6TH ANNUAL GCC INNOVATIVE DRUG DISCOVERY AND DEVELOPMENT CONFERENCE: PIONEERING NEW APPROACHES FOR HEALTHCARE INNOVATION

MAY 6-7, 2025

BIOSCIENCE RESEARCH COLLABORATIVE
HOUSTON, TEXAS

Gulf Coast Consortia

QUANTITATIVE BIOMEDICAL SCIENCES

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The Gulf Coast Consortia (GCC), located in Houston, Texas, is a dynamic, multi-institution collaboration of basic and translational scientists, researchers, clinicians, and students in the quantitative biomedical sciences, who benefit from joint training programs, topic-focused research consortia, shared facilities and equipment, and exchange of scientific knowledge. Working together, GCC member institutions provide a cutting-edge collaborative training environment and research infrastructure beyond the capability of any single institution. GCC research consortia gather interested faculty around research foci within the quantitative biomedical sciences and currently include Innovative Drug Discovery and Development, Antimicrobial Resistance, Cellular and Molecular Biophysics, Immunology, Integrative Development, Regeneration and Repair, Mental Health Research, Single Cell & Spatial Omics, and Translational Pain Research. GCC training programs focus on Antimicrobial Resistance Training, Biomedical Informatics, Cancer Therapeutics, Interdisciplinary Pharmacology Scientists, Molecular Basis of Infectious Diseases, Molecular Biophysics, and Precision Environmental Health Sciences. Current members include Baylor College of Medicine, Rice University, University of Houston, The University of Texas Health Science Center at Houston, The University of Texas Medical Branch at Galveston, The University of Texas M. D. Anderson Cancer Center, The Institute of Biosciences and Technology of Texas A&M Health Science Center and Houston Methodist Research Institute.

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Agenda

Day 1 Tuesday, May 6

7:30-8:20 Mentoring Breakfast-Event Hall (Academic Careers)
Jin Wang, Baylor College of Medicine
Reid Powell, Institute of Biosciences and Technology, Texas A&M University
Suzanne Tomlinson-Mathis, Gulf Coast Consortia

8:30 am Welcome
Suzanne Tomlinson-Mathis, Gulf Coast Consortia

Keynote Introduction Mohanad Albayyaa, Univ of Texas Medical Branch at Galveston

8:35-9:10 **Keynote Presentation**
Statistical Significance for Causal Inference: How Decision Makers Hijacked Science
Miguel Hernán, Harvard University

Session 1 **Preclinical to Clinical: Observed Translational Differences**
Moderator Scott Widmann, Texas Southern University

9:10 *When Humans Do Not Behave Like Lab Animals*
Jeff Larson, Tvardi Therapeutics

9:30 *Leveraging Clinical Data to Reimagine Novel Therapies for Stem Cell Transplant*
Siddhartha De, 7Hills Pharma

9:50 Panel Discussion
Siddhartha De, 7Hills Pharma
Jeff Larson, Tvardi Therapeutics
Elaine Lea-Chou, ELC Private Consulting
Reid Powell, Institute of Biosciences and Technology, Texas A&M University

10:30 Vendor Session and Networking Break-Event Hall

Session 2 **Real World Evidence to Inform Preclinical Development**
Moderator Mohanad Albayyaa, University of Texas Medical Branch, Galveston

11:00 *Clinical Trials and Registries: Driving Scientific Innovation and Medical Breakthroughs*
Wissam Khalife, University of Texas Medical Branch at Galveston

11:20 *How Early Data Can Help Determine Future Study Designs*
Long Doan, SpyGlass Pharma Inc.

11:40 Panel Discussion
Lynda Chin, Apricity Health Inc.
Long Doan, SpyGlass Pharma Inc.
George Golovko, University of Texas Medical Branch
Wissam Khalife, University of Texas Medical Branch at Galveston

Moderator Dillon Fritz, GCC Research Evaluation and Commercialization Hub

12:15 **Rapid Fire Presentations- even-numbered posters**

Agenda

Digital Spatial Profiling Identifies Novel Targets in Patients with Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension
Phoebe Andrew, University of Texas Health Science Center, Houston, Poster 6

Investigating the Role of SSRIs' as a Potential Therapeutic for Neurodegenerative Diseases
Olivia Reed, Rice University, Poster 4

Two-Pronged Precision: Evaluating a Novel Dual-Targeting Antibody-Drug-Conjugate Based Therapy to Combat Colorectal Cancer
Shraddha Subramanian, MD Anderson Cancer Center, Poster 2

12:30 ***Lunch and* even-numbered posters** – Event Hall
12:30-1:30 Lunch
1:30-2:30 Poster presentations, even-numbered posters

Session 3 ***Innovative Methods for Identifying New Targets***
Moderator Scott Gilbertson, University of Houston

2:30-2:50 *Phenotypic Drug Discovery Revisited*
Deepak Nijhawan, University of Texas Southwestern

2:50-3:10 *Discovery of Novel First-in-Class Medicines with a Suite of AI-Enabled Platform Technologies*
Aimee Iberg, Recursion Pharmaceutical

3:10-3:50 Panel Discussion
Dillon Fritz, GCC Research Evaluation and Commercialization Hub
Matthew Gibson, Hogan Lovells
Aimee Iberg, Recursion Pharmaceutical
Elaine Lea-Chou, ELC Private Consulting
Deepak Nijhawan, University of Texas Southwestern
Reid Powell, Institute of Biosciences and Technology, Texas A&M University

Session 4 ***Houston-Based Resources for Healthcare Innovation***
Moderator Suzanne Tomlinson-Mathis, Gulf Coast Consortia

3:50 **Jennifer Roohi,** TMC Innovation
3:55 **Lacey Tezino**, GCC Research Evaluation and Commercialization Hub
4:00 **Colby Suire**, K2 Bio
4:05 **Allison Rhines,** Johnson & Johnson Innovation, JLABS TMC
4:10 **Zach Hightower,** Portal Innovation
4:15 **Will Tankersley,** Levit Green
4:20 **Jeffrey Wade**, BioHouston
4:25 **Megan Liles**, HGI Clinical
4:30 **Atul Varadhachary**, Fannin Innovation
4:35 **David Maxwell**, CanSAR platform/MD Anderson Cancer Center

4:40-6:00 ***Reception and BioConnect***-Pre-Function

Agenda

Day 2 Wednesday, May 7

8:00-8:50 am Mentoring Breakfast-Event Hall (Industry Careers)
Nassim Beiranvand, Texas Medical Center, Accelerator for Cancer Therapeutics
Jason Cross, MD Anderson Cancer Center
David Kummer, MD Anderson Cancer Center

Keynote Introduction Suzanne Tomlinson-Mathis, Gulf Coast Consortia

9:00 **Keynote Presentation**
The Fun of Academic Drug Discovery - Novel Targets, New Technologies
Michelle Arkin, University of California, San Francisco

Session 5 ***New Therapeutic Strategies***
Moderator Reid Powell, Institute of Biosciences and Technology, Texas A&M University

9:35 *New Strategies for Small Molecule Development*
Stanton McHardy, University of Texas, San Antonio

9:55 *New Strategies for Antibody Drug Modalities*
Chen-Ni Chin, IGM Biosciences, Inc.

10:20 Panel Discussion
Bissan Al-Lazikani, MD Anderson Cancer Center
Cheryl Beal Anderson, ACE Regulatory Affairs Consulting
Chen-Ni Chin, IGM Biosciences, Inc.
Matthew Gibson, Hogan Lovells
Stanton McHardy, University of Texas, San Antonio

11:00 ***Vendor Session and Networking Break***-Event Hall

Session 6 ***GCC IDDD Core Network Showcase***
Moderator Suzanne Tomlinson-Mathis, Gulf Coast Consortia

11:30 *GCC IDDD Core Network*
Suzanne Tomlinson-Mathis, Gulf Coast Consortia

11:40 *GCC Drug Discovery Resource Center*
Cliff Stephan, Texas A&M Institute of Bioscience and Technology

11:50 *GCC Center for Comprehensive PK/PD and Formulation*
Dong Liang, Texas Southern University

11:55 *Center for Innovative Drug Discovery*
Stanton McHardy, University of Texas San Antonio

12:00 *Advanced Protein Therapeutics*
Jennifer Maynard, University of Texas

12:05 *Advanced Cancer Antibody Drug Modalities Core*
Zhiqiang An, University of Texas Health Science Center, Houston

12:10 *Preclinical Development Core for Large Molecules*

Agenda

Qingyun "Jim" Liu, University of Texas Health Science Center, Houston

12:15 *Accelerator for Cancer Therapeutics*
Supriya Sinha, TMC Innovation

12:20 *Targeted Therapeutics Drug Discovery and Development*
Kevin Dalby, University of Texas

Moderator Dillon Fritz, GCC Research Evaluation and Commercialization Hub

12:25 **Rapid Fire Presentations, odd-numbered posters**
Expanding the IMiD-induced CRBN Degradome: Identifying Novel Neosubstrates of Molecular Glue Degraders Using Proximity-based Proteomics
Adebowale Alade, Baylor College of Medicine, Poster 1

Intratumoral biodegradable-Nanofluidic Platform for Localized Multimodal Immunotherapy Enhances Tumor Eradication and Immune Memory
Francesco Manfredi, Houston Methodist Research Institute, Poster 5

12:35 ***Lunch and* odd-numbered posters**-Event Hall
12:35-1:30 Lunch
1:30-2:30 Poster presentations, odd-numbered posters

Session 7 ***Innovative Medical Devices***
Moderator Jiaxin Feng, Texas A&M University

2:30 *Precision Medicine at 3 A.M.*
Onur Kilic, Bairitone Health

2:50 *Leveraging Wearable Devices to Monitor Disease Progression and Acute Events in Stroke Patients*
Sandra Saldana, Alva Health

3:10 Panel Discussion
Kevin Coker, MD Anderson Cancer Center
Abbas Dhilawala, Galendata
Mohammad Ghasemi Rad, Baylor College of Medicine
Gabrielle Guttman, TMC Venture Fund
Onur Kilic, Bairitone Health
Meagan Pitcher, Bairitone Health
Sandra Saldana, Alva Health

4:00 Closing Remarks

Michelle Arkin, PhD
Executive Director of the Small Molecule Discovery Center
University of California at San Francisco
The Fun of Academic Drug Discovery - Novel Targets, New Technologies

Michelle Arkin is a chemical biologist and Executive Director of the Small Molecule Discovery Center at UCSF. Her research focuses on developing methods and molecules that target currently 'undruggable proteins,' including protein-protein interactions and dynamic or intrinsically disordered proteins. For this work, in 2024 she received the ACS Cope Scholar Award and ACS/Biochemistry Gordon Hammes Lecturer Award. Michelle has been highly involved academic drug discovery community as past President of the Academic Drug Discovery Consortium, editor of the Assay Guidance Manual, member of the joint research committee for the Accelerating Therapeutics for Opportunities in Medicine (ATOM) consortium, and past director of the Society for Laboratory Automation and Screening. Prior to UCSF, Michelle was a founding scientist at Sunesis Pharmaceuticals, where she helped discover small molecule inhibitors of IL-2/IL-2R and LFA/ICAM (the anti-inflammatory drug lifitigrast, marketed by Novartis). She serves on the advisory boards for several pharmaceutical companies and is a co-founder of Elgia Therapeutics and co-founder and director of Ambagon Therapeutics.

