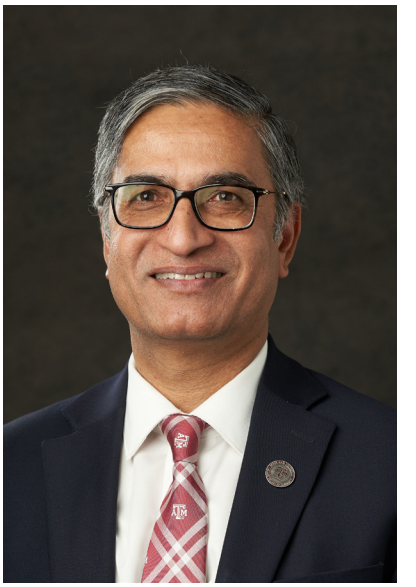


Table of Contents

Research at the Irma Lerma Rangel College of Pharmacy is at the forefront of preclinical and 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!

It is my distinct honor and privilege to welcome you to the second Research Colloquium of the Texas A&M University Irma Lerma Rangel College of Pharmacy.

I sincerely appreciate your participation in this event, which aims to showcase advancements and discoveries within a multitude of focus areas, including drug development, design, and delivery, pharmacogenomics, pharmacotherapy, cancer research, and precision medicine. Your presence and contributions will significantly enrich our discussions and the overall experience of the colloquium.

This year's colloquium features dynamic keynote speakers who are experts in their respective fields and leaders in pharmaceutical sciences and pharmacy practice throughout the United States. They have each been invited to deliver thought-provoking presentations, engage in robust discussions with their audiences, and promote networking and collaboration. Their insights and perspectives will be of tremendous value to researchers, clinicians, residents, students, and healthcare and scientific professionals.

I am eagerly looking forward to hosting researchers, educators, practitioners, pharmacy residents, graduate, and professional pharmacy students so they may share their latest research discoveries, innovations, and methods in pharmacy practice, pharmaceutical sciences, and pharmacy administration. The exchange of knowledge and ideas that will take place during this event is something I am particularly excited about.

The abstracts presented in this book are meant to foster reflection and inspire conversations on the meaningful contributions the authors have made. Their work and insights are of tremendous value to the advancement and understanding of the scientific and clinical world, and I am confident that you will find the discoveries shared here vital to your own research and practice.

Over the next two days, we have a packed four sessions, including keynote speeches, panel discussions, and networking opportunities. On behalf of the Research Colloquium organizing committee, thank you for joining the Texas A&M University Irma Lerma Rangel College of Pharmacy on this endeavor.

Gig 'em!

Mansoor A. Khan, Ph.D.

Program Schedule

Thursday, March 27, 2025

1:00 – 3:00 p.m. | **Registration/Poster Setup**

3:00 – 5:00 p.m. | **Poster Presentations**

5:30 – 5:40 p.m. | **Welcome**
Mansoor Khan, Ph.D.
Interim Dean, Irma Lerma Rangel College of Pharmacy

5:40 - 5:45 p.m. | **Moderator: Zhenyu Li, Ph.D.** | *Professor, Pharmaceutical Sciences*

5:45 – 6:45 p.m. | **Keynote Address**
Fetal and Neonatal Alloimmune Thrombocytopenia
Peter Newman, Ph.D.
Vice President of Research and Associate Director, Versiti Blood Research Institute

7:00 – 9:00 p.m. | **Welcome Reception & Dinner**

Friday, March 28, 2025

7:00 – 8:20 a.m. | Registration/Breakfast

8:30 – 9:40 a.m. | Scientific Session I
Moderator: Lin Zhu, Ph.D. | *Associate Professor, Pharmaceutical Sciences*

8:30 – 9:00 a.m. | **Keynote Address**
Discovery of Small Peptides for Cancer Immunotherapy
Kun Cheng, Pharm.D., Ph.D.
Endowed Chair & Distinguished Professor, School of Pharmacy, University of Missouri-Kansas City

9:00 – 9:20 a.m. | **Multimodal Strategies for Designing BBB-Penetrant Kinase Inhibitors For Effective CNS Tumor and Brain Metastases Therapy**
Hamed Ismail Ali, Ph.D. | *Associate Professor, Pharmaceutical Sciences*

9:20 – 9:40 a.m. | **Developing PROTAC-Based Next-Generation Antivirals against Coronavirus**
Shiqing Xu, Ph.D. | *Assistant Professor, Pharmaceutical Sciences*

9:45 – 11:00 a.m. | Scientific Session II
Moderator: Fatima Alshbool, Pharm.D., Ph.D. | *Associate Professor, Pharmacy Practice*

9:45 – 10:15 a.m. | **Keynote Address**
Biomarkers to Targeted Therapy for Bladder Cancer
Vinata Lokeshwar, Ph.D.
Chair, Department of Biochemistry and Molecular Biology, Medical College of Georgia, Augusta University

10:20-10:40 a.m. | ***Role of Tyrosine Kinases in Inter-Organ-Communication (IOC) in Diabetes-Linked Alzheimer's Disease***
Narendra Kumar, Ph.D. | *Associate Professor, Pharmaceutical Sciences*

10:40 – 11:00 a.m. | ***Unlocking the Gut-Cardiac Axis: TMAO as a Key Mediator in Cardiovascular Pathogenesis***
Sai Sudha Koka, Ph.D. | *Associate Professor, Pharmaceutical Science*

11:00 – 11:15 a.m. | **Coffee/Refreshment Break**

11:20 – 12:30 p.m. | **Scientific Session III**
Moderator: Stephen Lee, PharmD. | *Instructional Professor, Associate Head, Department Pharmacy Practice*

11:20 – 11:50 a.m. | **Keynote Address**
Integrating Research into Clinical Pharmacy Practice, Never Stop Asking Why
Judith A. Smith, Pharm.D.,
Professor, Department of Obstetrics, Gynecology & Reproductive Sciences, UTHSC Houston

11:50 – 12:10 p.m. | **Clinical and Economic Impact of Circulating Tumor DNA and Comprehensive Genomic Profiling in Cancer Management**
George Udeani, Pharm.D., D.Sc. | *Professor, Pharmacy Practice*

12:10 – 12:30 a.m. | **AI-Driven Prediction of Serum Creatinine for Enhanced Pharmacokinetic Modeling in Narrow-Therapeutic Drugs**
Merlyn Joseph, Pharm.D. | *Clinical Associate Professor, Pharmacy Practice*

12:30 – 1:45 p.m. | **Lunch**

2:00 – 2:40 p.m. | **Scientific Session IV Rapid Fire Presentations**
Moderator: Theresa Ofili, Pharm.D. | *Assistant Instructional Professor, Pharmacy Practice*

2:00 - 2:10 p.m. | **TAM and Mitochondria Dual-targeted Drug Delivery for Cancer Immunotherapy**
Nishat Ara, *Graduate student*

2:10 - 2:20 p.m. | **Pathological Mechanisms & Potential Therapeutic Targets of *E. coli* K1-Induced Sepsis**
Zhuodong Chai, *Graduate student*

2:20 - 2:30 p.m. | **Targeting Platelet Serotonin 5-HT2AR via Selective Vaccination: A Novel Strategy for Thrombosis Management**
Ahmed Alarabi, Ph.D., *Postdoctoral fellow*

2:30 - 2:40 p.m. | **Arsenic Exposure Alters the Signatures of the Microbiome and Metabolome, Facilitating Bladder Carcinogenesis**
Bhawna Tyagi, Ph.D., *Postdoctoral Fellow*

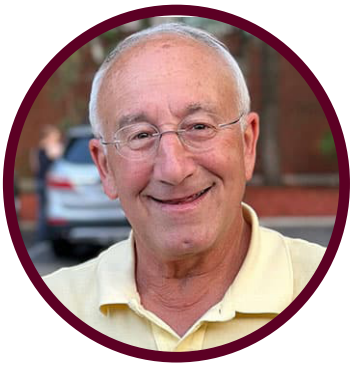
2:45 – 2:50 p.m. | **Closing Remarks**
Chendil Damodaran, Ph.D.
Associate Dean for Research & Innovation and Professor, Pharmaceutical Sciences

2:50 – 3:00 p.m. | **Awards Ceremony**
Indra K. Reddy, Ph.D.
Interim Chief Operating Officer and Senior Vice President, Texas A&M Health
Founding Dean Emeritus of Texas A&M Irma Lerma Rangel College of Pharmacy

Speaker Biographies

Keynote Speakers

Peter J. Newman, Ph.D.

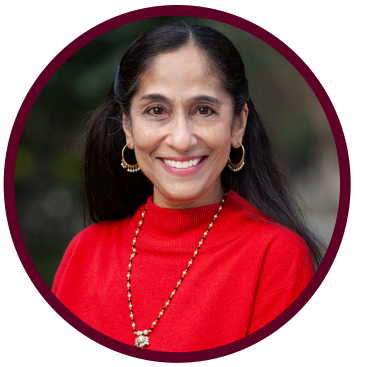


Peter J. Newman, Ph.D. is the recent past Vice President for Research and Associate Director of the Versiti's Blood Research Institute, serving in this capacity from 1998-2022. His major research accomplishments include elucidation of the molecular basis of the major human platelet alloantigen systems, including the PlA1/PlA2 polymorphism, the discovery of PECAM-1, and numerous contributions to the understanding of the role of activating and inhibitory receptors that control platelet activation. During the course of his nearly 40-year career in research, he has trained more than 30 pre- and post-doctoral fellows, including three MSTP trainees (Rich Gumina (1991-1995), Carmen Bergom (2002-2006), and Jamie Privratsky (2006-2010). Dr. Newman has published more than 200 original research articles, book chapters and reviews on the subject of platelet and endothelial cell biology, cell adhesion, and signal transduction, and his work has been cited more than 23,000 times (*h*-index 82). Dr. Newman has been on the editorial board of *Blood*, has reviewed dozens of grants for both the NIH and the AHA, and served the AHA as Associate Editor of the platelet and thrombosis section of the journal ATVB from 2012-2020. He was an Established Investigator of the AHA from 1992-1997, and received a Special Recognition Award from their ATVB Council in 2001. Dr. Newman received an Investigator Recognition Medal from the International Society of Thrombosis (ISTH) in 1997, the Emil von Behring Award from the German Society for Transfusion Medicine in 2007, the E.T.S. Walton Award from Science Foundation of Ireland for his studies on the Molecular Mechanisms of Platelet Activation and Adhesion in 2008, and a Distinguished Career Award from the ISTH in 2013. He is the recipient of a seven-year Outstanding Investigator award from the National Heart Lung and Blood Institute of the National Institutes of Health that supports the majority of his current research program through year 2025. Current research activities include the structural biology of PECAM-1, the role of PECAM-1 in endothelial cell junctional integrity, novel applications of CRISPR/ Cas9 gene editing technology to modify platelet- and megakaryocyte-specific signaling molecules and alloantigens in induced pluripotent stem (iPS) cells, and preclinical research evaluating novel therapeutic modalities to treat and/or prevent Fetal/Neonatal Alloimmune Thrombocytopenia.

Kun Cheng, Ph.D., FAAPS, FAIMBE

Dr. Kun Cheng is a Curators' Distinguished Professor at the University of Missouri-Kansas City (UMKC) School of Pharmacy. He has diverse research experiences in phage display, peptide drug, drug delivery, nanotechnology, and cancer immunotherapy. His research focuses on the development of novel therapeutics for breast cancer, prostate cancer, pancreatic cancer, and liver fibrosis. One of his primary research interests is using phage display to discover peptides that can serve as therapeutic agents or targeting ligands for drug delivery and cancer diagnosis. He is an American Association of Pharmaceutical Sciences (AAPS) Fellow and an American Institute for Medical and Biological Engineering (AIMBE) Fellow.

Vinata B. Lokeshwar, Ph.D.



Dr. Lokeshwar is a tenured Professor and the Chair of the Department of Biochemistry and Molecular Biology (BMB) and a Professor of Urology at the Medical College of Georgia, Augusta University. At MCG-AU, she is the first woman chair of the BMB department, established in 1829. The research projects in her lab begin with a clinical problem and the workflow always is "clinic to lab and back again". The current focus of Dr. Lokeshwar's lab is on biomarkers and experimental therapeutics related to bladder and renal cell carcinomas, and collaborative projects on benign prostatic hyperplasia and prostate cancer. Dr. Lokeshwar's lab has been continuously funded by grants from the NIH, and other agencies. She has published over 100 original research and review articles, book chapters and has co-edited a book on bladder cancer. Dr. Lokeshwar has mentored more than 80 graduate and medical students, residents, postdoctoral and clinical fellows, and faculty. Dr. Lokeshwar was the President of the Society for Basic Urologic Research (SBUR). She has serves/served on numerous national and international research panels, editorial boards of several journals, and grant review panels. Dr. Lokeshwar has received numerous awards including, Augusta University's Outstanding Research Scholarship and/or Creative Activity Award, Exemplary Teaching Awards, SBUR/SWIU Research Award for Excellence in Urologic Research, SBUR Distinguished Service Award and Female Leaders in Urology. Dr. Lokeshwar credits basic science and clinical collaborators, and her mentees/staff for the research programs in her lab. Bench-to-bedside research is Dr. Lokeshwar's passion, as is teaching and mentoring.

Judith A. Smith, Pharm.D., BCOP, CPHQ, FCCP, FHOPA, FISOPP

Dr. Judith A. Smith is a Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at UTHealth McGovern Medical School. She also has faculty appointments at the University of Houston, College of Pharmacy and the UTHSC Graduate School of Biomedical Sciences. Dr. Smith received a Bachelor of Science in Pharmacy and her Doctor of Pharmacy degree from Union University Albany College of Pharmacy. She completed residency in Pharmacy Practice and Oncology Pharmacy Practice at the National Institutes of Health followed by a fellowship in Clinical Pharmacology at The University of Texas M.D. Anderson Cancer Center (UT MDACC). Upon completion of her fellowship, she joined the Faculty at UT MDACC. She has been Board Certified in Oncology Pharmacy for 25 years and Certified Professional in Healthcare Quality for over 14 years. She has served in professional leadership roles in many nationals as well as international pharmacy and oncology associations and has earned recognition as Fellow in clinical pharmacy and oncology clinical pharmacy. Her research focus is to advance the progress of the safe and effective use of nutritional and herbal supplements with pharmacologic modalities as it relates to women's health and cancer.

Speaker Abstracts

Shiqing Xu, Ph.D. | Assistant Professor, Department of Pharmaceutical Sciences

Developing PROTAC-Based Next-Generation Antivirals against Coronaviruses

Over the past two decades, three major coronavirus outbreaks, including COVID-19, have underscored the urgent need for effective antiviral therapies. Main protease (MPro), a highly conserved protease among various coronaviruses, is essential for viral replication and pathogenesis, making it a prime target for antiviral drug development. While MPro inhibitors have shown efficacy against SARS-CoV-2, emerging drug resistance due to viral mutations presents a significant challenge. In this talk, I will present our recent advances in antiviral drug discovery using Proteolysis Targeting Chimera (PROTAC) technology to develop a novel class of small-molecule antivirals that selectively degrade SARS-CoV-2 MPro within cells. By integrating our reversible covalent MPro inhibitors with a CRBN E3 ligand, we designed and synthesized the first MPro-targeting PROTACs, which demonstrate potent antiviral activity against multiple SARS-CoV-2 variants, including those resistant to nirmatrelvir. Notably, PROTAC MPD2 is now commercially available through Bio-techne/Tocris and MedChemExpress, providing a valuable tool for both fundamental virology research and drug discovery. Our findings highlight the potential of PROTAC-based MPro degraders as a transformative approach for developing next-generation broad-spectrum antivirals to overcome drug resistance and enhance pandemic preparedness.

Hamed Ismail Ali, B.Pharm, Ph.D. | Associate Professor, Department of Pharmaceutical Sciences

Multimodal Strategies for Designing BBB-Penetrant Kinase Inhibitors for Effective CNS Tumor and Brain Metastases Therapy

Brain malignancies, particularly breast cancer brain metastases (BCBM), represent a major clinical challenge due to the protective nature of the blood-brain barrier (BBB) and the development of resistance to existing therapies. Approximately 30–50% of HER2+ BC develop BM, often accompanied by HER2L755S and HER2T798I(M) mutations that confer resistance to FDA-approved HER2 inhibitors. Overexpression VEGFR2 exacerbates disease progression by promoting angiogenesis. Therefore, there is an urgent need for novel therapies capable of crossing the BBB and targeting key oncogenic pathways. Our study focuses on designing BBB-penetrant tyrosine kinase inhibitors (TKIs) for CNS malignancies and BMs. Novel quinazoline and pyrrolotriazine derivatives were synthesized, targeting HER2 and VEGFR2, as two critical pathways implicated in brain tumor progression. HA17 demonstrated substantial tumor growth inhibition and prolonged half-life, while HA31 and HA32 showed significant VEGFR2 inhibition, outperforming sorafenib. In vivo, HA31 combined with sorafenib led to a 58.2% tumor growth reduction with minimal toxicity. To optimize these promising compounds for CNS applications, in silico PK modeling was employed, focusing on molecular properties: lipophilicity, Mol.Wt, and HB donors. HA-149 demonstrated potent inhibition of TNBC MDA-MB-468 cells and high BBB permeability in Parallel Artificial Permeability Assays (PAMPA). Our current research includes extensive in vitro and in vivo studies to optimize efficacy, selectivity, and minimize drug efflux by P-glycoprotein to enhance intracerebral drug concentrations. This research represents a significant step toward overcoming CNS oncology challenges, offering a promising therapeutic avenue to improve outcomes for patients with brain tumors and metastatic diseases, and potentially revolutionizing CNS cancer treatment.

