College of Pharmacy
UNIVERSITY OF HOUSTON

Clinical and Translational Reserach Symposium

Friday, May 22, 2026

University of Houston, Health 2 Building

Keynote Speakers

Pamela Hill
Open Innovation,
A straZeneca

Christine Colvis
Officeof DrugDevelopment
Partnership Programs, NCATS/NIH

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KEYNOTE SPEAKER

Christine M. Colvis, Ph.D.

Director Office of Drug Development Partnership Programs, NCATS/NIH

22ND MAY

FRIDAY | 1:30PM

Location:Room 3050

"Rethinking Translational Science: Disrupting the Status Quo"

Christine serves as Director of the Office of Drug Development Partnership Programs (ODDPP) at the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health. The office leads a broad portfolio focused on accelerating therapeutic discovery and early-stage development through innovative partnerships, data-driven approaches, and cross-sector collaboration. Her office spans activities from expanding the target landscape through clinical evaluation as well as catalyzing the development of high-impact, next-generation tools and platforms that will improve the efficiency of diagnostic and therapeutic development. The small office also oversees biomedical AI and AI-enabling initiatives, including the Biomedical Data Translator program and LitCoin.

Dr. Colvis also serves as Acting Director of the NCATS Office of Special Initiatives, which leads transformative programs including microphysiological systems ("tissue chips"), automated chemistry platforms, quantum-enabled biomedical applications, advanced diagnostic technologies, and novel biomarker strategies.

Through extensive collaborations across NIH, federal partners such as FDA, CMS and NASA, as well as industry, Dr. Colvis advances innovative strategies to make translational science faster, more predictive, and more efficient.

KEYNOTE SPEAKER

Pamela Hill, M.S.

Senior Director, Global Head of Open Innovation, AstraZeneca

22ND MAY

FRIDAY | 8:15AM

Location:Room 3050

"DrivingInnovation Through Industry-Academic Partnerships"

Pamela Hill is a seasoned biopharmaceutical leader with more than two decades of experience advancing scientific innovation, external partnerships, and early stage drug discovery. As Head of Open Innovation at AstraZeneca, she leads an externally-aligend program that elevates the company's global scientific reputation, expands access to external expertise, and delivers scientificacross preclinical and clinical portfolios. Pam is widely recognized as a trusted collaborator and expert in academic engagement, public–private partnerships, and cross functional leadership, drawing on her extensive scientific background and early career contributions leading antiviral and antibacterial discovery programs through candidate selection. Her work has established AstraZeneca as a longstanding industry leader in Open Innovation, and her influence extends beyond R&D through her deep commitment to mentoring, community engagement, and STEM outreach.

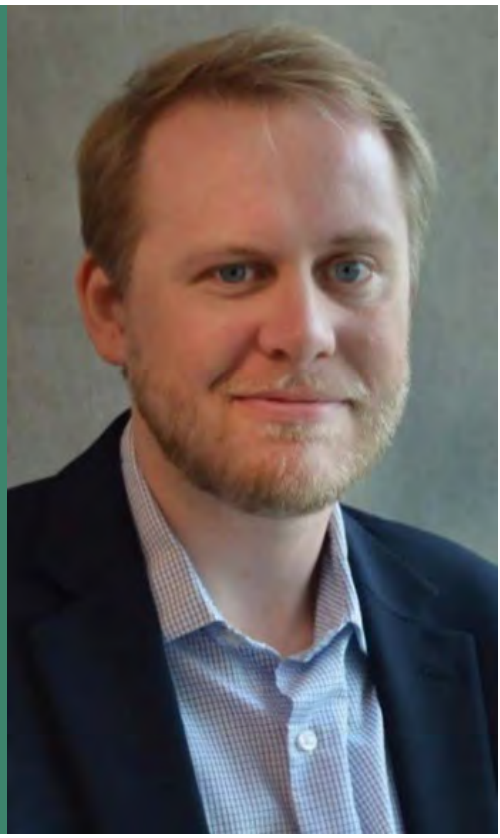
Target & Drug Discovery

LOCATION: ROOM 3050 | TIME: 9:15AM

"AI-Directed Molecular Probe Discovery"

Reid T. Powell, PhD

Assistant Professor, Institute of Biosciences & Technology, Texas A&M University; Alkek Fellow, Texas A&M Institute of Biosciences and Technology; Assistant Professor, Texas A&M Institute of Biosciences and Technology; Director of Artificial Intelligence and Data Science, Gulf Coast Consortia Drug Discovery Resource Center (GCC-DDRC); Research Coordination Fellow, Texas A&M University Institute of Data Science (TAMIDS); Acting Director, Computational Medicine Makers Space, Texas A&M School of Engineering Medicine (EnMED); Chief Technology Officer, Esperanza Therapeutics, Inc.



Speaker's Bio:

Dr. Reid T. Powell is a computational scientist and translational drug discovery expert at the forefront of AI- enabled therapeutic development, spanning academic and small biotech. With undergraduate training in biochemistry at Texas Tech University, his current role as Assistant Professor at the Texas A&M Institute of Biosciences and Technology (IBT) and Head of Artificial Intelligence and Data Science at the Gulf Coast Consortia's Drug Discovery and Development Resource Center (3DRC) in Houston's TMC3 Collaborative Research Building, and founding role in Esperanza Therapeutics, an early-stage small molecule company focusing on brain health and cancer. His research heavily leverages high-performance computing to enable a multitude of therapeutic discovery and repositioning efforts. At the 3DRC, Dr. Powell leads the integration of machine learning, cheminformatics, and high-throughput screening analytics across several CPRIT-funded translational cores, including the Drug Discovery Resource Center (DDRC), Combinatorial Drug Discovery Program (CDDP), and the High-Throughput Flow Cytometry Program (HtFCP). His team develops and implements modular analytical pipelines that support structure-activity relationship (SAR) modeling, iterative design-make-test-analyze cycles, phenotypic assay interpretation, mechanism-of-action clustering, and multi-omics inference.

"AI-Based Drug Design and Repurposing"

Yejin Kim, PhD

Associate Professor ofInformatics,
Associate Director of theCenterforSecureArtificialIntelligenceforHealthcare

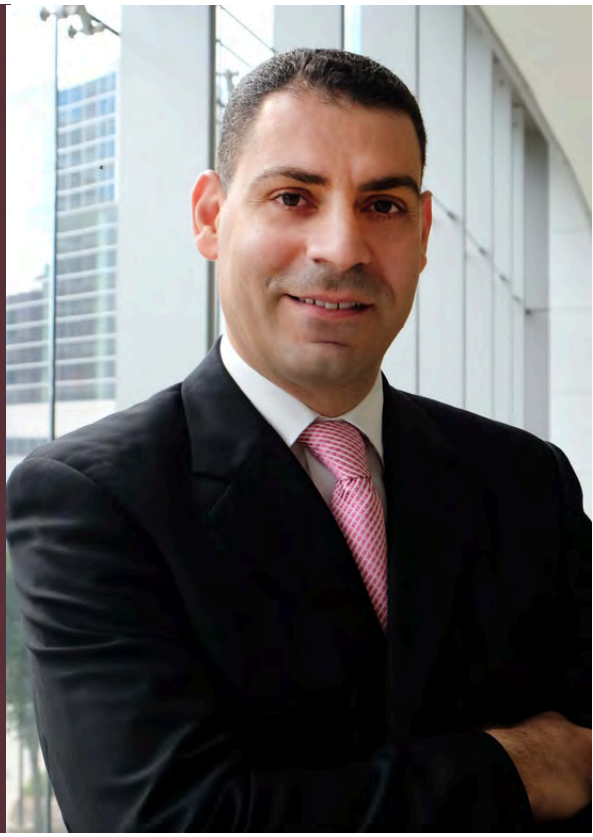
Speaker's Bio:

Dr. Yejin Kim is a tenured Associate Professor in the Department of Health Data Science and Artificial Intelligence and Associate Director of the Center for Secure Artificial Intelligence for Healthcare at UTHealth Houston. She received her PhD in Machine Learning from POSTECH
in 2018 and leads a multidisciplinary lab developing AI/ML models for therapeutic antibody discovery and validation. Her group recently ranked among the top five teams globally in the IQVIA AIntibody Challenge for AI-based antibody design. Dr. Kim has secured over $8 million
in extramural funding, including multiple NIH R01s as principal investigator, and published more than 50 peer-reviewed papers in top biomedical informatics journals and AI conferences. She serves on numerous NIH study sections and international grant panels, and as an editor for PLoS Biology and BMC Medical Informatics and Decision Making. Her work bridges experimental biology and AI to accelerate therapeutic innovation.

Drug & Biomarker Development

LOCATION: ROOM 3050 | TIME: 10:30AM

"New Mechanism Based Drug Development for GI Cancer Treatment and Prevention"



Maen Abdelrahim, MD, PhD, PharmD

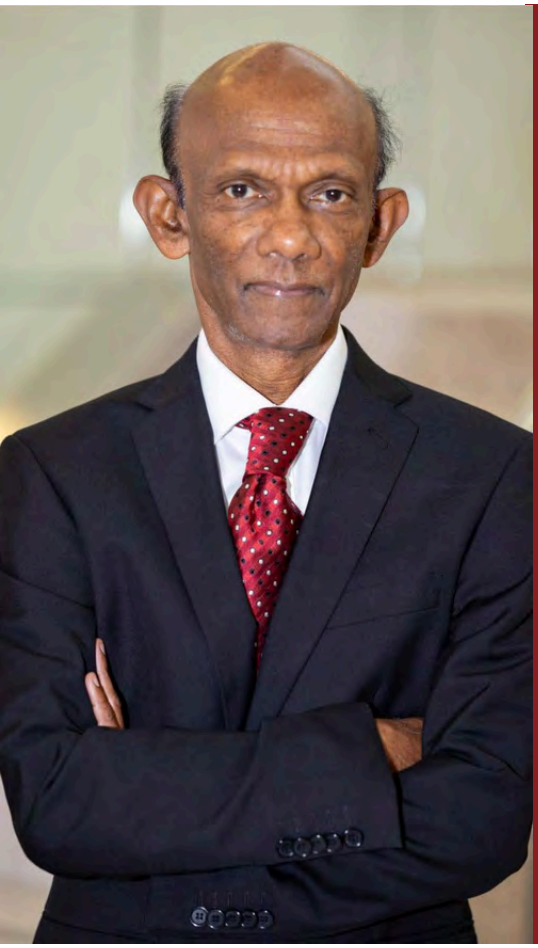
Professor of Medicine, Chief of GI Medica Oncology, Director of The Cockrell Center for Advanced Therapeutics Phase I

Speaker's Bio:

Dr. Maen Abdelrahim is a leading gastrointestinal (GI) medical and transplant oncologist specializing in upper and lower GI malignancies, including colorectal cancer (CRC), cholangiocarcinoma (CCA), and liver transplantation-related cancers. He is Professor of Medicine in GI Oncology at Weill Cornell Medical College and Chief of GI Medical Oncology at Houston Methodist Neal Cancer Center, where he leads a multidisciplinary team focused on innovative Phase I–III clinical trials. As Medical Director of the Cockrell Centers for Advanced Therapeutics, Dr. Abdelrahim directs the Phase I Clinical Trial Program at Houston Methodist, advancing novel mechanism-based therapies for GI cancers. His work includes developing a new structural class of compounds targeting selective transcription factors, with a lead agent now in Phase I clinical testing.

Dr. Abdelrahim has authored over 300 research articles, reviews, and book chapters. He is Editor-in-Chief of the "Transplant Oncology" section of Cancers, Associate Editor of Frontiers in Oncology, and editor of the first textbook on transplant oncology, Transplant Oncology: A Frontier in Multidisciplinary Cancer Care (Academic Press, Elsevier, 2024). He serves as principal investigator for multiple chemotherapy, targeted therapy, and immunotherapy trials through the Southwest Oncology Cooperative Group.

A member of the American Society of Clinical Oncology, American Association for Cancer Research, and International Liver Transplant Society, he is recognized globally in oncology and transplant oncology. Dr. Abdelrahim holds a Pharm.D. and PhD in pharmacology and toxicology from Texas A&M University, an MD from Texas A&M, completed residency at Baylor College of Medicine, and a Medical Oncology fellowship at Duke University.



"Leveraging proteomics for novel biomarkers, early diagnostics and therapeutic leads"

Chandra Mohan, MD, PhD

Professor at the University of Houston

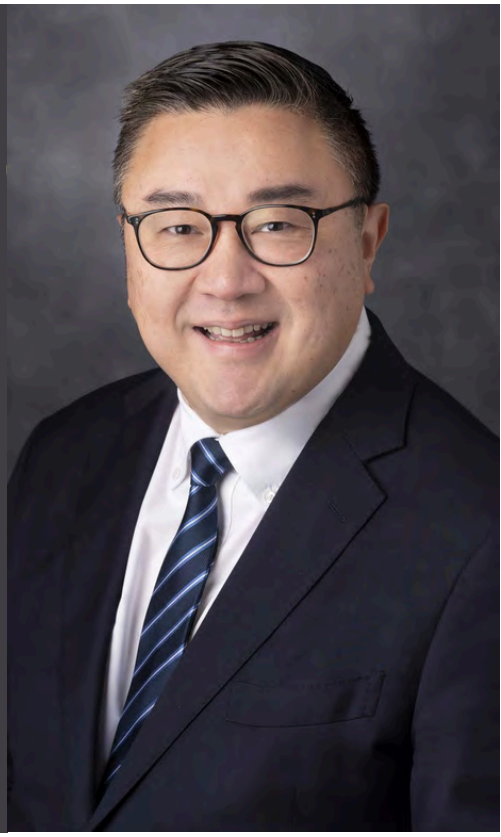
Speaker's Bio:

Dr. Mohan is a Cullen Distinguished Professor at the University of Houston in Houston, TX. Following his medical training in Pathology and Rheumatology at the National University of Singapore and the Singapore General Hospital in Singapore, he undertook his doctoral thesis focusing on the immunology of lupus. Dr. Mohan's ongoing studies are aimed at tapping leads from various proteomic platforms to mine new biomarkers and targets in chronic rheumatic diseases and selected cancers. Dr. Mohan is an elected member of the American Society of Clinical Investigation and the Henry Kunkel Society. He has published >350 articles, largely in the area of lupus genetics, autoimmunity, and biomarkers.

Clinical Studies & Health Outcomes

LOCATION: ROOM 3050 | TIME: 2:30PM

"Impact of the FDA's Project Optimus on Biomarker-Driven Early-Phase Drug Development."

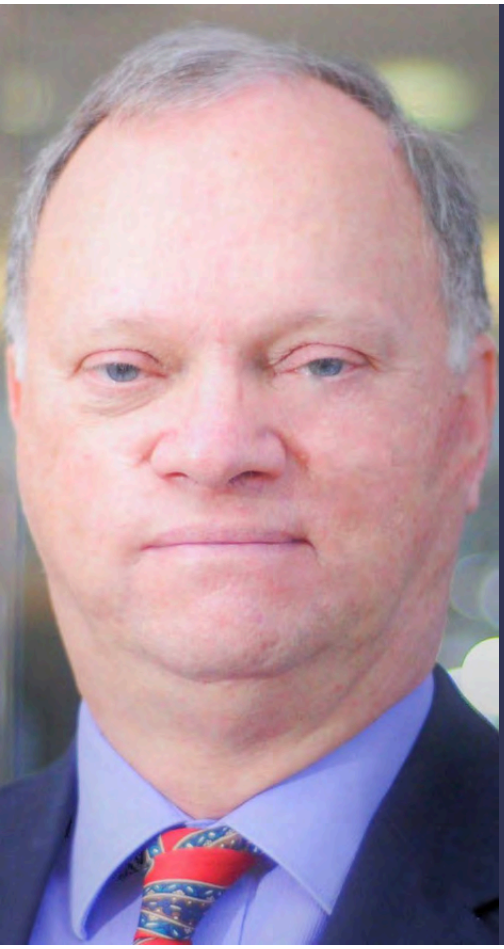


Timothy A. Yap MBBS, PhD, FRCP

Ransom Horne, Jr. Endowed Professor for Cancer Research, Vice President and Head of Clinical Development, Therapeutics Discovery Division, Professor, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center

Speaker's Bio:

Dr. Timothy Yap is a Medical Oncologist and Physician-Scientist, and the Ransom Horne, Jr. Endowed Professor for Cancer Research at the University of Texas MD Anderson Cancer Center. He serves as Vice President and Head of
Clinical Development, Therapeutics Discovery Division, a drug discovery biopharmaceutical division where drug discovery and clinical translation are seamlessly integrated. Dr. Yap is a Professor in the Department of Investigational Cancer Therapeutics (Phase I Program) where he leads the design and conduct of phase 1/2 clinical trials and translational studies. Dr. Yap's main research focuses on the first-in-human and combinatorial development of molecularly targeted agents and immunotherapies, and their acceleration through clinical studies using novel predictive and pharmacodynamic biomarkers. His main interests include the targeting of the DNA damage response (DDR) with novel therapeutics, such as Werner Helicase, ATR, PARP1, WEE1, POLQ, USP1, PKMYT1, PARG, CHK1, ATM and DNA-PK inhibitors, next generation CDK2, CDK4 and CDK7-selective inhibitors, YAP/TEAD inhibitors, SMARCA2 degraders, as well as the development of novel Immunotherapeutics.



"Clinical Trial Design and Health Outcomes for Novel Addiction Pharmacotherapies"

Thomas R Kosten MD,

Waggoner Professor of Psychiatry, Pharmacology, Neuroscience, Immunology at Baylor College of Medicine; Epidemiology and Behavioral Science at University of Texas, MD Anderson Cancer Center; Psychology at University of Houston

Speaker's Bio:

Thomas R. Kosten, MD, is the JH Waggoner Chair and Professor of Psychiatry, Neuroscience, Pharmacology, and Immunology, Director of the Division of Alcohol and Addiction Psychiatry, and Founding Director of the Dan L. Duncan Institute for Clinical and Translational Research (ICTR) at Baylor College of Medicine. He previously served as Vice Chair for Research at Baylor, Professor at Yale University School of Medicine, and Chief of Mental Health at the Connecticut VA. He is the founding Vice Chair for Addiction Psychiatry of the American Board of Psychiatry and Neurology (ABPN) and past president of both the American Academy of Addiction Psychiatry (AAAP) and the College on Problems of Drug Dependence (CPDD). Dr. Kosten is a Distinguished Life Fellow of the American Psychiatric Association (APA) and a Fellow of both the American College of Neuropsychopharmacology (ACNP) and the American Society of Clinical Psychopharmacology (ASCP). He also served as a Congressional Fellow in the US House of Representatives. He is the recent-past Editor-in-Chief of the American Journal on Addictions (AJA) and has authored over 950 publications on addiction pharmacotherapies. His research has been supported by over 75 grants from the NIH, VA, DoD, and various foundations, which also form the basis of ongoing funding support. His scientific contributions include development of an anti-cocaine vaccine, pharmacotherapies for stimulant and opioid use disorders, and advances in pharmacogenetics and microRNA research in addictions and suicidality. He has been recognized as a "Top Doc" by U.S. News & World Report and Castle Connolly, ranked in the top 10% of addiction medicine physicians, and in the top 1%, of U.S. physicians nationwide. A 2024 Scholar GPS ranking places him in 10th place worldwide in the field of addictions, and in the top 0.03% worldwide across all specialties for the quantity and quality of his research.