Keynote presenter

Miguel Hernán, MD, MPH, ScM, DrPh
Professor, Harvard T.H Chan School of Public Health

Miguel Hernán is the Director of CAUSALab, the Kolokotrones Professor of Biostatistics and Epidemiology at the Harvard T.H. Chan School of Public Health, and faculty at the Harvard-MIT Division of Health Sciences and Technology. He and his collaborators repurpose real world data into evidence for the prevention and treatment of infectious diseases, cancer, cardiovascular disease, and mental illness. This work has contributed to shape health research methodology worldwide.

Miguel teaches causal inference methods to generate and analyze data for health policy and clinical decision making. At Harvard, he has mentored dozens of trainees. His free online course Causal Diagrams and book Causal Inference: What If, co-authored with James Robins, are widely used for the training of researchers.

Miguel has received several awards, including the Rousseeuw Prize for Statistics, the Rothman Epidemiology Prize, and a MERIT award from the U.S. National Institutes of Health. He is elected Fellow of the American Association for the Advancement of Science and the American Statistical Association, member of the Advisory Board of ADIA Lab, and Associate Editor of Annals of Internal Medicine. He was Special Government Employee of the U.S. Food and Drug Administration, Editor of Epidemiology, and Associate Editor of Biometrics, American Journal of Epidemiology, and Journal of the American Statistical Association.

Keynote presenter

Bissan Al-Lazikani, PhD, FRSB, FISCB, MBCS
Professor
Genomic Medicine, Division of Cancer Medicine
MD Anderson Cancer Center
New Therapeutic Strategies Panel

Dr. Al-Lazikani is a data scientist and drug discoverer. She applies data science and machine learning to address key challenges in cancer drug discovery and development. Dr. Al-Lazikani has drug discovery experience in both academia and the biotechnology industry. Through this experience, she encountered the myriad of hurdles faced through drug discovery and development pipelines. Dr Al-Lazikani's research focuses on bringing the power of Data and Artificial Intelligence to address these hurdles, accelerating drug discovery and de-risking innovation. Specifically, she applies data science approaches to integrate multi-disciplinary and multi-modal data to inform all aspects of cancer translational research; and to develop novel machine learning algorithms that learn from these integrated data. Together, her approaches inform decision-making and experimental design throughout the drug discovery and development pipeline. She led the development of the world's largest public cancer drug discovery platform (canSAR.ai) to inform target selection and prioritization for drug discovery. She now leads the Therapeutics Data Science Initiative at MD Anderson Cancer Center to maximally exploit data to discovery novel drugs and individualize drugs and drug combinations for patients.

Zhiqiang An, PhD
Vice President of Drug Discovery
University of Texas Health Science Center
Houston *GCC IDDD Core Network Showcase-*
Advanced Cancer Antibody Drug Modalities Core

Dr. Zhiqiang An is a professor and the Robert A. Welch Distinguished University Chair in Chemistry, director of the Texas Therapeutics Institute, and vice president of drug discovery at the University of Texas Health Science Center at Houston. His laboratory focuses on antibody drug discovery. During the last 10 years, he has advanced more than 10 innovative antibody-based therapies to preclinical and clinical development for diseases ranging from acute myeloid leukemia, cancer bone metastasis, solid tumor, spinal cord injury, fibrosis, and COVID-19. Previously, he served as Chief Scientific Officer at Epitomics, Inc., and was Director of Biologics Research at Merck. Dr. An is an elected fellow of the Society for Industrial Microbiology and Biotechnology (SIMB), the American Academy of Microbiology (ASM), the American Association for the Advancement of Science (AAAS), and the National Academy of Inventors (NAI). He received the 2024 Scientific Achievement Award in Drug Discovery and Development from the American Society for Pharmacology and Experimental Therapeutics (ASPET). Dr. An received his Ph.D. from the University of Kentucky and his postdoctoral training at the University of Wisconsin-Madison.

Cheryl Beal Anderson, PharmD, MBA
Founder & CEO
ACE Regulatory Affairs Consulting, LLC
New Therapeutic Strategies Panel

Dr. Cheryl Beal Anderson is the founder and CEO of ACE Regulatory Affairs Consulting and serves as a Fractional Chief Regulatory Officer. She partners with companies to streamline regulatory approvals and accelerate market access for programs in development. With over 25 years of experience, Anderson brings deep expertise in regulatory strategy, drug development, quality systems, and navigating global regulatory landscapes. Her therapeutic focus spans CNS, oncology, and rare diseases, gained through leadership roles at Parke-Davis, Pfizer, Eli Lilly, Lundbeck, and Upsher-Smith Laboratories. As former SVP & Global Head of Regulatory Affairs, Drug Safety, and Quality at Upsher-Smith, Anderson served on the CEO executive team while leading regulatory and quality functions. She supports biotech founders—especially first-time teams—with FDA meeting strategy, briefing documents, IND planning, expedited designation requests, and broader regulatory execution. She also advises seed-stage companies and consults with therapeutics accelerator programs in Houston. Anderson is a member of the Dean's Advisory Council at the University of Texas at Austin College of Pharmacy. She holds degrees from Texas A&M University (BS, Biomedical Science), UT Austin (BS, Pharmacy; Doctor of Pharmacy), and Saint Joseph's University (MBA, Pharmaceutical & Healthcare Marketing), with executive training from UVA, Simmons, and Michigan. A 2021 Women in Business honoree, Anderson is recognized for her collaborative, solution-focused leadership.

Chen-Ni Chin, PhD
VP of R&D
Rock BioTherapeutics
Fc Engineering to Enhance Antibody Functions

Chen-Ni has nearly 20 years' experiences in antibody drug discovery and engineering across different therapeutic areas. She has recently joined Rock BioTherapeutics in Boston as VP of R&D. Prior to RockBio, Chen-Ni was with IGM Biosciences where she worked on novel multivalent and multispecific antibody platforms for potential treatments for ant-infectious diseases and autoimmune diseases. At IGM, she has led multiple projects involving alliances with different organizations such as Gates foundation, Sanofi, Stanford University and Fred Hutch. In addition to antibody discovery and engineering, Chen-Ni also has extensive experience in exploratory target biology. One of such efforts has led to the development of a novel ADC XMT-1660 targeting B7H4, currently being developed to treat breast, ovarian and endometrial cancers by Mersana Therapeutics. Prior to entering the world of biotech business, Chen-Ni gained deep experience in drug discovery through roles at Merck and JnJ where she focused on building efficient organizations and training scientific personnel to establish in vivo and in vitro antibody discovery platforms and contributed to companies' therapeutic pipelines.

Chen-Ni earned her Bachelor of Science degree in Botany from the National Taiwan University, followed by a PhD in Biochemistry at the University of Connecticut. She completed postdoc fellowships at Yale University and Stockholm University in Biophysics.

Lynda Chin, MD
Founder-CEO
Apricity Health
Real World Evidence to Inform Preclinical Development Panel

Dr. Chin, a member of the National Academy of Medicine and Fellow of the Association of American Physicians, is a dermatologist scientist who helped catalyze modern cancer genomics. At Dana Farber Cancer Institute, Harvard Medical School, and the Broad Institute, she co-led the first TCGA project, pioneered its team science model, and built the open data platform that made TCGA a global resource. At MD Anderson, she founded the Department of Genomic Medicine and later served as the University of Texas System's first Chief Innovation Officer for Health. Today, as founder CEO of Apricity Health, Dr. Chin harnesses technology, AI, and real world patient data to deliver precision oncology at scale and accelerate therapeutic discovery, closing the loop between care delivery and drug discovery.

Kevin Dalby, PhD
Professor of Chemical Biology & Medicinal Chemistry
Johnson & Johnson Centennial Professor in Pharmacy
Research Service Core
University of Texas, Austin
Targeted Therapeutics Drug Discovery and Development

Dr. Dalby is the Johnson & Johnson Professor of Pharmacy at UT Austin. He is a distinguished chemist and a recognized expert in protein kinase biochemistry, signaling, and enzymology. He directs the Targeted Therapeutic Drug Discovery & Development Program (TTP). Dr. Dalby's current research is dedicated to developing novel covalent ERK inhibitors to target the ERK pathway, driven by RAS mutations. His work aims to characterize the chemical and allosteric mechanisms involved in this process. Additionally, Dr. Dalby investigates the dysregulation of translation elongation in chronic neurological conditions and various cancers. His studies focus on the phosphorylation of eEF2 on Thr-56, a crucial regulatory mechanism affecting protein synthesis. He has discovered novel regulatory mechanisms of eEF2K, an atypical protein kinase, and is working on therapeutic strategies targeting eEF2K for the treatment of neurodegenerative diseases and malignancies. Since 2011, Dr. Dalby has led TTP, providing specialized resources for cancer drug discovery to Texas institutions. TTP supports preclinical research, high-throughput screening, lead development, and target validation.

Siddhartha De, PhD
Vice President of R&D
7 Hills Pharma
Leveraging Clinical Data to Reimagine Novel Therapies for Stem Cell Transplant

Siddhartha De, Ph.D. is the Vice President of R&D at 7 Hills Pharma, a Houston-based clinical-stage drug development company advancing first-in-class integrin-targeted agonists designed to safely augment immunotherapies for cancer, stem cell transplantation, and infectious diseases. He has spent over two decades in drug discovery and development, advancing multiple drugs to the clinic for cancer, metabolic disorders, inflammation, CNS diseases, and pain. Additionally, he has extensive experience in project management and business development, representing out-licensing strategy, partnerships, and contract services. He is an avid photographer, having led photography workshops as far afield as the Himalayas and Iceland, and is currently finishing an MBA from Boston University.

Abbas Dhilawala, MSc
Co-Founder and CTO
Galen Data
Innovative Medical Devices Panel

Abbas is a Co-Founder and CTO of Galen Data, a software company providing compliant data management solution for medical device industry. Abbas has over 20 years' experience developing enterprise grade software for the medical device industry. He is well versed with technology and industry standards regulating security and privacy of data. His expertise lies in programming, cloud, cyber security, data storage and regulated medical device software.

Prior to Galen Data, Abbas worked as a Software Architect at Tietronix Software, where he led technical teams in creating medical device software that were successfully cleared for FDA Class I, II, and III and CE Marking.

Long Doan, PhD
Global Vice President and Head of Clinical Research
SpyGlass Pharma
How Early Data Can Help Determine Future Study Designs

Long Doan is the Global Vice President and Head of Clinical Research for SpyGlass Pharma. He designs and manages studies to try to get new drugs and Devices FDA approved. He has mainly worked in Ophthalmology, Dermatology, and in the Central Nervous System on mental illnesses like Depression, Bipolar Disorders, Parkinson's, and Alzheimer's. He has worked on big name products like Botox, Latisse, Restasis, Acular, Zymar, Zymaxid, and the Advair Diskus Inhaler, and various Ophthalmology, Dermatology, Oncology, and Respiratory therapies. Most recently Long led the clinical trials for iDose, an innovative micro drug delivery system that not only received FDA approval as a Drug/Device combination delivery system, but also ended up being nominated for the Prix Galien Award for Best Pharmaceutical Product in 2024. In his spare time, he works with youths from low socio-economic backgrounds to help motivate them to improve their lives (usually at the Jr HS and HS levels). He has been featured in magazines, print advertisements, and commercials for various universities and has done a public service announcement health education video for the LA unified school district. He also teaches Clinical Research to Pharmacy Students at USC, Loma Linda University and is a guest lecturer at UCI and Mt. Sac College.