Narendra Kumar, Ph.D. | Associate Professor, Department of Pharmaceutical Sciences

Role of Tyrosine Kinases in inter-organ-communication (IOC) in diabetes-linked Alzheimer's disease

The incidence of Alzheimer's disease-related dementia (ADRD) continues to rise and is expected to quadruple worldwide by 2050. Nearly 6 million Americans have ADRD where over half a million among them are veterans. On the other hand, over 29.3 million Americans have type-2 diabetes (T2D) and 115.9 million are pre-diabetic where over 25% of them are veterans. In our home state, nearly 2.7 million Texans have T2D and 0.6 million have ADRD. Diabetic people have 65% higher risk of developing ADRD and 85% of ADRD have diabetes. To understand how diabetes progresses to ADRD, recently we reported a first of its kind novel mouse model that shows symptoms of both T2D, and phenotypic brain abnormalities as seen in ADRD patients. Using pathology and behavioral studies data from the novel mouse model and human tissues, I will speak on the current state of possible mechanistic understanding of Gut-Liver-brain communication in the progression of the symptoms of ADRD in T2D subjects. Having a better understanding the IOC in T2D-linked ADRD will not only impact significant population nationwide but also bring mitigation values to our own local south Texas population where both these diseases are highly prevalent.

Sai Sudha Koka, Ph.D., R.Ph. | Associate Professor, Department of Pharmaceutical Sciences

Unlocking the Gut-Cardiac Axis: TMAO as a Key Mediator in Cardiovascular Pathogenesis

The intestinal microbiota and microbe-derived metabolites play a pivotal role in cardiovascular health and disease. However, the molecular mechanisms through which intestinal microbiota and their metabolic products alter systemic homoeostasis and promote cardiovascular disease (CVD) progression are yet beginning to be dissected. Recent reports highlight intestinal microbe-derived metabolites such as trimethylamine-N-oxide (TMAO), as a novel source of risk factors for CVD. TMAO, a gut microbe-derived metabolite of dietary choline/carnitine is elevated in the circulation of CVD patients and has been associated with atherosclerosis in rodents and humans. The molecular mechanisms of how TMAO induces atherosclerosis and CVD progression are still unclear. Our studies have identified that TMAO acts as an endogenous danger signal leading to the formation and activation of NLRP3 (nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing protein 3) inflammasomes which produce molecules like interleukin-1β. TMAO-induced NLRP3 inflammasomes activation is associated with redox regulation, tight junctional protein disruption, enhanced cell permeability and endothelial dysfunction. We found that direct infusion of TMAO in mice with partially ligated carotid artery increased NLRP3 inflammasome formation and IL-1β production in the intima of wild type mice, and endothelial specific Nlrp3 knockout mice were protected against atherosclerosis. Therefore, formation and activation of NLRP3 inflammasomes by TMAO may be an important initiating mechanism to turn on the endothelial inflammatory response in the arterial wall leading to endothelial dysfunction, vascular inflammation, and consequent atherogenesis. This presentation will highlight the gut-cardiac axis and focuses on a key gut-derived metabolite trimethylamine-N-Oxide (TMAO) and its relationship with cardiovascular injury.

Speaker Abstracts

George Udeani, Pharm.D., D.Sc., FCP, FCCP | Clinical Professor, Department of Pharmacy Practice

Clinical and Economic Impact of Circulating Tumor DNA and Comprehensive Genomic Profiling in Cancer Management

Cancer is the second leading cause of death in the United States, with approximately 618,120 deaths expected in 2025. Cancer remains one of the most pressing challenges, in terms of its clinical management and economic impact on individuals, families, and healthcare systems globally. Despite significant advancements in cancer research and treatment modalities, timely diagnosis, accurate monitoring, and personalized therapy selection continue to pose formidable challenges. Imaging procedures remain the mainstay of cancer diagnosis and monitoring but are associated with costs and access issues. Circulating tumor DNA (ctDNA) which are small fragments released from tumor cells into the bloodstream through processes such as apoptosis, necrosis, and active secretion, represents a promising biomarker in cancer diagnosis and management. The release of ctDNA into circulation provides a dynamic snapshot of tumor biology and evolution, offering valuable insights into disease progression and treatment response as well as analysis of the tumor size. Comprehensive genomic profiling (CGP) is a next-generation sequencing (NGS) method that employs a single assay to evaluate several genes and applicable cancer biomarkers, guiding antineoplastic therapy selection and clinical trial recommendations for patients. Our preliminary experience in the clinics, with these approaches and potential economic impact, are discussed.

Merlyn Joseph, PharmD | Clinical Associate Professor, Department of Pharmacy Practice

AI-Driven Prediction of Serum Creatinine for Enhanced Pharmacokinetic Modeling in Narrow-Therapeutic Drugs

Narrow-therapeutic drugs requiring renal clearance demand careful monitoring due to the risk of adverse effects, particularly in patients with acute kidney injury (AKI). To enhance pharmacokinetic modeling for such drugs, we developed a deep-learning model, an artificial intelligence (AI) approach, to predict serum creatinine levels, a key renal function indicator. The study cohort comprised 9,710 patients from Memorial Hermann Health System, aged ≥18 years with serum creatinine <3 mg/dL on admission, excluding those with end-stage renal disease or dialysis. Our model incorporated patient-specific features such as vital signs, laboratory results, medications, and diagnostic codes. A gated recurrent unit (GRU)-based AI architecture was employed alongside a one-compartment pharmacokinetic model to account for creatinine production and elimination dynamics. After training the model, the GRU-based AI model achieved a Root Mean Square Error (RMSE) of 0.294. Given that AKI is defined as a serum creatinine increase of 0.3 or more, this pilot model shows promise in detecting acute changes in renal function with further refinement. This approach seeks to advance pharmacokinetic modeling for narrow-therapeutic drugs, ultimately reducing adverse effects and improving patient care through more accurate renal function prediction. Future work will focus on training the model on a larger database of patients, evaluating the model on an external patient dataset to improve external validity, and enhancing model performance by integrating MedBERT. MedBERT leverages AI techniques to create contextualized embeddings from structured electronic health records (EHRs), enabling improved performance in predictive healthcare tasks.

Acknowledgements

Mansoor Khan, Ph.D.

Chendil Damodaran, Ph.D.

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Abstracts

1. Effects of the Thirdhand Smoke Toxicant Nicotine-derived Nitrosamine Ketone (NNK) on Platelet Activation

Lanam Millican, Reina De La Paz, Shelby Umphres, Ahmed B. Alarabi, Fatima Z. Alshbool, Fadi T. Khasawneh
Department of Pharmaceutical Sciences

Cardiovascular disease (CVD) is the leading global cause of death, with platelets playing a crucial role in thrombosis-dependent CVD. Thirdhand smoke (THS)- the residual toxicants from tobacco smoke- contributes to ongoing exposure even after smoking has ceased and can persist in indoor environments for months. Previous research from our laboratory showed that THS exposure increases platelet activity and the risk of thrombotic CVD. To this end, while the nicotine-derived nitrosamine ketone (NNK), a significant THS toxicant, is linked to increased cancer risk and tumor growth, nothing is known regarding its effect on platelet function. Thus, we sought to examine the effects of NNK on platelet function, in order to address the implications of THS constituents for CVD. Utilizing blood from healthy human donors, our results showed that platelets treated with NNK exhibited enhanced aggregation when compared to the vehicle control, in response to the agonist ADP. Similar results were observed when the NNK-treated platelets were stimulated with another agonist, thrombin, suggesting that the effects manifest regardless of the agonist used. Additionally, platelets treated with NNK also exhibited enhanced P-selectin expression/secretion in response to agonist stimulation. Consist with the aggregation and secretion data, our thrombosis T-TAS01 system revealed an increase in the area under the curve (AUC) in NNK treated platelets relative to the vehicle, which indicates enhanced platelet reactivity. These results suggest that NNK is responsible-at least in part- for the enhancement of platelet activation due to THS exposure and that the effects manifest regardless of the agonist employed.

2. Impact of Smoking on Drug Metabolism for Disease States

Miguel Delgado, Mykel Colbert, Jerry Xie, Simon Chibueze Ezeudu, Elizabeth Pan, Sofía Ferguson, Hamed Ali
Department of Pharmaceutical Sciences

Introduction: Smoking poses a major global health challenge, affecting 1.3 billion individuals worldwide and contributing significantly to morbidity and mortality, especially in those with chronic diseases. This study explores how smoking interferes with drug metabolism and impacts therapeutic outcomes, emphasizing the need for personalized treatment strategies. Understand the effects of smoking in crucial pathways.

Methods: A comprehensive review of literature was conducted using PubMed and EMBASE databases to examine the interactions between smoking, drug metabolism, and disease states. Articles were selected based on their relevance to smoking's effects on pharmacokinetics and disease states. The analysis aimed to synthesize findings related to the modulation of metabolic pathways by cigarette smoke constituents. We also extensively evaluated data on the E-cigarette & Texas youth tobacco survey provided by Texas Health and Human Services of 202312.

Results: A literature review of smoking's effects on pharmacokinetics revealed that cigarette smoke induces key enzymes such as cytochrome P450 and uridine diphosphate-glucuronosyltransferases (UGTs), altering the metabolism of many medications. For instance, smokers consuming 11–20 cigarettes daily exhibit a 1.66-fold increase in CYP1A2 activity, reducing the efficacy of drugs metabolized by this enzyme. Smoking also induces CYP3A4, impacting oral contraceptives and increasing thrombotic risk.

Conclusion: Understanding the interplay between smoking and drug metabolism is essential for optimizing therapeutic outcomes. Collaboration among healthcare professionals is critical in developing personalized cessation strategies to enhance patient safety and improve health outcomes.

3. Understanding Medication Adherence Among Pharmacy Students: A Social Cognitive Perspective

Shelby Ruggles, Makenna Kleibrink, Kayla Mok, Mitchell Barnett,
Department of Pharmaceutical Sciences

Introduction: Medication adherence is influenced by cognitive, behavioral, and environmental factors, as described by Social Cognitive Theory (SCT). Despite their education on adherence, pharmacy students may still face real-world challenges in consistently taking medications. This study applies SCT to examine the gap between knowledge and adherence by exploring self-efficacy, outcome expectations, and environmental barriers among third-year pharmacy students at Texas A&M University.

Methods: A total of 63 third-year pharmacy students were randomly assigned one of six simulated medication regimens using jellybeans and instructed to adhere to it for one week. Afterward, participants completed a post-regimen survey assessing:
-Self-reported adherence rates
-Perceived barriers, including motivation, forgetfulness, and schedule disruptions
-SCT-related factors, such as self-efficacy, outcome expectations, and environmental influences
Results: Despite their education, only 47.7% of students reported being somewhat to mostly adherent, illustrating that knowledge alone does not ensure adherence.
-Students with prior chronic medication use exhibited higher adherence, likely due to habit formation and greater self-efficacy.
-Male and older students had greater adherence, possibly due to structured routines and prior reinforcement.
-Unexpectedly, regimen complexity was associated with adherence, suggesting some students performed better with more structured dosing schedules.
-Common barriers included self-regulation challenges, social and environmental disruptions, and low motivation, aligning with SCT.

Conclusion: These findings reinforce the complexity of adherence behaviors and highlight the role of self-efficacy, external reinforcement, and environmental factors. SCT-informed strategies, such as habit-building exercises, accountability mechanisms, and adaptive adherence techniques, may improve adherence among pharmacy students and their future patients.

4. Challenges and Current Strategies in Treatment of Drug-Resistant, Metabolically Reprogrammed Triple Negative Breast Cancer Cells

Irma Garcia-Rios, Viviana Ramos, Hamed Ali
Department of Pharmaceutical Sciences

Background: HER2-positive breast cancer (BC) caused by a mutant growth factor, HER2, is an aggressive form of cancer that has shown significant drug resistance. Eliminating steric clashes at the ortho-steric site of HER2L755S and HER2T798I(M)I could be key to overcoming resistance by improving drug binding. This study aimed to design novel lapatinib analogs that effectively bind to the HER2L755S and HER2T798I(M)I Mutants and reduce anti-HER2 resistance in HER2-positive breast cancer treatment.

Methods: Molecular docking and dynamics simulations were applied to screen a library of 1,474,068 compounds using the Schrödinger suite of the Maestro software. This study used ligand stability and the interaction between ligands and proteins. The pharmacokinetic properties of the molecules that produced the best docking scores were further assessed using Swiss ADME.

Results: In comparison to the reference drug, 10 of the screened compounds showed significant docking scores. Compound 856174 demonstrated a high docking score (-9.921 kcal/mol) as well as strong hydrogen bonding to key residues (THR 862, MET 801). Molecular dynamics simulation shows the formation of a stable protein complex. The data from Swiss ADME indicates moderate aqueous solubility, low hepatotoxicity (inactive), high gastrointestinal absorption, and no blood-brain barrier (BBB) penetration. In addition, the pharmacokinetics study classified compound 856174 as Class VI or Non-toxic (LD50 > 5000 mg/kg).

Conclusions: Compound 856174 shows promise as a potential inhibitor of HER2T798I, with favorable pharmacokinetic and binding properties. Additional in-vitro and in-vivo studies are required to validate its therapeutic potential for overcoming anti-HER2 resistance in breast cancer.

5. Optimization of Buchwald Amination Condition in the Synthesis of 3-Arylamino-2-aryl Indoles for Developing Novel Analgesics from Positive Allosteric ligands of the Cannabinoid CB1 receptor

Pedro Ochoa IV, Priscilla Gracia, Christabel Igwe, Vivian Rios, Rajpal Vangala, Zhixing Wu, Dai Lu
Department of Pharmaceutical Sciences

Introduction: A novel class of positive allosteric ligands (PAL) of the cannabinoid CB1 receptor, 3-arylamino-2-aryl indoles, was discovered in our lab. The representative compounds, such as PTDP-131 and PTDP-947 showed robust pain suppression effects without inducing cannabimimetic adverse effects and addictive liabilities. The synthesis of this class of compounds involves indole synthesis via Sonogashira coupling reaction followed by Buchwald-Hartwig amination at indole C-3 position, which is a key step to access the 3-aryalamino-2-aryl indole scaffold. The variables of Buchwald-Hartwig amination including the choices of aryl halide, Pd pre-catalyst, phosphine ligand, base and solvent are all interrelated. Changes to one can impact the relative energies of multiple steps within the catalytic cycle, and consequently affects the product yield. To optimize this reaction, we investigated amination condition. To effectively solubilize the amination product, toluene was selected as reaction solvent. The reaction was optimized by variations including Pd pre-catalysts, phosphine ligands, and bases to optimize the synthesis of this key intermediate 3-arylamino-2-phenyl indole.

Methods: Over 12 Pd pre-catalysts, and corresponding biphenylphosphine ligands, strong base t-BuONa and weak base Cs2CO3 to investigate the reaction condition for optimization.

Results and Conclusion: The nature of the pre-catalyst and the corresponding phosphine ligands are critical factors for an optimal yield in synthesizing the desired Buchwald-Hartwig amination product. It was found that Brettphos Pd-G1 in the presence of t-BuONa and Brettphos provided the optimal yield up to 92%. The optimization supported the synthesis of 3-aryalamino-2-aryl indoles for the development of novel analgesics from CB1 PALs.

6. Precision Targeting of Anti-HER2 Resistance in Breast Cancer via Eliminating Steric Clashes in HER2L755S and HER2T798I(M)I Mutants

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Background: HER2-positive breast cancer (BC) caused by a mutant growth factor, HER2, is an aggressive form of cancer that has shown significant drug resistance. Eliminating steric clashes at the ortho-steric site of HER2L755S and HER2T798I(M)I could be key to overcoming resistance by improving drug binding. This study aimed to design novel lapatinib analogs that effectively bind to the HER2L755S and HER2T798I(M)I Mutants and reduce anti-HER2 resistance in HER2-positive breast cancer treatment.

Methods: Molecular docking and dynamics simulations were applied to screen a library of 1,474,068 compounds using the Schrödinger suite of the Maestro software. This study used ligand stability and the interaction between ligands and proteins. The pharmacokinetic properties of the molecules that produced the best docking scores were further assessed using Swiss ADME.

Results: In comparison to the reference drug, 10 of the screened compounds showed significant docking scores. Compound 856174 demonstrated a high docking score (-9.921 kcal/mol) as well as strong hydrogen bonding to key residues (THR 862, MET 801). Molecular dynamics simulation shows the formation of a stable protein complex. The data from Swiss ADME indicates moderate aqueous solubility, low hepatotoxicity (inactive), high gastrointestinal absorption, and no blood-brain barrier (BBB) penetration. In addition, the pharmacokinetics study classified compound 856174 as Class VI or Non-toxic (LD50 > 5000 mg/kg).