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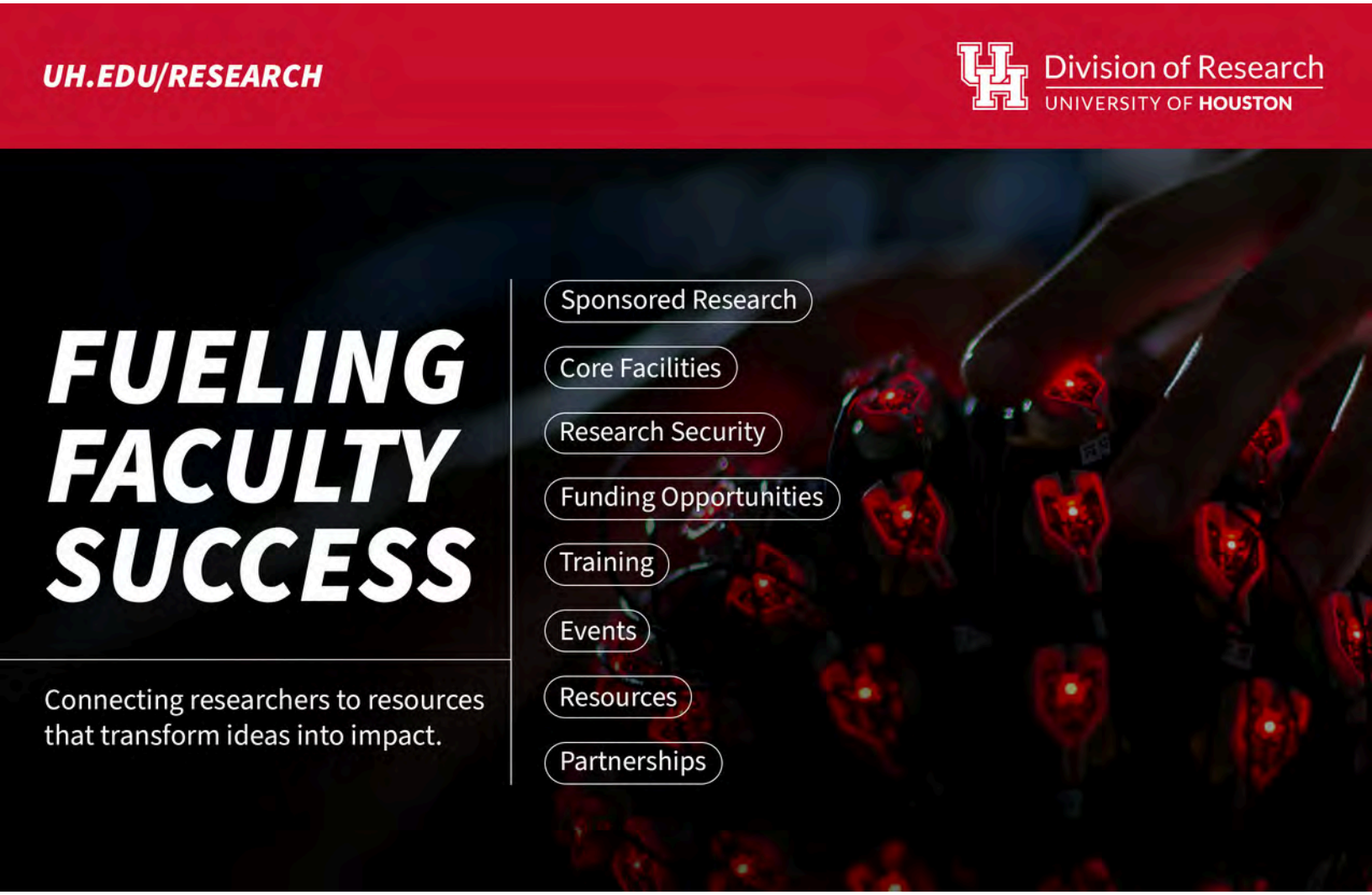
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ABSTRACTS

Prognostic Impact of CTNNB1 Mutations on Immunotherapy Outcomes in Hepatocellular Carcinoma: A Multi-Cohort Genomic Analysis

Waseem Abdelrahim[1], Rubaa Hameed[2], Abdullah Esmail[3]
[1]Michael E. DeBakey HS for Health Professions, [2]Baylor College of Medicine, [3]Weill Cornell Medical College Section of Gastrointestinal Oncology Dr. Mary and Ron Neal Cancer Center Charles W. Duncan Jr. Department of Medicine Houston Methodist Hospital Houston Methodist Academic Institute Houston Methodist Research Institute

Poster 35

Background: Hepatocellular Carcinoma (HCC) remains a highly lethal malignancy characterized by heterogeneous responses to systemic therapy. Recent genomic insights have identified the Wnt/β-catenin signaling pathway as a key driver of HCC oncogenesis. Mutations in the *CTNNB1* gene (encoding β-catenin) occur in 20–40% of cases and are increasingly recognized as critical determinants of tumor behavior and therapeutic sensitivity. This study investigates the impact of *CTNNB1* mutations on treatment response and overall survival (OS) in HCC patients, particularly those treated with immunotherapy.

Methods: A retrospective analysis was conducted using the cBioPortal for Cancer Genomics, aggregating data from 2,453 samples across five major studies (2018–2024). We assessed the prevalence of *CTNNB1* mutations and compared their impact on survival outcomes against other common genomic alterations, specifically *TP53*. Survival analysis for patients receiving immunotherapy was performed using Kaplan-Meier curves and the log-rank test. Statistical significance was defined as $p < 0.05$.

Results: The study cohort was predominantly male (64.2%) and white (55.7%). Within the immunotherapy-treated subgroup, *TP53* and *CTNNB1* mutations were identified in 540 and 174 patients, respectively. Patients harboring *CTNNB1* mutations demonstrated a significantly superior median OS of 39.78 months (95% CI: 32.56–53.33) compared to 25.15 months (95% CI: 22.61–28.15) for those with *TP53* mutations ($p = 0.00314$).

Conclusion: Our findings indicate that *CTNNB1* mutations are associated with a significantly improved median OS compared to *TP53* mutations in the context of HCC immunotherapy. These results highlight the potential of the Wnt/β-catenin pathway as both a prognostic biomarker and a viable therapeutic target. Further prospective research is required to validate these findings and integrate *CTNNB1* mutational profiling into personalized treatment algorithms to optimize patient care.

Association Between Gender Difference in Outcomes and Immune Checkpoint Inhibitors in Colorectal Cancer and Esophagogastric Cancer

Saifudeen Abdelrahim[1], Abdullah Esmail[2]
[1]University of Houston, Houston, [2]Weill Cornell Medical College Section of Gastrointestinal Oncology Dr. Mary and Ron Neal Cancer Center Charles W. Duncan Jr. Department of Medicine Houston Methodist Hospital Houston Methodist Academic Institute Houston Methodist Research Institute

Poster 9

Background: Immunity, encompassing both cellular and humoral responses, is significantly influenced by sex. Factors such as genetic differences, hormonal variations, environmental influences, and the composition of the commensal microbiome all contribute to these differences. Although numerous studies have examined the relationship between gender and the effectiveness of immunotherapy, the results have often been inconsistent. This study aimed to explore whether an association exists between gender and the therapeutic effect of immune checkpoint inhibitors (ICIs) in Colorectal Cancer (CRC) and Esophagogastric Cancer.

Methods: We conducted a cohort study using data from the cBioPortal database, focusing on patients with CRC and esophagogastric cancer who received ICIs. Patients included in the study had been treated with ICIs such as atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, or tremelimumab, either as monotherapy or in combination. We excluded other cancer types from our analysis. Overall survival (OS) was measured from the date of first ICI treatment to the time of death or most recent follow-up, with a median follow-up period of 19 months. To assess gender differences in OS, we calculated median OS separately for male and female patients. Survival analysis was performed using the Kaplan–Meier (KM) method, and we calculated pooled 95% confidence intervals (CIs) to determine the reliability and precision of our findings. The log-rank P-value was used to assess differences in OS between genders.

Results: In cohort study of a total of 1,661 patients, we focused on 110 (6.6%) CRC patients and 126 (7.6%) patients with esophagogastric cancer. Among the CRC patients, 62 (56.4%) were male and 48 (43.6%) were female. In the esophagogastric cancer patients 98 (77%) males and 28 (22%) females. The most common genetic mutations identified in CRC patients were APC 80 (72%), KRAS 57 (51%), and TP53 56 (50%). Among esophagogastric cancer patients, TP53 mutations were found in 92 (72%) patients, and CDKN2A mutations were present in 20 (15%) patients. Out of these patients, 99 (90%) of CRC patients and 93(73%) of esophagogastric cancer patients received PD-1/ PD-L1 inhibitors and the remaining patients received either anti-CTLA-4 or combination of anti-CTLA-4 and anti-PD-1/PD-L1 therapies, as part of their treatment. In studies measuring median OS for CRC patients treated with ICIs, male patients had a median OS of 31 months (95% CI: 13.00–NA), compared to 12 months (95% CI: 8.00–NA) for female patients (p=0.03). For esophagogastric cancer patients, the median OS was 13 months (95% CI: 7.00–21.00) for male patients, while for female patients, it was 20 months (95% CI: 10.00–NA) (p=0.32).

Conclusion: Our study highlighted that ICI therapy improves survival outcomes, with males showing greater benefit as, indicated by a longer OS, compared to females in CRC, while the opposite result was observed in esophagogastric cancer.

Macrophage Ferroptotic Susceptibility and Polarization Are Linked to Adaptive Radiation Resistance in Esophageal Adenocarcinoma

Sadhna Aggarwal[1], Rui Ye[1], Jared K Burks[1], Steven H Lin[1]
[1]MD Anderson Cancer Center

Poster 55

Radiation resistance remains a major obstacle to improving outcomes after chemoradiation therapy (CRT) in esophageal adenocarcinoma (EAC). Ferroptosis, a lipid peroxidation–driven cell death pathway, is increasingly recognized as a regulator of tumor–immune interactions. We investigated whether macrophage ferroptotic susceptibility differs between good responders (GR) and non-responders (NR) to CRT.

Single-cell RNA sequencing (scRNA-seq) and multiplex immunofluorescence (COMET) were performed on patient biopsies collected before, during, and after CRT to define immune subsets and ferroptosis-related markers. In vitro assays were conducted in THP-1 and human PBMC-derived M1/M2 macrophages exposed to 0–12 Gy radiation ± RSL3 or ferrostatin. Ferroptosis was assessed by CellTiter-Glo, BODIPY-C11 oxidation, and GPX4 expression.

scRNA-seq revealed expansion of myeloid populations in both GR and NR. Pro-ferroptotic gene programs (BH4 biosynthesis, iron metabolism, glycolysis) were enriched in NR at baseline and during CRT, particularly in macrophages, while anti-ferroptotic pathways (GPX4) were higher in GR. Spatial analysis showed increased baseline M2 macrophage density and elevated 4-HNE in NR tumors. During CRT, NR exhibited further M2 enrichment, consistent with an immunosuppressive microenvironment, whereas GR maintained higher M1 representation. In vitro, radiation enhanced RSL3-induced ferroptosis, while ferrostatin rescued viability. M2 macrophages were more sensitive to radiation-induced ferroptosis, whereas M1 macrophages were relatively resistant.

CRT response in EAC is associated with macrophage polarization and ferroptotic susceptibility. NR tumors display M2 dominance, increased lipid peroxidation, and activation of pro-ferroptotic pathways. Targeting macrophage ferroptosis may represent a strategy to improve radiosensitivity in EAC.

Institutional and Community Impact of NIH-funded Community Engagement Core of the Center for Biomedical and Health Research (CBMHR CEC) from December 2020 to November 2025

Adams Akilah[1], Monique Gongora[1], Mark Ibarra-Garza[1], Kassie Thompsom[1], Sneha George[1], Maria Mejia[1], Rosalia Guerrero[1], Rodney Hunter[1], Veronica Ajewole-Mwema[1]*.
[1]Texas Southern University

Poster 1

Texas Southern University (TSU) has built unparalleled trust within the community through a long history of meaningful outreach and engagement to address health concerns. Although TSU has received Research Center for Minority Institutions funding from the National Institutes of Health for over 30 years, a Community Engagement Core (CEC) was not established until 2020. In September 2020, the NIH- funded Center for Biomedical and Health Research, led by Drs. Ester Olaleye, Xie Huan, Dong Liang, established TSU's first CEC with Dr. Veronica Ajewole-Mwema as its founding Director to strengthen efforts in addressing community health priorities through focused outreach and collaboration.

Since 2020, the CBMHR CEC has built trusted partnerships with more than 75 organizations, including faith-based and community groups, Federally Qualified Health Centers, healthcare systems, industry partners, and governmental and non-governmental organizations. Collaborations include health education events, steering committee participation, community grants, Community Health Worker (CHW) training, and support for clinical research initiatives. To date, CEC has hosted over 100 outreach events reaching more than 6,000 attendees, issued approximately 1,500 CHW continuing education credits, generated over 3 million media impressions, and received nearly 15 proclamations and formal recognitions from elected officials. CEC has strengthened clinical research awareness through its annual conference, drawing >1,000 attendees, and recently established the 1st-ever TSU Center for Clinical Research and Translational Sciences (TSU CCRTS). CEC also led to the establishment of the 1st-ever TSU Mobile Health Unit.

With its recently renewed funding, CBMHR CEC is positioned for continued and lasting health impact in the community.

Cardioprotective roles of Mas and MrgD axis activation by Angiotensin-(1–7) and Alamandine in cardiac remodeling

Tabish Ali[1], Bradly McConnell[1]
[1]Department of Pharmacological & Pharmaceutical Sciences, Collage of Pharmacy, University of Houston

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Pathological cardiac remodeling, characterized by hypertrophy, fibrosis, and progressive dysfunction, is a major driver of heart failure and arrhythmia. While Angiotensin II (Ang-II) signaling through the classical renin–angiotensin system promotes maladaptive remodeling, the protective arm of the RAS, mediated by Angiotensin-(1–7)/Mas and Alamandine/MrgD signaling, remains incompletely understood.

This study investigates the cardioprotective roles of Angiotensin-(1–7) and Alamandine in complementary in vitro and in vivo models of cardiac stress. Human AC16 cardiomyocytes and hiPSC-derived cardiomyocytes were subjected to Ang-II–induced hypertrophic stress, followed by peptide treatment to assess receptor-specific protective effects on remodeling-associated gene expression.

In vivo, cardiac dysfunction and remodeling were induced in C57BL/6J mice using continuous Ang-II infusion (1.5 mg/kg/day) via ALZET osmotic pumps for 14 days. Separate groups received Angiotensin-(1–7) or Alamandine (0.6 mg/kg/day). Cardiac function was assessed by echocardiography, while structural remodeling was evaluated by heart weight to tibia length ratio and RT-qPCR–based analysis of hypertrophic and fibrotic markers.

Both peptides significantly attenuated Ang-II–induced cardiac remodeling, reducing hypertrophic and fibrotic gene expression while improving functional parameters. These findings support the therapeutic potential of Mas and MrgD axis activation as novel strategies to counter pathological remodeling and heart failure progression. Ongoing studies are focused on receptor-specific knockdown, RNA sequencing, and mitochondrial analyses to define the underlying molecular mechanisms.

SP-16, an LRP1 Agonist Peptide, Protects Against Pseudomonas Aeruginosa-Induced Acute Respiratory Distress Syndrome

Sundus Jabeen Amina[1], Fatima Dagher[1], James E. Smith[1], Mikayla Skillman[1], Vincent H. Tam[1], Diana S-L Chow[1], Bin Guo[1]

[1]University of Houston

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Acute respiratory distress syndrome (ARDS) caused by severe bacteria-induced pneumonia is associated with high mortality and limited treatment options, particularly in the context of antimicrobial resistance. Host-directed therapies that preserve immune homeostasis while maintaining antimicrobial defense represent a promising strategy. Here, we evaluated the therapeutic efficacy and immunomodulatory effects of SP-16, a synthetic peptide agonist of low-density lipoprotein receptor–related protein-1 (LRP-1), in a mouse model of Pseudomonas aeruginosa–induced ARDS. In a drug-susceptible strain (PA27853), SP-16 administered after disease onset significantly improved survival compared with untreated controls. Among the dosing regimens tested, a 2.5 mg/kg daily regimen showed greater survival benefit than a 5 mg/kg every-other-day regimen. SP-16 treatment significantly reduced pulmonary bacterial burden at 24 h post-intubation and at later stages, including in animals that ultimately succumbed to infection. In addition, SP-16 improved physiological parameters, including body temperature and clinical disease severity scores. Mechanistically, SP-16 suppressed pro-inflammatory cytokines (IL-1β, IL-6) and modulated immune cell populations. Flow cytometric analyses indicated activation of Akt signaling and modulation of NF-κB pathways in myeloid cells. In a drug-resistant strain (PA42), SP-16 and its cyclic analog 7G produced comparable reductions in bacterial burden and similarly improved blood gas parameters at 36 h post-intubation. Both compounds also showed comparable modulation of immune responses and signaling pathways. In survival studies, SP-16 achieved the highest survival rate (87.5%), while 7G showed partial protection (75%), both outperforming meropenem (42.85%). Collectively, SP-16 provides robust host-directed protection in pneumonia-induced ARDS and retains efficacy in drug-resistant infection.

The DAMPRs: DNA-Damage Ameliorating Proteins and Cell Health

Sofia Aramburu[1], Julian Perren[2], Mu Lin[1], Jun Xia[3], Dorothy Shippen[4], Daniel Jarosz[5], Vishnu Dileep[1], Reuben Harris[6], Kyle Miller[2], Susan Rosnberg[1]

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As organisms age, their genetic integrity erodes and physiological cell functions decline, creating a disease prone environment. Although DNA-repair machinery can cope with some DNA-damaging events, repair can be error-prone or overwhelmed by excessive damage events, leading to elevated somatic-cell mutation rates.

We hypothesized the existence of proteins that protect macromolecules – including nucleic acids, proteins and lipids – from endogenous and exogenous damage. Using flow cytometry, we screened for reduced markers of DNA-damage response: γH2AX and phosphorylated p53 levels in two separate cell lines. We identified 15 DNA Damage Ameliorating Proteins (DAMPRs) that reduce DNA-damage markers upon over-expression, 12 of them further protect against X-ray-induced DNA damage.

To understand the mechanisms underlying the DNA-damage-reducing effects of DAMPRs we assessed their effect on known cellular stressors. We identified 9 DAMPRs that reduce reactive oxygen species (ROS) in either one or both cell lines; and a second group that reduces aggregated proteins when compared with over-expressed random human genes. 2 DAMPRs have not shown a stress-reducing phenotype, hinting at additional untested mechanisms.

Ongoing work aims to determine whether DAMPRs reduce mutation rates when overproduced. Using a modified human cell line engineered to express the HSV-1 thymidine kinase gene, that when mutated confers ganciclovir resistance, we obtained preliminary data showing that at least 2 DAMPRs might reduce somatic mutation rates in human cells.

We predict that understanding how DAMPRs affect cellular stressors and mutagenesis can aid in the development of novel preventative strategies against age-related diseases. Greater access to genetic screening has increased awareness of individual cellular vulnerabilities and could allow physicians to choose upregulation of DAMPRs to treat specific individuals whose risk profiles justify intervention.

Retinal Arterioles and Venules are Remodeled in Type 2 Diabetes but Not Prediabetes

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Purpose: It is established that retinal arterioles are remodeled in type 2 diabetes (T2DM), yet microvascular remodeling in venules and in prediabetes (preDM) remain largely uncharacterized. We used adaptive optics scanning light ophthalmoscopy (AOSLO) to investigate structural remodeling in retinal arterioles and venules in individuals with preDM and T2DM.
Methods: One eye of 15 participants (44.93±11.56 years) was imaged with AOSLO. Participants were divided into three groups: controls (HbA1c ≤ 5.6%, N = 7), preDM (HbA1c 5.7 - 6.4%, N = 4), and T2DM (HbA1c ≥ 6.5%, N = 4). Videos were acquired over 9° × 9° (fovea-centered) region, and split-detector images of 62 arterioles and 67 venules were analyzed using semi-automated custom MATLAB software. Structural vascular metrics, including wall thickness (WT), wall-to-lumen ratio (WLR), and wall cross-sectional area (WCSA), were quantified. Measurements were corrected for retinal magnification and group differences were assessed using Kruskal–Wallis tests with post hoc comparisons.
Results: Arteriolar WT (p = 0.11), arteriolar WCSA (p = 0.72), and venular WLR (p = 0.10) did not differ significantly among the groups. Arteriolar WLR (p = 0.02), venular WT (p < 0.01), and venular WCSA (p = 0.01) were significantly higher in T2DM compared to controls.
Conclusion: We show that retinal venular WT and WCSA, and arteriolar WLR are increased in T2DM. This data suggests that venular wall remodeling also occurs in T2DM and may serve as a potential retinal vascular biomarker in T2DM.
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Educate Before You Medicate: Preventing Prescription Misuse Through Community Pharmacy Interventions

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Background: Community pharmacists are highly accessible healthcare professionals who play an important role in educating patients on safe use of controlled substances. However, counseling practices related to controlled substances vary widely between pharmacies. The Educate Before You Medicate initiative aims to improve pharmacist awareness of safe medication practices and increase availability of disposal resources available to patients from community pharmacies.
Methods: PharmD students from the University of Houston College of Pharmacy were recruited to conduct a telephone-based intervention targeting community pharmacies in Texas from Dec. 2025 – Jan. 2026. Pharmacists were asked questions regarding counseling about controlled substances, counseling points as compared to non-controlled medications, and their recommendations for the disposal of unused medications. Pharmacies were also offered single-use disposal systems (SUDS) for patients at no cost.
Results: A total of 154 pharmacies were contacted by five pharmacy students, with students ultimately speaking with 84 (55%) of pharmacies. The main counseling points reported for controlled substances were on direction for use (71%), adverse effects (61%), and emphasizing use only as directed and by the intended patient (44%). Counseling points for controlled substances were modified by emphasizing directions for use (45%), overdose risk (21%), and safe disposal (19%) as reported. A total of 39% of pharmacies reported they already provide safe disposal options to patients, and 62% said they would provide free SUDS and educational materials if supplied.
Conclusion: Most community pharmacists reported consistently counseling patients on directions for use and adverse effects; however, fewer addressed overdose risk, naloxone, and safe disposal. Relatively few pharmacies offer an on-site disposal bin and education materials, with many pharmacists expressing willingness to provide SUDS to patients.