Dillon Fritz, PhD
Entrepreneur-in-Residence
GCC Research Evaluation and Commercialization Hub
Innovative Methods for Identifying New Targets Panel

Dillon Fritz, PhD, is the Entrepreneur-in-Residence for the GCC-REACH Program. In this role, he will work closely with and provide comprehensive support for all GCC-REACH stakeholders and biomedical entrepreneurs to facilitate the translation of early-stage life science innovations into commercially successful products and companies. Dillon has spent the past 15 years working at the interface of academia - industry - entrepreneurship, including roles as Head of Bio Innovation at King Abdullah University of Science and Technology (KAUST), developing strategic research partnerships and early-stage innovation programs at Saudi Aramco, and most recently as co-founder and CEO at a clinical genomics company (NoorDx). Dillon is a molecular biochemist by training, receiving his PhD from the Florida State University College of Medicine. He continued his research training as a National Cancer Institute Postdoctoral Fellow at the H Lee Moffitt Cancer Center, focusing on the molecular mechanisms of cancer metastasis and development of genome-driven therapeutics.

Mohammad Ghasemi Rad, MD, PhD
Assistant Professor
Radiology
Interventional Radiology
Baylor College of Medicine
Medical Devices Panel

Dr. Mohammad Ghasemi Rad is a physician-scientist and innovator dedicated to advancing minimally invasive therapies and medical device development in interventional radiology. He earned his medical degree from Urmia University, completed a postdoctoral fellowship in bioengineering at MIT, and trained in Vascular and Interventional Radiology at Baylor College of Medicine and Massachusetts General Hospital, Harvard Medical School.

At Baylor College of Medicine, Dr. Ghasemi Rad serves as faculty in the Department of Minimally Invasive Vascular and Interventional Radiology. His research and clinical work focus on complex vascular and image-guided interventions. He is the inventor on several patents and actively mentors both medical and engineering trainees in translational research and device innovation. He leads multiple cutting-edge projects, including devices for portal hypertension (such as a peritoneovenous shunt and a novel TIPS access device), multifunctional balloon catheters, advanced embolic materials, and pneumothorax management device.

Matthew Gibson, JD, PhD
Counsel
Hogan Lovells
Innovative Methods for Identifying New Targets Panel
New Therapeutic Strategies Panel

Matt serves clients primarily in the life sciences industry focusing on development of therapeutic assets, mainly biologics such as antibodies, cell therapies, and gene therapies. Matt's practice is focused on intellectual property protection, patent counseling, diligence and the various business and research transactions that accompany drug development as well as IP licensing, joint development projects, strategic partnerships and M&A.

George Golovko, PhD
Assistant Professor
Pharmacology and Toxicology
University of Texas Medical Branch at Galveston
Session 2 Real World Evidence to Inform Preclinical Development Panel

Dr. George Golovko is an Assistant Professor in the Department of Pharmacology and Toxicology at the University of Texas Medical Branch (UTMB), specializing in bioinformatics, genomics, and computational biology. With over ten years of experience, Dr. Golovko is a recognized expert in leveraging Real World Evidence (RWE) derived from large-scale electronic health records (EHR), genomic data integration, and advanced statistical learning methods to support infectious disease research, vaccine surveillance, and clinical decision-making. His substantial contributions include developing and optimizing workflows for pathogen detection, multiomics analyses, and predictive modeling of disease progression and vaccine outcomes utilizing TriNetX and Epic Cosmos data platforms. Dr. Golovko has also led biomedical infrastructure projects, facilitated international research collaborations, and mentored the next generation of bioinformatics scientists.

Gabrielle Guttman, BSE, MBA
Business Strategy and Analytics Manager
Texas Medical Center
Medical Devices Panel

Gabrielle Guttman is the Business Strategy and Analytics Manager at TMC. In this role, she helps drive TMC's strategic projects, including the Center for Device Innovation, as well as being an active member of the TMC Venture Fund.

Prior to this, she worked at Johnson and Johnson Innovation as a Business Operations Manager at JLABS @ TMC in Houston, Texas. In that role, she managed the JLABS local site and ran global portfolio management. Gabrielle started at J&J in various operations roles across the pharmaceutical, medical device and consumer healthcare sectors through the Global Operations Leadership Development Program.

Gabrielle received a Bachelor of Science and Engineering in Chemical and Biomolecular Engineering from the University of Pennsylvania and an MBA from Rice University.

Zach Hightower, BS
Director of Business Development
Portal Innovations
Houston-Based Resources for Healthcare Innovation

Zach is the Director of Business Development at Portal Innovations, a role he has held since September 2024. With a focus on fostering the Portal ecosystem and supporting the venture team, he brings extensive experience in the life sciences industry, particularly within the Houston ecosystem. A 2014 graduate of Texas A&M University, Zach has held various business and sales roles, including a position in sales at Eppendorf, where he also managed part of the business development team. His expertise and network drive innovation and collaboration in the life sciences sector.

Aimee Iberg, PhD
Senior Director, Oncology Industrialized Drug Discovery
Recursion Pharmaceuticals
Discovery of Novel First-in-Class Medicines with a Suite of AI-Enabled Platform Technologies

Dr. Aimee Iberg has over 20 years of combined industry and academic experience in the biotech sector, specializing in epigenetics and cancer biology. Currently, she is a leader at Recursion, using systems biology approaches to transform drug discovery.

Aimee's educational journey began at The University of Texas at Austin, where she earned a B.S. in Chemical Engineering in 2004. She later obtained a Ph.D. in Molecular Carcinogenesis from The University of Texas Graduate School of Biomedical Sciences and MD Anderson in 2010. Her doctoral dissertation focused on discovering epigenetic regulatory molecules during a period of rapid advancement in understanding gene expression regulation by external environmental inputs. During her postdoctoral research at Harvard Medical School, Aimee worked to decipher epigenetic mechanisms controlling cellular fate, differentiation, and trans-differentiation.

In her current role at Recursion Pharmaceuticals, Aimee leads cross-functional teams and establishes workflows to rapidly validate and advance hit compounds. She also contributes as the Bio Lead on the multi-year Roche/Genentech oncology partnership.

Throughout her career, Aimee has demonstrated remarkable leadership in discovering new cancer treatment options.

Wissam Khalife, MD, FACC, MACC
Professor
Cardiology
University of Texas Medical Branch at Galveston
Clinical Trials and Registries: Driving Scientific Innovation and Medical Breakthroughs

Dr. Khalife attended medical school in Lebanon, attended an internal medicine residence at the University of South Dakota, received a cardiology fellowship at UTMB, and received a heart failure/transplant fellowship at Baylor College of Medicine/Texas Heart Institute.

He is board-certified in Internal Medicine, Cardiovascular disease, Heart Failure and transplantation, Echocardiography, and Nuclear Cardiology.

He is currently a professor of medicine at UTMB, in the cardiovascular medicine division, the section head of the heart failure program (since 2011), and the director of the cardiovascular fellowship program (since 2019). His current interests include invasive cardiology, invasive heart failure, and advanced heart failure.

Clinically, he has been practicing heart failure for the last 16 years as a faculty at UTMB with a very good local and regional reputation, resulting in multiple referrals from different areas.

He has received multiple awards, including the Super Doctors in Texas award for multiple consecutive years, as a testimony of clinical expertise and excellent patient care.

He has been part of multiple national and international clinical trials (total 15) with multiple ongoing clinical projects and has many publications (n=103) and presentations in national and international conferences (> 200 posters/oral presentations).

Onur Kilic, PhD
CTO
Bairitone Health
Precision Medicine at 3 A.M.

Onur Kilic is the co-founder and CTO of Bairitone Health, which redefines sleep apnea care with AI-guided therapy matching. His PhD work at Stanford focused on record-setting defense technologies and was featured in Popular Science. At Johns Hopkins Medical School, he developed breakthrough biomedical technologies that appeared on the cover of Nature BME. A serial inventor with 70+ issued patents, he previously co-founded Sidera Medicine, an oncology spin-out from Mayo Clinic and Yale.

Jeffrey Larson, PhD, DABT
Senior Vice President of Research & Development
Tvardi Therapeutics
When Humans Do Not Behave Like Lab Animals

Dr. Jeffrey Larson is an accomplished and experienced toxicologist who has worked for over 30 years in companies, both large and small. He graduated from Washington State University with a PhD in Pharmacology and Toxicology. Dr. Larson has held positions at numerous pharmaceutical companies, including large pharma (Rhone-Poulenc Rorer, now Sanofi Aventis), mid-size pharma (Allergan), and small startup pharma (NexBio, Aronex Pharmaceuticals). He has served as President and Vice President of numerous consulting firms and product development companies, such as Parady Consulting, Inc., Texas BioAlliance, Beta Cat Pharmaceuticals (now Iterion Therapeutics), and Salarius Pharmaceuticals. He is currently the Senior VP of R&D at Tvardi Therapeutics. His expertise in preclinical product development, including studies performed under Good Laboratory Practice conditions, such as acute to chronic toxicology studies, carcinogenicity studies, reproductive toxicology studies, and in vitro safety studies, has been invaluable to the companies and academic researchers with whom he works. In addition to preclinical efficacy model planning and execution, he also takes an active role in clinical study design focusing on clinical pharmacology and clinical biomarkers.

Elaine Lea-Chou, PhD
CEO, FounderCEO, Founder
ELC Private Consulting
Preclinical to Clinical: Observed Translational Differences Panel
Innovative Methods for Identifying New Targets Panel

Dr. Lea-Chou is a Silicon Valley-based Life Sciences and Biotech Consultant with a distinct mix of scientific, entrepreneurial, and communications expertise. She has a PhD in cancer signal transduction from UC San Diego and an MS in tumor metastasis from Northwestern's Lurie Cancer Center. Dr. Lea-Chou has worked in settings ranging from industry, academia, and the private sector, and specializes in assessing technology, and business development in the interest of creating and nurturing vibrant partnerships. She has consulted with numerous startups and companies located across the US in Texas, Biotech Bay, Biotech Beach, Genetown, and BioCapital. Her focus is currently directed on cancer therapeutics and diagnostics. In the last 5 years, Dr. Lea-Chou has advised 40+ companies contemplating a CPRIT Product Development Award, and has successfully won $75+M in non-dilutive funding for 9 companies, including the inaugural New Technology Category award that went to CTMC, a pioneering joint biotech venture between MD Anderson Cancer Center and Resilience.

Dong Liang, PhD
Professor and Interim Associate Dean for Research
College of Pharmacy and Health Sciences Texas Southern University
GCC IDDD Core Network Showcase-GCC Center for Comprehensive PK/PD and Formulation

Dr. Dong Liang is Professor and Interim Associate Dean for Research in the College of Pharmacy and Health Sciences at Texas Southern University (TSU). He received his BS and MS from Zhejiang University, and PhD from the University of Houston. Dr. Liang has expertise and experience in preclinical and clinical Phase I pharmacokinetic and drug development studies. He serves as Program Director of NIH funded Center for Biomedical and Health Research Excellent at TSU. He is Co-Director of the CPRIT funded GCC Center for Comprehensive PK/PD and Formulation, providing support in preclinical dosage formulation and PK/PD studies. He was formerly a clinical pharmacokineticist at Mylan Pharmaceuticals Inc.

Megan Liles, MS
VP, Clinical Delivery
HGI Clinical
Houston-Based Resources for Healthcare Innovation

Megan Liles is a clinical research industry veteran with over 25 years of experience on global clinical trials across a range of therapeutic areas. She began her career as a Research Coordinator at Wayne State University, working with patients living with HIV/AIDS—an experience that sparked her lifelong commitment to improving patient access to innovative treatments.

Throughout her career, Megan has held strategic roles across both sponsor and CRO settings—including Clinical Program Manager, Director of Project Management, and Head of Clinical Operations —where she developed a strong foundation in building and managing cross-functional teams and partnerships. For the last 10 years, Megan has focused primarily in the early phase oncology space with deep expertise in the conduct of biomarker-driven and cell therapy trials.