Conclusions: Compound 856174 shows promise as a potential inhibitor of HER2T798I, with favorable pharmacokinetic and binding properties. Additional in-vitro and in-vivo studies are required to validate its therapeutic potential for overcoming anti-HER2 resistance in breast cancer.

7. Targeting Triple-Negative Breast Cancer: Screening and Mechanistic Evaluation of a Novel Scaffolds Library Using NCI-60 Cell Lines

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Background: Triple-negative breast cancer (TNBC) is a highly aggressive and difficult-to-treat form of breast cancer, characterized by the absence of estrogen receptors (ER-), progesterone receptors (PR-), and HER2 expression (HER2-). It is often associated with poor prognosis and resistance to conventional therapies, so discovering targeted treatment options is crucial. The objective of this study was to screen a library of novel kinase inhibitors for their potential anticancer activity against a variety of human cancer cell lines, with a particular focus on triple-negative breast cancer cell lines, to identify promising compounds for further development.

Methods: The National Cancer Institute's (NCI) 60 human tumor cell lines were utilized to screen 160 novel compounds. The screening focused on assessing the growth inhibition of various cancer cell lines, including TNBC, by measuring the GI50 values (the concentration of compound required to inhibit 50% of cell growth). Selected compounds showing significant activity were further investigated for kinase selectivity and mechanisms of action using in-silico molecular docking and simulation studies.

Results: Among the compounds tested, several demonstrated potent anticancer activity in TNBC cell lines, including the MDA-MB-231 and BT-549 cell lines, with GI50 values in the nanomolar range. Notably, compounds HA45 and HA46 exhibited strong selectivity and efficacy, targeting key signaling pathways involved in cancer progression. Conclusions: The results highlight several promising kinase inhibitors that could serve as potential targeted therapies for triple-negative breast cancer. These compounds are undergoing further preclinical evaluation to confirm their therapeutic potential.

8. Bruton's Tyrosine Kinase (BTK) Inhibitor, Acalabrutinib, Disrupts Endothelial Junctional Proteins and Promotes Endothelial Dysfunction

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Introduction: Emerging evidence has shown that a class of drugs known as Bruton Tyrosine Kinase (BTK) inhibitors have been associated with cardiotoxic effects, increasing the number of patients suffering with cardiovascular diseases. Acalabrutinib, a second-generation BTK inhibitor used in B-cell malignancies was designed to be less toxic than its previous generation of BTK inhibitors but was recently associated with hypertension, arrhythmia and endothelial dysfunction. However, the mechanisms by which it causes cardiotoxic effects are unknown. This study investigates the impact of acalabrutinib on endothelial integrity and evaluates the potential effect of an antihypertensive, amlodipine, in protection against acalabrutinib-induced endothelial injury.

Methods: Endothelial cells (EOMA) were cultured and were treated with or without acalabrutinib (10 μM), amlodipine (5 μM), and combination therapy of acalabrutinib+ amlodipine for 24h. Endothelial nitric oxide synthetase (eNOS) was determined by western blotting, Nitric Oxide was analyzed by Nitric Oxide assay kit. Endothelial junctional proteins ZO-1 and VE-cadherin were detected by immunofluorescence and western blotting. Endothelial cell permeability was determined by FITC-dextran permeability.

Results: Acalabrutinib reduced NO production, correlating with decreased phospho-eNOS/eNOS ratio. Immunofluorescence analysis showed disruption of tight junction protein ZO-1 and VE-cadherin which was confirmed by western blotting. Notably, co-treatment with amlodipine partially restored ZO-1 expression and NO levels, mitigating acalabrutinib-induced endothelial dysfunction. Acalabrutinib significantly increased endothelial permeability which was diminished by amlodipine.

Conclusion: Acalabrutinib disrupts endothelial homeostasis by reducing NO availability and impairing tight junction integrity, contributing to increased vascular permeability. Amlodipine may offer protective effects against the adverse outcomes of acalabrutinib.

9. A Small Molecule Inhibitor of Notch1, Chemo Sensitizes Triple-Negative Breast Cancer

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Background: Triple-negative breast cancer (TNBC) exhibits high chemoresistance, particularly in the mesenchymal stem-like (MSL) and basal-like 1 (BL1) subtypes, due to ligand-independent activation of Notch1. Current Notch1 inhibitors are associated with significant toxicity and an off-target profile. This study evaluates a small-molecule inhibitor of Notch1 (ASR490) as a potential chemosensitizer in TNBC subtypes.

Methods: We performed cell viability assays, immunoblotting, RNA sequencing (bulk and spatial; 10X Genomics), and mass spectrometry imaging. The TNBC patient-derived xenograft (PDX) mouse model was used for in vivo studies.

Results: ASR490 inhibits Notch1 expression by binding to and stabilizing the negative regulatory region (NRR), showing a lower IC50 than doxorubicin (DXR), docetaxel, and carboplatin. Chemotherapeutic agents induce Notch1, which leads to poor prognosis and increased toxicity. However, combining a low amount of ASR490 with chemotherapy decreased Notch1 expression and exhibited synergistic effects in several TNBC cell lines. Furthermore, ASR490 enhanced the sensitivity of TNBC tumors to DXR in the TNBC-PDX mice model, consistent with our in vitro data. Intratumoral analysis of spatial features, including NOTCH1 expression, revealed heterogeneous transcriptional substructures. However, integrated analysis of all samples resulted in eight transcriptionally distinct clusters that mapped across all individual sections. Comparison of clusters with distinct NOTCH1 expression identified pathways, including Apoptotic cleavage, Mitophagy, Nucleotide excision repair, Cell cycle and DNA Repair were significantly altered indicating a restructuring of transcriptional program leading to chemosensitization.

Conclusion: ASR490 enhances the chemotherapy response by stabilizing the NRR and inhibiting Notch1 signaling, providing a novel strategy to overcome chemoresistance in TNBC.

10. Quality Assessment of FDA-Approved Products of Divalproex

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Introduction: Seizures remission has been reported in epileptic patients upon switching to another generic product. This may be caused by underlying quality differences among the interchangeable generics upon storage. In this study, a number of modified-release commercial products of Divalproex sodium, a narrow therapeutic index antiepileptic agent, was assessed.

Methods: Products were stored at three different conditions: a. ambient conditions (25±0.5oC/65%RH) to simulate pharmacy storage conditions, b. patients' in-use conditions (30oC/75%RH), and c. accelerated stability testing conditions (40oC/75%RH), for predetermined periods up to 3 months. The products were then analyzed for in-vitro dissolution profiles. Changes in physicochemical properties were studied using near infrared (NIR) chemical imaging, surface morphology (scanning electron microscopy, SEM), Fourier transformed infrared spectroscopy (FTIR), and X-ray powder diffraction (XRPD).

Results: All the selected products satisfied the US Pharmacopeia drug release limits prior to storage according to their respective monographs. After storage, significant changes in the dissolution profiles were observed. The FTIR spectra confirmed the integrity of the drug substance. NIR chemical imaging of the unit doses indicated compositional changes during storage. SEM images showed changes in their morphology as well as in the solid state of the drug (drug crystals) further confirmed by XRPD.

Conclusions: The study revealed that bioequivalent Divalproex sodium modified-release products stored at conditions seen as normal and/or short-lived can significantly affect the quality attributes of the unit doses due to changes in the solid state of the drug and the physical qualities of the unit doses.

11. Targeting Metastatic Prostate Cancer with Antiandrogen- equipped Histone Deacetylase Inhibitor

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Background: Prostate cancer (CaP) heavily depends on the androgen receptor (AR), and standard treatments for advanced cases include androgen deprivation therapies (ADT) such as enzalutamide (ENZ) and abiraterone. However, CaP can develop into castration-resistant prostate cancer (CRPC) even with ADT. Researchers are exploring new treatments, particularly those that aim to downregulate AR and HDAC expression epigenetically. Hence, we have developed a novel molecule, KK62, which combines ENZ and HDAC inhibitors. This combination is designed to inhibit both AR and AR-V7 expression, ultimately reducing the growth of CRPC.

Methods: We synthesized the target antiandrogen-equipped histone deacetylase inhibitors, adapting the convergent chemistry we used to synthesize the first-generation compounds. The final compounds were characterized using 1H-NMR, 13C-NMR, and high-resolution mass spectrometry. We synthesized and analyzed several compounds, in which KK62 emerged as the lead compound.

Results: KK62 effectively inhibits various CRPC cell lines at nanomolar concentrations without harming healthy prostate cells. Molecular analysis indicates that KK62 inhibits AR and AR-V7 activation and leads to growth inhibition of CRPC cells. KK62 achieves this therapeutic effect by degrading the AR through the ubiquitin-proteasome pathway and reducing the expression of HDAC markers 2, 3, and 6. In vivo, studies using castrated and non-castrated xenografted CRPC models further support KK62's potential as a therapeutic agent for CRPC.

Conclusion: KK62 is a novel compound that epigenetically inhibits AR, AR-V7 activation compared to conventional ADT. The preclinical results from CRPC models suggest that KK62 is a promising agent that can be translated to clinical settings.

12. Identification of Novel Small Molecules Targeting FOXM1 in Chemo-resistant Colorectal Cancer

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Introduction: Colorectal cancer (CRC) is a leading cause of mortality in the United States. The development of chemoresistance to 5-fluorouracil (5FU), the first-line treatment, contributes to the metastatic progression of the disease. FOXM1, a transcription factor that regulates critical cellular functions, may play a significant role in the resistance to 5FU (5FUR). Consequently, we have identified novel inhibitors, ASR458 and SAC53, which effectively inhibit FOXM1 expression and significantly reduce growth in metastatic CRC and 5FUR-CRC cell lines and tumors.

Method: We conducted cell viability assays in metastatic CRC and 5FU-resistant CRC followed by Western blotting, immunofluorescence, FACS analysis, and xenograft studies.

Results: Our results show that FOXM1 expression is markedly elevated in patients with metastatic CRC compared to primary tumors. Notably, treatment with 5FU induced the expression of FOXM1 in mCRC cell lines. Our newly identified small molecules, ASR458 and SAC53, inhibited the growth of HCT-116 and HCT-5FUR at nanomolar concentrations without causing significant toxicity to normal colon epithelial cells. Their efficacy surpassed the currently available FOXM1 inhibitor, FDI-6, which requires mM concentrations to inhibit the growth of the 5FUR cell line. Western blot analysis corroborated that treating ASR458 and SAC53 led to a downregulation of FOXM1 expression, and in silico analysis suggested that ASR458 may directly bind to FOXM1. Moreover, ASR458 demonstrated the ability to inhibit tumor growth in mCRC xenograft models, while further studies on SAC53's efficacy are underway.

Conclusion: The suppression of FOXM1 in 5FUR-CRC suggests a promising therapeutic potential for overcoming chemoresistance in CR cancer.

13. Exploration of Protein Kinase Inhibitors as Antibacterial Agents: Targeting MRSA and VRE Resistance

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Introduction: Antimicrobial-resistant (AMR) strains like Methicillin-Resistant Staphylococcus Aureus (MRSA) and Vancomycin-Resistant Enterococcus (VRE) are becoming more virulent, which makes it urgent to find innovative approaches to overcome their resistance. Protein kinase inhibitors have recently arisen as promising antibacterial agents. We initiated our study by screening the antibacterial activities of the in-house hits, initially designed as kinase inhibitors, compared to PK-150. Our first diarylurea hit, HA-52, showed considerable anti-staphylococcal activity with a MIC value of less than 6.25 μg/mL compared to PK-150 (MIC < 0.4 μg/mL). The initial screening results motivated us to explore the essential structural features of the active compounds and to optimize the tested diarylureas to target bacterial menaquinone biosynthesis through the structural modification of our compounds to have a similar binding mode to PK-150 in the menaquinone methyltransferase (MenG) enzyme.

Methods: We designed, synthesized, and evaluated structurally optimized scaffolds bearing diarylurea moieties. The novel series of optimized compounds were screened against various bacterial strains using single- and multi-strain screening, including MRSA & VRE strains.

Results: The screening of the optimized compounds showed promising results, particularly HA-167 and HA-163, against MRSA and VRE strains, with MIC values as low as 0.25 μg/mL.

Conclusion: The findings highlighted the antimicrobial screening of kinase inhibitors' potential against resistant bacterial strains. We found promising analogs with outstanding antibacterial activity against gram-positive resistant strains such as MRSA and VRE while exploring a series of modified diarylurea compounds compared to PK-150 as our model drug.

14. Psychostimulants Cocaine and Methamphetamine: Acute and Chronic Effects on DNA Repair Pathways and the Epigenetic Landscape in Microglia

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Introduction: Psychostimulants, such as cocaine and methamphetamine (METH), are known to affect several cellular functions, including those involved in DNA damage and repair. DNA damage and repair proteins (DRPs) regulate transcription, replication, and chromatin modifications by shaping the epigenomic landscape. However, the effects of chronic cocaine and METH exposure on DNA damage and repair pathways in brain immune cells, particularly microglia, remain poorly understood. This study investigates how cocaine and METH affect genomic stability, DNA repair mechanisms, and epigenomic modifications under acute (24 hours) and chronic (5 days) exposure conditions.

Methods: Human microglial cells (HMC3) were treated with cocaine (2 μM) and METH (10 μM), and the levels of DNA repair proteins—including ATM kinase, phosphorylated H2AX (Ser139), ERCC proteins, H2AX, KAT5, and NBS1—were assessed via western blot analysis. Epigenetic markers such as H3K9me and H3K27ac were evaluated using immunocytochemistry.

Results: These observations strongly demonstrate that acute exposure increases the expression of DNA repair proteins, including phosphorylated H2AX (p-H2AX), ATM, ERCC2, ERCC3, ERCC6, and KAT5. In contrast, chronic exposure significantly reduces these markers, impairing DNA repair and genomic stability. Concurrently, epigenetic alterations, marked by increased H3K9me and H3K27ac, were observed, indicating a disruption of the epigenetic landscape.

Conclusion: These findings reveal that while acute cocaine and METH exposure activate protective DNA repair responses, chronic exposure leads to impaired repair mechanisms, DNA damage accumulation, and epigenetic changes. This disruption of DNA integrity and repair pathways underscores the detrimental effects of chronic drug abuse on microglial function and its potential contribution to neurodegeneration.

15. Design and Synthesis of Novel oxazoline derivatives as Targeted Kinase Inhibitors with improved Blood-Brain Barrier

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Introduction: The blood-brain barrier (BBB) poses a significant challenge in CNS disorders and brain metastatic cancer, which limits pharmacokinetics (PK) of targeted-kinase therapy. This study explores these challenges via designing and synthesizing oxazoline derivatives. This study aims to design and synthesize oxazoline derivatives optimized for pharmacodynamic (PD) kinase inhibition and PK BBB permeability, trying to address these limitations of the current cancer therapies.

Methods: A structure-based drug design approach was employed, utilizing computational modeling to optimize key physicochemical properties, including lipophilicity and hydrogen bond potential to guide the synthesis of target compounds. Structural elucidation of the synthesized derivatives was conducted using 1HNMR, 13C NMR, 13C DEPT, HRMS, and FTIR spectroscopy. Early kinase profiling, molecular modeling, and Structure-activity Relationship (SAR) significantly improve our rational design for lead optimization. Further in vitro PK and PD validation for BBB permeability via PAMP assay, kinase profiling, and MTT assay are in process

Results: The oxazoline derivative demonstrated potential BBB penetration and potent kinase inhibitory activity. Computational predictions aligned strongly with experimental findings, confirming the design's efficacy.

Conclusion: This study establishes a dual-approach framework combining rational design and CADD-chemical synthesis to develop effective CNS-targeted therapeutics. The findings demonstrate the potential of oxazolines as a versatile chemical platform for addressing metastatic cancer in the brain, contributing to improved treatment outcomes.

16. Learning Mouse Work to Investigate Epigenetic Regulation of Cardiometabolic Diseases

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Introduction: Epigenetics, the study of gene expression without changes to the genetic sequence, has been a fast-growing field due to its applications in studying and diagnosing cardiometabolic diseases prevalent in the modern population. With the rise of obesity, insulin resistance, and metabolic dysfunction-associated steatotic liver disease, exploring if there is an epigenetic explanation for these disorders has become a high priority. With this research, we aim to find an answer to the prevalence of the above-mentioned metabolic disorders, and determine if there are biological and epigenetic markers present for preventative screening of such diseases.

Methods: After a series of CITI trainings in animal studies, we, a team of undergrads, started to learn how to carry out mice studies. Daily activities include ensuring each mouse has adequate food, water, and bedding. We also learned weaning of mice after 3 weeks of their birth. Further, hands-on training on weaning, breeding, and single/group housing were provided by our postdoctoral mentor. Lastly, a series of safety techniques are being trained to investigate cardiometabolic diseases.

Results: To ensure our tissues of study, white and brown adipose tissue and heart, are in the best condition for analysis, it is essential to our study that our animal model is properly cared for and housed. Through the study we have learned how to maintain the quality of our experimental tissues.

Conclusion: The proper maintenance of animal models is the most crucial aspect of an experimental design to ensure the scientific integrity and efficacy of the study.