Structure-Activity Relationship and Binding Mode Analysis of a New Class of Receptor-Interacting Protein Kinase 3 Inhibitors

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Necroptosis is a form of programmed cell death triggered by death receptors when apoptosis fails to occur. It has been linked to numerous diseases, such as cancers, liver diseases, cardiovascular diseases, neurodegenerative disorders, pancreatic diseases, lung diseases, and kidney diseases. Necroptosis is highly dependent on the protein receptor-interacting protein kinase 3 (RIPK3) and its substrate, the mixed lineage kinase domain-like (MLKL) pseudo-kinase, which are fundamental players in the necroptotic pathway. Activated RIPK3 leads to MLKL phosphorylation, which results in MLKL oligomerization and translocation to the plasma membrane, triggering cell rupture and release of chemokines, cytokines, and damage-associated molecular patterns (DAMPs).

Our previous studies identified UH15-38 as a potent inhibitor of RIPK3-mediated necroptosis (e.g., TNF-induced cell death in FADD-deficient JK cells), with an IC50 of 205 nM. Herein, we report a structure–activity relationship (SAR) and binding mode analysis of UH15-38 and its analogs. Substitution of the phenol ring with a benzothiazole moiety significantly enhanced RIPK3 inhibitory activity, yielding MB-2-03 with an IC50 of 49 nM. Additionally, derivatives with a piperidine substituent at the 3- or 4-positions of the solvent-exposed phenyl ring retained comparable potency. Molecular docking studies of the optimized compound MB-2-03 demonstrated a strong binding affinity to the DFG-in active conformation of RIPK3, consistent with the binding mode of the lead compound UH15-38.

Pharmacokinetic/Pharmacodynamic Correlation and Biodistribution of Paclitaxel and Cyclopamine from M-CPA/PTX in HCC Mice Following Multiple Dosing

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Hepatocellular Carcinoma (HCC) is the most common form of liver cancer, highly aggressive and heterogenous. Due to lack of effective diagnostic techniques, HCC is often detected when surgical and chemotherapeutic interventions are inadequate. To address this, we developed a polymeric micelle containing Paclitaxel (PTX), a microtubule-stabilizer, and Cyclopamine (CPA), a Hedgehog pathway inhibitor, termed M-CPA/PTX. The M-CPA/PTX contained 2.5 mg each of PTX and CPA, with size of 70.6 ± 3.4 nm, PDI of 0.12 ± 0.04 (n = 3), and encapsulation efficiency of ± 80% for both agents. The biodistribution (BD) of PTX and CPA in tumor, liver, lung, spleen and kidney were characterized following IV dosing of 5 mg/kg M-CPA/PTX in C-MYC expressing transgenic mice which were randomized into four groups: vehicle (n = 10), 1 dose (n = 8), 2 doses (n = 7), and 3 doses (n = 9). ANOVA with Tukey's post hoc test was for statistical analysis with p-value < 0.05 for significance. The BD data were compiled in Table 1. The blood concentrations for each agent were substantially lower than those in tumor and organs at 24 hours post the last dose. The BD patterns were distinct between PTX and CPA. The PTX concentrations were the highest in tumor, 369-443 ng/g, followed by liver >>lung > kidney >> spleen, 11-15 ng/g. The CPA concentrations were high in lungs, 537-751 ng/g, and kidney, 305-339 ng/g, followed by tumor, 218-300 ng/g, and liver, 206-328 ng/g. The BD levels were not significantly altered among the dosing groups.

The 3D PK/PD correlation was established for tumor growth inhibition (%), with tumor concentrations of PTX and CPA in individual mice, while that with the systemic exposures (AUC0-∞) of PTX and CPA in blood was not promising. In conclusion, the biodistributions of PTX and CPA following multiple IV dosing in an HCC mouse model were characterized, and a 3D PK/PD correlation was established with PX and CPA uptakes in tumor, potentially enabling future efficacy projection.

Pomegranate-Derived Bioactive Compounds Mitigate Mycophenolate Mofetil–Induced Gastrointestinal Toxicity: An AI-Assisted Discovery Approach

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Mycophenolate mofetil (MMF) is an immunosuppressant for organ transplantation and autoimmune diseases; however, its clinical utility is limited by gastrointestinal (GI) toxicity, particularly diarrhea, which reduces patient adherence and therapeutic outcomes. Punica granatum (pomegranate) is rich in bioactive polyphenols, flavonoids, and tannins with anti-inflammatory and mucosal-protective properties. This study evaluated the therapeutic potential of P. granatum extract in mitigating MMF-induced GI toxicity in a rat model. Female Wistar rats were used to establish an MMF-induced diarrhea model. MMF was administered orally to induce GI toxicity. Following MMF cessation, P. granatum extract was administered to assess protective effects. Body weight and fecal consistency were monitored daily to evaluate diarrhea severity and treatment efficacy. Extract quality and phytochemical composition were characterized using UPLC and LC–MS. In parallel, a curated library of P. granatum–derived compounds was developed and is being integrated with AI-assisted cheminformatics to identify bioactive constituents. Inflammatory status in colon tissue was quantified using ELISA to assess cytokine modulation. MMF administration-induced diarrhea was observed as early as Day 5 in 40% of control animals, progressing to 90% incidence in the vehicle-treated group, with severe cases noted. In contrast, rats treated with P. granatum extract demonstrated improved stool consistency and reduced diarrhea severity, with 80% of rats exhibiting symptoms by Day 8. Treatment groups maintained body weight compared with controls, and stool consistency improved to 100% with continuous co-administration. The antidiarrheal efficacy was dose-dependent. P. granatum mitigated GI toxicity through anti-inflammatory pathways, with reduced pro-inflammatory cytokines. This study established a reproducible MMF-induced diarrhea model in rats and demonstrate that P. granatum extract mitigates GI toxicity.

Preliminary investigation into treatment failure in patients receiving intravenous vancomycin prior to Clostridioides difficile and treated with oral vancomycin

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Poster 5

Background: Intravenous (IV) vancomycin is not used as a treatment for *Clostridioides difficile* infections (CDI) due to the lack of penetration into the gut and localized antibacterial effects. However, our group recently demonstrated that 10% of patients with diarrhea had measurable concentrations of vancomycin in their stool. We hypothesize that patients receiving IV vancomycin and have measurable concentrations in the stool will have treatment failure with oral vancomycin potentially due to resistance generation. The purpose of this study is to describe a preliminary cohort of patients receiving IV vancomycin and the rate of delayed resolution of diarrhea at day 6 and day 14.

Methods: This is a retrospective, observational cohort study including patients who tested positive CDI at two health systems between 2017-2024. Patients were included if they received IV vancomycin for >48 hours immediately prior to *C. difficile* test and were treated with oral vancomycin monotherapy. Vancomycin monotherapy was defined as <72 hours of metronidazole in combination with definitive oral vancomycin. Primary endpoint was total patients who had diarrhea at day 6 for delayed resolution and day 14 for treatment failure.

Results: Sixty-one patients were included in this study. Delayed resolution of diarrhea occurred in 14/61 (23%) of patients and treatment failure occurred in 6/61 (10%) of patients. Baseline demographics were similar between those who had delayed resolution compared to those who had resolution at day 6.

Conclusion: In patients who received IV vancomycin prior to CDI treatment with oral vancomycin, 1 out of 5 patients had delayed resolution of diarrhea and 1 out of 10 had treatment failure at day 14. This correlates with previous findings that 10% of patients have detectable vancomycin in their stool following IV administration. Future directions include quantifying vancomycin by LC-MS on available stool samples from this cohort as well as susceptibility testing.

Impact of treatment on 30-day mortality in patients with discordant two-step CDI results

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Clostridioides difficile discordant results (GDH+/EIA-) have historically been interpreted as colonization not necessitating treatment. However, patients are often treated, and the clinical impact of this is conflicting. Previous studies have shown conflicting results surrounding treating patients with discordant C. difficile results and associated patient outcomes. This study's objective was to evaluate our preliminary cohort of GDH+/EIA- patients to determine if treatment is correlated to decreased 30-day mortality. This study was a retrospective, observational cohort study looking at patients with GDH+/EIA- results at Baylor St. Luke Health System from 2020 to 2026. The primary endpoint was comparing 30-day mortality in patients who received treatment against those who did not. Electronic medical records were manually reviewed, and clinical values of interests were gathered. Analysis was performed using R studio (version 4.5.3).

Four hundred patients were included in this preliminary analysis with 36.75% receiving treatment and 63.25% not. The overall study population had a mean age of 57.6±17.6 years, 57% Female, 19% Hispanic. The majority of the population was treated with oral vancomycin (142/147, 96.60%). Overall, 30-day all-cause mortality was 10% (40/400). Mortality was significantly higher in patients receiving therapy (25/147 (17%) vs 15/253 (6%); p<0.001). In this preliminary analysis, patients with discordant results receiving treatment were associated with higher rates of 30-day mortality. Future directions include expansion of the cohort, sub analysis by treatment selection and dosing, and inclusion of a severity score for deeper comparison of the study groups.

Nebivolol Triggers Apoptosis, Ferroptosis and Necroptosis in Triple-Negative Breast Cancer

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Triple-negative breast cancer (TNBC) lacks effective targeted therapies and is associated with poor outcomes. We are investigating nebivolol (NEB), an FDA-approved third-generation β-blocker, as a repurposed therapeutic candidate for TNBC. We previously reported that NEB inhibits TNBC cell growth, proliferation, clonogenic potential and disrupts autophagic flux. RNA-seq analysis revealed enrichment of ferroptosis (FDR = 0.076), apoptosis (FDR = 0.111), and necroptosis (FDR = 0.133) pathways following NEB treatment. Here, we investigated NEB-induced cell death mechanisms using 2 TNBC cell lines (MDA-MB-231 and SUM159) treated with vehicle or NEB. Ferroptosis was assessed by BODIPY C11 lipid peroxidation assay at 24h and confirmed using western blotting (WB) for ACSL4, SLC7A11, and GPX4. NEB-induced apoptosis was evaluated at 24-72h using Annexin V/PI-stained flow cytometry and confirmed by WB for cleaved/total PARP and caspase-3/7. Necroptosis was assessed by LDH release following 3-100 μM NEB treatment at 24h. Statistical significance was determined by one-way ANOVA with multiple comparisons or unpaired t-test using at least 3 biological replicates. NEB (10 μM) significantly increased lipid peroxidation (1.5-2-fold), confirming ferroptosis induction. WB analysis showed time-dependent upregulation of SLC7A11 and downregulation of GPX4, without changes in ACSL4. NEB significantly increased both Annexin V+/PI- and Annexin V+/PI+ populations in a time-dependent manner, indicating early and late apoptosis induction. NEB elevated cleaved PARP and caspase-7, but not caspase-3, in a time-dependent manner. NEB 30 and 100 μM significantly increased LDH release indicating necroptosis-mediated membrane rupture. Overall, NEB induces TNBC cell death by activating both apoptotic and non-apoptotic pathways. These findings support NEB as a promising repurposed drug candidate for TNBC and identify ferroptosis and necroptosis as novel components of its antitumor mechanism.

Dual-targeting LGR5 and EREG using Bispecific Antibody-based Approaches for the Treatment of Colorectal Cancer

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Colorectal cancer (CRC) remains the second-leading cause of cancer deaths worldwide. Significant challenges in the treatment of CRC include tumor heterogeneity and the persistence of cancer stem-like cells (CSCs) that drive relapse, metastasis, and therapeutic resistance through their dynamic cellular plasticity. These factors highlight the need for novel bispecific therapeutics capable of targeting multiple tumor-associated antigens and pathways. Leucine-rich repeat containing, G protein-coupled Receptor 5 (LGR5) is a well-established CSC marker known to regulate Wnt signaling and drive tumor initiation. Interconversion of $LGR5^{+}$ CSCs to $LGR5^{-}$ non-CSC states has been shown to be essential for tumor progression and metastasis, as well as contribute to treatment resistance. The EGFR ligand epiregulin (EREG) is broadly expressed on the surface of both CSC and non-CSC populations and is upregulated with the loss of LGR5. We previously showed antibody-drug conjugates (ADCs) targeting LGR5 or EREG effectively inhibited tumor growth, yet tumors eventually grew back due to target downregulation and plasticity. This project focuses on the development of EREG:LGR5 bispecific ADCs (bsADCs) to simultaneously eliminate both LGR5- and EREG-expressing CRC cells to improve antitumor efficacy and prevent resistance and relapse. RNA-seq and western blot showed LGR5 and EREG are highly expressed in CRC patient tumors and cell lines, with minimal expression in normal tissues. EREG:LGR5 bispecific antibodies (bsAbs) were engineered, produced, and purified as shown by Coomassie staining and mass spectroscopy. Immunocytochemistry demonstrated that bsAbs specifically bound both EREG and LGR5 and rapidly internalized into lysosomes, which is essential for bsADC payload release. Effects of EREG:LGR5 bsAbs on downstream signaling were also assessed. Future work will focus on the generation of EREG:LGR5 bsADCs and evaluation in patient-derived tumor models for the improved treatment of CRC.

Vascular-Targeted Liposomal Delivery for Modulating Neurovascular Inflammation in Vascular Dementia

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Vascular dementia (VaD) accounts for approximately 15-20% of all dementia cases and affects an estimated 1.5-2 million individuals in the United States. Despite its high prevalence, effective clinical treatments remain lacking, largely because the molecular mechanisms linking cerebrovascular injury to neurovascular inflammation and white-matter degeneration are not fully understood. Increasing evidence suggests that vascular inflammation plays a central role in VaD progression.

In experimental models of VaD, we observed pronounced inflammatory activation within the cerebral vasculature, characterized by markedly elevated expression of the endothelial adhesion molecule VCAM-1 along brain blood vessels. This vascular inflammatory phenotype suggests that activated brain endothelial cells may represent an important driver of neurovascular inflammation during VaD progression.

Motivated by this observation, we sought to develop a vascular-targeted therapeutic strategy aimed at selectively modulating endothelial inflammation. Building upon our laboratory's liposome engineering platform, we designed a high–drug-loading liposomal system incorporating the ionizable lipid SM-102 to enhance nanoparticle stability and encapsulation efficiency. The engineered nanoparticles demonstrated robust formulation performance, achieving approximately 80% drug loading (DL) and encapsulation efficiency (EE) with a uniform particle size of ~150 nm. To enable selective targeting of inflamed vasculature, the liposomes were functionalized with VCAM-1–binding ligands, allowing preferential interaction with activated endothelial cells. In vitro targeting assays using OGD-treated bEnd.3 endothelial cells, a model of ischemic vascular stress, demonstrated that VCAM-targeted liposomes exhibited 46.7% higher cellular uptake compared with non-targeted liposomes after only 1 hour of incubation.

Role of Gastrointestinal Recycling in Modulating Buprenorphine Exposure Following Sublingual Administration

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Objective: Buprenorphine (BUPE), co-formulated with naloxone and administered as a sublingual film, is a cornerstone therapy for opioid use disorder (OUD) but exhibits substantial interindividual pharmacokinetic variability. Although designed to bypass hepatic first-pass metabolism, a swallowed fraction may contribute to systemic exposure via gastrointestinal (GI) mechanisms. This study evaluated the role of intestinal metabolism and recycling in BUPE disposition following sublingual administration.

Methods: Pharmacokinetics of BUPE and buprenorphine glucuronide (BUPE-G) were evaluated in rats following sublingual administration (2 mg/kg) with or without activated charcoal (1 g/kg, p.o.) to interrupt GI reabsorption. Rats (n = 8) received daily dosing for 7 days, with sampling on Days 1, 3, and 7. A crossover design minimized interindividual variability. After completion, tissues (liver and intestinal segments) were collected to assess distribution and GI contributions.

Results: Activated charcoal reduced systemic exposure of BUPE and BUPE-G (decreased AUC and Cmax) and eliminated secondary peaks in concentration–time profiles, indicating disruption of recycling. Control animals showed increased exposure with repeated dosing. Tissue levels were markedly reduced after charcoal, particularly in intestine and liver. Duodenal BUPE-G decreased from ~1120 to ~194 pmol/g and hepatic BUPE-G from ~166 to ~16 pmol/g. Distinct regional patterns were observed, with BUPE-G highest in the duodenum and BUPE highest in the colon (e.g., colon ~2510 vs. duodenum ~139 pmol/g), supporting rapid intestinal glucuronidation and potential colonic deconjugation.

Conclusion: GI metabolism and recycling play a key role in buprenorphine disposition after sublingual dosing. These findings highlight the importance of intestinal contributions to systemic exposure and suggest that altered GI function may contribute to variability in buprenorphine pharmacokinetics and clinical response.

Targeting GPR56 to Suppress Colorectal Cancer Stemness and Metastasis through Next-Generation Antibody–Drug Conjugates

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Distant metastasis and relapse are the leading causes of mortality in Colorectal cancer (CRC), as approximately 20-25% of patients develop metastatic disease, where the 5-year overall survival is about 15%. Despite available therapies for specific mCRC subtypes, outcomes remain poor due to tumor heterogeneity, therapy-related toxicity and resistance, and the persistence of cancer stem-like cells (CSCs), highlighting the urgent need for new targeted therapeutics. Antibody-drug conjugates (ADCs) deliver potent cytotoxic payloads to tumor cells with improved specificity and reduced systemic toxicity. Our previous studies identified GPR56 as a viable therapeutic target for CRC. GPR56 is overexpressed in 65–80% of CRCs, enriched in the MSS subtype and associated with poor clinical outcomes. We showed that GPR56 promotes tumor growth, chemoresistance, and alters CSC marker expression. Furthermore, we developed GPR56-targeted ADCs incorporating in-house mAb 10C7 with duocarmycin, which showed strong selectivity and potent antitumor activity in GPR56-high CRC cells and PDXs without overt toxicity. However, incomplete tumor elimination indicates the need for improved therapeutic efficacy and strategies. We therefore hypothesize that GPR56 helps promote cell plasticity and the metastatic potential of CRC, which can be effectively inhibited using a novel optimized GPR56 ADC with enhanced efficacy. Using CRISPR/Cas9, we generated GPR56 knockout metastatic CRC cells expressing mCherry–luciferase for orthotopic implantation and in vivo imaging of metastatic progression. We also generated GPR56-overexpressing human and murine CRC cell lines showing enhanced proliferation and are evaluating effects on CSC phenotypes, clonogenicity, migration/invasion and chemoresistance. In parallel, we are developing optimized GPR56 ADCs and generated a novel anti-GPR56 mAb, M6, with >6-fold higher binding affinity than parental 10C7 and engineered for site-specific conjugation.

A Computational Fluid Dynamics Framework for Optimizing Microchannel Oxygenator Architectures in Artificial Placenta Systems

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The placenta is a temporary organ that develops in the uterus of pregnant women to provide the developing fetus with oxygen and nutrients while removing waste through the umbilical cord. In preterm infants, organs are underdeveloped, which can lead to a number of physiological problems. Thus, artificial placenta systems have been theorized to support and improve prognostic outcomes for preterm infants post-pregnancy. Current research in artificial placenta systems have demonstrated promise in large animal models, but have yet to translate to human clinical use. This is largely due to the lack of a systematic optimization of oxygenator microchannel design for gas exchange efficiency and hemocompatibility. In this study, a computational fluid dynamics (CFD) framework was developed to evaluate and optimize oxygenator architectures that vary in geometry, flow rate, and other features. Four geometric configurations based on biological design were assessed. Steady-state incompressible laminar flow simulations were performed at three physiologically relevant inlet velocities, and passive scalar transport was simulated to assess CO2 behavior. The results of the study reveal design recommendations that can increase gas transport efficiency while controlling pressure drop and wall shear.

Mapping Multi-Level Stigma Across the Patients' Journey in Accessing Medications for Opioid Use Disorder (MOUD)

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Poster 6

Stigma toward medications for opioid use disorder (MOUD) is a known barrier to treatment and although stigma is often linked to opioid use disorder (OUD), intervention stigma toward MOUD remains prevalent throughout patients' recovery process. This study aims to show how stigma persistently constrains patients' engagement with MOUD and develop a stigma-informed patient journey map to showcase patients' experiences. A qualitative study was conducted using semi-structured interviews with 31 stakeholders including patients, peer recovery coaches, and clinicians at an office-based addiction treatment program. Interviews were designed to explore participants' experiences with stigma and their impact on patients' journey in opioid use disorder (OUD) treatment. Data were analyzed using thematic analysis.