In her role at HGI Clinical, Megan oversees the Clinical Operations department and advises biotechs on trial execution and vendor oversight to provide fit for purpose vendor solutions as well as conducting gap assessments and optimizing governance structures to ensure alignment, quality and accountability across all study stakeholders.

Qingyun (Jim) Liu, PhD
Professor and Director, IMM-Center for Translational Cancer Research
University of Texas Health Science Center, Houston
GCC IDDD Core Network Showcase-Preclinical Development Core for Large Molecules

Dr. Liu's research has primarily been focused on the identification and characterization of function and signaling mechanism of novel receptors and enzymes for the discovery and development of therapeutics in the area of cancer and immunology. His current research is to continue to investigate the roles and mechanism of RSPO/LGR ligand-receptor system in normal and cancer development with the ultimate goal of validating them as potential drug targets and discovering therapeutic leads. In addition, he is the director of a core facility called "A Preclinical Development Core for Large Molecule Therapeutics" at UTHealth-Houston that is funded by the Cancer Prevention and Institute of Texas (CPRIT). The core's capabilities include detailed pharmacokinetics and toxicology studies of protein drug candidates in rodents and monkeys with complete blood analysis and tissue histopathology report.

David Maxwell, PhD
Principal Data Scientist
CanSAR platform/MD Anderson Cancer Center
Houston-Based Resources for Healthcare Innovation

Dr. Maxwell is an expert in molecular modeling and data analysis, with nearly 30 years of Industrial and Academic post-graduate experience in the pharmaceutical and healthcare areas. Skilled in communicating technical findings to researchers and clinicians, and summarizing key aspects for the layperson. Currently, he works as a Data Scientist/Data Engineer in the healthcare industry.

Jennifer Maynard, PhD
Professor
Z. D. Bonner Professorship of Chemical Engineering
University of Texas at Austin
GCC IDDD Core Network Showcase-Advanced Protein Therapeutics

Dr. Jennifer Maynard is the ZD Bonner Professor of Chemical Engineering. Her research focuses on the development of protein therapeutics to address unmet medical needs, with a specific interests in development of antibodies with selective activity in the solid tumor micro-environment. She co-invented the approved inhalation anthrax drug ANTHIM® (olbitoxaximab), antibody cocktails for the prevention or treatment of pertussis (whooping cough) which received orphan drug designation, vaccine candidates for pertussis and COVID-19 that are in clinical testing. Maynard is a cofounder of Texas Biologics, established in 2021 to promote the discovery and development of biologics at UT Austin. In 2022 Maynard established and currently leads the Advanced Protein Therapeutics Core Facility funded the Cancer Prevention and Research Institute of Texas (CPRIT).

Stanton F. McHardy, PhD, FNAI
Professor
Director, Center For Innovative Drug Discovery
Department of Chemistry
University of Texas San Antonio
New Strategies for Small Molecule Development

Dr. Stan McHardy is the Director of the Center for Innovative Drug Discovery, and Professor and Assistant Chair in the Department of Chemistry at the University of Texas San Antonio (UTSA). Dr. McHardy has over 28 years' experience in the pharmaceutical R&D and academic areas of drug discovery, including >16 years of pharmaceutical industry experience from Pfizer Global Research and Development and Southwest Research Institute. After receiving his Ph.D. in organic chemistry, followed by a post-doctoral study at the University of Utah in 1996, he started his career at Pfizer Global Research in the Neuroscience drug discovery group, where he led research teams in the development of novel small molecules for CNS disorders such as addiction, schizophrenia and ADHD. Dr. McHardy became a leader in the CNS group at Pfizer and helped discover and develop several small molecule drug candidates that advanced into multiple phase II clinical trials. After a family move returned him to his home state of Texas, Dr. McHardy was recruited by UTSA to build a collaborative, state-of-the-art drug discovery research center called the Center for Innovative Drug Discovery (CIDD), a joint research center between UTSA and UT Health San Antonio. As the original Director of the CIDD since 2012, Dr. McHardy established, expanded and maintained this state-recognized drug discovery research center and core discovery facilities on the campuses of UTSA and UT Health SA, and developed numerous state and national research collaborations with both academic and private industry partners, securing over $24 million in collaborative extramural funding to date. In his current academic role, he holds adjoining positions as an Adjunct Professor in the Department of Microbiology, Immunology and Molecular Genetics, and the Department of Pharmacology at UT Health San Antonio (UTHSA). Demonstrating a profound spirit of innovation, he has proven himself to be an exemplary leader, greatly dedicated to advancing and improving the health and well-being of society while also brilliantly devoting himself to mentoring rising STEM scholars. He embodies the core values of UTSA, leading his research with integrity, inclusiveness, excellence, respect, collaboration, and innovation. Due to his extensive patent and research accomplishments, in 2024 he received the honor of being inducted as a Fellow into the National Academy of Inventors.

Currently, the private, state, and federally funded collaborative research programs in Dr. McHardy's CIDD labs at UTSA are focused on various small molecule drug

discovery approaches to cancer, psychotherapeutic and neurodegenerative diseases, non-opioid pain and infectious diseases. Dr. McHardy is an author or co-author on 59 peer reviewed publications in synthesis, medicinal chemistry and drug discovery and is inventor or co-inventor on 42 patents.

Deepak Nijhawan, MD, PhD
Professor and Vice-Chair and Joseph P Sambrook Distinguished Chair in Biomedical Science
University of Texas Southwestern
Phenotypic Drug Discovery Revisited

Dr. Deepak Nijhawan is a physician-scientist who has challenged the generally accepted paradigm for drug discovery which is to start with a well-defined drug target and then to use a variety of biochemical, structural, and pharmacological tools to develop new therapeutics. His laboratory has undertaken the opposite approach by starting with molecules that have well established anti-tumor effects and using forward genetics/chemical proteomics/and classical biochemistry to elucidate their mechanism of action. He has pinpointed the molecular targets for multiple small molecules which have led to new strategies for cancer therapeutics. In 2024, Dr. Nijhawan fused his program with Jef De Brabander in the newly formed Section in Molecular Medicine in the Department of Radiation Oncology at UT Southwestern Medical Center. Deepak Nijhawan is currently Professor and Vice-Chair and Joseph P Sambrook Distinguished Chair in Biomedical Science.

Meagan Pitcher, PhD
CEO & Co-Founder
Bairitone Health
Medical Devices Panel

Meagan Pitcher is the co-founder and CEO of Bairitone Health, which brings advanced imaging diagnostics into the home environment. Meagan worked on several neurology and ophthalmology projects at Lexicon Pharmaceuticals and managed a diverse intellectual property portfolio as a Baylor College of Medicine technology transfer officer. She holds a Ph.D. in translational biology and molecular medicine from Baylor College of Medicine and a B.S. in genetics from Texas A&M University.

Reid T. Powell, PhD

Research Assistant Professor at the Texas A&M Institute of Bioscience and Technology

Preclinical to Clinical: Observed Translational Differences Panel

Innovative Methods for Identifying New Targets Panel

Dr. Reid T. Powell is a Research Assistant Professor at the Texas A&M Institute of Bioscience and Technology, situated in the TMC3 Collaborative Research Building. He holds a Ph.D. in Medical Science from Texas A&M Health Science Center and a B.S. in Biochemistry from Texas Tech University. His interdisciplinary career sits at the intersection of cancer biology, high-throughput screening, and AI-driven drug discovery. Trained as a biochemist and computational biologist, Dr. Powell specializes in the development of scalable discovery platforms that integrate phenotypic screening, pharmacogenomics, cheminformatics, and machine learning. He serves as the lead data scientist for two Cancer Prevention and Research Institute of Texas (CPRIT)-funded core facilities—the Combinatorial Drug Discovery Program (CDDP) and the High-throughput Flow Cytometry Program (HtFCP)—where he has architected analytical pipelines for real-time, high-dimensional assay interpretation and compound prioritization. His translational work has directly contributed to multiple preclinical programs targeting chemoresistance in triple-negative breast cancer (TNBC) and novel therapeutic vulnerabilities across a variety of solid tumors.

Beyond experimental screening, Dr. Powell's current research expands into virtual screening, AI-enabled generative drug design, and predictive modeling to accelerate therapeutic lead identification. He has led or contributed to multi-institutional initiatives spanning drug repurposing, structure-activity relationship (SAR) modeling, and the design of AI/ML pipelines for phenotypic and molecular datasets. His work has appeared in Cell, Nature Communications, NPJ Breast Cancer, Scientific Reports, and Clinical Cancer Research.

Dr. Powell is a member of the Innovative Drug Discovery and Development (IDDD) Steering Committee and actively works to promote the integration of computation, automation, and biology to redefine early-stage drug discovery frameworks.

Allison Rhines, PhD
Head
Johnson & Johnson Innovation, JLABS TMC
Houston-Based Resources for Healthcare Innovation

As Head of Johnson & Johnson Innovation – JLABS TMC, Dr. Rhines leads the JLABS TMC team in incubating and growing the JLABS community of companies, as well as in enabling strategic partnerships between JLABS companies and the broader ecosystem.

Prior to this role, Dr. Rhines served as Early Innovation Partnering Lead for Infectious Disease, Vaccines, and Global Public Health within Johnson & Johnson Innovation, based in the San Francisco Innovation Center. She re-joined J&J in this role from the Gates Foundation's early innovation organization, now known as the Gates Biotech Accelerator. There, she managed the Foundation's SARS-CoV-2 transmission biology portfolio at the onset of the pandemic, followed by diverse biopharma investments in early-stage platform technologies. Prior to joining the Gates Foundation, Dr. Rhines held various venture-backed startup operating responsibilities.

Dr. Rhines completed her postdoctoral fellowship within Johnson & Johnson's Global Public Health group. She holds her PhD in Biology with a mathematical and computational focus, as well as her BA, from Stanford University. She holds her MBA from INSEAD and her MPhil from the University of Cambridge.

Jennifer Roohi, BBA
ACT Program Manager
Innovation at Texas Medical Center
Houston-Based Resources for Healthcare Innovation

Jennifer is the Program Manager for the TMCi Accelerator for Cancer Therapeutics, funded by the Cancer Prevention and Research Institute of Texas (CPRIT) and launched in collaboration with the Gulf Coast Consortia (GCC) and the University of Texas Medical Branch (UTMB) to support Texas-based biotech entrepreneurs and researchers contemplating translations alongside institutional technology transfer teams. Jennifer comes to TMCi as a solutions-driven general manager with 13 years of multi-industry experience leading operational initiatives, developing high-producing teams, and driving results through engagement and collaboration.

Before joining TMCi, Jennifer worked in business development for a recruiting firm. She established a new market position on the west side of Houston and orchestrated many networking and marketing events to build brand awareness. Before that, Jennifer worked for several prestigious brands in the retail industry, spanning over 11 years. She was in the direct-to-consumer space, working in general manager roles, leading operations, and merchandising with buying and planning teams, opening new brand locations, and directing special projects. Jennifer brings vast experience centered around process refinement, organizational development to benefit multiple stakeholders, people development, and optimization of workflows.

Jennifer is passionate about her professional growth and delivering meaningful work. She is thrilled to have found a role that combines her passions and, most importantly, where the Texas healthcare community directly benefits. Jennifer holds a double bachelor's degree in finance and marketing from the University of Houston.