17. Design and Optimization of Dose-Flexible Tolfenamic Acid Dosage Forms with Real-Time Coating Process Monitoring Using PAT Tools

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Introduction: Tolfenamic acid (TA), an NSAID recognized for its potential in modulating cancer-related molecular pathways, faces limited clinical application due to poor bioavailability and gastric irritation. This research focuses on developing a dose-flexible enteric-coated TA formulation to enhance its anti-cancer efficacy and mitigate side effects. The study aims to design enteric-coated and non-enteric-coated TA dosage forms, optimize their manufacturing processes using Process Analytical Technology (PAT), and evaluate pharmacokinetics to establish a personalized cancer treatment regimen.

Methods: Formulations were developed using advanced pharmaceutical techniques, incorporating PAT tools like Near-Infrared (NIR) spectroscopy for real-time monitoring of coating processes. Preclinical studies included in vitro characterization of formulations and in vivo pharmacokinetic profiling to evaluate bioavailability and systemic exposure. Statistical methods, including regression analysis and ANOVA, were employed to optimize formulation variables and validate analytical techniques.

Results: The enteric-coated TA formulations demonstrated significant improvements in in-vitro Drug release profile and reduced gastric irritation compared to non-coated forms. PAT integration ensured consistent coating quality and minimized off-line testing variability. The dose-flexible system enables customized dosing, which supports its application in combination therapies, potentially reducing side effects and improving clinical outcomes.

Conclusion: This research establishes a novel dose-flexible, enteric-coated TA formulation as a promising adjunct therapy for advanced cancers. The innovative integration of advanced formulation techniques with real-time PAT monitoring enhances manufacturing precision, ensuring therapeutic efficacy and patient safety. This approach addresses the limitations of fixed-dose regimens, paving the way for tolfenamic acid to serve as a viable and effective cancer treatment adjunct.

18. Development of Biorelevant Multimodal In vitro Characterization Techniques for Assessing the Adhesiveness Performance of Transdermal Patches

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Introduction: Adhesion is a pivotal determinant of the quality, efficacy, and safety of transdermal patches. The adhesive properties of the patch have a direct correlation with drug permeation and flux notably for matrix system patches. For potent therapeutics, the quality, adhesion strength and minor tampering during wear can significantly impact patch's in vivo performance. Adhesive performance can fluctuate over the duration of wear. To investigate the feasibility of using interferometry, and infra-red thermography for assessing the structural and adhesive deficiencies of transdermal patches.

Methods: In this study, surface topography was characterized using a Zygo NewView 600 interferometer. Thermal properties of the patches were assessed via thermal analysis using a Fluke Ti480 Pro Infrared Camera. Permeation profiles of nicotine patches (both intact and tampered) were evaluated using vertical Franz diffusion cells with a receiver orifice-area of 1.77 cm^2.

Results: Interferometry showed significant roughness differences between un-tampered and tampered patches ($p<0.05$, 95% CI) among test patches. Specifically, 2R and 10R tampered sets differed significantly. No significant differences were found among reference patches ($p>0.05$, 95% CI), which was confirmed by roughness profiles. Tampered test patches exhibited higher peaks, suggesting greater loss of adhesive than reference patches, indicating superior quality of the adhesive used in the manufacturing of reference patches.

Conclusions: Transdermal patch performance was assessed via interferometry, infrared spectroscopy, probe-tack test, and IVPT for drug permeation across porcine skin. The above comprehensive series of tests offers valuable insights to industry and academia in developing generic transdermal patches.

19. Screening and Mechanistic Evaluation of Novel Kinase Inhibitors with Selective Anticancer Activity in NCI-60 Cell Lines

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Background: Targeted cancer therapies aim to improve effectiveness while minimizing adverse effects. The NCI-60 Human Tumor Cell Line Screen provides a powerful platform for discovering compounds with selective anticancer activity across various cancer subtypes. Identify potent compounds from a library of 160 novel compounds, focusing on molecular selectivity, mechanistic insights, and preclinical efficacy.

Methods: 60 human cancer cell lines derived from nine different types of cancer; leukemia, melanoma, and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. Initial screening was done at a dose of 10 μM. Compounds showing more than 50% growth inhibition were selected for the five-dose study. Compounds showing IC50 in the nanomolar range were subjected to kinase selectivity, and in-silico studies to identify their mode of action.

Results: Among 160 compounds 53 compounds were selected for five dose studies. Seventeen compounds exhibited significant selectivity, with GI50 values in the nanomolar range. Compounds HA45 and HA46 demonstrated potent kinase inhibition profiles against CNS SNB 74 cell lines. Compounds HA9,10,12 and 23 showed high selectivity against LOX-IMVI and Sk-MEI-5 melanoma cell lines. Compound HA88-97 showed high level of non-selective growth inhibition. Compound HA57-58 showed selective growth inhibition against the MDA-MB-468 cell line. Molecular docking and dynamics simulations revealed stable interactions with target kinases, corroborating structure-activity relationships.

Conclusions: The screening identified 19 compounds showing high potency and significant selectivity, highlighting their potential as promising candidates for targeted cancer therapy with minimal toxicity. They are currently undergoing further in vivo and in vitro investigations.

20. Formulation Study and Pharmacokinetic Characterization of PTDP-15 as A Preclinical Candidate for Non-Addictive and Non-Opiate Analgesics

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Background: PTDP-15, a lead compound for a new class of positive allosteric modulator (PAM) of the cannabinoid CB1 receptor, was discovered in our lab. The compound showed potent allosteric modulation on cannabinoid CB1 receptor, indicative for potential application in pain suppression. However, it's a highly lipophilic and displayed poor aqueous solubility. To validate whether the compound is a viable lead compound for drug discovery, formulation methods are needed for parenteral and intravenous administration of the experimental drug. While DMSO can be a valuable co-solvent in vivo efficacy studies, it is crucial to optimize its concentration and exposure duration to minimize potential biological effects. Additionally, DMSO containing media is not suitable for PK and behavioral studies that typically involve intravenous administration of drug candidate.

Methods: We measure the aqueous solubility of PTDP-15 through a standard protocol and investigated the formulation methods for parental administration with minimum involvement of DMSO by the combination of various cosolvent with 10-20% DMSO. For intravenous administration need, we investigated the DMSO-free formulation methods using a variety of co-solvents including Tween-80, tween-40, PEG200, PEG400, Cremophor EL and propylene glycol.

Conclusion: Using the combination of DMSO and Cremophor EL, ethanol and PBS, a method suitable for parenteral administration of the drug up to 3 mg/mL (equivalent to 60 mg/Kg dose need). Through the combination of non-DMSO cosolvent we are able to solubilize the drug up to 2 mg/mL that is well suited for intravenous drug administration. The formulation methods successfully supported in vivo efficacy, PK & behavioral studies.

21. Metabolic Cartography: Biochemical Mapping of Type-2 diabetes Linked Alzheimer's Disease Related Dementia

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Introduction: Liquid chromatography-mass spectrometry (LC-MS) has emerged as a powerful tool for metabolic profiling and providing critical insights into physiological and pathological processes. This study focuses on metabolic alterations in a novel genetically modified mouse model of type 2 diabetes (T2D)-linked Alzheimer's disease related dementia (ADRD) with an aim to explore potential diagnostic and prognostic biomarkers. To comprehensively map the metabolomic shifts in serum and urine samples to identify diagnostic markers for T2D linked ADRD-like changes in brain. Methods: Serum and urine samples from control and diseased mice were analysed using high-resolution LC-MS with positive electrospray ionization (ESI) in MSE mode. The analysis focused on two mass-to-charge (m/z) ranges: 50–250 and 500–2000, enabling untargeted profiling of small and medium-range metabolites. Advanced data processing was conducted using MassLynx software and the NIST database for detailed metabolite characterization.

Results: Preliminary findings revealed distinct and specific spectral peak shifts that distinguished diseased and control groups in both serum and urine. The 50–250 m/z range showed significantly altered peak intensities for low molecular weight metabolites, highlighting potential disease-associated changes. In the 500–2000 m/z range, potential modifications in peptides or lipid profiles were observed, indicative of disease-related metabolic disruptions.

Conclusion: This study demonstrates the potential of LC-MS-based metabolomics in revealing metabolic disturbances associated with T2D and Alzheimer's-related dementia. The innovative approach provides a foundational framework for identifying novel diagnostic and prognostic markers, advancing our understanding of the complex metabolic mechanisms underlying interconnected metabolic and neurodegenerative disorders.

22. Exosomes from Trimethylamine-N-Oxide (TMAO) Stimulated Endothelial Cells Contributes to Endothelial Dysfunction

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Introduction: Gut microbe metabolite, Trimethylamine-N-Oxide (TMAO), has been identified as an independent risk factor for adverse cardiovascular events. In recent years, extracellular vesicles have gained attention due to their involvement in physiological and pathological processes in cardiovascular diseases. The role of TMAO in synthesis and release of exosomes from endothelial cells (ECs) remains unclear. Based on our preliminary results, we hypothesized, TMAO stimulation results in enhanced exosomal release from ECs and these EC-derived exosomes (TMAO-Exos) have the potential to induce endothelial dysfunction.

Methods: Exosomes were isolated from EC culture and plasma with or without TMAO treatment, using exosome isolation kit. Exosomes markers like CD63, CD9 were analysed by western blot. Isolated exosomes were characterized by Nano Sight NS300 analyser, transmission electron microscope (TEM) and Cryo-TEM. Immunophenotyping of exosomes was measured by nano-flow cytometry. ECs were treated with these isolated exosomes for 24hr and endothelial barrier integrity was determined by FITC-dextran permeability and trans-endothelial electrical resistance (TEER). Cytokine production in ECs was measured by ELISA. In addition, tight junctional disruption was examined by immunofluorescent staining.

Results: TMAO treatment enhanced both CD9 and CD63 protein levels in ECs as compared to control. TMAO-Exos induced damage to the endothelial barrier integrity was demonstrated by cell permeability assay and TEER experiments. TMAO-Exos also increased production of interleukin-1β in ECs. Immunofluorescence revealed that TMAO-Exos markedly reduced tight junctional proteins.

Conclusion: TMAO induced formation and release of exosomes from ECs both in-vitro and in-vivo. These TMAO-Exos contribute to endothelial dysfunction and vascular injury.

23. Epigenetic Technologies to Investigate Cardiometabolic Diseases: A Tale from the Enthusiastic and Motivated Undergraduate Students

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Introduction: Epigenetics, an emerging frontier in science, focuses on the study of changes in gene regulation without altering the genetic sequence. As newer scientists in this field, our research laboratory utilizes various techniques to explore these mechanisms and gain insight into gene expression and epigenetic modifications.

Methods: This project showcases essential methodologies in our epigenetics lab. Genotyping identifies genetic variants to determine the mice's genetic and epigenetic background. mRNA and miRNA extraction examine gene activation and transcriptional regulation. Nanodrop spectrophotometry ensures RNA purity and concentration for downstream experiments. Specific buffers stabilize biological molecules during RNA extraction and electrophoresis. Gel electrophoresis detects protein levels, reflecting translational changes.

Results: To ensure high-quality data, we implement rigorous quality control at each step. Genotyping accuracy is verified to prevent misidentification. During RNA extraction, contamination is minimized by using RNase-free reagents, maintaining a sterile workspace, and wearing face masks and gloves. Nanodrop measurements confirm RNA purity and concentration for downstream applications. Buffers are carefully prepared to maintain molecular stability, and gel electrophoresis is performed under standardized conditions to ensure reproducibility. These measures enhance data reliability for epigenetic studies.

Conclusion: Together, these techniques provide a comprehensive toolkit for studying epigenetics, enhancing our understanding of gene regulation. While used in our lab to explore cardiometabolic diseases, this presentation will guide other undergraduate researchers in applying these methodologies across various fields.

24. Epigenetic Research in Obesity: From Bench Science to Bioinformatics

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Introduction: The obesity epidemic demands expansion from foundational approaches with its ever surging rates. Concomitantly, comorbidities, such as metabolic dysfunction-associated steatotic liver disease and type 2 diabetes, are also mounting. By harnessing the powers of modern technology and epigenetics, opportunities to enhance patient care begins to arise. Epigenetics involves modulation of gene expression through reorganization of DNA rather than altering the sequence itself. Epigenetic regulations are mediated by noncoding-RNAs, DNA methylation, and histone modification. Previously, our lab first discovered the metabolic role for the long noncoding-RNA Deleted in Leukemia 2 (Dleu2) and its hosted microRNA (miR) cluster, containing miR-15a/miR-16-1, presenting prospective targets. We aimed to investigate the contribution of Dleu2 and its miR cluster to epigenetic regulations in obesity and its comorbidities.

Methods: Two global knockout models MiR-/- and MDR-/-, where MiR-/- has only the miR cluster deleted and MDR-/- has the deletion of Dleu2 and the miR cluster, were fed a chow diet. After 10 weeks, both models became obese and insulin resistant. To uncover the underpinning epigenetic dysregulations, we employed a combinatorial bench side and bioinformatic approach. Using liver tissue, we coded and analyzed RNA-sequencing, ATAC-sequencing, and reverse phase protein array.

Results: We revealed prominent changes to chromatin accessibility, gene expression, and protein expression in pathways relating to lipid metabolism. We are currently validating our findings via qRT-PCR, western blot, and cell culture.

Conclusion: Through this integrated approach, we intend to discover therapeutic targets for the treatment of obesity and its comorbidities before the onset of disease.

25. Molecular Roadmap for Navigating Sex, Age, and Normalization Marker: A Comprehensive Atlas of a Complex Noncoding RNA-miRNA Cluster

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Introduction: Understanding which tissue and under what conditions a gene of interest is being expressed allows researchers to determine the presence or absence of a diseased state. Characterizing patterns of a non-diseased state provides a baseline for comparison. Here, we created a comprehensive atlas of the complex non-coding RNA cluster Dleu2-mir15/16 and how it changes in a time, tissue, and sex specific manner after establishing the most stably expressed normalization control.

Methods: Both male and female C57/BL6 mice were maintained on a control chow diet for 4-weeks, 8-weeks, 12-weeks, 4-months, and 6-8-months in age. Total RNA with miRNA extraction was carried out in metabolic and non-metabolic tissues. Three homogeneous controls were tested to establish two most consistent normalization controls. qRT-PCR analysis was then employed to evaluate the gene and miRNA expression of five genes of interest: Dleu2, KCNRG, Dleu5, miR15a, and miR16-1.

Results: Our study demonstrated that, out of three commonly used homogeneous controls, Beta Actin is the most consistent and reliable normalization control in two metabolic tissues. Significant changes were observed in all genes in an age, sex, and tissue dependent manner. Metabolic tissues showed the most dynamic up and down regulation of all genes, with Dleu2 showing the significant alterations across all categories.

Conclusion: Our results suggest two major conclusions; 1. The establishment of a reliable control is critical when dealing with multiple factors and 2. Dleu2 expression shows the most significant changes of all five genes of interest in an age, tissue, and sex specific manner.

26. Pathological Mechanisms and Potential Therapeutic Targets of E. coli K1-Induced Sepsis

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Introduction: Escherichia coli (E. coli) is a leading cause of invasive bacterial infections in humans, frequently resulting in sepsis and meningitis. Although extensively studied, the precise mechanisms governing E. coli–induced immune responses and sepsis remain incomplete. This study explores how E. coli triggers cell death and inflammation, focusing on caspase-8.

Methods: Bone marrow–derived macrophages (BMDMs) from genetically modified mice and gene-mutated E. coli strains were used to examine cell death and inflammatory pathways. In vitro assays measured apoptosis, cytokine release, and NF-κB activation. In vivo murine sepsis models assessed survival, cytokine storms, and organ damage. Molecular signaling events were evaluated by standard biochemical techniques.

Results: E. coli infection induced caspase-8–dependent apoptosis in BMDMs. Mice lacking both RIPK3 and caspase-8, but not RIPK3 alone, showed improved survival, reduced cytokine release, and lower NF-κB activation. Caspase-8 activation relied on TLR4/TRIF signaling, highlighting TLR4's pivotal role in orchestrating the immune response during infection.

Conclusions: Caspase-8 is central to macrophage apoptosis, cytokine production, and NF-κB signaling in E. coli sepsis, driven by TLR4/TRIF pathways. Targeting caspase-8 could be a therapeutic strategy to mitigate cytokine storms and enhance survival. Further investigations will clarify the detailed mechanism of caspase-8 activation and explore broader applications in inflammatory diseases.

27. Development of Tofacitinib Loaded Oral Zein Nanoparticles for Inflammatory Bowel Disease

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Introduction: Tofacitinib is one of the most effective therapies for acute, severe steroid refractory ulcerative colitis. Whilst therapy with tofacitinib was shown to reduce the probability to avoid colectomy, systemic side effects such as including nephrotoxicity, hypertension, seizures and neurotoxicity, limit its long-term use. To develop stable, tofacitinib-loaded nanoparticles using a natural protein from corn, zein and study its efficacy.

Methods: Amphiphilic nature of zein with prominent hydrophobic character was advantageous for the encapsulation of lipophilic drug like tofacitinib, while its resistance towards digestive enzymes exploited for slow and sustained drug delivery. Physicochemical characterization such as was conducted. *In vivo* efficacy of the NP was tested in DSS-induced colitis mouse model.