Participants described patients' experiences with stigma while interacting with peers, family members, friends, pharmacies, employers, law enforcement, and the healthcare system. Stigma was identified at the following points of patients' treatment journey, including: 1) treatment or ongoing care, 2) accessing MOUD, and 3) return to community. Participants reported that court-mandated MOUD dose reductions, negative perceptions of higher dosing among providers, and refusal to treat OUD and pain led to inadequate treatment and relapses. Negative interactions at pharmacies and MOUD confiscation by law enforcement and treatment facilities led to treatment gaps and non-adherence. Stigma within patients' community led to the lack of support for receiving MOUD and loss of employment. Showcasing a stigma journey map surrounding MOUD helps to identify pain points in patients' treatment journey in accessing treatment for OUD and empower patients in making informed health decisions. Findings from this research will shape training modules and educational materials designed to reduce stigma.

From Analysis to Action: Arts-Based Practices in Translational Health Research

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Poster 7

Since the early twenty-first century, research has demonstrated that arts engagement can improve human health and wellbeing. Yet the field of arts in health continues to face a central challenge: translating interdisciplinary knowledge into effective, real-world interventions. My poster presentation argues that dramaturgy—a methodological practice rooted in theatre—offers a distinctive framework for advancing translational research in healthcare. Grounded in rigorous observation, interpretive analysis, and collaborative design, dramaturgical methods support the movement of knowledge from research contexts into applied settings by shaping how information is communicated, interpreted, and enacted. Drawing on case studies of arts-based interventions, including work with youth audiences and healthcare partners, this presentation demonstrates how dramaturgy facilitates three critical dimensions of translational research: the interpretation of complex qualitative data, the translation of research findings into accessible and engaging forms, and the collaborative design of context-responsive interventions. By positioning dramaturgs as partners within interdisciplinary teams, this approach expands current models of translational research to include arts-based practices that address the social and cultural dimensions of health. In doing so, it offers a structure for designing interventions that are not only evidence-informed but also responsive to the lived experiences of the communities they serve.

Antibody-Functionalized Bismuth Nanoparticles for Targeted X-ray Imaging of the Myocardium

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Introduction: Bismuth nanoparticles (Bi NPs) are gaining attention as versatile contrast agents for biomedical imaging. Their high atomic number (Z = 83) permits strong X-ray attenuation, enhancing radiographic contrast compared to conventional iodinated contrast agents (ICAs). ICAs are limited by rapid systemic clearance, lack of tissue specificity, and risks of nephrotoxicity. In contrast, Bi NPs provide tunable surface chemistry and the capacity for conjugation with targeting ligands. Here, we engineered PEGylated Bi NPs functionalized with anti-contactin-2 (CNTN2) antibodies for targeted imaging of the cardiac conduction system (CCS), which remains challenging to visualize during procedures.

Methods: Bi NPs were synthesized via chemical reduction of bismuth (III) nitrate pentahydrate. A layer-by-layer surface engineering approach was employed with PAH and PAA, followed by PEGylation using NH_2-PEG-COOH via EDC coupling to improve stability and retain carboxyl groups for bioconjugation. Morphology was examined using TEM, while DLS and ζ-potential measurements determined hydrodynamic size, polydispersity, and surface charge. Antibody conjugation used EDC/sulfo-NHS chemistry, while nano differential scanning fluorimetry (NanoDSF) assessed protein conjugation and thermal stability. MicroCT imaging quantified X-ray attenuation performance.

Results: Bi NPs showed a hydrodynamic diameter of 105.1 ± 0.64 nm with low PDI (0.19 ± 0.006), indicating a uniform size distribution. FT-IR, ζ-potential shift, and TEM imaging confirmed successful PEGylation. MicroCT imaging demonstrated higher X-ray attenuation compared to conventional contrast agents. NanoDSF confirmed antibody conjugation via protein unfolding thermal signatures.

Conclusion: PEGylated, antibody-functionalized Bi nanoparticles show high stability and radiopacity, with X-ray attenuation exceeding iodine. They enable targeted myocardial imaging for conduction system visualization and image-guided therapy.

Molecular Mechanisms and Neural Impact of Human Microglia Immune Tolerance

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Tightly regulated microglial activity is essential for normal circuit refinement, and dysregulated activation can disrupt synaptic pruning and promote neurodegeneration in brain and visual disease. Microglia play a critical role in developmental axonal refinement of retinal ganglion cells (RGCs), and disruptions through maternal immune activation (MIA) impair synaptic pruning in visual targets such as the lateral geniculate nucleus (LGN). Paradoxically, this leads to attenuated refinement, resulting in excessive RGC connectivity, noisy neural signaling, and reduced visual thalamic responses in offspring, suggesting that inflammatory exposure suppresses microglial function by reprogramming their states. However, the mechanisms underlying MIA-induced microglial reprogramming remain unclear. To address this, we investigate how immune exposure alters visual circuit refinement through microglial tolerization, a state in which repeated inflammatory signaling suppresses phagocytosis and cytokine production. We hypothesize that prior inflammatory stimulation reduces microglial activity through the antiphagocytic SIRPα–SHP-2 signaling pathway. To test this, we generated human microglia-like cells (iMGLs) from iPSCs and evaluated tolerance in primary mouse microglia stimulated with LPS by assessing CD68, SIRPα, and cytokine secretion. We also established a human eye–brain circuit model using microfluidic devices, where iPSC-derived RGCs formed polarized projections and synapses with postnatal mouse LGN neurons, with functional connectivity confirmed via synapse quantification, viral tracing, and calcium imaging. Together, these studies define how microglial tolerization disrupts visual circuit development and identify tolerance pathways as therapeutic targets for visual disorders.

SGLTi discontinuation rate among high-risk populations: A systematic review

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Poster 8

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are approved for cardio-kidney-metabolic indications, with an increase in their uptake over the past several years. However, they are often discontinued for various reasons, including side effects. We conducted a systematic review to examine the SGLT2i discontinuation rates across multiple populations, including people with type 2 diabetes (T2DM), cardiovascular disease (CVD), and/or chronic kidney disease (CKD). We searched for relevant studies (e.g., observational studies, secondary analyses of clinical trials) in PubMed, Cochrane library, and EMBASE using search terms synonymous to SGLT2i discontinuation. Studies published between 2013-2025 were included. Given their heterogeneity (enrolling different patient populations from various countries with different coverage and indications), we did not pool the results from individual studies.

We included 23 studies. Among those, 60% of the eligible studies (n=13) reported discontinuation rates at 1 year that ranged from 5-45%. The reported range of discontinuation rates at 1 year was 24-33% among those with T2DM,18-23% with CVD, and 26-45% with multiple comorbid conditions (Figure 1). The 3 studies from North America reported discontinuation rates of 23-27% at 1 year, vs. 5-45% among 8 studies enrolling European populations. Notably, though CKD was often present among those with T2DM and CVD, dedicated studies in the CKD population were lacking. SGLT2i discontinuation rates at 1 year varied, with higher discontinuation rates among those with multiple indications and lower discontinuation rates in heart failure populations. Further studies are needed to examine rates and reasons for SGLT2i discontinuation among those with CKD.

Factors Associated with Adherence to Cyclosporine Ophthalmic Therapy Among Patients with Dry Eye Disease

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Dry eye disease (DED) is a chronic ocular surface disorder requiring persistent anti-inflammatory therapy, with cyclosporine ophthalmic agents commonly prescribed for patients with moderate-to-severe DED. The objective of this study was to evaluate factors associated with medication adherence among patients initiating cyclosporine ophthalmic therapy. A retrospective cohort study using the Merative™ MarketScan® Commercial Database (2022–2024) included adults with at least one incident cyclosporine ophthalmic prescription fill and continuous enrollment for 12 months pre-index and 6 months post-index. Adherence was defined as the proportion of days covered (PDC) ≥80% during the 6-month follow-up. Multivariable logistic regression evaluated factors associated with adherence, with sensitivity analysis conducted at PDC ≥90%.

Among 24,434 eligible patients, 20.9% achieved adherence (PDC≥80%). Brand Restasis accounted for 72.7% of initiators and generic cyclosporine for 27.3% and no significant difference in adherence was observed between generic and brand users (aOR:0.93, 95%CI:0.87–1.01). Compared with patients aged 18–34 years, older age (55+ years: aOR: 1.38, 95% CI: 1.21–1.57) was associated with higher adherence. Compared with patients with out-of-pocket costs <$25, higher costs were associated with lower adherence ($25–$100: aOR: 0.83; >$100: aOR: 0.82). Positive predictors of adherence included glaucoma, punctate keratitis, Sjögren's syndrome, Xiidra use, and glaucoma medications. Findings were consistent with PDC≥90%. Overall, adherence to cyclosporine ophthalmic therapy was low in DED. Higher out-of-pocket costs were associated with reduced adherence, while markers of greater ocular disease burden were associated with improved adherence. These findings highlight the need to address cost barriers and provide early treatment support to improve long term management of DED.

Strengthening Cancer-related career options at an HBCU.

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Poster 12

Cancer has a disproportionate impact on socially disadvantaged community members; the underrepresentation of this population in biomedical and cancer-related careers persists. The P20 NCI-funded Collaborative Union of Cancer Research and Educational Development (CURED) program is a collaborative initiative between Texas Southern University and Baylor College of Medicine that aims to promote the biomedical research workforce through education, mentorship, and community engagement. P20 CURED launched its summer 2025 8-week mentored cancer research program for 20 scholars. Specific aims for the P20 CURED summer research experience included: (i) Providing hands-on cancer research training and professional development (ii) Creating an educational curriculum focused on emerging cancer research technologies and (iii) Implementing a comprehensive outreach program to raise cancer awareness among TSU/BCM students, faculty, and the community. Each student is completing 16 hours of cancer-related outreach, projected to conclude in April 2026. Out of 75 applicants, 37 were eligible, and 20 were selected to participate. 16 completed the program, 81% female and 19% male. Participants represented undergraduate (73%), graduate (25%), and PharmD (13%) programs spanning across the biomedical sciences, biology, chemistry, and environmental sciences continuum. Topics presented during the end-of-summer research experience symposium included induced pluripotent stem cells (iPSCs), pharmacogenomics, lymphoblastic Leukemia, T-cell dysfunction, estrogen-receptor-positive breast cancer, nanoparticles (NPs), esophageal cancer, pediatric brain tumor survivors, prostate cancer, DMS-MaPseq, Cachexia, and gynecological cancer.

Lipid Nanoparticle–Mediated Targeting of Liver Sinusoidal Endothelial Cells for Therapeutic Intervention in Liver Fibrosis

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Liver fibrosis is driven by dysregulated interactions among hepatic cell populations, with liver sinusoidal endothelial cells (LSECs) acting as key regulators of both disease progression and resolution. Under physiological conditions, LSECs possess fenestrations that facilitate exchange of nutrients and signaling molecules with hepatocytes. Upon injury, LSECs undergo capillarization, losing fenestrations and promoting fibrogenesis through secretion of pro-fibrotic mediators such as TGF-β and CCL2, which drive hepatic stellate cell activation. In contrast, restoration of LSEC function suppresses stellate cell activation and promotes fibrosis resolution by recruiting macrophages to clear extracellular matrix.

Despite their central role, selective targeting of LSECs remains challenging. Here, we study how disease context and nanoparticle design influence intrahepatic biodistribution. Using a commercially available nanoparticle as a reference, we evaluate differences in hepatic uptake between normal and fibrotic conditions. We further develop a lipid-based nanoparticle platform and explore how formulation parameters, including lipid composition and active loading strategies, modulate interactions within the hepatic microenvironment.

These findings highlight that nanoparticle distribution within the liver is not static but is shaped by both microenvironmental changes and material design. More broadly, this work supports a strategy of leveraging nanoparticle engineering to access specific hepatic cell populations, enabling upstream modulation of cellular networks that govern fibrosis.

Establishing a Community-Focused Clinical Research Site in a Low-Resourced HBCU: Lessons through Collaboration and Capacity Building

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Poster 13

Background: Texas Southern University, a prominent HBCU without an affiliated hospital, clinic network, or existing patient population, established a community-focused clinical research site. The primary goal was to educate, recruit, and expand research participation, specifically among those with unmet health needs.
Approach: The implementation process involved strategic planning in four key areas as below:
Collaboration: Partnered with mentor site to align site capabilities with industry standards.
Workforce Training: Hired and strengthened research personnel expertise through training, certification, and mentorship.
Community Engagement: Enhanced trusted relationships with community members, key stakeholders, and advisory board members.
Infrastructure Development: Defined site capabilities: regulatory processes, data management, IRB optimization, budgeting, contract management, and prospective study feasibility assessments. Developed standard operating procedures and clinical research registry for site readiness.
Findings/Insights: TSU successfully launched this first-of-its-kind research infrastructure. A participant registry implemented in May 2025 has yielded 250+ expressions of interest and 110 full enrollments to date. Key challenges involved enhancing institutional feasibility, navigating the development of a new clinical research infrastructure, and managing complex regulatory and contracting approval timelines.
Implications: Building research capacity in low-resourced HBCUs requires intentional community trust and cross-disciplinary partnerships. TSU's site serves as a replicable model for non-traditional academic institutions seeking to increase clinical trial access.
Keywords: HBCU, Clinical Research, Community Engagement, Capacity Building
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Clostridioides difficile infection disease severity association with 30-day recurrence: A real-world observational cohort and scoping review

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Clostridioides difficile infection (CDI) is a leading cause of healthcare-associated infectious diarrhea with recurrence posing a persistent challenge in clinical management. Whether CDI disease severity is an independent risk factor of recurrence is unclear. This study aims to evaluate whether CDI disease severity is independently associated with increased risk of 30-day recurrence. A search query in PubMed was conducted with search terms: “severity”, “recurrence”, “risk factors”, and “Clostridioides difficile” and results summarized. A real-world observational cohort included adults hospitalized at 14 Houston hospitals (2016 - 2021) testing positive for CDI. Stool samples underwent culturing and strain typing then respective clinical data collected from the electronic health record. Statistics were performed in R.

A total of 951 patients were included with 38 (4%) experienced 30-day recurrence. In the univariate and multivariable logistic regression analyses, Charlson Comorbidity Index (CCI) was significantly higher in patients with recurrence (5.82 vs 4.80; p=0.03; OR: 1.13 (95% CI: 1.01-1.27)). No other demographic or CDI-specific factors, including disease severity and strain type, were significantly associated with recurrence. The scoping review results (n=8) were conflicting with 3 reporting increased recurrence, while 4 were no independent effect, and 1 was not evaluated. In this cohort, CDI disease severity was not associated with increased risk of 30-day recurrence. However, patient-specific and treatment-specific factors, such as gut microbiome composition, prior antibiotic exposure, or CDI therapy may be better predictors and were not feasible to evaluate in the current dataset yet remain for future studies.

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Mechanistic insights into post-endosomal barriers in LNP-mediated mRNA delivery

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Messenger RNA (mRNA) therapeutics represent a transformative platform for the prevention and treatment of infectious diseases, cancer, and immune disorders. However, efficient intracellular delivery remains a major challenge due to mRNA instability and limited cytosolic accessibility. Lipid nanoparticles (LNPs) enable protection, cellular uptake, and endosomal escape of mRNA and are essential to clinically approved mRNA medicines. While endosomal escape is widely regarded as the principal barrier to delivery, the subsequent intracellular dissociation of mRNA from LNPs, which is required for translation, remains poorly understood. To investigate the mechanistic role of ionizable lipid content in mRNA release, we systematically modulated the molar fraction of clinically validated ionizable lipids (SM-102 and ALC-0315) within benchmark LNP formulations. We evaluated physicochemical properties, cellular uptake, endosomal escape, intracellular mRNA release, protein expression, and immunogenicity. Reducing ionizable lipid content below that used in clinically approved formulations (46.3–50 mol%) unexpectedly enhanced mRNA transfection efficiency and in vivo immunogenicity. Notably, endosomal escape remained comparable across formulations, whereas intracellular mRNA release was significantly increased in lower ionizable lipid LNPs, indicating that post-escape dissociation rather than escape itself can limit translation efficiency. These findings identify intracellular mRNA–LNP dissociation as a previously underappreciated determinant of functional mRNA delivery and suggest that balancing electrostatic interactions, rather than maximizing ionizable lipid content, may improve LNP performance. This work provides mechanistic guidance for next-generation mRNA-LNP design beyond conventional optimization of uptake and endosomal escape.

Peer Recovery Coaches in MOUD Treatment: Attitudes, Practices, and Their Influence on Patient Engagement and Outcomes

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Poster 15

Although medications for opioid use disorder (MOUD) have demonstrated substantial efficacy in reducing opioid-related mortality and improving treatment retention, patient engagement remains a persistent challenge. Peer recovery coaches (PRCs), increasingly integrated into interdisciplinary treatment teams, serve a dual role as boundary spanners and patient advocates, bridging the gap between clinical providers and individuals with opioid use disorder (OUD). While research has begun to characterize PRC attitudes toward MOUD, less is known about the underlying factors shaping these attitudes and practices. We conducted a qualitative study utilizing semi-structured interviews with PRCs and healthcare providers, including prescribers and therapists, involved in MOUD treatment. Interviews explored perceptions of MOUD, PRC boundary spanning and advocacy roles, and barriers and facilitators to evidence-based care within interdisciplinary teams. Data was analyzed using thematic analysis.

PRCs facilitated MOUD engagement through trust building and lived experience, addressing patient concerns including fear of precipitated withdrawal during MOUD initiation. However, persistent intervention stigma including beliefs that MOUD replaces one drug with another and preferences for abstinence-based recovery contributed to patient ambivalence and premature discontinuation. Structural gaps in standardized MOUD training led to inconsistent and conflicting patient messaging, which providers identified as a potential risk for relapse and overdose. Formalized, evidence based MOUD training and stronger PRC integration within multidisciplinary teams are essential to reducing intervention related stigma, ensuring consistent patient messaging, and reconciling lived experience with clinical evidence to optimize patient centered outcomes for individuals with OUD.

An Epidemiological Investigation of Clostridioides difficile Biofilm

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Biofilm formation contributes to persistence in Clostridioides difficile infection (CDI), but its variability and clinical relevance remain unclear. This study examined how vancomycin (VAN) susceptibility and ribotype influence biofilm phenotypes and clinical outcomes. We analyzed 511 toxigenic clinical C. difficile isolates (Houston, 2016-2021) with linked metadata. VAN MICs were determined by CLSI agar dilution (reduced susceptibility: MIC >2 µg/mL). Ribotypes were identified by fluorescent PCR. Biofilm was quantified using a 48-h crystal violet assay and classified as low vs high. Clinical outcomes were compared, and multivariable logistic regression identified predictors of high biofilm phenotype.

Biofilm formation was highly prevalent (93%), with ~80% moderate-to-strong phenotypes. Baseline characteristics were similar across biofilm groups. Reduced VAN susceptibility was significantly enriched among low-biofilm isolates (45% vs 24%, p<0.001). Ribotype strongly structured biofilm behavior: RT106 was associated with strong biofilm formation, whereas RT027 showed reduced capacity. Clinically, low-biofilm isolates had worse outcomes, including higher persistent diarrhea at day 14 (15% vs 6.1%, p=0.003) and reduced sustained response at 90 days (37% vs 26%, p=0.026). In multivariable analysis, RT027 was independently associated with reduced odds of high biofilm (OR=0.38, 95% CI 0.20-0.71, p=0.003). Marginal effect modeling showed increasing VAN MICs were associated with higher predicted probability of high biofilm among susceptible isolates, whereas reduced-susceptible isolates exhibited a blunted response. Biofilm formation in C. difficile is a heterogeneous, clinically relevant phenotype shaped by ribotype and antimicrobial susceptibility.

Enhancing Myogenic Progenitor Cell Function Through Co-culture with hiPSC-Derived Endothelial Cells

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Background: Human induced pluripotent stem cells (hiPSCs) are a promising source for regenerative therapies; however, poor survival and engraftment of hiPSC-derived myogenic progenitor cells (MPCs) limit their therapeutic potential. Endothelial cells (ECs) are key regulators of the muscle microenvironment through vascular support and paracrine signaling.
Hypothesis: We hypothesize that hiPSC-derived ECs enhance MPC survival and function through paracrine interactions, thereby improving outcomes relevant to skeletal muscle regeneration.
Experimental Plan: hiPSCs were differentiated into MPCs and ECs using established protocols. MPC identity was confirmed by differentiation into multinucleated myotubes, while ECs were validated by endothelial marker expression. A transwell co-culture system was established to investigate EC–MPC crosstalk while preventing direct cell contact. MPCs cultured alone served as controls.
Findings: Co-culture with ECs significantly improved MPC survival under stress conditions, as indicated by reduced apoptotic signaling compared to monoculture. These results suggest that EC-derived paracrine factors play a protective role in MPC viability. Additionally, co-culture conditions showed improved functional characteristics of MPCs, supporting the importance of a physiologically relevant microenvironment.
Future Directions: Future studies will focus on identifying key signaling pathways mediating EC–MPC interactions using transcriptomic and proteomic approaches, as well as evaluating the therapeutic potential of combined EC and MPC transplantation in vivo.