Sandra Saldana, PhD, MBA
CEO & Co-Founder
Alva Health
Leveraging Wearable Devices to Monitor Disease Progression and Acute Events in Stroke Patients

Dr. Sandra Saldana is the CEO and Co-Founder of Alva Health, a medical device company and Yale University spinout that is developing a wearable device for real-time stroke detection. Dr. Saldana is a scientist by training with a mission to improve human health through the development, application, and commercialization of innovative technologies. She is responsible for planning and execution of the company's strategy and vision, fundraising and day-to-day operations, and has served as Principal Investigator on multiple innovative SBIR grants funded by the National Science Foundation and National Institutes of Health. During her tenure at Alva Health, the company developed a novel AI/ML-enabled wearable medical device, conducted proof-of-concept clinical research studies, and engaged the FDA in preparation for submission of the company's first product. Dr. Saldana has led Alva Health through several elite business accelerators and secured funding from top venture capital investors, including Techstars, the Cedars Sinai Accelerator, and the American Heart Association's emPOWERED to Serve business accelerator. In 2021, Dr. Saldana was named the Grand Prize winner of $350,000 out of over 1100 global applicants in the MedTech Innovator competition, the largest global accelerator for medical device startups. Before founding Alva Health, Dr. Saldana was Vice President of sales and account management at Brand Institute's Boston office, the top branding agency in the pharmaceutical and medical device industries. In her role, she advised pharma, biotech and med device executives on strategic branding, marketing and communications initiatives, while being responsible for territory sales growth. Dr. Saldana completed a BA in Biological Sciences at Cornell University, a PhD in Cancer Biology at the University of Texas MD Anderson Cancer Center, and an MBA in Healthcare Management at the Yale School of Management.

Supriya Sinha, PhD
Entrepreneur in Residence
TMC Innovation
GCC IDDD Core Network Showcase

Passionate about catalyzing innovation in cancer therapeutics and empowering early-stage startups, Supriya Sinha, Ph.D., now serves as an Entrepreneur in Residence (EIR) at TMC. With a dynamic background spanning technology transfer, venture capital, and biotech entrepreneurship, Supriya brings expertise in translating scientific discoveries into tangible patient and commercial benefits. Formerly serving as the Assistant Director of Commercialization Relations at UT Southwestern Medical Center, Supriya played a pivotal role in expanding commercialization opportunities and fostering strategic partnerships to nurture the biotech ecosystem in North Texas. With prior experience at Bios Partners, Supriya honed her expertise in biotech and life science investing, contributing to significant advancements in innovative technologies aimed at positively impacting patients' lives. Now, in her role at TMC, Supriya is committed to supporting and promoting the acceleration of novel cancer therapeutics, providing invaluable mentorship and strategic guidance to participating companies. Supriya holds a Ph.D. in Molecular Medicine from the University of Texas Health Science Center at San Antonio.

Clifford Stephan, PhD
Research Associate Professor
Translational Medical
Texas A&M College of Medicine
Core Network Showcase-GCC Drug Discovery Resource Center

Clifford Stephan, Ph.D. is a Research Associate Professor in the Department of Translational Medical Sciences at the Texas A&M College of Medicine. He is the Director of the Texas A&M Microphysiological Lead Optimization and Toxicity Screening (MLOTS) ‘ program and Scientific Director of the Texas A&M Drug Discovery and Development Resource Center (3DRC). MLOTS is a CPRIT funded (RP210108) ‘Fail Early’ in vitro toxicity and efficacy drug testing resource center specifically created to support new drug and new drug discovery to enhance drug portfolio enhancement , support new drug combination discovery prior to in vivo testing, and for supporting Go/No Go decision making for lead optimization selection and prioritization. MLOTS provides resources to test drug and drug cocktail efficacy in complex in vitro models and toxicity profiling for cardio-, neuro-, and hepato-toxicity. The 3DRC program combines the drug discovery and repurposing resources of two additional CPRIT-funded core facilities supporting combinatorial drug discovery and repurposing for translational research, automated and high throughput imaging and flow cytometry for phenotypic drug discovery in 2D, 3D, and cellular therapeutics models, traditional high throughput screening supporting target-based drug discovery, and an x-ray generator for radiosensitizer and radioprotectant research. The 3DRC also has a full Design-Make-Test-Analyze program for small molecule and peptide creation supporting new probe discovery research driven by its data science program and in-house synthetic capabilities. Dr. Stephan holds a Ph.D. in Pharmacology from Vanderbilt University and has been involved in drug discovery and repurposing in the pharmaceutical industry at Encysive Pharmaceuticals and in academic research at the University of Texas Health Science Center in Houston.

Lacey Tezino, MHA
Program Manager
GCC Research Evaluation and Commercialization Hub
Houston-Based Resources for Healthcare Innovation

Lacey Tezino is a Program Manager for the Gulf Coast Consortia's REACH program, where she supports early-stage biomedical innovators in advancing drug discovery and development efforts toward commercialization. With a background spanning mental health innovation, clinical research operations, and technology implementation, she brings a unique blend of scientific, operational, and strategic expertise to accelerating breakthrough therapies. Lacey collaborates closely with academic researchers, startups, and industry partners to help bridge the gap between laboratory discoveries and real-world solutions. Her work is driven by a passion for improving health outcomes through innovation, collaboration, and translation of cutting-edge research into impact.

Suzanne Tomlinson-Mathis, PhD, MBA
Director, Research Programs and Strategic Initiatives
Gulf Coast Consortia for Quantitative Biomedical Science
Executive Director, GCC Research Evaluation and Commercialization Hub
GCC IDDD Core Network Showcase

Dr. Suzanne Tomlinson-Mathis, PhD, MBA is a seasoned leader in drug development with over two decades of experience advancing innovative treatments for critical health challenges. Her scientific expertise encompasses diverse therapeutic areas, including antivirals targeting dengue and West Nile virus protease, oncology agents focused on treating colon and triple-negative breast cancer, and neurotherapeutic programs involving treatments for substance use disorder and neuroinflammation. Beyond her scientific contributions, Dr. Tomlinson-Mathis possesses extensive experience in biotech startup operations, strategic financing, and regulatory planning.

As Executive Director of the Gulf Coast Consortium (GCC) Research Evaluation and Commercialization Hub (GCC REACH), Dr. Tomlinson-Mathis plays a pivotal role in mentoring early-stage investigators in translating high-impact biomedical innovations into commercially viable products. She has spearheaded the development of numerous transformative programs, including the Accelerator for Cancer Therapeutics—the first therapeutics accelerator in Houston—the Cancer Therapeutics Training Program (CTTP), and the GCC Center for Comprehensive PK/PD and Formulation. Additionally, she directs the AAMC award-winning GCC Rigor and Reproducibility in Research Program, underscoring her commitment to research excellence and scientific integrity.

Dr. Tomlinson-Mathis also leads the GCC Innovative Drug Discovery and Development (IDDD) program, supporting a network of specialized core facilities in medicinal chemistry, PK/PD analysis, formulation, and toxicology among others. Her efforts have been instrumental in securing millions in funding to support these translational initiatives. Under her guidance, the GCC has expanded its collaborative research programs to include areas such as Mental Health, Antimicrobial Resistance, Pain, Immunology, Single Cell and Spatial Omics, Integrative Development, Regeneration and Repair, and Cellular and Molecular Biophysics. Emerging initiatives under her leadership focus on Aging and Geroscience, Neuroinflammation, and Rare Disease Research, reflecting her dedication to addressing complex biomedical challenges through interdisciplinary collaboration.

Atul Varadhachary, PhD
Managing Partner
Fannin Innovations
Houston-Based Resources for Healthcare Innovation

Dr. Atul Varadhachary is Managing Partner at Fannin, a leading early-stage life sciences development group, with multiple programs and spinouts at various stages of development ranging from discovery to commercial.

Atul previously served as President & COO of Agennix, Inc., where he helped advance the company's lead molecule from preclinical studies to pivotal Phase 3 trials and facilitated its sale. His career also includes roles as President of U.S. Operations at Reliance Life Sciences, and as a management consultant at McKinsey & Co.

Atul has held Adjunct Professor appointments at Rice University, the Baylor College of Medicine and the University Texas. His current company board memberships include, Allterum, Brevitest, Goldenrod, Pulmotect, Radiomer and RDG. He has also served on non-profit boards including BioHouston, Harris Health System, and Every Texan, and as President at TiE Houston, the Indo-American Chamber of Commerce of Greater Houston (IACCGH), and Pratham USA. Organizations where he has held an advisory roles including ACS, BIO, CPRIT, GHP, MDACC, Rice, TCH, UH and UT.

Atul received his medical training at the University of Bombay and holds a Ph.D. in Physiology from the Johns Hopkins School of Medicine, where he was also a postdoctoral fellow in Biological Chemistry.

Jeffrey L. Wade, JD
Chairman
BioHouston
Houston-Based Resources for Healthcare Innovation

Jeff Wade is the chairman of the board of BioHouston and an experienced, innovative and entrepreneurial biopharma executive with expertise in setting strategic direction, raising capital, and leveraging strategic partnerships to drive competitive advantage and growth. He served in a range of senior leadership roles at Lexicon Pharmaceuticals (Nasdaq: LXRX), most recently as president and chief operating officer, taking the company from start-up through commercialization of two internally-discovered drugs with a strong pipeline. During his tenure at Lexicon, he was responsible for securing over $1B in equity capital; establishing high-value strategic alliances with industry leaders including Bristol-Myers Squibb, Sanofi and Genentech; overseeing key product launches, bringing Xermelo (telotristat ethyl) and Inpefa (sotagliflozin) to market; and building the company's therapeutic portfolio.

Before joining Lexicon, Mr. Wade was a partner with the law firm of Andrews & Kurth, where his practice consisted primarily of corporate finance and securities transactions, mergers and acquisitions, and partnerships and alliances. In addition to BioHouston, he is a member of the board of directors of the Texas Healthcare and Bioscience Institute. Mr. Wade received his B.A. (Plan II) and J.D. from The University of Texas.

Lightning Poster Talk Presenters
in order of presentation

Day one
Even-numbered posters

Digital Spatial Profiling Identifies Novel Targets in Patients with Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension
Phoebe Andrew, University of Texas Health Science Center
Poster 6

Investigating the Role of SSRIs' as a Potential Therapeutic for Neurodegenerative Diseases
Olivia Reed, Rice University
Poster 4

Two-Pronged Precision: Evaluating a Novel Dual-Targeting Antibody-Drug-Conjugate Based Therapy to Combat Colorectal Cancer
Shraddha Subramanian, MD Anderson Cancer Center
Poster 2

Day two
Odd-numbered posters

Expanding the IMiD-induced CRBN Degradome: Identifying Novel Neosubstrates of Molecular Glue Degraders Using Proximity-based Proteomics
Adebowale Alade, Baylor College of Medicine
Poster 1

Intratumoral biodegradable-Nanofluidic Platform for Localized Multimodal Immunotherapy Enhances Tumor Eradication and Immune Memory
Francesco Manfredi, Houston Methodist Research Institute
Poster 5