Results: Zein NP with an average diameter of 165 nm, polydispersity index of 0.067 and a zeta potential of -15 mv at pH 7.4 were prepared. Hydrophobic interaction between tofacitinib and zein was confirmed by FTIR, but it did not change the confirmation of zein protein as analyzed by DSC. Rate of tofacitinib release from the NP was pH dependent, with highest release in PBS pH 7.4 followed by simulated intestinal fluid (SIF, pH 6.8) and least in simulated gastric fluid (SGF pH 1.2). Pharmacokinetic profile, disease activity index, and the cytokine estimation was conducted to study the efficacy of the zein nanoparticles formulated.

Conclusion: In conclusion, a stable tofacitinib-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 control.

28. Atomistic Insights Into MenG Inhibition: Design and Synthesis of Novel Inhibitors with Enhanced Antibacterial Activity Against Drug-Resistant Pathogens

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Introduction: Antimicrobial resistance (AMR) is a global health crisis, responsible for over 1.2 million deaths annually and projected to cause over 10 million deaths by 2050. PK-150, a promising antibacterial candidate, inhibits bacterial demethylmenaquinone methyltransferase (MenG), a key enzyme in the electron transport chain. However, the lack of a 3D crystal structure for MenG has hindered PK-150 optimization. This study aims to generate a homology model of MenG, investigate PK-150's binding mode and dynamic effects via molecular dynamics (MD) simulations, and apply these insights to guide the synthesis of optimized analogs.

Method: A homology model of MenG was developed and validated for structural stability through MD simulations. Conformational dynamics of both apo and ligand-bound states were analyzed to characterize key interactions and structural changes.

Results: Molecular modeling revealed an omega-like loop (residues 106–116), essential for enzyme activity, transitioning from an open to a closed conformation upon ligand binding. The diarylurea motif of PK-150 formed a crucial hydrogen bond interaction with the conserved D81 residue. Replacing the 2,2-difluorobenzo[1,3]dioxo fragment of PK-150 with a two-atom flexible spacer linked to a hydrophobic moiety enhanced binding affinity and promoted loop closure. These insights guided the design and synthesis of HA-163, which exhibited enhanced antibacterial activity against MRSA and VRE (0.25 μg/ml), comparable to levofloxacin.

Conclusion: This study advances MenG-targeted rational drug design, providing a potential strategy to combat AMR.

29. Real Time Monitoring of Content Uniformity of Lamivudine in Selective Laser Sintering

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Introduction: Selective Laser Sintering (SLS) of medication is a novel and promising way of developing personalized medication. It is capable of accurately dispensing medication according to patient's dose, tablet size and taste needs. It is ease-of-use allows it to be utilized at point-of-care, where personalized medication can be dispensed shortly after it is prescribed. However, ensuring the quality of the 3D-printed medication at point-of-care wouldn't be feasible since gold standard quality control (QC) methods require expensive equipment and highly trained personnel. Process Analytical Technology (PAT) is a QC method that is used to quantify the drug and identify any impurities. Near Infrared Spectroscopy (NIR) is a commonly used PAT tool can quantify the drug or detect impurities in a dosage form. To incorporate a PAT tool that can detect impurities and quantify lamivudine content in real-time without interfering with the 3D printing process.

Methods: In-house programmable control arm was build using a linear stage and Arduino to move the probe in-and-out. Standard QC methods to confirm the drug content and developing a chemometric model.

Results: Chemometric model accurately predicted the drug concentration in each layer as it prints using the spectral data collected real-time.

Conclusion: For the first time ever, a non-contact NIR probe was implemented into SLS and collected spectral data real-time, without interfering with the printing process. Non-contact probe scanned freshly sintered layer without interfering with the laser or powder deposition. Collected spectral data used to quantify the lamivudine amount successfully in each layer using chemometric modelling.

30. Caspase-11 and NLRP3 Exacerbate Systemic Klebsiella Infection through Reducing Mitochondrial ROS Production

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Introduction: Gram-negative bacterium Klebsiella pneumoniae is the third most commonly isolated microorganism in blood cultures from septic patients and can cause serious epidemics and endemic nosocomial infections. Despite intensive investigation, pathogenesis and mechanism of K. pneumoniae-induced sepsis remains elusive.

Methods: We used a systemic infection model via intraperitoneal inoculation of K. pneumoniae.

Results: Using a systemic infection model through intraperitoneal injection, we found that K. pneumoniae induced severe lung injury and a high level of bacteria accumulated in all key organs, especially in the lung. Deficiency of caspase-11 or NLRP3 led to prolonged survival, a reduction of the pulmonary bacterial load, increase in the blood oxygen levels, and reduction of the pulmonary IL-6 level compared to the WT counterparts in vivo. Caspase-11 or NLRP3-deficient macrophages produced elevated levels of mitochondrial ROS compared to wild type cells in response to K. pneumoniae, correlated with more effective K. pneumoniae clearance.

Conclusions: Our data suggest that the acute respiratory failure is the main cause of death following K. pneumoniae systemic infection. Upon activation by K. pneumoniae, Caspase-11 and NLRP3 impair mitochondria function, leading to reduction in ROS production in macrophages, thereby reducing their capacity in bacteria clearance.

31. Innovative SLS 3D Printing for Pediatric-Friendly HIV Combination Therapy

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Introduction: In the pediatric population, HIV-related morbidity and mortality have been significantly reduced by using combination antiretroviral (ARV) therapy. However, due to a lack of dose flexibility and pediatric-friendly formulations, adherence to ARV treatment is a barrier. Different drugs have different physicochemical properties; thus, incorporating them into a single dosage form is particularly challenging, especially when targeting personalized pediatric needs. Selective laser sintering (SLS) 3D printing enables the fabrication of customizable, stable, and effective drug delivery systems. To develop and optimize a dose-flexible co-delivery system of ARV drugs using SLS 3D printing using a rational and holistic approach to ensure the system's quality, stability, and therapeutic efficacy.

Method: SLS 3D printing will be employed to formulate a co-delivery system using FDA-approved excipients. The critical process parameters and the critical material attributes would be optimized using the design of experiments (DOE). The quality and stability of the formulation will be evaluated using various analytical techniques.

Results: Preliminary studies demonstrated the feasibility of incorporating up to 40% of combination drug tenofovir disoproxil fumarate and lamivudine into a single dosage form in a 1:1 ratio. Disintegration and dissolution profiles showed the desired outcomes. Despite the drugs' differing melting points, the formulations were stable and exhibited dose flexibility through printed layer thickness and geometry adjustments.

Conclusion: The study successfully demonstrates the potential of SLS 3D printing to formulate a stable, dose-flexible combination therapy for treating HIV in pediatrics, overcoming the challenges. This innovation improves adherence and therapeutic outcomes and broadens its application.

32. Overcoming Cancer MDR by Carbon Nanotube-based Intracellular Drug Delivery

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Introduction: Multi-drug resistance (MDR) in cancer is caused by many factors, such as insufficient intracellular drug concentration, a result of low drug uptake and high drug efflux. Nanoparticle-based drug delivery is a straightforward way to circumvent the cancer MDR. We studied discrete multiwalled carbon nanotubes' (dMWCNTs) capability of intracellularly delivering doxorubicin (DOX) and inhibiting P-glycoprotein (P-gp) mediated drug efflux, for effective MDR cancer treatment.

Methods: DOX was loaded to dMWCNTs and unloaded DOX was removed by dialysis. To study the effects against MDR, the P-gp-overexpressed MDR cells (MES-SA/DX5) were treated with dMWCNT/DOX and the intracellular DOX was determined by flow cytometry/microscopy. A Caco-2 transwell model was also used to confirm dMWCNTs' impact on drug efflux. Their anticancer activity was estimated by cell viability assay. Intracellular localization of the nanoparticles was identified by confocal microscopy. DOX retention in tumor was determined in tumor-bearing mice.

Results: About 96% of DOX was loaded to the dMWCNTs. More intracellular DOX was observed in the MDR cells treated with dMWCNTs (60%) than free DOX (35%). The dMWCNTs were 2-fold permeable compared to DOX in the transwell model and significantly enhanced DOX's anticancer activity in the MDR cells. The dMWCNTs were co-localized with the organelles, mainly ER. Loaded DOX was retained 2-fold more than free DOX in tumors.

Conclusions: The dMWCNTs could enhance DOX uptake and decrease its efflux through organelle binding, resulting in the elevated drug concentration and prolonged drug retention time inside the MDR cells. The strategy might effectively overcome cancer MDR.

33. Effect of Process Variables on the Quality Attributes of Digoxin Formulations

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Introduction: Digoxin, one of the oldest cardiac medications, was first approved by the FDA in 1954 under the brand name LANOXIN® (NDA 020405). Evaluating the impact of manufacturing processes, process variables, and their combined effects on pharmaceutical products during storage and usage is essential to ensure consistent drug performance. Critical properties such as stability, dissolution, bioavailability, and clinical efficacy are influenced by the physical, mechanical, and chemical characteristics of the drug. This study aimed to evaluate the effects of process parameters, including particle size, binder type (lactose anhydrous vs. lactose monohydrate), and granulating fluid (water vs. ethanol), on Digoxin immediate-release formulations and their critical quality attributes. Ten formulations, including eight using wet granulation and two using direct compression, were prepared and stored under accelerated stability conditions (40°C/75% RH) for 10 days.

Methods: Formulations were evaluated for hardness, disintegration, assay, impurities, dissolution, and x-ray powder diffraction.

Results: The study demonstrated that particle size significantly influences dissolution across all formulations. Specifically, formulations with 32-micrometer particles exhibited higher dissolution rates compared to those with 75-micrometer particles. Furthermore, lactose anhydrous contributed to enhanced dissolution in the respective formulations, whereas lactose monohydrate was associated with lower dissolution rates. Interestingly, the choice of solvent did not exhibit a significant impact on dissolution outcomes.

Conclusion: Particle size and excipient selection are critical factors influencing the dissolution profile of digoxin formulations. Optimizing these parameters could enhance drug release performance.

34. TAM and Mitochondria Dual-targeted Drug Delivery for Cancer Immunotherapy

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Introduction: Tumor associated macrophages (TAMs) play a key role in tumor growth, metastasis, and immune escape, which are highly influenced by mitochondrial functions. Targeting TAMs and mitochondria to reprogram the immunity against cancer is a promising anticancer strategy. However, such studies are currently rare. The work aims to design a nanoparticle (NP)-based system for TAM and mitochondria dual-targeted delivery of immunomodulators.

Methods: The fluoroamphiphile (PEG-F7) NPs were engineered with a matrix metalloproteinase 2 (MMP2)-sensitive polymer, PEG-pp-PE, and phosphatidylserine (PS). In this design, PEG-pp-PE responds to overexpressed MMP2 for tumor targeting; PS, an "eat-me" signal, enables phagocytosis by macrophages, allowing TAM targeting; and fluoroamphiphile NPs facilitate mitochondrial targeting. PEG-pp-PE/PS/PEG-F7 NPs were characterized by physicochemical properties. The macrophage and mitochondrial targetability were evaluated in individual cell lines, co-cultured cells, and 3D cell spheroids by confocal microscopy and flow cytometry. The NIR dye-labeled NPs' biodistribution in tumor-bearing mice was studied by animal imaging. The antianginal drug, perhexiline, was repurposed using PEG-pp-PE/PS/PEG-F7 NPs for macrophage-centered cancer immunotherapy.

Results: PEG-pp-PE/PS/PEG-F7 NPs (particle size: ≤ 200nm and ζ-potential: ~-40 mV) showed a doubled phagocytosis compared with non-targeting NPs. The internalized NPs were mainly accumulated in mitochondria. In vivo, the NPs exhibited excellent tumor accumulation. Perhexiline-loaded NPs could effectively re-polarize protumor M2 TAMs to antitumor M1 phenotype, as evidenced by upregulated TNF-α IL-β, CD80, CD86, MHC-2, and glycolysis and downregulated IL-10, TGF-β, CD-206, NF-kB, and NRf2.

Conclusion: The TAM and mitochondria dual-targeted NPs are a promising drug platform for drug delivery and cancer treatment.

35. Macrophage-targeted Drug Delivery for Rheumatoid Arthritis Treatment

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Introduction: Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammation of the joints and surrounding tissues, affecting 1% of the global population. It primarily impacts the synovium, a membrane composed of activated macrophages and fibroblast-like synoviocytes (FLS), which is crucial in maintaining joint function. In RA, the macrophages and FLS lead to hyperplastic synovium and excessive proliferation, contributing to the secretion of inflammatory cytokines and matrix metalloproteinases (MMPs), that perpetuates joint destruction. This study aims to develop a novel nanomedicine for targeted delivery of coenzyme Q10 (CoQ10) to macrophages in RA. The nanomedicine, incorporating MMP-responsive polymers (PEG2k-pp-PE) and phosphatidylserine (PS), could respond to the MMP-2/9 overexpression in inflamed synovium, triggering PS-mediated phagocytosis for precise drug delivery.

Method: The PEG2k-pp-PE/PS nanoparticles were developed to load hydrophobic CoQ10 via the thin film hydration method. The CoQ10 nanomedicine was characterized by particle size, zeta potential, drug loading, and drug release. Using macrophages and fibroblasts as the models, the nanomedicine-induced cellular uptake, cytokine production, and macrophage activation were studied by flow cytometry, confocal microscopy, ELISA, and cell-surface marker.

Results: CoQ10 was loaded into nanoparticles (~9.5%) with a particle size of <200 nm and zeta potential of ~-40 mV. The PEG-pp-PE/PS nanoparticles showed MMP2-dependent macrophage-selective uptake. The CoQ10 nanomedicine significantly suppressed pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β, enhanced anti-inflammatory cytokine IL-10 production, and downregulated macrophage activation markers including CD80, CD86, and MHCII.

Conclusion: The inflammation and macrophage dual-targeted nanomedicine holds great potential for further development in treating inflammatory diseases, such as RA.

36. Mothers-to-be: Thirdhand E-Cigarette Exposure During Pregnancy Enhances Platelet Function and the Risk of Thrombosis in Offspring Mice Later in Life

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Introduction: It was recently shown that e-cigarettes (ECs) use during pregnancy increases the risk of cardiovascular disease (CVD) in the offspring. While ECs usage has been on the rise among pregnant women, this is not the only means by which innocent fetuses get exposed. Indeed, there is evidence that ECs are also a source of thirdhand exposure (THEC), which is formed from toxicants "produced" by vapor that accumulate on surfaces and elsewhere. However, whether THEC exposure during pregnancy poses any health effects remains unknown. Thus, we characterized the impact of maternal THEC on platelet function and thrombotic CVD.

Methods: Mice were housed with the EC-exposed or clean air material (i.e., carpet, cotton and upholstery) for one week prior to mating and throughout the pregnancy to mimic real-life exposure scenarios, and experiments were conducted on the adult offsprings.

Results: Our results indicate that maternal THEC exposed mice exhibit shortened bleeding and occlusion times measured by two widely used models (tail bleeding time and ferric chloride induced thrombosis models), in comparison to clean air. In terms of mechanism, platelet aggregation and dense & alpha granule secretion were potentiated in the maternal THEC exposed mice upon agonist stimulation. Furthermore, integrin activation and phosphatidylserine exposure, were also found to be enhanced. Notably, no detecatble differences were observed in platelet number and mean platelet value.

Conclusion: These data together demonstrate, for the first time, that maternal THEC increases thrombogenicity by modulating platelet reactivity, which highlights it as an underestimated risk factor for CVD in the offspring.

37. Paternal Exposure to E-Hookah Increases the Risk of Thrombosis Via Altering the mRNA/miRNA Expression Profile in C57BL/6J Offspring Mice

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Cardiovascular disease (CVD) is the leading cause of death worldwide, with smoking being the most preventable risk factor. While traditional smoking has declined, other novel products- including e-hookah- have gained popularity due to their "false safety claims". Moreover, while maternal/in utero exposure to tobacco has been extensively studied, little is known about paternal exposure, and the mechanisms underlying these "intergenerational" effects.

Methodology: To address this issue, we employed a model in which male mice are exposed to e-hookah/e-liquid for six weeks before mating, and throughout the mating period. We utilized the Beirut protocol which involves the delivery of 171 puffs at 2.6s puff duration and 17s puff interval, with experiments performed on the offspring at 10-12 weeks of age.

Results: The exposed mice exhibited shortened bleeding and occlusion times when compared to clean air controls. Investigation of the mechanism underlying this phenotype showed enhanced agonist-triggered aggregation, granule secretion, integrin activation, spreading, and phosphatidylserine exposure, indicating platelet hyperactivity. Finally, we carried out an analysis of the platelet transcriptome by establishing both the mRNA and miRNA expression patterns, which revealed a significant number of differentially expressed genes (DEGs), many of which are involved in platelet signaling. We also performed an integrated analysis of these DEGs and identified some functional pathways impacted by our exposure.

Conclusion: Collectively, we document that paternal e-hookah exposure exerts negative health effects in the context of platelet biology, impacting the F1 generation and beyond. Hence, e-hookah should not be considered a safe alternative to cigarette smoking.

38. Development and Optimization of Nanoparticles for siRNA Delivery to Endothelial Cells

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Introduction: Recent studies have identified that intestinal microbe-derived metabolites such as Trimethylamine-N-oxide (TMAO), are a source of novel risk factors for cardiovascular diseases such as atherosclerosis, hypertension, and heart diseases. We have recently identified that increased TMAO levels resulted in enhanced NLRP3 inflammasome formation leading to endothelial dysfunction. However, none of the inflammasome inhibitors developed so far have proven translational potential. We hypothesized that treatment with Lipid Nanoparticles (LNPs) encapsulating NLRP3-siRNA would protect against TMAO-induced endothelial dysfunction.