Cardiovascular Safety of First-Line Nucleot(s)ide Analogues in Older Adults with Chronic Hepatitis B

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Background: Older adults with chronic hepatitis B (CHB) frequently require long-term nucleos(t)ide analogue (NA) therapy. Tenofovir alafenamide (TAF) is increasingly used as a first-line agent for CHB due to its improved renal and bone safety profile; however, TAF has been associated with adverse lipid changes. Therefore, we aim to compare the risk of major adverse cardiovascular events (MACE) among older adults initiating first-line NA for CHB.
Methods: This target trial emulation study used Medicare fee-for-service claims data from 2014 to 2019. Beneficiaries aged ≥65 years with CHB initiating entecavir (ETV), tenofovir disproxil fumarate (TDF), or TAF between 2014-2019 were followed from treatment initiation for a MACE outcome (i.e., hospitalization for acute myocardial infarction or ischemic stroke, or revascularization). Death was modeled as a competing event using Fine-Gray sub-distribution hazards models involving stabilized inverse probability of treatment weights to evaluate the risk of MACE.
Results: The cohort included 4,679 beneficiaries (TDF:1,710; ETV:2,218; TAF:751). Mean follow-up was 21.9 months for TDF, 21.3 months for ETV, and 13.5 months for TAF. In intention-to-treat analyses, TAF initiation was associated with higher MACE risk compared with TDF (sHR,1.77;95%CI, 1.07–2.93), whereas ETV was not (sHR:1.13; 95%CI:0.85–1.50). At 36 months, direct-adjusted absolute risks of MACE were 6.64% (95%CI:5.32%–8.27%) for TDF, 7.36% (95%CI:6.10%–8.89%) for ETV, and 10.43% (95%CI:6.96%–15.63%) for TAF. Similar results were observed for the per-protocol analysis: TAF vs. TDF (sHR:1.86; 95%CI:1.05–3.28) and ETV vs. TDF (sHR:1.23; 95%CI:0.81–1.87). Sensitivity analyses were consistent with the primary findings.
Conclusions: This study found that TAF was associated with a higher risk of MACE than TDF, whereas ETV had a risk similar to TDF. These findings suggest cardiovascular risk may warrant additional considerations when selecting NAs in old adults with HBV.

CDK5 Inhibition by the Novel Small-Molecule TK22 Suppresses Endothelial-to-Mesenchymal Transition in Idiopathic Pulmonary Arterial Hypertension

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Idiopathic pulmonary arterial hypertension (IPAH) is a progressive vascular disease driven by endothelial dysfunction, smooth muscle cell proliferation, and endothelial-to-mesenchymal transition (EndMT). Cyclin-dependent kinase 5 (CDK5) has emerged as a potential regulator of vascular remodeling, although its role in EndMT remains unclear.

Here, we report the design, synthesis, and evaluation of TK22, a novel ATP-competitive CDK5 inhibitor. Docking studies (PDB: 7VDP) predicted stable binding within the ATP pocket, supported by key hydrogen bonding and hydrophobic interactions. TK22 was synthesized in three steps with high purity (57%) and showed potent CDK5 inhibition (IC_{50} = 181.3 nM).

In GFP Mouse Endothelial Cells, TK22 suppressed TGF-β1 induced EndMT, reducing mesenchymal markers (α-SMA, SM22α, calponin), decreasing proliferation, restoring angiogenesis, and limiting contractility.

Single-cell sequencing revealed that TGF-β1 drives EndMT from a proliferative $Mki67^{+}$ endothelial population and induces a hypoxia-adaptive state. TK22 selectively eliminated the EndMT-competent subpopulation, disrupted the transition trajectory, and restored endothelial identity without broadly affecting other cell states.

These findings identify CDK5 as a key regulator of endothelial plasticity and position TK22 as a promising therapeutic strategy for IPAH and other EndMT-driven diseases.

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Bioanalytical Quantification and Evaluation of Pharmacokinetics of Semaglutide in Rat Models

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Purpose: Semaglutide (a glucagon-like peptide-1 receptor agonist (GLP-1RA)) is approved by the US Food and Drug Administration primarily for enhancing glycemic control in adults with and without T2DM (Ozempic®) and promoting weight loss in individuals dealing with obesity and overweight (Wegovy®). According to clinical trials, the average body weight loss of individuals with overweight or obesity using 2.4 mg semaglutide weekly was approximately 10% to 17.4%. In the United States, around 6% of American adults (15 million individuals) currently use a GLP-1 drug. GLP-1 drug use has increased in recent years, driven by growing demand for both diabetes treatment and off-label weight management, with prescriptions increasing more than 400% between 2021 and 2023. GLP-1 receptor agonists demonstrate established efficacy in glycemic control and body weight reduction; given the favorable safety profile of semaglutide, its potential additional therapeutic indications may need to be investigated. This study aimed to apply a LC–MS/MS method to quantify semaglutide in plasma, characterize its pharmacokinetics, and evaluate tolerability following 5 days of administration in rats, with the objective of dose selection for subsequent studies exploring additional therapeutic indications.

Method: 3 female rats were fed a normal diet of Teklad F6 rodent diet (W) from Harlan Laboratories (Madison, WI) (ad libitum) since weaning. At week 8, Female F344 rats (n=3) received daily subcutaneous (s.c.) injections of semaglutide following an escalating dose regimen (120 μg/kg for 2 days, 240 μg/kg for the next 2 days, and 400 μg/kg for 1 day). Rats were euthanized on day 7.

Results: In a five-day dose ramping study, semaglutide exhibited a peak plasma concentration Cmax of 4129.85 ± 733.3 ng/mL, with AUCall and AUCinf values of 74392.41 ± 6909.76 and 78291.38 ± 5586.25 h*ng/mL, respectively. Animals maintained normal behavior, indicating that the escalating dosing regimen was well tolerated.

Pharmacokinetic interactions between Nebivolol and Dasatinib in the 4T1 Triple-Negative Breast Cancer Model

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In our recent in-vitro study, nebivolol (NEB) and dasatinib (DAS) synergistically inhibited the growth of 4T1 cell line. However, the in vivo disposition and potential for drug-drug interactions (DDI) are not well defined. This study aimed to characterize the pharmacokinetics (PK) and biodistribution of NEB and DAS in 4T1 tumor-bearing mice and evaluate whether co-administration modifies plasma or tissue concentrations.

Methods: Female BALB/c mice were inoculated with 4T1 cells orthotopically and treated with NEB and DAS for 3 weeks. Blood and tissues were collected, then quantified using a validated LC-MS/MS method. Phoenix (8.5.1) and GraphPad 10 was used to analyze data.

Results: Co-administration significantly increased both NEB and DAS exposure in blood. The area under curve (AUC normalized by dose) of NEB was 2294.5±1509.8 hr*ng/mL/(mg/kg), compared to 445.1±102.1 hr*ng/mL/(mg/kg) in the NEB alone group (p<0.05), and DAS 864.1±631.7 vs. 288.4±60.8. The NEB clearance and volume of distribution (V) was decreased from 2.9±0.5 to 0.6±0.3 L/(kg*hr) and 11.4±8.7 to 4.7±0.4 L/kg, respectively (p<0.05). DAS clearance was from 3.6±0.8 L/(kg*hr) in alone group to 1.6±0.8 L/(kg*hr) in combination. NEB concentrations in all tissues were higher in combination group than NEB alone group (p>0.05 due to the large variance). Even though Tissue-to-Blood (T/B) ratios of both drugs in tumor, liver, lung, spleen, kidney and pancreas were over 1, indicating preferential tissue accumulation, no significant difference was observed due to the large variance. T/B of DAS in the kidney was significantly elevated under combination dosing compared with DAS alone, which indicated more DAS accumulation in combination treatment.

Conclusions: Combination increased NEB and DAS exposure in blood. It suggests that dose reduction or interval prolongation may be necessary to prevent drug accumulation and minimize potential organ-specific toxicity, particularly renal toxicity associated with DAS.

Structure-Guided Discovery of Covalent Inhibitors Targeting SARS-CoV-2 Proteases with Potent Antiviral Activities

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The continued emergence of SARS-CoV-2 variants and the development of resistance to current antivirals underscore the urgent need for novel therapeutics. The viral papain-like protease (PLpro) is an essential enzyme for viral replication and host immune evasion, yet it remains an underexplored therapeutic target with only a few reported classes of small-molecule inhibitors. Here, we report the structure-guided design, synthesis, and biological evaluation of a series of small-molecule inhibitors targeting the S1′ pocket of PLpro. Structure–activity relationship (SAR) studies identified fumaramide-based compounds with potent enzymatic inhibition (IC50 as low as 16 nM). The lead compound exhibited robust antiviral efficacy in cellular assays (EC50 = 96 nM), excellent selectivity over human deubiquitinase, and no detectable cytotoxicity. Mechanistic studies and X-ray crystallographic analyses revealed that the incorporation of electron-deficient pyridine moieties significantly enhances potency by promoting favorable π–π stacking and electrostatic interactions with Trp106 in PLpro. In parallel, structure-guided efforts identified chloroacetamide- and epoxide-based covalent inhibitors of the main protease (Mpro) targeting Cys145 (IC50 as low as 490 nM) with robust antiviral activity; mechanistic and X-ray crystallographic analyses revealed that Cys145 preferentially attacks the sterically hindered epoxide carbon, while Cys44 lacks sufficient nucleophilicity for covalent targeting. Overall, this work establishes PLpro as a compelling antiviral target and provides highly potent, structurally validated lead compounds for the development of next-generation SARS-CoV-2 therapeutics.

Rational Dose Modification of Atorvastatin and Rosuvastatin in Obese Patients Post - Gastric Bypass Surgery

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Background: Roux-en-Y Gastric Bypass (RYGB) surgery is a recommended treatment for patients with a body mass index (BMI) ≥ 40, or ≥ 35 with obesity-related comorbidities. This procedure significantly alters gastrointestinal physiology, potentially impacting the pharmacokinetics (PK) and pharmacodynamics (PD) of orally administered drugs such as statins. In this study, we recruited twelve Hispanic patients from DHR who have undergone or are scheduled to undergo bariatric surgery. The primary objective is to characterize the PK/PD relationship of statins pre- and post-surgery and evaluate whether medication discontinuation, maintenance of the same regimen, or individualized dose adjustments result in improved therapeutic outcomes.

Methods: To date, twelve obese patients have been enrolled (target enrollment: 20). Two blood samples were collected per visit, with a two-hour interval. Clinical parameters, including body weights, heights, vital sign, and lipid profiles of low-density lipoprotein (LDL), Triglyceride (TG) were recorded at pre-surgery (baseline), and 3, 6 and 12 months (M) post-surgery. Plasma concentrations of ATV and its active metabolites 2-hydroxy atorvastatin (2-OH-ATV) and 4-hydroxy atorvastatin (4-OH-ATV), and rosuvastatin (RSV) were quantified using a validated LC-MS/MS assay with a lower limit of quantification (LLOQ) of 0.25 ng/ml. Correlations between PD parameters (BMI, LDL, TG) and PK profiles and exposures were evaluated.

Results and Discussion: Ten patients completed the 3-month follow-up and six of them discontinued statin therapy according to their primary care physicians' instructions. Initial weight loss is likely attributable to surgical effects. Patients who discontinued statins post-surgery showed poor lipid control based on their lipid panel results. Additionally, the monitored half-life of RSV showed an increasing trend in one patient, indicating the potential need for personalized dose adjustments. Longitudinal monitoring is ongoing.

Investigating the Role of AR SUMOylation in Triple-Negative Breast Cancer Progression

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Triple-negative breast cancer (TNBC) is defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression. Its aggressive nature is characterized by rapid growth, early recurrence, and poor prognosis. TNBC accounts for approximately 15 – 20% of breast cancers and lacks effective therapeutics. Recent studies with AR-targeted strategies have shown promising outcomes, supporting the androgen receptor (AR) as a potential therapeutic target, as its signaling may contribute to TNBC progression.

SUMOylation is a reversible post-translational modification in which small ubiquitin-like modifier (SUMO) proteins are covalently attached to lysine residues on targeted proteins, regulating transcription, chromatin organization, and cellular stress responses. Dysregulation of the SUMOylation pathway has been reported in multiple cancers, including breast cancer, where increased expression of components such as UBC9 is associated with aggressive disease features. Notably, elevated SUMO3 expression has been observed in TNBC and correlates with poor clinical outcomes. In parallel, AR is a well-characterized SUMO substrate whose activity can be modulated by SUMOylation.

Based on these observations, we aim to determine the functional relationship between AR and SUMO3 expression in TNBC. We hypothesize that elevated SUMO3 may alter AR activity and downstream signaling, contributing to the progression of TNBC.

To investigate this, a conditional multicistronic SUMO transgenic mouse model will be utilized, in which SUMO1/2/3 expression is activated by Cre/lox recombination. Crossing these mice with MMTV-Cre mice will enable mammary-specific SUMO overexpression to determine whether elevated SUMO promotes early mammary tumorigenic events in vivo.

Together, this study will elucidate the role of SUMO3 in TNBC and evaluate whether AR SUMOylation represents a therapeutic vulnerability.

TAK1 promotes cancer stem cell homeostasis and proliferation in Rhabdomyosarcoma

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Rhabdomyosarcoma (RMS) is an aggressive pediatric soft tissue sarcoma characterized by skeletal muscle lineage features, defective terminal myogenic differentiation, and the presence of stem-like tumor cell populations that may promote tumor progression, recurrence, and therapeutic resistance. Transforming growth factor β-activated kinase 1 (TAK1/MAP3K7) is an important central signaling kinase that integrates multiple intracellular pathways involved in cell proliferation, survival, and oncogenic transformation; however, the role of TAK1 in maintaining RMS stemness remains unclear. In this study, we demonstrate that TAK1 plays an important role in sustaining the stem-like properties of RMS cells. Genetic knockdown or pharmacological inhibition of TAK1 significantly reduces RMS sphere-forming capacity and downregulates the expression of stemness-associated genes. Transcriptomic and pathway enrichment analyses further reveal that TAK1-associated signaling is closely linked to cell cycle regulation, tumor cell proliferation, and activation of oncogenic signaling pathways. In addition, TAK1 inhibition attenuates PI3K–AKT–mTOR signaling and suppresses non-canonical Wnt-associated signaling, suggesting that TAK1 may promote RMS stemness maintenance through coordinated regulation of proliferative and stemness-related pathways. Collectively, these findings identify TAK1 as an important regulator of the RMS stem-like phenotype and suggest that targeting TAK1 may suppress RMS tumor progression by disrupting stemness maintenance, cell cycle progression, and oncogenic signaling networks.

Human HLHS-causing gene Myrf is expressed in multiple cardiac cell types and is sufficient to induce HLHS in mice

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Hypoplastic left heart syndrome (HLHS) is clinically and genetically heterogeneous and attributed to multigenetic mutations. Recent studies have identified point mutations in the myelin regulatory factor (Myrf) associated with HLHS, suggesting a potential monogenic origin. However, the mechanism by which single Myrf mutation causes HLHS remains unknown.

We integrated single-cell RNA sequencing (scRNA-seq), RNAscope, and lineage tracing to delineate the spatiotemporal expression of Myrf during cardiac morphogenesis. We generated and systematically characterized global Myrf knockout mice alongside multiple cell type–specific conditional knockout models. Underlying molecular mechanisms were interrogated through scRNA-seq analyses, complemented by targeted phenotypic characterization and experimental validation.

In embryonic hearts, Myrf expression was selectively enriched in pro-epicardial cells, epicardial cells, endocardial cells overlying the atrioventricular canal (AVC), and the dorsal mesenchymal protrusion. Homozygous global Myrf knockout embryos died before E10.5, prior to the developmental stage at which HLHS phenotypes typically emerge. Endocardial Myrf knockout hearts showed a shortened AVC but survived into adulthood. Notably, Endocardial/epicardial Myrf knockout hearts displayed outflow tract alignment defects, double outlet right ventricle, a narrowed aorta, atrioventricular valve abnormalities, and hypoplastic ventricular myocardium, closely recapitulating key structural features of HLHS.

Although global loss of Myrf results in early embryonic lethality prior to the full manifestation of canonical HLHS features, lineage-specific deletions recapitulate discrete components of the HLHS spectrum. Collectively, these findings demonstrate that HLHS can arise from a single-gene defect with essential functions across multiple cardiac lineages, highlighting a multicellular pathogenesis even in a nominally monogenic congenital heart disease.

A novel molecular mechanism for coronary arteriolar constriction to endothelin-1 guides drug development to classify and treat coronary microvascular dysfunction

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Elevated plasma levels of potent vasoconstrictor endothelin-1 (ET-1) are associated with coronary microvascular dysfunction (CMD) in myocardial ischemic patients. Recent randomized controlled trials with endothelin receptor antagonist zibotentan (NCT04097314) or L-type calcium channel (LTCC) blocker diltiazem (NCT04777045) failed to improve clinical outcomes, partly due to limited understanding of mechanistic signaling underlying coronary microvascular constriction. Herein, we probed the molecular mechanisms responsible for coronary arteriolar constriction at clinically relevant ET-1 concentrations to identify potential new targets amenable to CMD management.

The vasoconstrictor response and signaling pathway of isolated, pressurized (at 44 mmHg) porcine coronary arterioles to ET-1 and protein kinase C (PKC) activator phorbol 12,13-dibutyrate (PDBu) were studied using videomicroscopic and pharmacological tools.

Coronary arterioles developed basal tone with a resting diameter (40±4 μm) about 50% of the maximal diameter (73±3 μm). ET-1 caused concentration-dependent vasoconstriction with a threshold at 0.1 pM and an EC50 at 10 pM. A clinical level of ET-1 (100 pM) caused sustained vasoconstriction to 20-25 μm (~25% of maximal diameter) for over 2 hours. The ETA receptor antagonist BQ123 (1 μM) prevented but failed to reverse vasoconstriction to ET-1. Rho kinase (ROCK) inhibitor H-1152 (3 μM) and conventional PKC inhibitor Ro 32-0432 (1 μM) prevented and reversed arteriolar constrictions to 100 pM ET-1 and 0.1 μM PDBu, respectively. LTCC blocker nifedipine (1 μM) prevented and reversed vasoconstriction to PDBu but not to ET-1.

A clinical level of ET-1 caused profound and long-lasting narrowing of coronary arterioles and was reversed by blockade of ROCK but not of PKC, ETA receptors, or LTCC. Thus, the current data may explain why zibotentan or diltiazem failed to show clinical benefit for CMD. A new drug target ROCK might be useful for abnormal ET-1 related CMD.

Investigating the Role of SENP7-SUMO Machinery on Extracellular Vesicle Signaling

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Postpartum Breast Cancer (PPBC) is an aggressive malignancy linked to the "window of susceptibility" (WOS) during parity and involution. Our research identifies SENP7S as a critical deSUMOylase in normal human mammary epithelium. Its loss induces a hyperSUMOylated state and triggers epithelial-to-mesenchymal transition (EMT). While EMT alters the cellular secretome, the role of SENP7-SUMO machinery in regulating Extracellular Vesicle (EV) signaling during postpartum remodeling remains undefined.

This study aims to characterize the SUMOylation landscape required for mammary homeostasis and define how SENP7-regulated pathways dictate EV cargo and activity.

We compared transcriptomic signatures from SENP7 catalytic knockout (7catKO) mice against clinical PPBC datasets to identify a SUMO-sensitive PPBC gene signature. To translate these findings, we utilized human breast milk cell culturing as a modeling system to analyze SENP7 and SUMO expression across 2D and 3D platforms. Simultaneously, EVs were isolated directly from human breast milk and characterized. Established assays were implemented to quantify EV uptake and activity.

Bioinformatic analysis revealed 7catKO parous mice exhibit a transcriptomic profile significantly overlapping with clinical PPBC signatures, specifically in pathways governing vesicle trafficking. We established cell culture systems for comparative 2D and 3D analysis of human breast milk. Preliminary work involves analysis of SENP7-SUMO machinery within these platforms. Characterized milk-derived EVs provide a validated foundation to test the impact of SENP7-SUMO machinery on EV-mediated communication.