Poster Presenters
In alphabetical order

Even posters white, day 1
Odd posters gray, day 2

Presenter First Name	Presenter Last Name	Presenter Institution	Title of Submission	Poster number
Edidiong	Abraham	Texas Southern University	Development and Validation of an LC-MS/MS Assay for the Quantification of Andrographolide in Rat Plasma and Tissues.	7
Tristan	Adamson	Southwest Research Institute	Research and Development of Oxime OPNA Antidotes	8
Tolulope	Adebuusyi	Texas Southern University	Development and Validation of a reliable LC-MS/MS Method for SLP-1A6	9
Stella	Adeyemo	Texas Southern University	Production Optimization, Stability, Molecular Weight Characterization and Protein Quantification of Bacteriocins from Weissella Paramesenteroides Using Bradford Assay and SDS-PAGE	10
Zamal	Ahmed	MD Anderson Cancer Center	Novel GRB2 Inhibitors to Expose DNA Replication-Repair Venerability of Cancer Cells for Immune Destruction	11
Adebowale	Alade	Baylor College of Medicine	Expanding the IMiD-induced CRBN Degradome: Identifying Novel Neosubstrates of Molecular Glue Degraders Using Proximity-based Proteomics	1
Mohanad	Albayyaa	University of Texas Medical Branch at Galveston	Patterns of Care in Prostate Cancer: Investigating Androgen Deprivation Therapy (ADT) Treatment Trends	74
Phoebe	Andrew	University of Texas Health Science Center at Houston	Digital Spatial Profiling Identifies Novel Targets in Patients with Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension	6
Eric	Asare	Texas Southern University	Development and Validation of a Novel LC-MS/MS Method for the Simultaneous Quantification of Alvocidib and its Glucuronide: Application to Pharmacokinetic and Tissue Distribution Study in Rats	13
Ashwaq	Bahkali	Texas Southern University	Synthesis and Characterization of Ethylenediamine Platinum(II) Complexes Containing Thiourea Derivatives	14
Kiara	Baldridge	Texas Southern University	Human vs. Robot: A Comparison of Manual Sample Preparation to Automated Andrew+ Pipetting Robot	15
Shinjini	Basu	University of Houston	Liver X Receptor Ligand Disrupts Proliferative Signaling in Luminal A Breast Cancer	16
Cara	Biddle	University of Texas Health Science Center at Houston	The Promise of Multi-targeted ADC Therapy in Colorectal Cancer: Epiregulin and Amphiregulin	17
Michael	Bolt	Baylor College of Medicine	A Phenotypic Screen Identifies Xanthohumol and Other Flavonoids as Killers of Bladder Cancer	18

Poster Presenters
In alphabetical order

Even posters white, day 1
Odd posters gray, day 2

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Sherlene	Brown	University of Texas Medical Branch at Galveston	Developing Novel Allosteric Integrin a3 Targeting Antibodies for Podocyte-Specific Delivery of Nanoparticles for Treatment of Proteinuric Kidney Disease	19
Charmeyce	Buck	Texas Southern University	Pomegranate Extract Mitigated MMF-Induced Diarrhea	20
Joseph	Cave	Houston Methodist Research Institute	Machine Learning-Based Rational Design of Inorganic Engineered Nanoparticles for Improved Safety in Biomedical Applications	21
Luis	Cervantes	MD Anderson Cancer Center	Extending the Alchemical Transfer Method (AToM) to Predict Intrinsic Aqueous Solubility During Lead Optimization	22
Jingjing	Chen	Baylor College of Medicine	Repaid Discovery of a Novel Acetylation Targeting Chimera (AceTAC) for Acetylation of P53 Via High-throughput Direct-To-Biology (DTB) Platform	23
Yuan	Chen	Texas Southern University	Formulation of Tunable PLGA/PEG Nanoparticles for Drug IV Delivery: Correlation Between Drug Solubility and Encapsulation Efficiency	24
Chih-Wei	Chu	MD Anderson Cancer Center	Mapping the Determinants of TCR Recognition in HER2-mutant NSCLC	25
Megan	Daneman	Rice University	Investigating Novel Small Molecules for Selective Cytotoxicity Against Acute Myeloid Leukemia	26
Basudeb	Das	University of Texas Health Science Center at Houston	Targeting Breast Cancer-Specific Enhancer RNA1-BCOE1 Inhibits Breast Cancer Progression	27
Ting	Du	Texas Southern University	Absolute Quantification of Rat Uridine-Diphosphate-Glucuronosyl Transferase Isoforms using LC-MS/MS	28
Shalom	Emmanuel	Texas Southern University	Clay Attenuates Fat-Induced Diarrhea via Fat Adsorption and Bile Acid Modulation in Mice	29
Yuanyuan	Fan	University of Texas Health Science Center at Houston	Blockade CHI3L1 Enhances Hepatocellular Carcinoma Response to Anti-PD1 Antibody	30
Jiaxin	Feng	Texas A&M University	On-tissue Spatial Profiling with Quantitative Mass Spectrometry Discovers Isomeric Lipid Alternations in Patient-derived orthotopic Medulloblastoma Mouse Models	31
Ayobami	Fidelix	University of Texas Health Science Center at Houston	In Silico Design of Novel Artocarpus Altilis Derived Compounds Targeting the c-Myc/Max Heterodimer	32
Megan	Fisher	University of Texas Health Science Center at Houston	Decoding p53(R249S)-Mutated Liver Cancer: From Developmental Origins to Targeted Therapies	33

Poster Presenters
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Even posters white, day 1
Odd posters gray, day 2

Presenter First Name	Presenter Last Name	Presenter Institution	Title of Submission	Poster number
Nana	Goode	University of Texas Medical Branch	Novel Protein Interactor of Voltage-Gated Sodium Channel 1.6 Modulates Medium Spiny Neurons Excitability: Impact on Neuropsychiatric Disorders Drug Discovery	3
Yin Yuen	Ha	University of Texas Health Science Center at Houston	A Glycine-based Tripeptide Linker for Maximizing the Therapeutic Index of Antibody–Drug Conjugates	35
Brinley	Harrington	University of Texas Medical Branch at Galveston	Characterization and Development of Human Cell Line-Derived Extracellular Vesicles Loaded with IL-10 to Mitigate Inflammation at the Fetal-Maternal Interface	36
Helen	Hernandez	KAL Research Initiatives	Accelerating Discovery in a Rare Neurodevelopmental Disorder: The Power of Patient-Driven Research in FAM177A1 Deficiency	37
Peyton	High	University of Texas Health Science Center at Houston	Evaluation of EGFR and LGR5 Dual-Targeting Therapeutic Strategies for the Improved Treatment of Colorectal Cancer	38
Mo-Fan (Elena)	Huang	University of Texas Health Science Center at Houston	Dissecting 3D Chromatin Dynamics in Li-Fraumeni Syndrome	39
Michelle	Kameda-Smith	Baylor College of Medicine and Texas Children's Hospital	Immunologically Targeting U1 Mutant Shh Medulloblastoma	40
Yuepeng	Ke	Institute of Biosciences and Technology, Texas A&M University	Development and Preclinical Evaluation of Novel CAR-T Cell Therapy for Prostate Cancer	41
Uffaf	Khan	Texas A&M University Institute of Biosciences and Technology	A Novel, Pleiotropic Nanozyme for Targeting Mitochondrial Deficits in Rare and Ultra Diseases exemplified by Friedreich’s Ataxia	42
Tahir	Khuroo	Texas A&M University	3D Printed Tablets of Dual Anti-HIV Drugs: A Step Toward Dose-Flexible Pediatric Therapy	43
Tetiana	Kolodiazhna	University of Houston	Development of Selective CDK5 Inhibitor for the Treatment of Idiopathic Pulmonary Hypertension.	44
Neo Judith	Lemme	Baylor College of Medicine	Expression and Production of Malaria CSP(Circumsporozoite) Recombinant Protein as a Vaccine Candidate in Pichia pastoris	45
Hanfeng	Lin	Baylor College of Medicine	COOKIE-Pro: Covalent Inhibitor Binding Kinetics Profiling on the Proteome Scale	12
Rulong	Ma	University of Houston	The Tilting Motion of the Central Core Reveals the Transport Mechanism of the Sarco/endoplasmic Reticulum Ca2+-ATPase	46

Poster Presenters
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Even posters white, day 1
Odd posters gray, day 2

Presenter First Name	Presenter Last Name	Presenter Institution	Title of Submission	Poster number
Francesco	Manfredi	Houston Methodist Research Institute	Biodegradable Nanofluidic Drug-Eluting Seed for Durable Intratumoral Drug Delivery and Potent Immune Activation	47
Francesco	Manfredi	Houston Methodist Research Institute	Intratumoral Biodegradable-Nanofluidic Platform for Localized Multimodal Immunotherapy Enhances Tumor Eradication and Immune Memory	5
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Poster 7

Development and Validation of an LC-MS/MS Assay for the Quantification of Andrographolide in Rat Plasma and Tissues.

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Introduction: Andrographolide is a natural compound with anti-inflammatory, antioxidant, and anti-viral properties. It is being used in the treatment of lung cancer, pneumonia and other pulmonary infections. The focus of this study is to develop LC-MS/MS method for the quantification of this drug in plasma and pulmonary tissue after inhalation of a spray-dried formulation targeting the rat airway. Similarly, it will be used to determine the Pharmacokinetic (pk) parameters of andrographolide after inhalation drug delivery, as there is no current publication leading to the choice of a wide range of concentration for its quantification. **Purpose**: The aim of this study is to develop and validate an accurate, sensitive, and robust assay method for the quantification of Andrographolide in rat plasma and pulmonary tissue using a liquid chromatography-tandem mass spectrometry (LC-MS/MS). **Methods**: The assay was performed using a SCIEX 4000 QTRAP® LC-MS/MS System and an AQUITY UPLC BEH C_{18} column (2.1 × 50 mm, 1.7 µm particle size) based on a gradient elution with mobile phases consisting of water as mobile phase A and Methanol as mobile phase B. Andrographolide (*m/z* 348.9 → 331.2; 348.9 → 287.2) and ibuprofen (Internal Standard, IS) (*m/z* 205 → 160.9) were by electrospray ionization (ESI) using multiple reaction monitoring (MRM) in a negative mode. Andrographolide concentration was in the range of 5-2500 ng/mL. Similarly, tissue homogenate from the lung tissue will be extracted and purified. The purified lung tissue homogenate will be spiked with the working solutions of different concentrations of andrographolide and internal standard in methanol to obtain a calibration curve to be used for the quantification of pulmonary delivered andrographolide. **Results and Conclusion**: The method is linear in the range of 5-2500 ng/ml in rat plasma. The LLOQ of the method is 5ng/ml in rat plasma. Andrographolide and ibuprofen have retention times of 2.01 and 3.25 min respectively. The LC-MS/MS method will be validated in accordance with FDA guidelines. Validation parameters of linearity, accuracy, precision, extraction recovery, matrix effects, and stability of the spiked analyte at different conditions (benchtop, processed, freeze-thaw, and long-term) will be determined. Further, the method will be applied to study the pharmacokinetics of andrographolide in a spray-dried formulation for pulmonary delivery in terms of its bioavailability.

Acknowledgement: This study was funded in part by the Cancer Prevention & Research Institute of Texas (CPRIT) Core Facilities Support Awards RP240430 (Liang) and the NIH/NIMHD grant U54MD007605 (Xie, Liang).

Poster 8

Research and Development of Oxime OPNA Antidotes

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Organophosphorus nerve agents (OPNA), used as chemical weapons and pesticides, cause an estimated 300,000 deaths per year worldwide. Mechanistically, the OPNA phosphorylates Serine-203 in the catalytic triad of acetylcholinesterase (AChE) which impairs neurotransmission. Mild exposure typically results in blurry vision, eye ache and runny nose which progresses to nausea, vomiting, and abdominal cramps upon moderate exposure and finally arrhythmias, loss of consciousness and death upon severe exposure. Oxime compounds have been shown to reactivate AChE, restoring normal enzyme function. Currently, the bis-pyridinium oximes HLo-7 dimethanesulfonate (DMS) (1), HI-6 DMS (2) and obidoxime DMS (3) are among the most effective reactivators of OPNA inhibited acetylcholinesterase (AChE) (Figure 1).