Methods: Endothelial cells were treated with or without TMAO (60μM) and NLRP3 siRNA loaded LNPs for 24 hours. We prepared siRNA loaded LNPs using MC3, by solvent injection method, a benchmark ionizable cationic lipid along with helper lipids at different N/P ratios and different micromolar concentrations of cationic lipid. We characterized the LNPs using dynamic light scattering and determined cellular uptake of CY5-siRNA loaded LNPs. We determined the gene knockdown ability of the most optimal formulation and observed its transfection efficiency. The effect of NLRP3 siRNA LNPs on TMAO induced dysfunction was analyzed by confocal microscopy, caspase activity, and ELISA.

Results: Particle size, PDI, Zeta potential was determined. All standard LNPs were ~150 nm in diameter with greater dispersion < 0.2 and had surface charge greater than +15 mV. All LNPs resulted in encapsulation efficiency greater than 80%. Cytocompatibility studies revealed no interaction between the blank and siRNA loaded LNPs. NLRP3 siRNA LNPs prevented inflammasome formation.

Conclusion: LNP is ideal system for delivery of NLRP3 siRNA against TMAO induced endothelial dysfunction.

39. Role of cGAS-STING Pathway in Platelet Activation and Thrombosis

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Introduction: The cGAS-STING signaling pathway, composed of Cyclic GMP–AMP synthase (cGAS), stimulator of interferon genes (STING), and tank-binding kinase 1 (TBK1), plays a crucial role in innate immunity by detecting double-stranded DNA (dsDNA) and triggering type I interferon responses. While extensively studied in immune cells and bacterial infections, its role in platelets and thrombosis remains unclear. We aim to determine whether cGAS-STING signaling influences platelet activation and thrombosis. Specifically, we hypothesize that mitochondrial DNA (mtDNA) released upon platelet activation stimulates cGAS, leading to cGAMP production and STING/TBK1 activation, ultimately enhancing platelet function and thrombus formation.

Methods: We assessed cGAS, STING, and TBK1 expressions in platelets using immunoblotting. Platelet activation was evaluated via aggregation assays and flow cytometry following stimulation with collagen, thrombin, and exogenous cGAMP. Thrombosis models were used to test the vivo relevance.

Results: Our preliminary findings confirm cGAS-STING pathway components are expressed in platelets. Platelets deficient in cGAS or STING exhibited impaired responses to physiological agonists, whereas cGAMP addition enhanced platelet activation. In vivo studies further suggest a role for cGAS signaling in thrombosis.

Conclusion: These findings indicate that cGAS-STING signaling contributes to platelet activation and thrombus formation, linking innate immune sensing to cardiovascular health. Targeting this pathway could provide novel therapeutic strategies for thrombotic disorders and cardiovascular diseases.

40. LDK2006, the First-in-class Inhibitor of CAMKV for the Treatment of Neuroblastoma

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Introduction: Neuroblastoma accounts for about 15% of childhood cancer-related mortality in the United States. Currently, multiple therapies including chemotherapy and targeted therapy have been developed for the treatment of neuroblastoma. However, the resistance to therapies is inevitable following long-term treatment, leading to treatment failure and cancer relapse. Calmodulin kinase-like vesicle-associated protein (CaMKV) was identified as a transcriptional target of MYCN/MYC in human NB cells. Though CAMKV was once characterized as a pseudokinase, its kinase activity was recently identified from its phosphorylation of proto-oncogene CREB, CAMKV knockdown in NB cells and knockout in NB experimental mice effectively suppressed NB cell proliferation in vitro and tumor growth in vivo. It was also shown that CAMKV is not expressed on normal tissues outside of the central nervous system. Targeting CAMKV was recently demonstrated as a viable approach for the treatment of NB.

Methods: Chemical scaffold hopping, computer-aided modeling, synthesis, cell viability, target protein expression, and in vivo investigation for tumor growth inhibition and mice survival span were employed in the discovery the first inhibitor of CAMKV.

Results: A novel class of CAMKV inhibitors have been identified through the combination of target computer-aided modeling, rational drug design and experimental analysis. The lead compound LDK2006 inhibits the CAMKV-mediated phosphorylation of CREB. Administration of LDK2006 (10 mg/Kg) in NB bearing mice resulted in tumor suppression and at least doubled survival life span.

Conclusion: LDK2006 represents a first-in-class inhibitor of CAMKV. Its tumor suppressing effects surpassed the effects from reported therapeutics used in NB treatment.

41. Discovery and Optimization of a Scaffold of Positive Allosteric Modulators of Cannabinoid CB1 Receptor towards the Development of Clinical Candidate of Non-Addictive and Non-Opiate Analgesics

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Introduction: PTDP-15 was discovered in our lab as a positive allosteric modulator (PAM) of the cannabinoid CB1 receptor (CB1R). The compound demonstrates superior analgesic activity in a preclinical neuropathic pain model in comparison with the FDA-approved gabapentin, showing promise as a non-addictive and non-opioid analgesic. However, further drug development of this preclinical candidate faces challenges, including poor kinetic solubility, high plasma protein binding (PPB), suboptimal metabolic stability in mice, limited cell (MDCK-MDR1) permeability, and marginal off-target inhibition of cyclooxygenase-2 (COX-2).

Methods: A comprehensive structure-activity relationship (SAR) study was performed to optimize the scaffold and functional groups of PTDP-15, aiming to improve its potency, ADME properties, drug efficacy, and overall safety.

Results: Optimized analogs of PTDP-15 demonstrated significant improvements of in vitro potency and metabolic stability, and significant improvements of in vivo analgesic efficacy. The therapeutic index over COX-2 inhibition improved by more than 100-fold. Our compounds exhibited no effects on hERG channels, cannabinoid CB2 receptor, opiate receptors, and an array of common drug targets (80 protein drug targets). Behavioral studies indicated that neither PTDP-15 nor its analogs exhibited adverse cannabimimetic liabilities and addictive liability.

Conclusion: PTDP-15 and its optimized analogs represent a promising class of candidates for non-addictive and non-opioid analgesics. Preliminary SAR and SPR data demonstrated their in vitro potency and in vivo efficacy, with notable improvements in pharmacological properties and eliminating off-target effects. Ongoing efforts are focused on optimizing this class to identify a suitable candidate for IND-enabling studies.

42. The expression of TMEM16A and TRPV4 in platelets reveals a new role in osmoregulation and thermoregulation A new Insight in platelet function

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Introduction: Platelets are the primary effectors of thrombosis and play a central role in preventing bleeding. Moreover, they also engage in other functions, such as the release pro-inflammatory molecules, chemokines, and the recruitment of immune cells. As a result of the aforementioned diverse functions, platelet activation has been linked to several other diseases. To this end, it is thought that normal functioning of platelets (all types of cells for that matter) is dependent on ambient temperatures (temperature perception), which allows for the selective transport of ions across the cell membrane to maintain homeostasis. Hence, this study focuses on the notion that the human body's exposure to heat stress, including through global warming, will affect platelet function. Thus, we hypothesize that TRPV4 and Ano1 regulate thermoregulation, and osmoregulation, respectively, in platelets.

Methods: Western blot technique, aggregometry and live cell Ca2+ imaging fluorescence microscopy are employed to characterize protein expression, platelet aggregation and calcium influx respectively.

Results: Our data revealed, for the first time, that TRPV4, Ca2+channel, and Ano1 (TMEM16A; a selective Cl- channel), are expressed in platelets, and they mediate transport of Ca2+/ Cl- ions respectively. Our studies did document that TRPV4 and Ano1 activation does enhance platelet aggregation, in a pharmacological, temperature and shear stress dependent manner.

Conclusion: Our data suggests that both TRPV4 and Ano1 could contribute to the thermoregulation and osmoregulation in platelets leading to enhanced platelet activation, while Ano1 is calcium dependent, downstream of TRPV4, and that they function in a synergistic manner.

43. Targeting Platelet Serotonin 5-HT2AR via Selective Vaccination: A Novel Strategy for Thrombosis Management

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Introduction: Cardiovascular disease (CVDs) is the leading global cause of death, largely attributable to thrombotic events that can result in conditions like myocardial infarction and stroke. The serotonin 2A receptor (5-HT2AR) has been identified as a key mediator in platelet aggregation and thrombogenesis, making it a promising target for anti-thrombotic therapies. Current 5-HT2AR antagonists, however, have been limited by non-selectivity and adverse effects.

Methods: This study introduces a novel vaccine-based approach- designed to target the ligand binding domain of 5-HT2AR, which resides in the second extracellular loop (EL2)- as an antithrombotic agent. This vaccine, referred to as "EL2-5HTVac" is expected to provide a long-lasting and selective therapeutic approach, without the complications of increased bleeding risk.

Results: In this study, we demonstrate that EL2-5HTVac induces a robust immune response with a significant elevation in EL2-specific antibodies, in comparison with the random EL2 peptide vaccinated mice/controls. Furthermore, vaccinated mice exhibited prolonged occlusion times in a FeCl3-induced carotid artery thrombosis model (EL2rVAC =350±33.4[sec], EL2-5HTVac=650±48.9[sec]), supporting the notion that this vaccine exhibits thromboprotective effects. Interestingly, these protective effects were observed without extending tail bleeding times (EL2rVAC =206±72.1[sec], EL2-5HTVac=201±39.1[sec]), indicating a potential favorable safety profile. Moreover, the EL2-5HTVac effectively inhibited the serotonin-induced platelet shape change, suggesting that its effects are specific to the 5-HT2AR. Additionally, it also blocked serotonin-enhanced ADP-induced platelet aggregation, suggesting an ability to prevent serotonin-facilitated amplification of platelet activation.

Conclusion: These findings suggest that EL2-5HTVac offers a dual advantage of thrombo-protection and maintenance of hemostasis, potentially overcoming limitations of existing anti-thrombotic strategies. Future studies should focus on the long-term efficacy and safety of EL2-5HTVac, as well as the feasibility of a vaccination approach in larger animal models for eventual clinical application.

44. H2A Histone Family Member X [H2AX] as a Therapeutic Target for DNA Damage and Neuroinflammation in HIV and Opioid Abuse

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Introduction: HIV infection, coupled with opioid abuse particularly morphine exacerbates neuroinflammation and DNA damage in the central nervous system (CNS). Microglia, the brain's primary immune cells, play a pivotal role in neuroimmune responses. This study explores the molecular mechanisms of DNA damage and repair in human microglial cells (HMC3) exposed to HIV-iTat and morphine, focusing on γH2Ax, a sensitive DNA damage response (DDR) marker. We hypothesized that HIV and morphine alter DDR proteins, leading to dysregulated pathways, and that silencing H2Ax could mitigate these effects.

Methods: HMC3 were treated with HIV-iTat (50ng/mL) and Morphine (10 μM) for 5days, and the levels of ATM, pH2AX (Ser139), Mre11a-RAD50-NBS1—were assessed via Immunoblotting. Additionally, the study aimed to investigate the effects of H2AX knockout in this model to further explore the cellular response to HIV and opioid exposure.

Results: After five days of HIV-iTat and morphine treatment, DNA repair proteins ERCC2, ERCC3, and ERCC8 were significantly downregulated, while DDR proteins such as ATM, phospho-H2AX, 53BP1, and KAT5 were markedly upregulated. mRNA levels of DDR-related genes, including RAD50, MRE11a, POLK, and TP53BP1, were also elevated compared to controls, indicating enhanced DDR in response to increased DNA damage. H2Ax knockdown via siRNA normalized DDR in HIV-iTat and morphine-treated cells by enhancing the non-homologous end-joining (NHEJ) repair pathway, reducing DSBs, and promoting effective DNA repair. Importantly, knockdown decreased activation of the AIM2 and NLRP3 inflammasomes, further linking DNA damage with neuroimmune dysregulation.

Conclusion: Targeting H2Ax holds therapeutic promise for alleviating neuroinflammatory and neurodegenerative effects in HIV-infected opioid users, offering new avenues for treating HIV-associated neurocognitive disorders (HAND).

45. LncRNA Dleu2 Modulates Macrophage Polarization through NFKB Signaling

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Introduction: Macrophages are highly adaptable immune cells whose polarization is shaped by their microenvironment. They can differentiate into classically activated (M1) or alternatively activated (M2) macrophages. M1 macrophages are linked to tissue inflammation and contribute to metabolic diseases such as obesity. Epigenetic regulation mediated by lncRNAs plays a crucial role in macrophage function. We previously reported that the lncRNA Dleu2 regulates metabolic health. In this study, we investigated Dleu2's role in macrophage polarization.

Methods: To evaluate the role of Dleu2 in macrophage polarization, we measured the expression level of Dleu2 in RAW 264.7 cell line and bone marrow-derived macrophages (BMDMs) under lipopolysaccharide (LPS)-induced M1 polarization. We performed siRNA-mediated knockdown of Dleu2 and assessed M1 macrophage marker expression and inflammatory signaling pathways.

Results: Dleu2 expression is significantly downregulated during M1 polarization in the RAW 264.7 cell line and BMDMs. In addition, Dleu2 suppression markedly increased Il6 and Nos2 expression in both untreated and LPS-stimulated macrophages, reinforcing its inhibitory role in pro-inflammatory responses. Furthermore, the nuclear factor kappa B (NFκB). Dleu2 knockdown resulted in increased levels of phosphorylated NFκB, along with decreased total IκBα protein level, which is a critical regulatory signaling pathway of macrophage-mediated inflammation. These changes suggest that Dleu2 regulates macrophage polarization by modulating NFκB activation.

Conclusion: Our findings reveal an anti-inflammatory role of lncRNA Dleu2 in macrophage polarization and identify it as a key modulator of NFκB signaling. These insights provide a basis for exploring Dleu2 as a potential therapeutic target for metabolic diseases driven by chronic inflammation.

46. NLRP3 Inflammasome Inhibitor Dapansutrile (OLT1177), Inhibits Trimethylamine N-oxide (TMAO) Induced Endothelial Dysfunction

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Introduction: Trimethylamine N-oxide (TMAO), a metabolite produced by gut microbiota, is widely recognized for its role in cardiovascular disorders. Previously, it was reported that TMAO induced endothelium damage by the formation and activation of NOD-like receptor protein 3 (NLRP3) inflammasome. This study aims to evaluate the effect of NLRP3 inflammasome inhibitor, Dapansutrile (OLT1177), on TMAO-induced activation of the NLRP3 inflammasome pathway.

Methods: Endothelial (EOMA) cells were treated with 1 μM, 5 μM, 10 μM, and 15 μM doses of OLT1177 to evaluate the cell viability. The integrity of endothelial cell monolayer was assessed by cell permeability to FITC dextran and transendothelial electrical resistance (TEER) was measured upon treatment with TMAO (60μM) and OLT1177 (10μM) for 24h. mRNA and protein levels of NLRP3, Caspase, ASC, ZO1, and VE-cadherin in response to TMAO and OLT1177 was evaluated by qPCR, immunoblotting, and immunofluorescent techniques.

Results: We observed that treatment with OLT1177 at concentrations of 1 μM, 5 μM, 10 μM, and 15 μM did not affect the endothelial cell viability. Cell permeability and TEER assays showed that TMAO triggered damage to endothelial monolayers which was notably reduced in cells treated with OLT1177. qPCR, immunofluorescence, and western blot analysis revealed that TMAO downregulated ZO1 and VE-cadherin expression and upregulated caspase, ASC, and NLRP3 expression whereas the transcript and protein levels of OLT1177 treated group were comparable to that of control.

Conclusion: Taken together, these results suggest that OLT1177 protects against TMAO-induced inflammation in endothelial cells and preserves endothelial cell tight junctional protein integrity.

47. Selective Laser Sintering-based 3D Printing of Poorly Flowable Drug by Applying Granulation Technique

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Introduction: The study aimed to improve the flow property of a drug for printing by selective laser sintering, using the 3D printing method, by making its granules, and characterization of printlets.

Methods: Drug was converted into granules to improve its flow property by wet granulation technique. Based on various preliminary 3D printing trials, sugar was selected as binder for granulation. By using fractional factorial design (JMP Pro 17), nine different runs were obtained. Surface temperature, chamber temperature, laser sintering speed, and Kollidon VA64 percentage were selected as independent factors. The printed printelts were analyzed for hardness, disintegration, and dissolution time, which were chosen as dependent factors. Chemical imaging of printlets and blends before and after printing was also performed using near-infrared hyperspectral imaging.

Results: Sulfadiazine granules were evaluated for flowability. Weight, hardness, disintegration, and dissolution of printlets varied from 76.5±2.6 to 94.6±3mg, 1.9±0.5 to 9.1±1.9N, 2.7±0.5 to 12.3±2.3s, and 98.8±1.3 to 101.5±1.2%, respectively. In the NIR chemical imaging, exhibited similar pixel distribution in the 3D printlets, suggesting homogeneity of formulation component distribution, but aggregation of ingredients was observed in formulation 4 and 7 due to high heat energy of slow laser sintering at printing site, and high surface temperature. Before and after printing blends showed non-significant differences.