Our data establish a robust framework for bridging murine 7catKO models with human milk-derived EVs and primary cultures. Ongoing work utilizes these validated platforms to investigate how SENP7 deficiency drives the release of pro-tumorigenic EVs, with the ultimate goal of identifying early-detection biomarkers for at-risk postpartum populations.

Turning Salt into a Delivery Engine: Osmotically Active Lipid Nanoparticles for Gene Therapeutics

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Poster 40

Lipid nanoparticles (LNPs) have enabled major advances in nucleic acid therapeutics; however, their clinical performance remains limited by inefficient endosomal escape, with typically less than 2% of internalized cargo reaching the cytosol. To address this fundamental barrier, we developed salt-loaded LNPs (SLNPs), a simple and scalable platform that leverages osmotic pressure to enhance intracellular delivery of nucleic acids. SLNPs are formulated by encapsulating sodium chloride within the aqueous core of LNPs, creating an ionic gradient upon endocytosis. These gradients drive water influx into endosomes, leading to endosomal swelling and membrane disruption, thereby facilitating the cytosolic release of nucleic acids. Using clinically relevant lipid compositions, SLNPs demonstrated significantly enhanced mRNA delivery across multiple cell types, including HEK-293 cells, dendritic cells, and tumor cells, compared to conventional LNPs. In vivo studies further showed markedly increased protein expression following both intramuscular and systemic administration. Mechanistic investigations confirmed that Na^+-induced osmotic stress promotes endosomal destabilization, representing a distinct physical strategy for overcoming intracellular delivery barriers. Importantly, SLNPs exhibited minimal cytotoxicity, negligible inflammatory responses, and no detectable systemic toxicity, even after repeated dosing. Additionally, enhanced antigen expression led to stronger humoral and cellular immune responses, highlighting its potential in immunotherapy. Overall, this work introduces a broadly applicable, translationally feasible approach to improve nucleic acid delivery via osmotic-pressure-driven endosomal escape. SLNPs provide a versatile platform for advancing gene-based therapies, with potential impact across vaccines, cancer immunotherapy, and genetic medicine.

Pharmacokinetic/Pharmacodynamic Correlation and Biodistribution of Re $(CO)_3$-phenformin Compared with Phenformin in Murine PDAC Model Following Equimolar Intravenous Dosing

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Re $(CO)_3$-phenformin (Re-phen) is a newly synthesized rhenium biguanide complex with potential anticancer activity; however, its in vivo pharmacokinetics (PK), biodistribution (BD), metabolic fate, and PK/pharmacodynamic (PK/PD) properties remain incompletely characterized. In this study, we performed an integrated PK, BD, and PK/PD evaluation of Re-phen compared with phenformin (Phen) following three consecutive equimolar intravenous doses (26.26 µmol/kg) in PDAC-bearing mice, including quantification of in vivo conversion of Re-phen to Phen to support parent–metabolite exposure modeling. Blood and major organs (tumor, pancreas, liver, kidney, spleen, lung) were analyzed using a validated LC–MS/MS assay. Re-phen showed markedly higher tissue accumulation than Phen across all organs, including tumor, pancreas, liver, kidney, spleen, and lung (all p<0.01), indicating extensive distribution and preferential retention. In vivo conversion to Phen was observed (Fm ≈ 11%; AUC ratio ≈ 0.22), demonstrating that both parent and metabolite contribute to systemic exposure. 2D PK/PD analysis showed a moderate, non-significant inverse correlation between Phen exposure and tumor weight ($r = -0.800$, $p = 0.1333$). In contrast, Re-phen exhibited a strong and statistically significant inverse correlation between tumor weight and potency-adjusted exposure, integrating parent and converted Phen to account for biotransformation and relative potency ($r = -1.000$, **$p = 0.0028$). These findings demonstrate a clear exposure–efficacy relationship for Re-phen and highlight the importance of integrating parent–metabolite exposure in PK/PD analysis. Collectively, this study provides the first comprehensive in vivo characterization of Re-phen, demonstrating its superior tumor delivery, parent–metabolite interplay, and exposure-driven antitumor activity, supporting its development as a rhenium-based therapeutic and as part of the Re/^{99m}Tc-phen theranostic platform for pancreatic cancer.

Comparison of colonoscopy using a multipurpose rigid endoscope with postmortem detection of polyps in Pirc rat model of familial adenomatous polyposis

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Background: Familial adenomatous polyposis (FAP) is a rare hereditary syndrome with an almost inevitable progression to colorectal cancer. The Pirc (polyposis in rat colon) model, which carries an Apc mutation analogous to human FAP, develops age-dependent intestinal polyps and is widely used for preclinical prevention studies. Longitudinal assessment of polyp burden is critical and can be performed using colonoscopy.

Objective: This study compared rigid endoscope-enabled colonoscopy with postmortem polyp assessment in Pirc rats.

Methods: Colons of 16-week-old male and female Pirc rats (n=8) were examined using a rigid endoscope (Small Coloview scope, 10 cm, Karl Storz, Tuttingen, Germany). In the video review, polyps were graded by degree of luminal obstruction (G1–G5). Postmortem images of excised colons were analyzed for total polyp counts and polyp diameters measured with digital calipers. Total and detectable polyp counts were compared between colonoscopy and postmortem evaluation using the Wilcoxon matched-pairs signed rank test. Mean ± SD polyp diameter was reported for each grade.

Results: Median total polyp counts were 2 (range: 0–5) by colonoscopy and 3 (range: 1–12) postmortem, with no significant difference ($p = 0.09$). Because the rigid endoscope visualizes only the distal 10 cm of colon, detectable polyps were compared; median detectable counts were 2 by colonoscopy and 2.5 (range: 0–7) postmortem ($p = 0.5$). Mean ± SD polyp diameters were 2.9 ± 0.7 mm (G2), 3.4 ± 0.5 mm (G3), 3.6 ± 0.6 mm (G4), and 3.6 ± 0.7 mm (G5). Limitations of colonoscopy included incomplete colonic visualization, difficulty distinguishing adjacent polyps, and challenges detecting rectal polyps.

Conclusion: Rigid endoscope colonoscopy provides feasible and comparable polyp detection to postmortem analysis, supporting its use for longitudinal monitoring in preclinical prevention studies. Flexible and extendable endoscopes may enhance polyp detection and monitoring.

Assessment of Simvastatin on Amyloid-β_{1-42}–Induced Cytotoxicity in SH-SY5Y Cells

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Background: Alzheimer's disease is defined by amyloid-β (Aβ) accumulation, mitochondrial dysfunction, and progressive neuronal loss. Cholesterol metabolism and neuroinflammation play important roles in Aβ production and toxicity, suggesting that lipid-lowering therapies may influence disease pathogenesis. Statins, widely used for cardiovascular disease, possess pleiotropic effects including modulation of cholesterol homeostasis, anti-inflammatory activity, and potential regulation of amyloid processing. However, despite these proposed mechanisms, the direct effects of statins on Aβ-induced neuronal injury remain unclear.

Objective: To evaluate whether simvastatin attenuates $A\beta_{1-42}$–induced cytotoxicity in SH-SY5Y human neuroblastoma cells.

Methods: SH-SY5Y cells were treated with $A\beta_{1-42}$ (3 μM), simvastatin (10–150 nM), or a combination of both. Simvastatin was administered as a 24-hour pretreatment followed by co-treatment with Aβ. Aβ oligomers were prepared by incubation at 4 °C for 24 hours. Cell viability was assessed using the MTT assay and normalized to untreated controls. Statistical analyses were performed using t-tests and one-way ANOVA with Tukey's post hoc test.

Results: Exposure to 3 μM $A\beta_{1-42}$ significantly reduced cell viability compared to control ($p < 0.05$). Simvastatin alone had no significant effect on cell viability. Pretreatment with simvastatin did not significantly reverse Aβ-induced cytotoxicity at any tested concentration, although a modest, non-significant trend toward improved viability was observed at 100 nM.

Conclusion: Simvastatin did not significantly attenuate $A\beta_{1-42}$–induced cytotoxicity in SH-SY5Y cells under the conditions tested. These findings suggest that any neuroprotective effects of simvastatin may be limited or dependent on specific experimental parameters such as dosing and timing. Further studies are needed to explore potential context-dependent mechanisms of statin-mediated neuroprotection in Alzheimer's disease models.

Mobile Mammography Outreach in Texas Communities with unmet health needs: Appointment Outcomes and Operational Insights (2022-2024)

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BACKGROUND: Breast cancer screening through mammography reduces mortality through early detection; however, communities with unmet health needs face lower screening rates and later-stage diagnoses due to socioeconomic, geographic, and systemic barriers. In Texas, these barriers disproportionately affect Hispanic, Black or African American, and low-income populations served by federally qualified health centers, community-based organizations, faith-based organizations, and university outreach programs. This project aimed to quantify mobile mammography screening uptake and attendance patterns, examine screening outcomes (normal vs. abnormal results), and identify operational trends to inform future community-based outreach strategies conducted by Texas Southern University's Breast Cancer Screening and Prevention Center.

APPROACH: A retrospective fieldwork analysis was conducted across four site types (Federally qualified health centers, Community-based organizations, Faith-based organizations, and Texas Southern University) and counties in Texas to evaluate appointment outcomes and screening mammogram outcomes through a mobile mammogram unit mobile mammography outreach from March 2022 to November 2024. Participants included individuals aged 40–75 years residing in various counties.

FINDINGS/INSIGHTS: Among 1,295 scheduled appointments during 56 mobile mammogram events, 64.3% were completed, 25.1% were no-shows, and 10.6% were cancelled. Federally qualified health centers accounted for the highest volume (701 schedules, 418 services provided) and the highest share of missed appointments. County level patterns mirrored overall rates. No significant monthly trends were observed (p > 0.45).

IMPLICATIONS: Qualitative feedback highlighted the role of faith-based outreach in trust building. Embedding services in established workflows and implementing reminder systems and transportation support may enhance uptake and reduce disproportionate outcomes.

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Buprenorphine Use and the Risk of Dental Adverse Events in Patients with Opioid Use Disorder

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Background: The US Food and Drug Administration (FDA) issued a drug safety communication in January 2022 warning of dental-related adverse events (DAE) reported in patients using buprenorphine films or tablets. This study utilized more recent data with a broad dental outcome definition beyond what has been previously reported to provide comprehensive evidence of this risk.

Objective: Assess the association between buprenorphine use and the risk of DAE among opioid use disorder (OUD) patients.

Methods: This was a retrospective cohort design. Using the Veradigm-MarketScan® linked dataset, adults aged ⩾18 years with an OUD diagnosis between June 30, 2018, and July 1, 2023, and who met our selection criteria were included. Patients were grouped as: (1) BUP users and (2) non-BUP users (control group). We used Prescription Time Distribution Matching (PTDM) and Inverse Probability Treatment Weighting (IPTW) methods to align follow-up and balance potential confounders between the 2 groups. The primary outcome was dental-related adverse events (DAE). Cox proportional hazards models estimated adjusted hazard ratios (HRs).

Results: A total of 14 495 OUD adult patients were included. Of these patients, 4199 (28.97%) initiated oral buprenorphine. Among the overall population, most were males, 8742 (60.3%), with an average age of 44.9 years. The absolute risk of DAE was slightly higher among buprenorphine users (2.17%) compared to controls (1.66%). We found an increased risk of DAE in buprenorphine users compared to the control group (adjusted HR, 1.36; 95%CI, 1.04-1.78).

Conclusions: There is an increased risk of DAE among buprenorphine users compared to non-users after 6 months of follow-up. Although this risk is modest, this finding suggests the need for increased awareness and preventive interventions among these users.

AI-based Drug Design to Target Allosteric Domains of the Androgen Receptor

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The androgen receptor (AR) is a nuclear receptor that plays critical roles in hormone regulation and development. AR activity accelerates hormone-driven malignancies and multiple cancers. AR function is highly regulated by post-translational modifications (PTMs). Our lab has published that in metastatic breast cancer, AR is modified by the protein PTM SUMOylation at lysine 386 (K386), and that SUMO-modified AR is 1) highly stable, 2) drives oncogenic transcriptional reprogramming, and 3) is resistant to FDA-approved AR-targeted therapies. More AR-targeted approaches for treatment are needed. The AR N-terminal domain (NTD) is responsible for PTM regulation of AR and facilitates both canonical and oncogenic AR activity, making it an attractive drug target. However, the NTD is an intrinsically disordered region (IDR), making conventional drug design ineffective.

We generated AI-diffusion models with ensembles of AR NTD (residues 101-485) using Boltz2, modeling six experimental states, including mono- and poly-SUMOylation identifying SUMO site K386 alone and in combination with covalent NTD-targeted binders. Our work 1) investigates how SUMO modification of AR impacts the structural dynamics of the Tau5 regulatory IDR and 2) develops new targeted approaches to treat malignancies driven by PTMs of the Tau5 IDR.

Our results validated that SUMOylation at K386 stabilizes the IDR Tau5 domain, increasing its fold confidence and maintains a compact stable structural state and alters protein surface accessibility, which could alter its transcriptional activity. Measuring targeted inhibition, the addition of NTD-binding, covalent small molecules to the poly-SUMOylated Tau5 resulted in structural compaction of the Tau5 helical domain. Our studies provide a structural basis for designing more effective allosteric AR inhibitors as well as targeted protein degraders (PROTACs) and next-generation covalent inhibitors for AR-driven malignancies.

Assessing Treatment Response Against Carbapenem-resistant Acinetobacter baumannii

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Poster 44

Background: Carbapenem-resistant Acinetobacter baumannii (CRAB) is a critical priority pathogen with few effective treatment options. Treatment efficacy against CRAB is commonly evaluated at 24h in preclinical infection models, but short-term assessment may not always predict long-term response. This study evaluated longitudinal CRAB response to treatment to characterize temporal patterns under antibiotic exposure.
Methods: Four clinical CRAB isolates (two unrelated clones by FTIR) were assessed, harboring OXA-23 or OXA-40/58. Bacterial response was evaluated in the hollow-fiber infection model (HFIM) using different β-lactam (e.g., sulbactam and ceftazidime) and β-lactamase inhibitor combinations (e.g., durlobactam and avibactam) at clinically relevant exposures. Baseline inocula of approximately 5.5 log cfu/ml were used. Duplicate samples were taken serially from the circulatory loop to verify simulated drug exposures, which were assayed by validated LC-MS/MS. Bacterial density was monitored for at least 72 hours through serial quantitative culture. Bacterial response (compared to baseline) at 24h were correlated to that at 72h.
Results: A total of 16 experiments with different drug combinations were evaluated. Pharmacokinetic simulations in the HFIM were satisfactory (r^2 > 0.84). Despite bacterial reduction of more than 1 log within the first 24 hours (in 15 out of 19 experiments), more than half of the isolates exhibited regrowth at 72h (9 out of 15). Sustained suppression was more likely in isolates harboring OXA-23, and with regimens dosed every 6 hours.
Conclusions: CRAB has a high propensity to regrow after initial treatment reduction. Bacterial suppression observed at 24 hours may not always reliably predict sustained suppression. Evaluation beyond 24 hours may provide more informative guidance on sustained treatment response by capturing delayed regrowth.

A Flexible, Wearable, Large-Area Dosimeter Array for Real-Time Radiation Dose Mapping

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Poster 45

Accurate, real-time verification of radiation dose delivery is essential for safe and effective radiotherapy. However, conventional dosimeters are rigid and unable to conform to complex patient anatomies, limiting continuous, spatially resolved dose monitoring. This creates a critical barrier to reliable in vivo dose verification, particularly for large or irregular treatment sites. To bridge this gap, we have developed a fully flexible, wearable dosimeter imager based on organic soft electronics, designed for real-time 1dimension (D) to 3D dose mapping directly on the patient. A flexible, wearable dosimeter array was fabricated using an elastomer–semiconductor–elastomer (ESE) stack architecture. The sensing region of the device is built from two thin organic semiconductor layers stacked on top of each other, a poly(3-hexylthiophene) (P3HT) nanofiber layer and poly[(N,N′-bis(2-octyldodecyl)-naphthalene-1,4,5,8-bis(dicarboximide)-2,6-diyl)-alt-5,5′(2,2′-bithiophene)] (P(NDI2OD-T2) or N2200) layer, each around 100 nm thick. Incident radiation generates scintillation light absorbed by the organic semiconductor bilayer; the P3HT/N2200 heterojunction facilitates efficient photocurrent generation, enabling quantitative dose detection. To make the device stretchable and wearable, we used silver nanowires embedded in a soft elastomer, polydimethylsiloxane (PDMS), as the electrical contacts, which is treated by heat at 90 °C to get good conductivity. A thin polyurethane coating (PU) was added on top to protect the sensitive N2200 layer from air exposure. The total device thickness was kept between 200–300 µm.

In this work, we fabricated a 2 × 3-inch prototype device incorporating an 8 × 8 array of photodetectors, demonstrating the core functionality of the system. Tiny transistors and resistors built into the device using the same flexible materials allow signals to be read from each individual pixel in real time. The device architecture is designed to scale toward larger.

Identification of Novel Upstream Activators of PAX7 in Human Skeletal Muscle Cells

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Skeletal muscle regeneration is governed by tightly regulated transcriptional networks, in which PAX7 plays a central role in the specification and maintenance of muscle stem cells (MuSCs). Dysregulation of these processes is associated with impaired muscle repair and a range of degenerative muscle diseases, highlighting the need to better understand the upstream mechanisms controlling PAX7 expression.

In this study, we aimed to identify and functionally characterize novel regulators of PAX7 using human skeletal muscle (HSkM) cells. Using a genome-wide activator gRNA library screen on a human ESC PAX7 reporter cell line, fourteen candidate genes were identified and systematically evaluated using a bidirectional (overexpression and knock down) perturbation approach. Gene knockdown was performed using siRNA-mediated silencing, while gene overexpression was achieved through lentiviral-based expression systems. Following these perturbations, changes in PAX7 and main myogenic genes' expression were assessed using qRT-PCR and/or protein-based assays to determine the regulatory role of each candidate gene. This strategy allowed us to distinguish between positive and negative regulators by comparing the effects observed under loss-of-function and gain-of-function conditions.

Preliminary results so far indicate that multiple candidate genes influence PAX7 expression, with several demonstrating consistent and reciprocal effects across both experimental approaches. These findings suggest that these genes may function as upstream regulators of PAX7 and contribute to the broader regulatory network governing myogenic processes. Ongoing work is focused on validating these candidate genes, improving reproducibility, and further characterizing their role in skeletal muscle biology using muscle-specific conditional knockout murine models. Ultimately, this study provides a foundation for identifying novel upstream PAX7 regulators, which can be leveraged to enhance muscle regeneration as therapeutic targets.

Re-Examining Doctors' Orders on Pain Killers Prior to Surgery

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Perioperative bleeding is a significant source of surgical morbidity, and patients are routinely instructed to discontinue all non-steroidal anti-inflammatory drugs (NSAIDs) prior to planned procedures. However, evidence supporting universal NSAID cessation is incongruent, and optimal discontinuation timing remains extensively debated. In patients with pain, this practice may be causing unnecessary harm.

NSAIDs inhibit cyclooxygenase (COX) enzymes, blocking conversion of arachidonic acid to prostanoids, including thromboxane A2, thereby inhibiting platelet aggregation. Following the discovery of the COX-2 isoform, it was established that platelets exclusively express COX-1. Inhibitory potencies of various NSAIDs towards COX-1 and COX-2 were also re-evaluated and found to be different among individual drugs. We propose that an NSAID's impact on primary hemostasis depends on its extent of COX-1 inhibition. We explore this by measuring collagen-induced platelet aggregation in platelet rich plasma after ex vivo incubation with therapeutically relevant concentrations of commonly used NSAIDs.

We show that COX-2 selective NSAID, celecoxib, did not affect platelet aggregation. In contrast, NSAIDs with slight COX-1 selectivity, ibuprofen, indomethacin, and naproxen, significantly attenuated platelet aggregation. While several studies reported that diclofenac had COX-2 selectivity comparable to celecoxib, therapeutically relevant concentrations of diclofenac inhibited platelet aggregation. This was likely observed because expected plasma concentrations of commonly administered diclofenac doses exceed reported COX-1 IC50 values by at least three-fold and can cause appreciable COX-1 inhibition.

These findings challenge the practice of universal preoperative NSAID cessation. Instead, a stratified approach based on the extent of COX-1 inhibition may allow for more comprehensive surgical decision-making, minimizing interruption of analgesia without increasing bleeding risk.