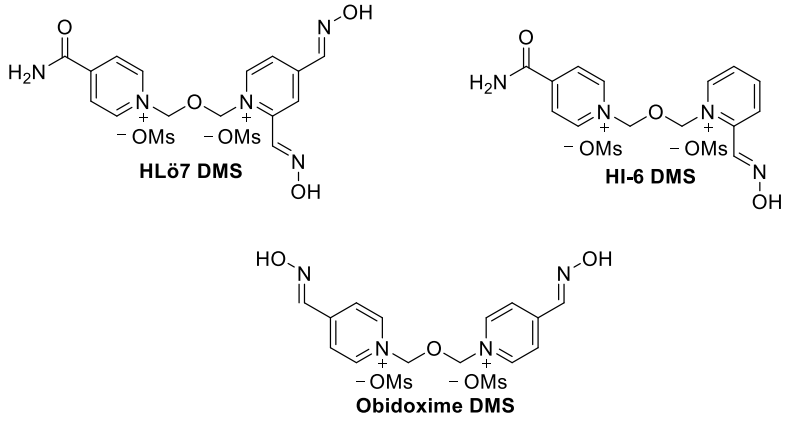

Figure 1: Leading Oxime Candidates for Organophosphorus Nerve Agent Antidotes

Despite a robust need, their preparation on scale has been hindered by the need for bis(2-chloromethyl) ether (BCME) which is one of 13 OSHA-regulated carcinogenic compounds, with an exposure limit of 0.0003 ppm. Other alkylating agents such as bis(2-methylsulfonoxymethyl) ether (BMME) have been investigated as alternatives, but their chemical instability and arduous synthesis precludes their use on scale. In this work, we demonstrate a new synthetic route based on a bench stable, non-toxic alkylating agent that has enabled multigram synthesis of bis-pyridinium oximes on multigram scale under CGMP.

Acknowledgements: This work was funded by Southwest Research Institute internal R&D projects 01-R8806 and 01-R8991.

Poster 9

Development and Validation of a reliable LC-MS/MS Method for SLP-1A6

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Prostate cancer (PCa) is a prevalent cancer in men that can progress to metastatic castration-resistant prostate cancer (mCRPC), leading to treatment challenges. While docetaxel chemotherapy can temporarily improve survival, many patients develop resistance. Recent studies reveal that the embryonic ectoderm development (EED) protein contributes to chemoresistance through interactions with enhancer of zeste homolog 2 (EZH2). Targeting EED may improve treatment outcomes and offer new drug development opportunities. SLP-1A6 is an analog of Nicardipine, a specific and potent inhibitor of chemoresistant PCa cells, and it also reduces tumor-associated bone growth in mouse models. Additionally, SLP-1A6 has demonstrated a nanomolar IC50 value of 3.08 nM in representative resistant cell lines. Herein, we developed and validated a highly sensitive and specific liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for quantifying SLP-1A6 in rat plasma to aid in its development as an anticancer drug. This method employs a Shimadzu LC-30AD system and a SCIEX API 4000 triple-quadrupole mass spectrometer. We utilized a protein precipitation approach with methanol, achieving high recovery rates while minimizing matrix interference. The linear dose response for quantification demonstrated the required precision and accuracy in rat plasma over 5-1000 ng/mL. Preliminary stability assessments under experimental conditions, including freeze-thaw cycles, stock solution, and long and short-term storage, confirmed the method's reliability. This validated LC/MS assay was used to quantify SLP-1A6 accurately in a pharmacokinetic study of Sprague-Dawley rats. The method's robustness and scalability make it a versatile tool for future pharmacokinetic and toxicokinetic evaluations.

Acknowledgments: This study was funded in part by the Cancer Prevention & Research Institute of Texas (CPRIT) Core Facilities Support Awards (RP240430) and the NIH/NIMHD grant U54MD007605. This study also acknowledges National Cancer Institute grants R01CA256058 and R42CA217491

Poster 10

Production Optimization, Stability, Molecular Weight Characterization, and Protein Quantification of Bacteriocins from *Weissella paramesenteroides* Using Bradford Assay and SDS-Page.

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Abstract

Bacteriocins are antimicrobial peptides synthesized by ribosomes, holding significant potential for food preservation. Bacteriocins from Weissella genus including *Weissella paramesenteriodes* have shown potential as biopreservative due to their antimicrobial properties against food borne pathogen and have been reported to be safe due to the absence of virulence factors. This study produced, determined stability at different conditions, molecular weight, and protein concentration of bacteriocin from *Weissella paramesenteroides* (BCN MT2). Optimization of culture parameters for bacteriocin production was done by subjecting the LAB to different carbon and nitrogen sources, incubation time, pH, temperature and bulk production was done using standard methods. The molecular weight and protein concentration of the bacteriocin were determined using SDS-PAGE and Bradford assay. The stability of BCN MT2 was determined at various temperatures, pH, metal ion concentrations, NaCl concentrations, and ethanol concentrations. Optimization results showed maltose and casein as best carbon and nitrogen source against *E.coli* (25 mm and 21 mm respectively), 37 ^{o}C incubation temperature and 6.5 pH as the best against *E.coli* (23 mm and 19 mm respectively). The stability result showed BCN MT2 to have enhanced activities when combined with metal ions $ZnSO_4$ and $MnSO_4$, at pH 6 and 8, temperature up to 100 ^{o}C, 4 % to 8 % NaCl concentration and ethanol concentration between 4 to 10 %. The result of the molecular weight and protein concentration showed that BCN MT2 is class II bacteriocin (9.29 kDa, 1.00mg/ml respectively). This study concludes that bacteriocin derived from *Weissella paramesenteroides* may serve as a natural food preservative and can be incorporated into active packaging materials for enhanced food safety during storage.

KEYWORDS: Bacteriocin, Bio preservation, Molecular weight, Protein concentration, Stability.

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Poster 11

Novel GRB2 Inhibitors to Expose DNA Replication-Repair Venerability of Cancer Cells for Immune Destruction

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Gross DNA damage and synthetic lethality limiting DNA repair in cancer cells are proven treatment strategies. The value of precisely targeting of DNA repair machines based on patient genetic mutational venerability has been realized by discovery of PARP inhibitor (PARPi) and its synthetic lethal relationship with BRCA genes. PARPi revolutionized cancer medicine and their value is underscored by the many new clinical trials directed against DNA damage response (DDR) proteins. We discovered a previously unsuspected key role for growth factor receptor binder 2 (GRB2) at the interface of DNA replication and DNA damage response pathways. We showed that nuclear GRB2 (nGRB2) roles are functionally separable from its canonical function in RAS signaling. In homology-directed repair (HDR), nGRB2 forms a functional GRB2-MRE11 complex for ample and timely MRE11 recruitment to DNA damaged sites marked by phosphorylated H2AX [1]. nGRB2 is thus critical for efficient error-free repair of DNA double-stranded breaks (DSBs) and for cellular resistance to PARPi. As such, PARPi sensitivity in most cells can be attained by GRB2 depletion. At stalled DNA replication forks (RFs), GRB2 binds and inhibits RAD51 ATPase activity, which stabilizes RFs to prevent their degradation [2]. This protects cancer cells from oncogenic replication stress and innate immunity: GRB2-RAD51 reduces release of DNA from broken RFs to the cytoplasm. Thus, at stalled RFs GRB2 blocks activation of cGAS/STING and the secretion of pro-inflammatory cytokines and chemo-attractants that together would promote cancer cell immune destruction. We previously determined that GRB2 adapter protein exists in an equilibrium between active monomer and auto-inhibited dimer [3]. Here, we identified, tested, and are optimizing small molecule GRB2 inhibitors (GRB2i) that act by stabilizing GRB2 dimers. Guided by experimental and computational structural biochemistry, we designed and synthesized >400 focused compounds. We identified GRB232 as lead GRB2i suitable for cell-biological and pre-clinical animal evaluation. Our data provided biomarkers for determining GRB2i efficacy and revealed GRB2i primarily impacts DNA damage and replication stress functions. Our multi-disciplinary methods from chemistry to cells to animals show: 1) GRB2i can be a standalone inhibitor or act in combination with other agents for precision molecular medicine targeting DDR; and 2) GRB2i can chemically generate HDR-deficiency to overcome PARPi resistance and to activate cancer immune surveillance. Thus, our work establishes a framework for GRB2i mono and/or combination therapy to unmask cancer cells for immune destruction.

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Poster 1

Expanding the IMiD-induced CRBN Degradome: Identifying Novel Neosubstrates of Molecular Glue Degraders Using Proximity-based Proteomics

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Molecular glue degraders are a class of small molecules that harness the cellular protein degradation machinery to eliminate disease-relevant proteins. These molecules induce interactions between E3 ubiquitin ligases and neosubstrates—proteins that would not normally be targeted—resulting in ubiquitination and subsequent degradation of the neosubstrates. Immunomodulatory imide drugs (IMiDs) are a well-established class of CRBN-binding molecular glues that recruit neosubstrates to CRBN for degradation. For instance, CC-885 induces CRBN-dependent degradation of GSPT1, exhibiting potent anti-leukemic activity. Beyond GSPT1, CDK4 and PLK1 have also been identified as CC-885 neosubstrates, implicating its broader antitumor potential in multiple myeloma and non-small-cell lung cancer. However, the full spectrum of IMiD-induced CRBN neosubstrates remains incompletely defined, underscoring the need for systematic discovery approaches.

To address this, we employed proximity labeling (TurboID) and proximity ubiquitination (BioE3) technologies to systematically map the IMiD-induced CRBN degradome and uncover novel neosubstrates. TurboID biotinylates CRBN-proximal proteins, whereas BioE3 selectively biotinylates CRBN-recruited ubiquitinated proteins upon IMiD treatment. As proof of concept, we applied TurboID- and BioE3-CRBN in HEK293T cells treated with CC-885 and observed a dose-dependent enrichment of GSPT1, validating our approach. Further BioE3-CRBN pulldown-mass spectrometry analysis identified a four-fold enrichment of GSPT1, reinforcing the method's sensitivity. Strikingly, we also observed a comparable enrichment of the 37kDa laminin receptor (LAMR/RPSA), a protein overexpressed in metastatic cancer, suggesting it as a previously unidentified CC-885 neosubstrate. Structural analysis revealed that LAMR harbors a G-loop degron motif similar to that of GSPT1, providing a mechanistic basis for its potential recruitment to CRBN.

These findings suggest that CC-885-induced CRBN degradome may extend beyond known targets, inducing the ubiquitination of LAMR, a previously unidentified neosubstrate. Our studies highlight the utility of proximity-based proteomic approaches in molecular glue neosubstrate discovery. Expanding the IMiD-induced CRBN degradome not only enhances our understanding of molecular glue mechanisms but also opens new avenues for the development of novel targeted protein degradation therapies. Future studies will investigate whether CC-885 can induce LAMR degradation to suppress metastatic potential in cancer models, further exploring its therapeutic relevance.