Conclusion: The sulfadiazine printlets were evaluated, where laser sintering speed and surface temperature showed their effects on the characteristics of printlets.

48. A Mechanistic Insight into Intracellular Drug Delivery and Mitochondrial Targeting of Fluoroamphiphile Nanoparticles

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Introduction: Mitochondria have emerged as a therapeutic target over the past decade. Different lipophilic cationic agents including triphenylphosphonium (TPP), dequalinium (DQA), rhodamine derivatives, peptides, etc. were developed to target the negatively charged mitochondria. In our previous study [ACS nano, 2022, 16 (1), 1409–1420], a type of charge-neutral di-block polymer, polyethylene glycol-fluoroalkyl (PEGm-Fn), particularly PEG(2k Da)-heptafluorobutyl (PEG2K-F7) was synthesized for effective intracellular delivery and mitochondrial targeting. In the current study, we aim to optimize the PEGm-Fn and decipher their mechanism behind intracellular drug delivery and mitochondrial targeting.

Methods: A library of PEGm-Fn analogues were synthesized with different chain lengths of PEG and fluoroalkyls. The polymers were characterized and fluorescently labeled to study their interactions with cells, organelles (mainly mitochondria), cellular components, and biomolecules, using confocal microscopy, flow cytometry, gel electrophoresis, and fluorometry.

Results: The fluoroamphiphiles could self-assemble into nanoparticles (mean size 115 ± 5 nm, zeta potential 1.5 ± 2 mV). The fluoroamphiphiles were efficiently internalized by the cells and preferentially accumulated in mitochondria. The flow cytometry study with isolated mitochondria indicated that the fluoroamphiphiles could rapidly interact with mitochondria. The fluoroamphiphiles showed negligible interaction with proteins, including serum albumins. Interestingly, the polymers significantly interacted or bound with the phospholipids, among which cardiolipin, a mitochondria-exclusive phospholipid was the strongest.

Conclusions: Initial studies suggested that the fluoroamphiphiles could interact with the mitochondria independent of charge. Phospholipids, particularly cardiolipin, present in the mitochondrial membrane, might have played a significant role in mitochondrial targeting of the fluoroamphiphiles.

49. Pharmacies as Conduits in Decentralized Clinical Trials: A Meta-Analysis

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Introduction: Clinical trials are a critical component of the drug development process. However, large medical centers are sometimes located hundreds of miles from residents. Approximately 90% of Americans reside within 5 miles of community pharmacies. Decentralized clinical trials (DCTs) are transforming the research landscape by making clinical trials more accessible, directly engaging targeted populations, and mitigating challenges large medical centers face. Thus, pharmacies could be leveraged as conduits in DCTs. This project aims to analyze the benefits of pharmacy involvement in clinical trials and assess whether such involvement promotes diversity and inclusion within clinical trials.

Methods: Medical Countermeasures.gov, Applied Clinical Trials, aspr.hhs.gov, National Library of Medicine (PubMed), and Google Scholar were searched. Relevant Reports were included for wider quantitative analysis. Keywords: Decentralized clinical trials, Pharmacies, Diversity, Benefits, Disadvantages

Results: The initial search generated 7 articles, 2 reports from websites, and 10 Google Scholar studies. Six (6) studies did not meet the search terms and were excluded. Selected studies, articles, and reports have demonstrated that pharmacy involvement in DCTs improved collaboration with study team, accessibility to pharmacists, and increased pharmacy consults relevant to patient care by 32.5 %. Additionally, this approach facilitated greater participation of diverse populations.

Conclusion: Current literature suggests that pharmacy involvement in DCTs enhances the feasibility of conducting research across diverse populations by providing accessible points of care for patients and upholding high standards of clinical research and data management. Further studies are warranted to characterize the disadvantages associated with this approach.

50. Repurposing the FDA-approved Agent, Rifamycin for the Treatment of Castration-resistant Prostate Cancer

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Introduction: Resistance to androgen ablation therapy in Castration-Resistant Prostate Cancer (CRPC) is mainly driven by the aberrant activation of the androgen receptor (AR) and spliced AR variants (AR-v7). Consequently, our objective is to identify small molecules or repurpose existing drugs to mitigate or eliminate CRPC. Recently, we discovered a novel derivative (RTI-79) of the FDA-approved agent rifamycin, which is primarily used for tuberculosis treatment. This derivative demonstrates significant therapeutic efficacy in preclinical models of resistant CRPC.

Methods: To assess the efficacy of RTI-79, we conducted cell viability assays followed by western blotting, immunofluorescence, real-time PCR, and xenograft studies. Additionally, we performed RNA sequencing on xenograft tumors to elucidate the mechanism.

Results: RTI-79 inhibited growth in CRPC cell lines, without causing toxicity to normal prostate cells. In castrated and non-castrated CRPC mouse models, RTI-79 (administered at 15 mg/kg and 30 mg/kg of body weight) significantly suppressed tumor growth. Notably, RTI-79 exhibited synergistic effects with low doses of androgen ablating agent, enzalutamide, in in-vitro and in-vivo models. Transcriptomic analysis suggests that FOXA1, a crucial regulator of AR, was downregulated in tumors treated with RTI-79, suggesting that RTI-79 modulates AR signaling through FOXA1. Comprehensive differential gene expression and KEGG pathway enrichment analyses revealed that RTI-79 downregulates androgen response signaling and upregulates ubiquitination-mediated proteolysis in CRPC.

Conclusion: RTI-79 effectively sensitizes CRPC by targeting AR and AR-V7 signaling pathways through FOXA1. Its synergistic interactions with enzalutamide and its regulation of critical molecular pathways present a promising approach for overcoming drug resistance in CRPC.

51. Physicochemical Characterization and *In Vitro/Ex Vivo* Evaluation of Transdermal Gels of Baricitinib for Rheumatoid Arthritis

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Introduction:Rheumatoid arthritis causes joint damage, and while Baricitinib (BCB) is effective, its oral use risks infections and gastrointestinal issues, but transdermal drug delivery with Choline Geranic Acid (CAGE) offers a safer alternative by improving bioavailability and addressing BCB's solubility and permeability challenges. To develop and optimize transdermal Baricitinib (BCB) gel formulations using Hyaluronic acid, Compritol, and Lactoferrin to improve drug solubility, permeability, and skin penetration while minimizing systemic effects. It also investigates the use of Choline Geranic acid (CAGE) as a solvent and evaluates controlled release strategies to enhance localized efficacy and therapeutic outcomes for rheumatoid arthritis treatment.

Methods:Compritol was used to create lipid nanoparticles in an o/w emulsion, which were incorporated into Carbopol gel matrices. Various physicochemical tests, including FTIR, particle size analysis, and rheological assessments, were conducted, along with IVRT and IVPT tests using different membranes and porcine skin.

Results: The results showed varying release and permeation kinetics: Compritol and HA gels followed the Higuchi model, while Lf gels exhibited first-order kinetics. Over 24 hours, the cumulative drug release from optimized gels in cellulose membrane was 96.19% (HA), 78% (Compritol), and 83% (Lf), and in Strat M membrane, it was 65.11%, 63%, and 74%, respectively. The cumulative permeation amounts were 1.35 μg/cm² (HA), 0.88 μg/cm² (Compritol), and 2.54 μg/cm² (Lf), with Lf gels showing significantly higher release, permeation, and flux.

Conclusion: HA gels showed better release profiles with cellulose membranes, while Lf gels exhibited superior permeation across Strat M® and porcine skin membranes.

52. Neutrophil-Derived S100A8/A9 Impairs Megakaryocyte Maturation in Immune Thrombocytopenia via TLR4–JNK/c-Jun Signaling

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Introduction: Immune thrombocytopenia (ITP) is frequently driven by autoantibody-mediated platelet destruction; however, the extent to which inflammatory mediators disrupt platelet production remains insufficiently understood. Emerging evidence suggests that dysregulated immune cells within the bone marrow niche—beyond lymphocytes—may contribute to impaired megakaryopoiesis in ITP.

Methods: We combined single-cell RNA sequencing of bone marrow samples from ITP patients with in vitro assays on CD34^+-derived megakaryocyte (MK) cultures exposed to ITP plasma. In parallel, we employed both active and passive ITP mouse models to investigate how neutrophil-derived factors affect MK maturation. Pharmacological blockade of S100A8/A9 or TLR4 was tested in vitro and in vivo to assess the therapeutic potential of targeting these pathways.

Results: Single-cell analysis revealed an aberrant neutrophil–megakaryocyte axis characterized by elevated S100A8/A9 in ITP bone marrow. Neutrophils secreted excessive S100A8/A9, which activated TLR4–JNK/c-Jun in MKs, suppressed the transcription factor GATA1, and impaired platelet production. In vitro, ITP plasma reduced MK polyploidization, surface marker expression, and platelet-like particle release. Pharmacological inhibition of S100A8/A9 or TLR4 rescued these deficits. In mouse models, the S100A8/A9 antagonist tasquinimod improved platelet recovery, restored MK maturation, and downregulated MAPK activity.

Conclusion: Our findings show that S100A8/A9 secretion by expanded neutrophils directly compromises megakaryopoiesis via TLR4–JNK/c-Jun signaling, thereby worsening thrombocytopenia in ITP. Targeting this neutrophil–megakaryocyte axis with S100A8/A9 antagonists or TLR4 inhibitors not only alleviates MK dysfunction but also offers a novel therapeutic avenue to complement current ITP treatments.

53. A Complex LncRNA-miRNA Differentially Regulates Heterogeneity in White Adipose Tissue Depots: A Single Cell Analysis

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Introduction: Obesity and diabetes have reached epidemic proportions over the past decade. However, the mechanisms underlying the depot-specific white adipose tissue associations with metabolic risks are not fully understood. Here, we investigated the role of a complex lncRNA Dleu2 which hosts miRNA15/16 cluster [Dleu2 and miRNA15/16 together called minimal deleted region (MDR)], in the depot-specific adipose tissue function.

Method: We performed a single-cell RNA sequencing of stromal vascular fraction from visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) of six-week-old WT and MDR knockout (MDR KO) male mice.

Result: Cluster analysis using scGEATool, an ideal algorithm prototyping tool developed by us to facilitate scRNA-seq data analyses under Matlab settings, showed increased macrophage and T cells subpopulation in MDR KO-VAT and SAT compared to their WTs. Additionally, M1 macrophage population was significantly upregulated along with significantly decreased M2 macrophage in MDR KO-VAT. Subsequently, we observed significantly high TNF, IL1β, and IFNϒ expression only in MDR KO-VAT. We also observed a significant reduction in IRS2 and IGF1R expression in MDR KO-VAT with a non-significant decreasing trend in MDR KO-SAT, indicating dysregulated insulin signaling. Interestingly, we identified that stemness was significantly reduced only in MDR KO-VAT suggesting differential stem cell-mediated metabolic dysregulation. We are currently confirming our above findings as well as cellular interaction and pseudotime analysis using R Studio.

Conclusion: Our data underscores lncRNA-miRNA cluster regulated intrinsic differences between VAT and SAT at progenitor stage which sets the foundation for an early therapeutic approach that is urgent and an unmet clinical need.

54. Application of a Validated LC-MS/MS Method for the Quantification of Varenicline in Plasma

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Background: Varenicline (VRN) is an FDA-approved prescription-only drug commonly used for smoke cessation. Accurate determination of plasma varenicline level is crucial to monitor therapeutic efficacy and ensure the safety of users. However, currently, available analytical methods for plasma varenicline analysis are either less sensitive to adequately quantify trace levels of varenicline and/or not specific to varenicline in the presence of other interfering analytes. The present study was aimed at developing a fast and selective LC-MS/MS method for the analysis of varenicline in plasma samples.

Methods: Plasma varenicline analysis was performed using Xevo-TQD Triple Quadrupole LC-MS with a Kinetex 2.6 um C8 AX (100 x 3mm) column maintained at 40°C using a mobile phase consisting of water with 0.1% formic acid (A) and methanol (B). The total run time was 3 min followed by 2 min equilibration. Multiple reaction monitoring (MRM) with a positive electrospray ionization mode was used for the mass spectrometric detection. Parent-to-daughter transition, m/z 212.26 → 43.93 and m/z 216.3 → 47.96 were used to monitor varenicline and varenicline-d4 (IS), respectively. The developed method was validated as per ICH guidelines.

Results: The developed method was found to be selective with excellent linearity (R^2 = 0.999) in the range of 0.5ng/mL to 10ng/mL, precise (%RSD <6%), and accurate (%Recovery, 95.5%-103.0%).

Conclusion: In this study, a fast, sensitive, and selective LC-MS/MS method with an easy sample preparation method has been developed and successfully applied to determine the content of varenicline in dog plasma samples.

55. Mitochondria Contribute to NAIP/NLRC4 Inflammasome Activation and Pyroptosis

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Introduction: Mitochondria play a pivotal role in apoptosis and have been implicated in inflammasome activation. However, their role in NAIP/NLRC4 inflammasome activation remains unclear. The NAIP/NLRC4 inflammasome responds to bacterial virulence factors such as flagellin and T3SS components, leading to caspase-1 activation and pyroptosis. This study investigates the role of mitochondria in NAIP/NLRC4 inflammasome assembly, activation, and subsequent cell death.

Methods: Mitochondria-deficient iBMDMs were generated. Macrophages were stimulated with Escherichia coli T3SS rod protein EprJ (LFn-EprJ/PA), and inflammasome activation was assessed by LDH release, caspase-1 activation, and ASC oligomerization via Western blot and fluorescence microscopy. Calcium chelation and BID inhibition were used to analyze regulatory mechanisms, while Salmonella infection models validated findings.

Results: Mitochondrial depletion reduced NLRC4-dependent caspase-1 activation, ASC speck formation, and pyroptosis. ASC recruitment to mitochondria was calcium-dependent, and inhibition of calcium signaling suppressed inflammasome activation. NLRC4 activation led to mitochondrial dysfunction, including membrane depolarization and increased ROS production. Both caspase-1 and caspase-8, but not GSDMD, contributed to mitochondrial damage via BID cleavage. TFAM deficiency impaired NLRC4 activation, highlighting the importance of mitochondrial integrity. Salmonella infection confirmed that mitochondrial depletion protects against NLRC4-driven pyroptosis.

Conclusion: Mitochondria are essential for NAIP/NLRC4 inflammasome activation and pyroptosis. Dysfunctional mitochondria amplify inflammasome signaling via caspase-1/-8 and BID-dependent pathways, while calcium signaling modulates inflammasome assembly. These findings provide insights into mitochondria-driven immune regulation, offering potential therapeutic targets for inflammatory diseases.

56. Arsenic Exposure Alters the Signatures of the Microbiome and Metabolome, Facilitating Bladder Carcinogenesis

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Introduction: Chronic exposure to inorganic arsenic (iAs) poses a significant risk factor for the development of bladder cancer (BCa); however, the underlying carcinogenic mechanisms remain poorly understood. Interactions between host and environment, particularly alterations in the microbiome and metabolism, may play a pivotal role in BCa progression. Utilizing a mouse model exposed to iAs, we investigated changes in the urinary microbiota and metabolomic profiles and linked these disruptions to iAs-induced carcinogenesis.

Methods: Male and female mice were exposed to sodium arsenite ($NaAsO_2$) at doses of 30 and 60 PPM in water over a year. Subsequently, urine and fecal samples were analyzed for Urinary arsenic species, 16S rDNA sequencing, and metabolic profiling to assess alterations in microbiome composition.

Results: Histopathological examination of bladder tissue revealed that iAs exposure resulted in lesions and hyperplasia in both male and female mice. The levels of urinary arsenic species (iAs, DMA(III), and MMA(III)) correlated with dosage, yet significant differences were observed between male and female mice. Importantly, iAs exposure altered the urinary microbiome composition and increased the abundance of Muribacter, a bacterium associated with hyperplasia, in both sexes. Cancer-associated microbes such as Enterococcus (in males) and Clostridium (in females) were also found to be enriched. Metabolomic profiling uncovered significant disruptions in amino acid and fatty acid metabolism, with notable sex-specific alterations in methylation pathways and cellular repair mechanisms, ultimately contributing to bladder carcinogenesis.

Conclusion: Exposure to arsenic results in sex-specific dysregulation of the urinary microbiome and metabolome, facilitating the development of bladder lesions.

57. Pyrroloquinoline Quinone primed Human Adipose-Derived Mesenchymal Stem Cells improves Metabolic Abnormalities along with Gut Microbiome in Phthalates-Mixture exposed High Fat Diet fed Mice

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Introduction: Phthalates, a group of plasticizers, can increase the risk of diabesity. Given high exposure to a variety of different phthalates daily, we investigated the efficacy of Pyrroloquinoline Quinone (PQQ)-primed Human Adipose-Derived Mesenchymal Stem Cells (hADMSCs) in mitigating the effect of environmentally relevant phthalate mixture (PM) induced metabolic dysregulation, along with gut microbiome alteration.

Methods: Six-week-old C57BL6 mice were fed on HFD with physiologically relevant PM doses. For the reversal experiment, we identified in vivo doses for PQQ by treating 3T3L1 cells with PM with or without hADMSCs or PQQ-primed hADMSCs.