Design of Blood-Brain Barrier Penetrating Peptide Macrocycles for Central Nervous System Drug Delivery

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The blood–brain barrier (BBB) remains a major obstacle to treating central nervous system (CNS) diseases, preventing over 98% of FDA-approved therapeutics from reaching the brain. While its selective permeability protects neural tissue, it also limits delivery of promising biologics. Receptor-mediated transcytosis (RMT), particularly via transferrin receptor protein 1 (TfR1), offers a viable transport mechanism, though antibody-based approaches are hindered by large size, immunogenicity, and manufacturing challenges. Macrocyclic peptides provide a compelling alternative, combining high affinity and specificity with smaller size, enhanced stability, and synthetic flexibility. Here, we present a generative AI–guided approach to design macrocyclic peptide ligands targeting the apical domain of TfR1. Using BindCraft, we generated domain-specific binders, and surface plasmon resonance (SPR) confirmed low- to sub-micromolar affinities, with subsequent optimization improving binding further. To evaluate functional BBB transport potential, we developed in-vitro assays to assess peptide internalization and transcytosis. Using HeLa cells and human brain endothelial hCMEC/D3 cells, we established platforms to quantify TfR1-dependent uptake and intracellular trafficking. These assays enable systematic evaluation of peptide-mediated internalization and provide insight into mechanisms governing receptor engagement and transport efficiency. In parallel, an in vitro BBB model was established to examine transcytosis across endothelial barriers under physiologically relevant conditions. Together, this work highlights the integration of AI-driven peptide design with robust in vitro validation to develop macrocyclic ligands as next-generation BBB shuttle vectors, advancing strategies for CNS drug delivery.

Molecular Risk Profiling of Postpartum Breast Cancer in High-Parity Women

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Background: Postpartum breast cancer (PPBC) is a type of breast cancer (BCa) that occurs within 5-10 years of delivery, affects 35-55% of younger women (<45), and exhibits poor prognosis with elevated metastasis risk. Emerging evidence suggests that higher parity among Latino women correlates with more aggressive, early-onset of PPBC. However, the molecular mechanisms underlying this epidemiological observation remain unclear. The objective of this study is to establish a relevant parity model and identify a gene signature that can predict PPBC risk within the Latino population.

Methods: We established a high-parity BCa genetically engineered mouse model (GEMM) and conducted RNA-seq analysis on tumors derived from multiparous female mice alongside mammary gland (MG) tissue from nulliparous age-matched control mice. The resulting mouse parity-associated gene set was filtered through publicly available human PPBC RNA-seq data to establish a parity-associated PPBC gene signature. Results: The high-parity GEMM exhibits impaired MG involution and tumor development in comparison to controls; suggesting that multiple parity is required for onset of BCa in this GEMM model. RNA-seq of high-parity mouse tumors, integrated with human PPBC datasets, identified an overlapping 18-gene signature. Current studies are leveraging additional publicly available datasets to evaluate the effectiveness of the 18-gene signature in identifying high-risk PPBS populations, with a particular focus on the Latino community. Conclusion: Our studies have identified a distinct molecular signature of parity-driven PPBC. This genes panel provides a foundation for detecting early PPBC susceptibility biomarkers in younger Latino women at risk and identify molecular drivers for targeted therapeutic interventions.

First In Vivo Evaluation of BPR0L075 Reveals ICD-Inducing Potential in an EO771 Triple-Negative Breast Cancer Model

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BPR0L075 (BPR) is a novel colchicine-site binding inhibitor with potent anti-tumor and vascular-disrupting activity. Previous studies showed that BPR overcomes paclitaxel resistance and induces hallmarks of immunogenic cell death (ICD) in vitro, including calreticulin exposure, ATP release, and HMGB1 secretion in multiple breast and ovarian cancer cell lines. Building on this foundation, we evaluated BPR's immunogenic potential in vivo using the EO771 murine breast cancer model, which closely resembles human triple-negative breast cancer (TNBC). To the best of our knowledge, this study represents the first evaluation of BPR0L075 in an immunocompetent model and the first use of EO771 in an ICD vaccination context.

To assess whether BPR triggers ICD in vivo, we conducted a prophylactic vaccination experiment in C57BL/6 mice. Animals were vaccinated with BPR-treated, dying EO771 cells and later challenged with live EO771 tumor cells. BPR vaccination significantly delayed tumor onset, reducing the risk of tumor development by more than elevenfold compared to unvaccinated controls in some animals. In several cases, BPR conferred strong protection, and in one instance, completely prevented tumor growth, highlighting its potential as an effective immunogenic agent. These results support further investigation of BPR-based combination therapies to enhance immune engagement and improve tumor control.

Toward Personalized Radiotherapy: A Cellular World Model from DNA Damage to Patient-Specific Tumor Response

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Radiotherapy remains a cornerstone of cancer treatment, and patient responses vary widely due to complex, multiscale biological processes that are not fully captured by current models. Here, we present a cellular world model that mechanistically links radiation dose to downstream cellular fate, enabling a new paradigm for personalized radiotherapy. Our framework integrates key biological modules—including DNA damage induction, repair pathway dynamics (HR/NHEJ), cell cycle checkpoints, oxidative stress, and apoptosis signaling—into a unified, interpretable system. Built on a structured network of interacting nodes and quantitatively defined edges, the model simulates how radiation and microenvironmental factors such as oxygenation propagate through intracellular pathways to determine probabilistic cell fate outcomes, including survival, apoptosis, senescence, and necrosis. Unlike empirical dose–response models, this approach captures the causal progression from DNA damage to phenotypic decision-making, providing mechanistic insight into treatment sensitivity and resistance. Importantly, the model is designed for personalization, allowing incorporation of patient-specific parameters such as tumor hypoxia, genetic alterations, and pathway dysregulation to generate individualized response predictions.
We demonstrate that this cellular world model can reproduce clinically relevant dose–response behaviors while revealing hidden drivers of variability in treatment outcomes. By bridging radiation physics with systems biology, our approach lays the foundation for a predictive, scalable framework capable of evolving toward patient-specific tumor modeling and, ultimately, clinical decision support. This work advances the concept of a computational “world model” of the cancer cell, offering a powerful tool to decode radiotherapy response and accelerate the transition toward precision oncology."

Significant Species Differences in Buprenorphine Metabolism: A Pharmacokinetic Comparison of Metabolite Exposure

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Purpose: Buprenorphine (BUP) metabolism differs across species, complicating translation to humans. We compared CYP-mediated N-dealkylation and UGT-mediated glucuronidation across species and routes.

Methods: Pharmacokinetics of BUP, norbuprenorphine (NBUP), and their glucuronides were evaluated in mice (in-house) and rats, with human data from literature. Pathway contribution and fraction metabolized (Fm) were calculated from AUC. Enzyme kinetics were assessed in liver and intestinal microsomes.

Results: Rats showed UGT-dominant metabolism, whereas mice and humans were CYP-dominant. After sublingual (SL) dosing, Fm increased (mice: 48%, rats: 62%; humans: 79–93%). CYP contribution was lower in rodents (rat: 14%, mouse: 42%) than in humans (71–88%). Microsomal data supported these findings: mouse liver microsomes showed high CYP activity, while rat liver and intestine showed strong UGT activity.

Conclusion: BUP metabolism is species-dependent. Rats overrepresent glucuronidation, whereas mice better reflect human oxidative metabolism. Route of administration influences metabolic balance. These findings support careful species selection and integration of in vivo and in vitro data for PBPK modeling.

Therapeutic targeting of adhesion receptor GPR56 for the treatment of triple-negative breast cancer

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Triple-negative breast cancer (TNBC) is an aggressive subtype lacking durable targeted therapies, and resistance drives poor outcomes. The clinical success of antibody–drug conjugates (ADCs), which combine antibody specificity with potent cytotoxic payloads, highlights their impact. The anti-TROP2 ADC sacituzumab govitecan provides clinical benefit but causes toxicity in normal tissues, highlighting the need for more selective strategies. Our previous study showed that GPR56, an adhesion G protein-coupled receptor (GPCR), activates the adhesion-mediated FAK–Src signaling and that targeting GPR56 with an ADC elicited antitumor efficacy in colorectal cancer models. Given these findings, we examined GPR56 as a therapeutic target in TNBC. While TROP2 is a validated ADC target, its normal tissue expression limits tumor selectivity. In contrast, GPR56 is significantly enriched in TNBC tumors and associated with poor prognosis. It exhibits limited expression in normal tissues, suggesting a superior therapeutic index. Functional studies showed that GPR56 knockdown suppressed FAK–Src phosphorylation, tumor cell growth, and invasion in TNBC cells. Our first-generation anti-GPR56 ADC (10C7-Duo), incorporating the DNA-damaging payload duocarmycin, exhibited target-dependent cytotoxicity in GPR56-positive TNBC cell lines, supporting GPR56 as a viable target. However, the monoclonal antibody (mAb) 10C7 displayed agonistic activity, which may limit its therapeutic potential. To address this, we developed 9E3, a non-agonist anti-GPR56 mAb that internalizes and traffics to lysosomes. 9E3 was conjugated to a pyrrolobenzodiazepine (PBD) payload using site-specific chemistry, with analyses confirming conjugation, stability, and preserved antigen binding. We are evaluating 9E3-PBD for in vitro and in vivo efficacy in TNBC models. These findings establish GPR56 as a clinically relevant target and support the development of GPR56-targeted therapeutics in TNBC.

Repurposing Nebivolol with CPI-613 for Triple-Negative Breast Cancer: Linking In Vitro Synergy to In Vivo Exposure

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Triple-negative breast cancer (TNBC) is associated with poor prognosis, high recurrence rates, and limited targeted treatment options, with chemotherapy remaining the standard of care despite significant toxicity. Drug repurposing offers a clinically translatable strategy to improve outcomes using agents with established safety profiles. Nebivolol (NEB), an FDA-approved β_1-blocker, has demonstrated anti-cancer activity, while CPI-613 (CPI) disrupts mitochondrial metabolism. We hypothesized that dual metabolic targeting would enhance TNBC inhibition.

Murine 4T1 cells were treated with NEB (0.5–16 µM) and CPI (5–250 µM). MTT assays (72 h) and Chou–Talalay analysis identified 4–8 µM NEB + 5–50 µM CPI as the optimal synergistic range (>90% inhibition, CI < 0.2).

In vivo, orthotopic 4T1-Luc tumors in BALB/c mice were treated with vehicle (N=5), NEB (10 mg/kg QD), CPI (25 mg/kg BID), or NEB + CPI (NC) (N=5–6), 5 days/week for 3 weeks. All treatments significantly reduced tumor growth versus vehicle ($p < 0.01$–0.001), with mean tumor volumes (mm^3 ± SD): Vehicle 1484.9 ± 492.4; NEB 595.8 ± 134.6; CPI 634.7 ± 116.9; NC 702.5 ± 352.0. Tumor weights showed similar trends ($p < 0.0001$), with no difference among treatment groups.

LC–MS/MS confirmed intratumoral drug exposure; however, tumor concentrations (µM) for NEB and CPI in all groups were below the in vitro synergistic range and did not achieve the optimal ratio.

NEB and CPI inhibited TNBC growth, but the combination did not outperform single agents. Sub-synergistic, ratio-mismatched tumor exposure likely explains this outcome. Ongoing tumor PK studies aim to optimize dosing to achieve synergistic exposure in vivo.

Dehydroepiandrosterone Sulfate Biliary Excretion: Sex and Species Differences Revealed by LC-MS/MS quantification.

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Dehydroepiandrosterone sulfate (DHEAS), a major circulating metabolite of dehydroepiandrosterone and precursor of sex hormones, has circulating levels associated with multiple endocrine and age-related conditions. The role of biliary excretion and enterohepatic recirculation in regulating systemic DHEAS exposure, particularly species-and sex-related differences, remains unclear.

We developed and validated a high sensitivity LC-MS/MS assay to quantify DHEAS in bile and whole blood and characterize interspecies and sex-dependent biliary excretion. Charcoal-stripped whole blood and rat bile were used as steroid-free matrices. Bile and blood were collected from male and female rats, and bovine and porcine bile were analyzed to assess cross-species differences.

The assay met US FDA bioanalytical validation criteria, with 80 – 110% recovery, 90 – 110% matrix effect, precision and accuracy within ± 20% over nanomolar linear range, and a lower limit of quantification of 0.24 nmol/L. We observed pronounced species differences in biliary DHEAS, with no significant differences between porcine and bovine bile, and consistently higher biliary DHEAS levels in females across all species examined. Also, we found a more than 10-fold difference in human bile samples between males and females. In contrast, whole blood DHEAS concentrations were largely below the LLOQ and did not significant difference between male and female.

This simple and robust LC-MS/MS method is, to our knowledge, the first to define species- and sex-dependent patterns of DHEAS biliary excretion, providing a translational basis for interpreting DHEAS profile in preclinical models, which is potentially extrapolatable to humans as guidance for future clinical studies of steroid hormone homeostasis.

Targeting MET–LGR5 Crosstalk using an Antibody-Drug Conjugate Combination with Diverse Payloads to Overcome Adaptive Resistance in Colorectal Cancer

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Off-target side effects and drug resistance limit the efficacy of current anti-cancer therapies against colorectal cancer (CRC), the second deadliest malignancy worldwide. CRCs harbor tumor-initiating cancer stem-like cells (CSCs) that survive cytotoxic insults and drive metastatic relapse. Antibody-drug conjugates (ADCs) exploit monoclonal antibody specificity to deliver potent payloads to tumor cells. We generated ADCs targeting leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5), a bona fide CSC biomarker frequently overexpressed in CRC. Our LGR5 ADC showed high potency in CRC xenografts with minimal toxicity. However, tumors relapsed after treatment cessation. Recurrent tumors evaded LGR5 ADC-mediated elimination by transiently adopting an LGR5-negative (LGR5-) state accompanied by MET downstream pathway activation. MET, a receptor tyrosine kinase often elevated in CRC, promotes metastatic progression. We found that activation of STAT3, a MET effector, undermines LGR5 ADC efficacy. To eliminate drug-resistant LGR5- cells, we developed MET-targeted ADCs by conjugating an antagonistic MET mAb (ABT700) to the DNA-crosslinking payload pyrrolobenzodiazepine (PBD). This MET ADC (ABT700-PBD) induced dose-dependent cytotoxicity in CRC cells and spared MET-ablated cells, confirming specificity. Safety studies in immunocompetent mice showed a favorable toxicity profile. In CRC xenografts, ABT700-PBD induced marked tumor regression. However, residual tumors exhibited increased LGR5 expression, suggesting MET-LGR5 crosstalk drives adaptive resistance. Cytotoxicity assays combining ABT700-PBD with our camptothecin-derived LGR5 ADC (8E11-CPT2) revealed synergistic killing. Combination therapy in CRC patient-derived xenografts extended survival and reduced tumor burden compared to monotherapies. These findings support dual MET and LGR5 ADC therapy as a strategy to overcome adaptive resistance-driven relapse in CRC.

A CTC-based multiplex immunofluorescence assay for monitoring of response to CDK4/6 inhibitors in HR+/HER2- breast cancer

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CDK4/6 inhibitors (CDk4/6i) are standard treatment for HR+/HER2- breast cancer, but ~50% of patients develop resistance. Altered retinoblastoma (Rb) pathway signaling due to loss of Rb or persistent phosphorylated Rb (pRb) has been associated with reduced CDK4/6i response. Circulating tumor cells (CTCs) provide a minimally invasive approach for serial tumor assessment. We have developed and optimized a quantitative multiplex immunofluorescence (mIF) assay integrated with image analysis to measure Rb and pRb in CTCs and evaluated its compatibility with CTC enrichment. The mIF assay included conjugated antibodies against Rb, pRb, cytokeratin, CD45, and DAPI. Antibody specificity and analytical performance was evaluated using internal control cell lines. Healthy donor leukocytes spiked with control cell lines were used to model patient-derived samples. Staining buffers and cell attachment methods were optimized. Cell recovery was evaluated using cancer cells-spiked blood after CTC enrichment and staining in HyPICC chambers. Mean fluorescence intensity was quantified using FIJI, and statistical analyses were performed in GraphPad Prism v10. The optimized assay demonstrated sensitivity of 84% for Rb and 83% for pRb, and specificity of 96% for Rb and 100% for pRb. SNRs were 5 for Rb and 50 for pRb, with dynamic ranges greater than 2 log units. Single-marker and isotype control staining confirmed target specificity with minimal non-specific binding. Among tested conditions, 1% BSA with 0.5% goat serum and a Triton-based buffer were selected as blocking and wash buffer. RareCyte® cell attachment yielded the highest cell retention (79%). After CTCeptor processing of spiked blood, recovery of tumor cells ranged from 40% to 60% in HyPICC chambers. In summary, we have developed an analytically validated mIF assay for single-cell measurement of Rb and pRb in CTCs. The assay is being evaluated in HR+/HER2- breast cancer patients on CDK4/6i therapy.

Evaluating Ceftriaxone as a Prophylactic Treatment Against Alzheimer's Disease Using Real-World Evidence

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Alzheimer's disease (AD) affected more than 7 million Americans in 2025, yet no preventive treatment exists against this detrimental disease. Previous studies have shown that the beta-lactam antibiotic Ceftriaxone protects against Alzheimer's disease (AD), potentially through reduction of neuroinflammation. However, these studies were performed in preclinical models, and Ceftriaxone has not yet been assessed in patient populations. Therefore, the objective of this research is to determine whether Ceftriaxone exposure is associated with reduced risk of developing AD using real-world evidence. Using TriNetX, we created two cohorts of inpatients aged ≥ 65 years old without prior AD: those who received Ceftriaxone and those who did not receive Ceftriaxone 5-10 years ago. Individuals diagnosed with AD within one year of initial Ceftriaxone usage were also excluded. Through a retrospective cohort study, we assessed the relative risk of developing AD. Propensity score matching was used to balance confounders such as age, race, and sex. In our preliminary findings, there were 342,712 individuals who met our inclusion criteria. Amongst this cohort, 2,142 patients (1%) developed AD. After propensity score matching, the relative risk of developing AD one year or more after the index event between our cohort of interest and control cohort was 1.3 (95% CI: 1.2, 1.3). Our preliminary findings suggest that the relative risk of developing AD is relatively higher in older adult inpatients who used the beta-lactam antibiotic Ceftriaxone compared to those who did not. Our research highlights the need to continue exploring potential preventative therapeutics against AD. These findings emphasize that repurposing drugs, such as antibiotics and antivirals, may be of interest in preventing neurodegenerative disorders.

Comparison of patient outcomes between fidaxomicin monotherapy vs vancomycin monotherapy in real world, matched population

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Poster 23

Background: Patients admitted with Clostridioides difficile infection (CDI) are often treated with oral vancomycin. However, in recent years, many institutions have adopted fidaxomicin as first-line therapy due to higher accessibility and affordability to patients following recent IDSA/SHEA guidelines update. In this study, we aimed to compare patient outcomes between fidaxomicin monotherapy vs vancomycin monotherapy in a real-world, matched population.

Methods: This was a retrospective, case-control study of patients with CDI from two hospital systems (14 hospitals) from 2017 to 2026. Patients with either fidaxomicin monotherapy or vancomycin monotherapy were matched 1:1 by age ±10 years, Charlson Comorbidity Index (CCI) score ±1, and disease severity (nonsevere, severe, or fulminant). The primary composite endpoint was 30-day sustained clinical response (SCR) defined as no diarrhea at day 14, no mortality at day

30, and no CDI recurrence at day 30. Electronic medical records were manually reviewed to collect data of interest. Analysis was performed using R studio (version 4.5.3).

Results: Fifty-two patients were included within this study. The majority of the selected cohort were female (61.3%) and white (40.1%). No differences in 30-day SCR were observed between the two groups (21 (81%) vs 23 (88%); p = 0.442). ICU admission within 48 hours of CDI diagnosis was higher in patients treated with fidaxomicin (2 (8%) vs 10 (38%); p = 0.008).

Conclusion: No significant difference in 30-day SCR was observed between fidaxomicin monotherapy vs vancomycin monotherapy group in our matched population. This likely reflects the clinical practice of utilizing fidaxomicin in patients with a higher acuity of illness and/or risk of recurrence. Future directions include an expanded cohort and continued surveillance on patient outcomes and resistance development as fidaxomicin use continues to increase.

Cadaveric Analysis of the Persistent Median Artery and Association in Carpal Tunnel Compression

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Poster 24

The persistent median artery (PMA) is a vessel present during early embryonic development via morphogenesis. Although it typically regresses through apoptosis, it may persist after birth. Due to its proximity to the median nerve, it is associated with pain related to carpal tunnel pressure. Prior studies have demonstrated important anatomical relationships between the PMA and surrounding structures, though variability in reported data remains. This study aims to assess the prevalence and anatomical patterns of the PMA through cadaveric analysis while collecting vessel parameter data relevant to carpal tunnel pressure. Cadaveric human forearms (n = 102) were dissected to determine the prevalence and orientation of the PMA. Vessel diameter measurements were obtained and compared with existing literature.

PMA prevalence was 12.7% (13/102). Orientation relative to the median nerve included antero-piercing 61.5% (8/13), lateral 30.8% (4/13), and medial 7.7% (1/13). The average diameter was 0.45 ± 0.15 mm. Findings are consistent with prior literature, particularly the predominance of the anterior-piercing type. Prevalence was comparable; however, the measured diameter was smaller than values reported in ultrasound and Doppler studies of asymptomatic individuals. Understanding PMA morphology is important due to its potential role in carpal tunnel compression and postoperative complications. Medications that increase fluid retention or thrombosis risk, such as systemic corticosteroids, estrogen-containing contraceptives, and certain cancer therapies such as tamoxifen and anti-angiogenesis TKIs, which may worsen symptoms of PMA. Symptoms may improve with NSAIDs, neuropathic pain medications, and corticosteroids injections. Rare thrombosis events may require anticoagulation. Diabetes may further exacerbate vascular and nerve compression.

Pilot Assessment of Changes in Saliva Characteristics in Response to Sublingual Buprenorphine Treatment and Chewing Gum Intervention in Patients with Opioid Use Disorder

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As per recent FDA warning and published studies, use of sublingual BUPE (sBUPE) increases the risk of caries and tooth loss in patients with opioid use disorders (OUD). This ongoing pilot study was aimed to determine the association between increased risk for tooth decay and compromised saliva characteristics (flow, acidity, buffering capacity, and microbiome) in patients due to sustained oral exposure to BUPE (N=7). We also explored the potential of Afairo™, a specialized chewing gum by Sanarentero, in improving saliva characteristics in the study subjects (N=2). Participants were recruited at the University of Houston and Texas Clinic Fulton using IRB-approved protocol (STUDY00004381) (Fig. 1). All collected biospecimens labeled with participant study codes were stored in -80°C freezer for BUPE analysis. Oral microbiome saliva samples were shipped to Bristle Health for analysis. 4 White and 3 Black patients (4 males and 3 females), 36-47 years old, were recruited for this study. Most patients had acidic saliva pH (5/7) and impaired buffering capacity (5/7) at baseline. CariScreen assessment showed high S. mutans burden (Index>1500) in patients (4/7). Presence of bacterial species associated with high risk of tooth decay (4/7) and/or gum inflammation (3/7) and lack of beneficial bacteria were confirmed in oral microbiome analysis of several patients. sBUPE treatment reduced saliva pH levels which remained low (5.5-5.6) even after 1 hour of dosing (N=2). Chewing Afairo™ for 6-8 minutes restored pH back to the basal levels (6.25-7.25), showing early proof-of-concept performance as preventative adjuvant therapy. Measurement of BUPE levels in saliva and blood are awaiting LCMS analysis. Most patients with OUD suffer with low saliva pH and buffering capacity, increasing the risk of tooth demineralization and growth of cariogenic bacteria. Afario™ has the potential to be used as preventative intervention to improve saliva characteristics in patients with OUD.

Lessons from behavioral and arts-integrated interventions to improve oral endocrine therapy adherence in HR+ breast cancer

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Poster 25

Background: Adherence to oral endocrine therapy (OET) in hormone receptor-positive breast cancer (HR+ BC) remains suboptimal despite its proven survival benefit. Common barriers include adverse effects, long treatment duration, low perceived benefit, and psychosocial factors. Traditional interventions, such as education and reminder systems, have demonstrated limited success in improving long-term adherence. The objective of this study was to evaluate the role of patient-centered and arts-integrated interventions in improving adherence to OET in patients with HR+ BC.

Methods: Relevant literature in PubMed on OET adherence in breast cancer was reviewed. The discussion focused on reported adherence-related outcomes and incorporated behavioral, patient-centered, or arts-integrated interventions. These factors were categorized into intervention type, adherence outcomes, and barriers addressed to identify opportunities for improving adherence.

Results: Interventions included educational/reminder-based, behavioral, digital, and arts-integrated approaches. Traditional strategies showed modest adherence improvements, while multicomponent interventions, such as those including behavioral counseling, mHealth, patient–provider communication, were more effective. Arts-integrated approaches improved engagement and medication-taking behaviors through culturally relevant and emotional pathways. Key barriers addressed included adverse effects, low perceived benefit, forgetfulness, low health literacy, and cultural mistrust.

Conclusion: These findings show how integrating culturally responsive, engagement-focused interventions into clinical practice can enhance adherence to OET in HR+ BC patients. Future research and efforts should focus on developing and evaluating scalable, arts-integrated models to improve adherence outcomes in patients with HR+ BC.

In Silico Evaluation of Metal-Organic Frameworks for Receptor- Mediated Drug Delivery Across the Blood-Brain Barrier, targeting Glioblastoma

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Glioblastoma is the most common and aggressive malignant primary brain tumor, and its treatment is constrained by the blood–brain barrier (BBB), which restricts drug delivery. This project aimed to computationally evaluate metal–organic frameworks (MOFs) as nanocarriers for receptor-mediated delivery of FDA-approved neurological drugs across the BBB to glioblastoma cells. Three-dimensional MOF structures were obtained from crystallographic databases, while C-X-C chemokine receptor type 4 (CXCR4) and the transferrin receptor (TfR) were modeled using AlphaFold. Molecular docking was performed with the HDOCK server to assess interactions among MOFs, drugs such as Temozolomide, and the receptors. Several MOF–drug complexes showed favorable binding energies and stable interaction patterns with CXCR4 and TfR, suggesting strong potential for BBB translocation and targeted delivery. These results support MOF-based nanocarriers as promising systems to enhance glioblastoma therapy, although conclusions are limited to in silico predictions and require experimental validation to confirm efficacy and safety.

Administration Route-Dependent Salivary Gland Accumulation of buprenorphine and Its Implications for Dental Toxicity

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Objective: Sublingual buprenorphine (BUP) is associated with increased risk of adverse dental outcomes compared with other formulations. This study evaluated the impact of administration route of BUP for opioid use disorder (OUD) treatment on oral tissue distribution of buprenorphine and its potential role in drug-induced dental toxicity.
Methods: F344 rats received BUP via sublingual film (2 mg/kg), intravenous injection (1 mg/kg), or subcutaneous implantation (5 mg/rat). The sublingual groups of rats were sacrificed at 3 and 6 h following single or multiple dosing, and 11 tissues were collected for distribution analysis. For implant studies, blood samples were collected weekly and tissues were harvested after 4 months. BUP and its metabolites were quantified using a validated UHPLC–MS method in accordance with FDA guidance.
Results: Following sublingual administration, tissue-to-blood ratios in the salivary glands were consistently above unity, ranging from 1.42 to 5.15 after single dosing and from 1.29 to 4.63 after repeated dosing, indicative of preferential salivary gland accumulation. Although the highest tissue enrichment is observed in tongue and cheek, Kp values are also highly variable due to their direct contact with the administrated films. Notably, elevated buprenorphine-glucuronide levels were detected in these direct-contact tissues while no comparable metabolite levels obeserved in salivary glands, suggesting that salivary glands may primarily serve as reservoirs for parent buprenorphine rather than significant sites of local metabolization like in the direct-contact tissues.
Conclusion: Administration route significantly influences salivary gland exposure of buprenorphine in rats. Elevated local concentrations following sublingual dosing may contribute to dental adverse effects. These findings provide mechanistic insight into formulation-dependent toxicity and support further evaluation of tissue-specific drug distribution in OUD therapies.

Effect of GLP-1 receptor agonists on incident dementia with and without SGLT2 inhibitors

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BACKGROUND: Real-world evidence suggests potential benefit of GLP-1 receptor agonists (GLP1RA) and SGLT2 inhibitors (SGLT2i) for Alzheimer's disease and related dementia (ADRD) prevention. However, their combined effect remains unknown.

OBJECTIVE: To assess the effect of GLP1RA vs. long-acting insulin (LAI) and sulfonylurea (SU), with and without SGLT2i, on incident ADRD.

METHODS: Using a 20% fee-for-service Medicare beneficiaries aged 70+ with parts A/B/D coverage (2013-2019), we conducted 3 active-comparator, new-user studies comparing GLP1RA with LAI and SU, assessing treatment effect among: 1) overall population; 2) patients with baseline SGLT2i (initiated within 180 days before GLP1RA or comparator); and 3) patients without baseline SGLT2i. Initiation required a 2nd prescriptions (Rx) and no ADRD during a 3-year baseline. We identified incident ADRD by 2 diagnosis codes or a code with a new ADRD Rx within 90 days of the code. Propensity scores computed from ~80 baseline covariates measured in the 1-year baseline period were used to estimated inverse probability treatment–weighted 3-year adjusted risk difference (aRD). Intention-to-treat analyses follow-up began at the 2nd Rx until disenrollment of any Medicare parts, death, ADRD, 3-year follow-up, or 12/31/2019, whichever came first.

RESULTS: Covariates were well balanced after weighting. GLP1RA was associated with lower ADRD risk vs LAI (N 22878 vs 50066; crude risk 4.3% vs 9.4%, aRD% -2.0 (-2.4, -1.6)) and SU (N 11825 vs 55246; crude risk 6.3% vs 9.5%, aRD% -2.4 (-2.9, -1.8). Results were similar when excluding baseline SGLT2i users. In combination with SGLT2i (N 464 v 535), ADRD risk was markedly lower (crude risk 2.4% v 5.4%) and GLP1RA benefit slightly increased vs LAI: aRD% -2.7 (-5.0, -0.4).

CONCLUSIONS: GLP1RA use was associated with reduced ADRD risk overall. SGLT2i showed potential added benefits, highlighting both promise and methodological challenges when evaluating combination therapies for ADRD.

Risk of Antipsychotic Initiation with Cholinesterase Inhibitor Use in Patients with Alzheimer's Disease and Related Dementia

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Cholinesterase Inhibitors (ChEIs) were widely used as the first-line pharmacotherapy for patients with Alzheimer's Disease and Related Dementias (ADRD). However, ChEIs may necessitate the use of antipsychotic medications for behavioral symptoms. This study aimed to evaluate the risk of antipsychotic initiation with the use of CHEIs among ADRD patients. We conducted a nested case-control study using 2013-2018 Medicare fee-for-service claims among patients aged 65 years or older with ADRD and no antipsychotic prescriptions in 2013. Controls were selected from patients without antipsychotic use using incidence density sampling, matched to cases on age and sex, with up to 5 controls per case. ChEI (donepezil, rivastigmine, and galantamine) exposure was assessed during the 180 days before the event date and further categorized by individual agents. Patients were required to have continuous enrollment between 2013 and the event dates. We used conditional logistic regression to examine the association between ChEI use and the risk of antipsychotic initiation, controlling key sociodemographic and clinical factors.

Among 1,763,433 patients with ADRD, 59,725 cases and 175,043 matched controls were identified after applying the selection criteria. ChEI use within 180 days before the event date was more common among cases than controls (18.15% vs 8.00%). In adjusted analysis, ChEI use was associated with a higher risk of antipsychotic initiation (Adjusted Odds Ratio [aOR]=3.69, 95% Confidence Interval [CI]:2.51-5.41). The risk of antipsychotic initiation was observed for donepezil (aOR=3.40, 95% CI:2.23-5.20) and rivastigmine (aOR=5.10, 95% CI:2.52-10.30), but not with galantamine users, compared to non-users. The study found an increasing risk of antipsychotic initiation with donepezil and rivastigmine. The findings highlighted the importance of medication monitoring and management to optimize ChEI use in ADRD.

Nebivolol exhibits cell growth inhibition in drug-resistant HR+/HER2- breast cancer and anti-tumoral synergism with abemaciclib in vitro

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We are investigating nebivolol, a third-generation beta-blocker, as a drug-repurposing candidate for breast cancer (BC). While prior studies focused on triple-negative BC, we evaluated its efficacy and potency in hormone receptor-positive, HER2-negative (HR+/HER2-) subtype. Since HR+/HER2- BC is typically treated with endocrine therapy (ET) alone or in combination with CDK4/6 inhibitors (CDK4/6i), we also assessed the effects of nebivolol in inhibiting the cell growth of estrogen deprivation-resistant (EDR) and palbociclib-resistant (PalboR) models, as well as in combination with CDK4/6i in parental cells. Nebivolol inhibited growth in parental, EDR, and palboR MCF7 and T47D cells in a concentration-dependent manner. The efficacy (%) and potency (μM) of nebivolol were 68.4-84.1 and 7.9-20.4 in MCF7 models, and 86.7-96.1 and 5.2-5.8 in T47D models. Additionally, nebivolol demonstrated better synergism with abemaciclib than palbociclib as assessed by multiple synergy models. Synergistic combinations in the HSA method were mainly centered on nebivolol 0.3-3 μM and abemaciclib 30-300 nM, with analyses using ZIP and Bliss independence models showing similar findings. Cell growth inhibition was significantly improved in 0.3-3 μM nebivolol with 30, 100, or 300 μM abemaciclib in MCF7P and with 30 nM abemaciclib in T47DP. Accordingly, 0.3-3 μM nebivolol with 30-300 nM abemaciclib were selected for MTT assay and analyzed with the HSA model to confirm synergism (synergy score > 10). The analysis suggested that the synergy plateau occurred at 1 and 3 μM nebivolol in combination with 100 and 300 nM abemaciclib. A significant reduction in colony formation was observed with 3 μM nebivolol combined with 300 nM abemaciclib compared to nebivolol alone. In summary, nebivolol inhibited the growth of HR+/HER2- BC parental and drug-resistant cell lines and synergized with abemaciclib. Ongoing studies are evaluating the combination of nebivolol with ET for enhanced therapeutic potential.

Trends in Mortality and Carbapenem Resistance among Pseudomonas aeruginosa Bloodstream Infections

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Pseudomonas aeruginosa (PSA) is a Gram-negative pathogen commonly implicated in healthcare-associated bloodstream infections (BSI). Its intrinsic and acquired resistance mechanisms limit treatment options, and carbapenem-resistant PSA has been recognized as a major public health threat associated with increased mortality. Although advances in diagnostics and antimicrobial therapies have emerged over the past decade, their impact on mortality remains unclear. This study aims to assess trends in in-hospital mortality associated with carbapenem-resistant PSA BSI over a 12-year period. This single-center retrospective cohort study was conducted at a tertiary teaching hospital. Adult patients with a positive blood culture for PSA between 2014 and 2025 were included. Demographic and clinical data were extracted from electronic medical records. The primary endpoint was 30-day mortality, and risk factors were analyzed using logistic regression.

Among 466 PSA BSI episodes, the overall 30-day mortality was 21.7%. Carbapenem resistance was identified in 104 (22.3%) episodes. The prevalence of carbapenem resistance decreased from the pre-COVID to the post-COVID period. COVID period was excluded due to pandemic-related healthcare disruption. Carbapenem resistance was associated with increased 30-day mortality (OR=1.77, p=0.026). Older age and higher APACHE score were also associated with higher mortality, whereas appropriate empiric therapy was protective (OR=0.47, p=0.002). In multivariable analysis, APACHE score and appropriate empiric therapy remained major predictors of mortality. Mortality associated with PSA BSI remains high over the study period. Carbapenem resistance declined over time, suggesting improvements in antimicrobial stewardship practices as well as advances in diagnostic and therapeutic approaches to PSA BSI

cAMP Colocalization with AKAP12 is Initiated by β2-Adrenergic Receptor (ADRB2) in Cardiomyocytes

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Background: Heart failure (HF) is the leading cause of death in the United States and is a major cause of death globally. In HF sympathetic stimulation of ADRB2 triggers cAMP-dependent Protein Kinase A (PKA) mediated phosphorylation of proteins that regulate cardiac function. cAMP levels are regulated in part by phosphodiesterases (PDEs). A Kinase Anchoring Proteins (AKAPs), a family of scaffolding proteins, play a crucial role in facilitating signal transduction by bringing together multiple signaling components. Previous studies have shown that AKAP12, also known as Gravin, couples to the ADRB2 and affects the agonist-induced association of AKAP12 and PDEs to the receptor. However, the interactive roles of AKAP12, ADRB2, and PDEs in cardiac function are unclear.

Methods: We indirectly investigated the interaction of AKAP12 with ADRB2 and cAMP using primary ventricular cardiomyocytes (CMs) isolated from transgenic mice (8-12 weeks old). Contractile properties of the CMs were assessed using a Multi-Cell Lite® system (IonOptix). We evaluated the cAMP basal levels in AKAP12WT and AKAP12OX CM using ELISA, then investigated cAMP distribution through confocal microscopy.

Results: We applied the ADRB1 selective inhibitor CGP-20712A and the non-selective β-adrenergic receptor agonist isoproterenol (ISO) together to isolated CMs and then measured the contractility and [Ca2+]i. The results are comparably similar to no inhibition condition in both AKAP12WT and AKAP12OX CMs, therefore indirectly validating ADRB2's participation instead of ADRB1's. cAMP colocalization level was significantly lower in AKAP12OX CMs upon ISO stimulation.

Conclusions: The ADRB1 signaling pathway behaves similarly in both AKAP12OX and AKAP12WT CMs. Therefore, ADRB1 is not likely associated with AKAP12. Instead, stimulation of the ADRB2 signaling pathway, and by interaction with AKAP12 to recruit PDE8A, reduce cAMP and to mediate PKA-dependent cardiomyocyte contractility.

Pharmacokinetics of Tirzepatide in Rats: Limited Tissue Distribution, No Sex Differences, and Translational Dosing Implications

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The long-acting dual GLP1 and GIP agonist Tirzepatide showed significantly dose regimen differences between human (weekly dosing) and rodents (daily dosing) in treatment of type 2 diabetes and obesity. These differences are majorly driven by species-specific pharmacokinetic properties. However, its pharmacokinetic profile, tissue distribution, sex differences and their effects on its efficacy in rats under multiple-dose conditions remain incompletely characterized. To address this issue, we first optimized the LC–MS/MS method for characterization the pharmacokinetics and tissue distribution of tirzepatide. Briefly, 3 male and 3 female rats received tirzepatide for 7 consecutive days (0.07 mg/kg/day for the first 3 days, followed by 0.14 mg/kg/day for the last 4 days). On Day 1, tirzepatide achieved a Cmax of 193.20 ± 32.90 ng/mL with AUCinf values of 5087.79 ± 372.71 h·ng/mL. After 7th dose, Cmax and AUCinf increased to 465.50 ± 37.83 ng/mL and 13,159.90 ± 522.15 h·ng/mL, respectively, while T1/2 remained comparable at 11.30 ± 1.40 h on day 7. Tirzepatide was detected in the liver, small intestine, heart, kidney, and colon, but not in the brain. Dose-normalized plasma exposure increased modestly (1.24-fold), indicating limited systemically accumulation and tissue distribution with tissue-to-blood concentration ratio lower than 0.2, which support that one-compartment model adequately described the PK profiles of tirzepatide. Overall, the optimized the LC–MS/MS method was successfully applied for characterization the pharmacokinetics and tissue distribution of tirzepatide without sex difference and tissue accumulation. The shorter half-life (t½) of Tirzepatide in rats may help explain differences in dosing regimens for in vivo efficacy studies compared to humans.

FN14 overexpression promotes proliferation, chemoresistance, and impaired differentiation in rhabdomyosarcoma

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Rhabdomyosarcoma (RMS) is the most common soft tissue malignancy in children and adolescents and is characterized by the expression of myogenic regulatory factors without progression to terminal differentiation. Treatment of RMS remains challenging, with nearly one-third of patients experiencing relapses due to resistance to standard chemotherapy primarily because the molecular mechanisms underlying RMS growth and chemoresistance remain less understood. Fibroblast growth factor-inducible 14 (FN14), a bona fide receptor for the TWEAK cytokine, is expressed in most mesenchymal cells. Aberrant expression of FN14 has been implicated in tumorigenesis and tumor growth in several cancer types. However, the role of FN14 in RMS remains unknown. Here, we demonstrate that FN14 expression is significantly elevated in human RMS samples and in the RD and RH30 RMS cell lines. Silencing FN14 in cultured RMS cells reduced their proliferation and survival. FN14 levels were further increased in vincristine-resistant RD cells, and FN14 knockdown impaired the proliferation and survival of these chemoresistant cells. FN14 enhanced ERK1/2, but not p38 MAPK signaling, in RD cells. Consistent with this, inhibition of ERK1/2 recapitulated FN14 silencing by reducing RD cell proliferation and survival. Additionally, knockdown of FN14 or inhibition of ERK1/2 significantly decreased mitochondrial function in RD cells. Finally, inhibition of either FN14 or ERK1/2 promoted differentiation in both parental and vincristine-resistant RD cells. Collectively, our study demonstrates that FN14-mediated signaling promotes proliferation, survival, and chemoresistance in RMS cells while concurrently suppressing their myogenic differentiation.