Results: At acute exposure, significant glucose intolerance was observed with 500 mg/kg. At chronic exposure, as early as week 3, 200µg and 200mg/kg doses showed a significant increase in body weight. Both lower doses of 200µg and 5mg/kg showed hyperglycemia at week 10. Additionally, glucose intolerance was evident at all doses, with insulin resistance at 200µg & 5mg/kg. In vitro adipogenesis experiments showed a dose-dependent increase in adipogenic status of 3T3L1, T37i, and C3H/10T1/2 treated with a range of PM concentrations. Thirty µM PQQ-primed hADMSCs reduced body weight and improved gut microbiome in PM-exposed HFD mice. Microbiome analysis revealed that the above therapy significantly decreased alpha, and beta diversity and promoted improvement in beneficial bacterial species. The alpha diversity was decreased in the PQQ-hADMSCs treated group at both the phylum and genus ($p < 0.05$), with a non-significant difference in beta diversity.

Conclusion: Investigation of PM-induced metabolic dysfunction along with finding early therapeutic strategies will significantly advance the field.

58. Exposure to Cadmium Transforms Benign Prostatic Hyperplasia (BPH) to Prostate Cancer

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Background: Chronic exposure to cadmium (Cd) poses a significant risk for the development and progression of prostate cancer (CaP). Previous research has indicated that exposure to Cd in benign prostatic hyperplasia (BPH1) cells can initiate malignant transformation within 12 months by activating the ZIC2 signaling pathway. The current study aims to explore how Cd activates the ZIC2 signaling cascade and to elucidate the molecular mechanisms that drive malignancy.

Methods: To investigate the molecular interaction between MTF1 and ZIC2, we established MTF1/ZIC2 overexpression and knockdown models in both BPH1 and cadmium-transformed benign prostatic hyperplasia cells (CTBPH1). In addition, we conducted phenotypic and molecular analyses to determine the interaction between MTF1 and ZIC2 in BPH1 and Cd-exposed BPH1 cells.

Results: Our findings demonstrate that Cd induces the metal regulatory element-binding transcription factor-1 (MTF1), which subsequently activates ZIC2 in BPH1 cells. Silencing the expression of ZIC2 does not affect MTF1 levels, suggesting that MTF1 functions upstream of the ZIC2 signaling pathway. Moreover, overexpressing MTF1 in untransformed BPH1 cells resulted in the induction of ZIC2 and stem cell activation, by promoting spheroid formation, confirm that MTF1 is a critical player in this process. Conversely, silencing MTF1 expression in transformed cells inhibited stem cell functions and tumor growth in nude mice. Further, RNA sequencing analysis of MTF1-silenced and ZIC2 knock out xenograft tumors corroborated our in vitro findings.

Conclusion: These results underscore the pivotal role of MTF1, which exerts its oncogenic function through ZIC2, thereby facilitating the malignant transformation of BPH cells.

59. Targeted Inhibition of Androgen Receptor Signaling Reprograms Tumor Microenvironment and Mechanics in Castration Resistant Prostate Cancer

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Background: Castration-Resistant Prostate Cancer (CRPC) remains a significant cause of morbidity and mortality among prostate cancer patients. AR splice variants lacking ligand-binding domains resist current androgen deprivation therapies, leading to metastasis and recurrence of the disease. We have identified a non-toxic inhibitor, ASR603, that targets the N-terminal domain of the AR, which alters the dynamics of AR signaling, leading to changes in the tumor metabolome and resulting in decreased tumor burden.

Methods: We used CRPC-mice models (Xenograft/PDX) to determine the efficacy of ASR603. Adjacent sections of PDX tissues were subjected to spatial-omics (transcriptomics, proteomics, metabolomics), and relevant validation techniques were used.

Results: ASR603 exhibited inhibitory effects in CRPC models (xenografts and PDX). Spatial gene expression profiling revealed eight transcriptionally distinct clusters in control and ASR603-treated tumors. Comparison of clusters with distinct AR expression identified pathways, including autophagic cell death and ubiquitin-mediated degradation. Further studies confirmed that ASR603 promotes AR and AR-variant degradation via ubiquitination at novel sites, specifically K301 and K313. Altering these sites rescued AR expression, highlighting the N-terminal domain as an ASR603 target. Our spatial proteomics data indicated altered subcellular localization of AR pathway proteins, such as PSA, restructuring the translational program. Additionally, when we integrated spatial metabolic profiles, we observed a significant increase in metabolites such as taurine, thymol, and naproxen, with significant alterations in pyrimidine, arginine, and phenylalanine pathways.

Conclusion: Inhibition of AR and its variants alters the tumor microenvironment while enriching metabolites that play a crucial role in ASR603-mediated inhibition of CRPC.

60. Identifying Epigenetic Therapy for Preeclampsia at the First Trimester

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Introduction: Preeclampsia (PE) is the leading cause of maternal, fetal, and neonatal mortality. Most 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.

Methods: A case-control biomarker study was conducted along with in vitro and in vivo work in mice and human placenta. Several advanced molecular, physiological, and bioinformatics methods were used to determine the early epigenetic biomarkers.

Results: In a case-control study of healthy and PE women's first trimester blood (Choudhury US Patent 11344121), we identified several epigenetic biomarkers including DNA methylation, histone modification, and microRNA (miR). To decipher the explicit mechanism of how miR 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 non-invading HUVECs. The results of both analyses 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.

Conclusion: These findings contribute to our understanding of PE etiology and may inform the development of early diagnostic biomarkers and therapeutics in the long run. Future intervention efforts targeting miR-17 inhibition during early pregnancy can provide therapeutic potential for PE and CVD prevention.

61. AI-Driven Prediction of Serum Creatinine for Enhanced Pharmacokinetic Modeling in Narrow-Therapeutic Drugs

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Introduction: Narrow-therapeutic drugs requiring renal clearance demand careful monitoring due to the risk of adverse effects, particularly in patients with acute kidney injury (AKI). To enhance pharmacokinetic modeling for such drugs, we developed a deep-learning model, an artificial intelligence (AI) approach, to predict serum creatinine levels, a key renal function indicator.

Methods: The study cohort comprised 9,710 patients from Memorial Hermann Health System, aged ≥18 years with serum creatinine <3 mg/dL on admission, excluding those with end-stage renal disease or dialysis. Our model incorporated patient-specific features such as vital signs, laboratory results, medications, and diagnostic codes. A gated recurrent unit (GRU)-based AI architecture was employed alongside a one-compartment pharmacokinetic model to account for creatinine production and elimination dynamics.

Results: After training the model, the GRU-based AI model achieved a Root Mean Square Error (RMSE) of 0.294. Given that AKI is defined as a serum creatinine increase of 0.3 or more, this pilot model shows promise in detecting acute changes in renal function with further refinement.

Conclusion: This approach seeks to advance pharmacokinetic modeling for narrow-therapeutic drugs, ultimately reducing adverse effects and improving patient care through more accurate renal function prediction. Future work will focus on training the model on a larger database of patients, evaluating the model on an external patient dataset to improve external validity, and enhancing model performance by integrating MedBERT. MedBERT leverages AI techniques to create contextualized embeddings from structured electronic health records (EHRs), enabling improved performance in predictive healthcare tasks.

62. Addressing Data Gaps in Opioid Overdose Reporting: Enhancing Systems to Protect Vulnerable Older Adults

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Introduction: Opioid overdoses impact all age groups, yet the full extent of the crisis's effect on older adults remains unclear due to significant gaps in data collection and reporting. Many drug poisoning deaths do not list opioids as primary or secondary causes, leading to underreporting. Non-fatal overdoses are also poorly documented due to inconsistent reporting standards and a lack of unified data systems. Addressing these gaps is essential for developing targeted prevention efforts for vulnerable populations, including older adults.

Methods: This commentary reviews opioid overdose prevalence rates, challenges in data reporting, and innovative approaches to integrating overdose data. Existing systems, such as the CDC's State Unintentional Drug Overdose Reporting System (SUDORS) and CDC WONDER, are examined alongside real-time tracking tools like the Opioid Detection Mapping Application Program (ODMAP). Texas A&M University (TAMU) serves as a case example, demonstrating efforts to link overdose event data with intervention outcomes through data integration techniques.

Results: Integrating diverse data sources enhances the identification of overdose hotspots and geographical risk factors. States utilizing ODMAP can track real-time overdose incidents and adjust responses accordingly. TAMU's approach highlights the potential of linking overdose data with targeted interventions to improve prevention strategies. However, challenges remain, including inconsistent reporting across jurisdictions and limited interoperability between public health agencies.

Conclusion: A standardized, interoperable data infrastructure is essential for accurately tracking opioid-related harms and informing prevention efforts. Strengthening these systems will improve intervention effectiveness and reduce the crisis's impact on older adults and their families.

63. Incorporating Population Health Concepts to Conduct Pharmaceutical Outcomes Research Using Big Data: Examples and a Demo of Nationally Representative Medical Expenditure Panel Survey

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Introduction: Integration of population and public health thinking in pharmaceutical research sciences can provide avenues for designing non-pharmaceutical interventions benefitting communities, inform resource allocation, and guide societal policy decisions. However, the terminology and measurement regarding what constitutes population vs. public health, the various domains that influences overall health, and how these domains can be incorporated in pharmaceutical health outcomes research remain unclear and therefore underutilized. The objectives are: 1) to describe and distinguish how population health differs from public health; 2) to provide a conceptual thinking on domains over the life-course (*e.g.* biological, behavioral, physical/built environment, sociocultural, healthcare system) and levels of influence (*e.g.* individual, family/interpersonal, community, societal) that can impact pharmacy outcomes (*e.g.* economic, clinical, or humanistic); and 3) introduce a publicly available nationally representative Medical Expenditure Panel Survey that can be utilized to design and conduct peer-reviewed scholarly research in pharmaceutical outcomes research.

Methods/Results: Dr. Zanwar will describe how she has incorporated MEPS in her research on access to clinical preventive services among various communities in the United States and the social and non-biological factors that have influenced the receipt of such services. Dr. Zanwar will provide a hands-on demo on how to access and download the MEPS data, and plan and design a research study to examine prescription medicine utilization and out-of-pocket costs among older adults during the Covid-19 pandemic.

Conclusion: This talk will develop big data skills for master's/doctoral students/fellows, and faculty interested in learning how to conduct Pharmacoeconomics and outcomes research.

64. Assessing the Pharmacoeconomic Impact of Pharmacist-led Antimicrobial Interventions in the Inpatient Setting

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Introduction: Several studies evaluate the importance of clinical pharmacists in Antimicrobial Stewardship Programs and their pharmacoeconomic impact on the institution, but no studies have been conducted in a primarily Hispanic setting. Results from this study will help understand the importance of pharmacist-led antimicrobial interventions and their impact on cost-avoidance in a community where antimicrobial resistance risk is higher.

Methods: A single-center retrospective post intervention analysis was conducted via a chart review of adult patients admitted to the hospital with a urine or blood culture report that had an antimicrobial intervention led by a clinical pharmacist. To complete the cost avoidance analysis, average cost avoidance values, based on literature, were multiplied by the number of interventions in each intervention type.

Results: A total of 408 antimicrobial interventions were found through the standardized review process documented by eight clinical pharmacists. The most common intervention type was de-escalation with 261 (63.97%) interventions, followed by 77 (18.87%) bug-drug mismatches, and 24 (5.88%) duration optimizations. A total cost avoidance of $26,456.35 was calculated for all adult patients admitted to the hospital with a urine or blood culture report that had an antimicrobial intervention led by a clinical pharmacist during the six month study.

Conclusion: Clinical pharmacists are pharmacotherapy experts that are instrumental in optimizing antimicrobial use and decreased nosocomial infections that can lead to a reduction in antimicrobial resistance. The guidance and recommendations provided by clinical pharmacists results in positive cost savings while enhancing the quality of patient care.

65. Understanding Metabolic Shifts from Primary Tumor to Brain Metastasis in TNBC

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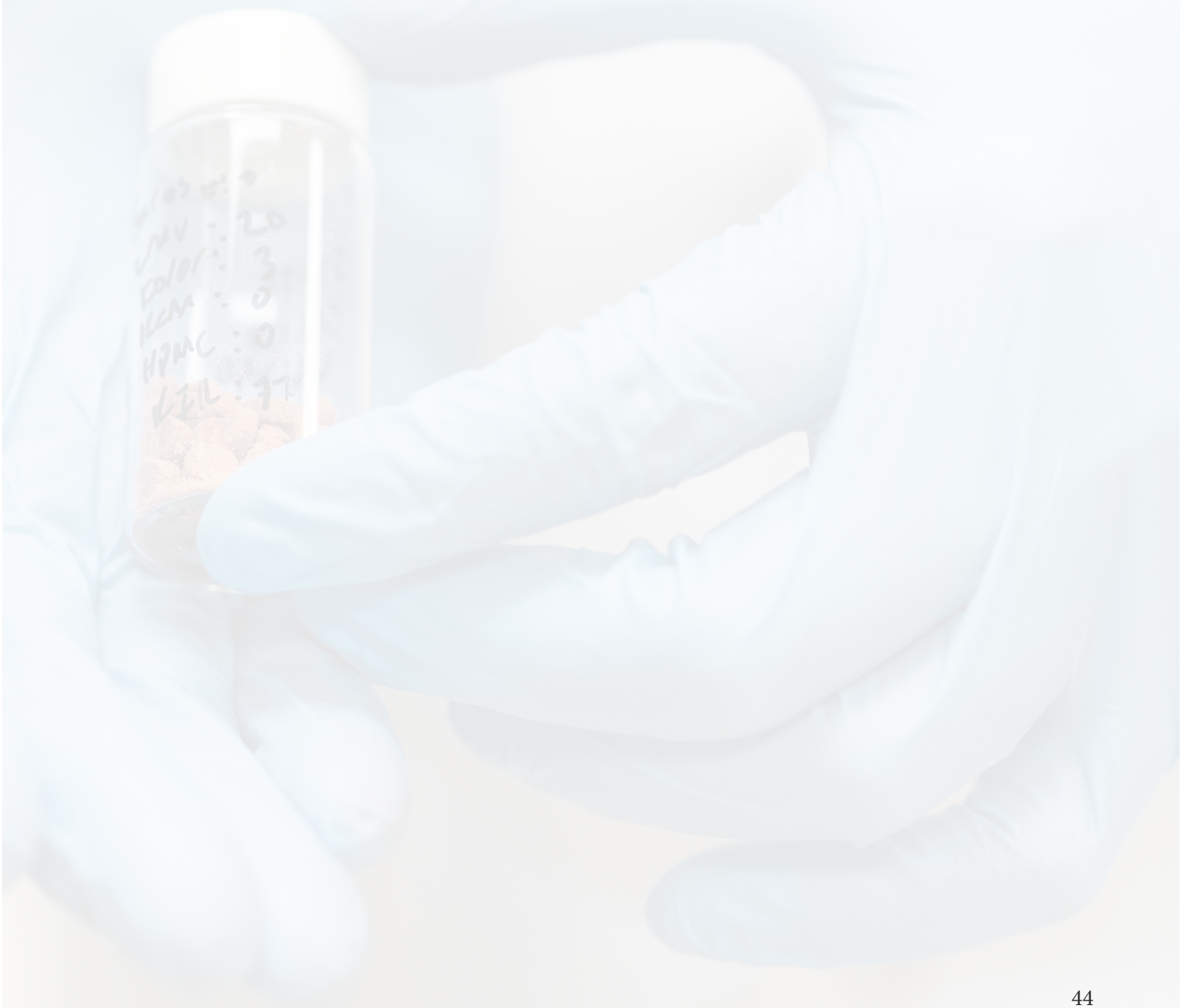
Introduction: Triple-negative breast cancer (TNBC) is an aggressive subtype with a high propensity for brain metastases (TNBC-BM). The metabolic alterations driving this progression remain unclear. Understanding these shifts could provide insights into tumor adaptation and survival, aiding biomarker discovery and therapeutic development. This study aims to characterize metabolic differences between primary TNBC tumors and brain metastases by analyzing both mice tissues and mice serum samples. Additionally, findings were validated in human TNBC serum to assess clinical relevance.

Methods: Tissue lysates and serum samples from a TNBC-BM mouse xenograft model and human TNBC patients were analyzed using liquid chromatography-mass spectrometry (LC-MS). Metabolites were identified using the Human Metabolome Database (HMDB) and MetaboAnalyst. Peak-stripping analysis was performed on both tissue lysates and serum samples (mouse and human) to distinguish shared and unique metabolites.

Results: Metabolic profiling revealed distinct shifts between primary tumor and brain metastatic samples. Six key metabolic pathways were identified. Peak-stripping analysis highlighted five metabolites unique to brain metastases in both tissue and serum, while three metabolites were shared between primary and metastatic samples, suggesting conserved metabolic adaptations. Human serum analysis validated these key metabolic differences, reinforcing their clinical significance.

Conclusion: This study highlights metabolic reprogramming in TNBC brain metastases across tissue and serum, identifying potential biomarkers and therapeutic targets. Further validation in human samples could enhance understanding and inform treatment strategies for TNBC-BM.

Notes



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Aroub Alfraihat
Hamed Ali
Mariame Ali
Agatha Alonso
Joy Alonzo
Fatima Alshbool
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Nishat Ara
Mostafa Aref
Aniqa Atta
Hima Bindu Atti
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Mitchell Barnett
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Gig 'em!

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