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Poster 74

Patterns of Care in Prostate Cancer: Investigating Androgen Deprivation Therapy (ADT) Treatment Trends

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Prostate cancer is the second leading cause of cancer death among men, with most diagnoses occurring at localized stages. Standard treatment options include radiation, androgen deprivation therapy (ADT), surgery, or conservative treatment. ADT, a mainstay therapy for advanced prostate cancer, can be administered medically via GnRH agonists, antagonists, antiandrogens, or surgically through orchiectomy. This study aims to assess patterns of care in men diagnosed with prostate cancer, focusing on the trends in ADT use, whether as primary or adjuvant therapy. We identified a cohort of 548,635 men aged ≥66 years diagnosed with prostate cancer between 2010 and 2019. The primary outcome was the proportion of men receiving at least one dose of ADT within 6 months of diagnosis. ADT initiation was examined per calendar year, stratified by age, race, stage, and treatment type. Multivariable logistic regression analysis was conducted, adjusting for patient demographics and cancer characteristics. Among men diagnosed with prostate cancer, 30.64% were aged 71-75, 79.33% were non-Hispanic White, and 64.25% were diagnosed at stage Ⅱ. ADT use was significantly associated with patient characteristics, including age, race, marital status, region, and comorbidity index. There was a notable increase in the use of GnRH agonists (31.92%), with gradual increases in GnRH antagonists (10.3%) and antiandrogens (11.8%) ($P < 0.001$). Our analyses showed an increase in the proportion of GnRH agonists and antiandrogens, followed by a gradual rise in the use of GnRH antagonists between 2010-2019. These observations align with established epidemiological trends, providing valuable insights into the sociodemographic and clinical determinants of prostate cancer patients. This study underscores the widespread adoption of ADT in clinical practice, with a noteworthy number of patients commencing treatment within 6 months of diagnosis. Therefore, clinicians should carefully consider the patterns of care and discuss the necessity for personalized treatment strategies.

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Poster 6

Digital Spatial Profiling Identifies Novel Targets in Patients with Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension.

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Background: Idiopathic Pulmonary Fibrosis (IPF) is a fatal lung disease characterized by fibrosis, leading to restrictive lung disease and impaired gas exchange. A common and fatal complication of IPF is Pulmonary Hypertension (PH), affecting 32-50% of IPF patients. PH results from increased pulmonary vascular resistance and pressure, causing eventually right-sided heart failure. The presence of PH in IPF greatly increases mortality. Current treatments, including Treprostinil, Pirfenidone, and Nintedanib, don't target the vascular remodelling central to PH, thus, understanding the mechanisms behind vascular remodelling is critical for developing new treatments.
Hypothesis: We hypothesize that gene expression in lung tissue differs between control, IPF, and IPF+PH patients, and digital spatial profiling will uncover novel transcriptomic differences between groups that could be exploited pharmacologically to target vascular remodelling.
Methods: Using spatial transcriptomics, we compared gene expression in lung vessels from control, IPF, and IPF+PH patients, and validated with qPCR and immunohistochemistry. We used spatial transcriptomics to reveal differences in the parenchyma, and confirmed this in vivo using RNA Polymerase 1 inhibitor CX-5461 to treat a chronic bleomycin induced pulmonary fibrosis murine model.
Results: We identified genes altered in the vasculature of IPF and IPF+PH lungs, revealing novel changes in gene expression. In IPF, downregulated genes included aquaporin 7 (AQP7) and FOS proto-oncogene (FOS), suggesting altered vascular processes like cell proliferation and apoptosis. In IPF+PH patients, we observed upregulation of metastasis-associated 1 family member 2 (MTA2) and serpin family E member 1 (SERPINE1), highlighting changes in RNA regulation, including mRNA deadenylation and transcriptional control, when PH is comorbid with IPF. Spatial transcriptomics revealed both upregulation and downregulation of ribosomal pathway genes in the parenchymal regions of IPF lungs, compared to IPF+PH. These genes, including translation initiation proteins and those involved in 40S and 60S ribosomal subunit synthesis, were notably affected. Treatment with CX-5461 in mice with bleomycin-induced pulmonary fibrosis improved lung mechanics, reducing whole lung elastance and resistance as measured with Flexivent, along with a decrease in right ventricular systolic pressure (RVSP), a key marker of PH. Our findings highlight novel targets for addressing vascular remodeling in both IPF and PH, suggesting ribosomal dysfunction plays a central role in PH development in IPF patients
Conclusion: Spatial transcriptomics accurately identifies novel targets specific to disease progression in IPF and IPF+PH. This helps us better understand localized gene expression and tissue heterogeneity in a spatial context to reduce target validation times in the drug discovery pipeline, hastening development of new therapeutic options.

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Poster 13

Development and Validation of a Novel LC-MS/MS Method for the Simultaneous Quantification of Alvocidib and its Glucuronide: Application to Pharmacokinetic and Tissue Distribution Study in Rats.

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Abstract:

Alvocidib (Flavopiridol) is a potent cyclin-dependent kinase (CDK) 9 inhibitor which has been approved for the treatment of acute myeloid leukemia (AML). Clinical studies have shown the occurrence of diarrhea in poor glucuronidators of Alvocidib. This has also been linked to a lower incidence of diarrhea in patients who are extensive glucuronidators. The purpose of this study is to develop a robust and sensitive LC-MS/MS method to simultaneously quantify Alvocidib and its metabolite, Alvocidib glucuronide and apply this method in a pharmacokinetic (PK) and tissue distribution study in rats to accurately quantify the levels of the parent compound, alvocidib and its metabolite (Alvo-G).

A Shimadzu UHPLC system coupled to an AB Sciex QTrap 4000 triple quadrupole mass spectrometer was used for the analysis. The rat plasma and tissue samples were processed using an organic-based protein precipitation method. The analytes were separated using an Ultra Biphenyl 5 µm column (50 × 2.1 mm) with 0.1% formic acid in water (A) and acetonitrile (B) as the mobile phases. They were then quantified under positive electrospray ionization (ESI) mode and a multiple reaction monitoring (MRM) approach.

The method showed a good linearity within the range of 2.4nM – 5000.00 nM for both analytes exhibiting correlation coefficient values, R> 0.99. The method was reproducible, with intra and inter-day accuracy and precision ranging from 84-98% and <13%, respectively, for all analytes in rat plasma. The extraction recovery and matrix effect of rat plasma using acetonitrile (100% v/v) achieved acceptable ranges (82-105%). Stability studies carried out on the analytes in plasma demonstrated that they were stable under bench-top (91-99%), freeze-thaw (83-110%), and long-term storage conditions (80-106%). This validated method was successfully applied to quantify Alvocidib and Alvocidib Glucuronide in rats. The PK results showed that after oral administration of alvocidib, both alvocidib and its glucuronide were detected in plasma, with the parent drug showing the highest disposition in the colon and lowest in the small intestine. In contrast, the glucuronide showed the highest disposition in the small intestine and the least amount in the colon as compared to the other tissues. This study established a robust and sensitive LC-MS/MS method for the simultaneous quantification of alvocidib and its metabolite, Alvo-G, and successfully applied it to pharmacokinetic and tissue distribution studies in rats.

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Poster 14

Synthesis and Characterization of Ethylenediamine Platinum(II) Complexes Containing Thiourea Derivatives.

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This study focuses on the synthesis and characterization of platinum(II) ethylenediamine complexes with thiourea-like ligands, targeting the development of improved anticancer drugs. Cancer remains a global health concern, and platinum-based drugs, particularly cisplatin, have played a key role in cancer treatment for decades. However, the limitations of cisplatin, such as severe side effects and low water solubility, have led researchers to explore new platinum-based compounds with better efficacy and reduced toxicity. This work synthesized and characterized 15 novel platinum(II) complexes. These complexes follow the general formula $[Pt(en)L_2](NO_3)_2$, where "en" represents ethylenediamine and "L" is thiourea or one of its derivatives, such as 1-benzyl-2-thiourea, 1-cyclohexyl-2-thiourea, and others. The complexes were synthesized via a reaction involving $[Pt(en)(H_2O)_2](NO_3)_2$, produced in situ by treating $Pt(en)I_2$ with silver nitrate and adding two equivalents of the desired thiourea derivative. Characterization was performed using elemental analysis, IR spectrometry, and NMR spectroscopy. Additionally, the crystal structures of five of these complexes were determined using single-crystal X-ray diffraction, revealing the monoclinic and orthorhombic space groups of the compounds. These new platinum(II) complexes are water-soluble, a crucial feature for potential therapeutic applications, making them promising candidates for further investigation in the development of more effective anticancer treatments.

Poster 15

Human vs Robot: Comparison of Manual Sample Preparation to Automation via Andrew+ Pipetting Robot

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Manual pipetting techniques can vary depending on the individual, leading to inconsistencies that reduce accuracy and extend experimental time. The Andrew+ pipetting robot by Waters Corporation, located at three Houston sites, including Texas Southern University, aims to deliver high accuracy and consistent results. Protocols for Andrew+ can be customized to accommodate the specifics of the sample being prepared and can execute a range of protocols such as serial dilutions, biological sample handling and solid phase extraction. This automation also enables hands-free experimentation, providing researchers with more flexibility for other tasks.

In the Biopharmaceutics/ Pharmacokinetics and nanotechnology laboratories, automation via Andrew+ is being used for sample preparation for analytical method validation for the novel compound PC257. Using the OneLab software, protocols can be created to direct Andrew+ through specific steps of the desired experiment. It is expected to outperform human performance in terms of accuracy, precision, and linearity during a standard curve protocol.

Triplicate serial dilutions were prepared manually by individuals with varying pipetting experience (novice, intermediate). These serial dilutions were then compared to a set of serial dilutions prepared via Andrew+, with the goal of achieving an ideal R^2 value of 0.999 in all standard curves. Manual Pipettor One (P1) had a mean R^2 value of 0.9978 ± 0.00704. Manual Pipettor Two (P2) produced a mean R^2 value of 0.9991 ± 0.0012. Andrew+ produced a mean R^2 value of 0.9997 ± 0.0002.

Consideration for human error is still a factor in implementing automation protocol design. This was observed in instances with automated serail dilutions produced an R^2 value less than 0.999. Upon this observation, protocols were reviewed and considerations such as input value, preparation order pipetting speed, liquid viscosity and repetitive pipetting increased accuracy and precision. While a high R^2 value has been attained by manual pipetting, Andrew+ can reduce the margin of error in multi-step processes and decrease the amount of time spent pipetting, ultimately easing laborious validation processes and allowing confidence in consistent results.

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Poster 16

Liver X Receptor Ligand Disrupts Proliferative Signaling in Luminal A Breast Cancer

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Abstract

Estrogen receptor α (ERα) is the primary oncogenic driver in ER+ breast cancer. Endocrine therapy (e.g., tamoxifen) can disrupt ER-dependent tumorigenic signaling and is commonly utilized as first-line treatment. However, endocrine resistance in patients remains a critical concern. This necessitates further investigation into alternative therapeutic approaches. Liver X receptors (LXRs) are nuclear receptors and ligand-dependent transcription factors that are involved in lipid metabolism and cholesterol homeostasis. LXR is linked with metabolic reprogramming and is frequently upregulated in cancer. Thus, targeting LXR with ligands could serve as a potential avenue for therapeutics. In the pursuit of developing cancer-specific LXR ligands, our lab conducted a focused library screening of putative LXR ligands in pancreatic cancer cells. The novel ligand GAC0001E5 (1E5) exhibited potent antiproliferative effects in pancreatic cancer and breast cancer. We observed that 1E5 functions as an inverse agonist, recruiting corepressors to downregulate LXR and LXR target gene expression. Since ERα drives tumorigenesis in ER-positive breast cancer, we hypothesized that the antiproliferative properties of 1E5 may be due to disruption of ER signaling. To test this hypothesis, we conducted protein and gene expression studies of estrogen receptor upon 1E5 treatment. Our studies revealed that 1E5 treatment led to significant downregulation of ESR1 gene and ERα protein, as well as reduced expression of ER-target genes. The development of endocrine resistance is complex, and other receptors like androgen receptor (AR) and human epidermal growth factor receptor 2 (HER2) have been implicated as potential contributors. AR and HER2 are known to be upregulated in endocrine-resistant breast cancer. Here, we show that 1E5 treatment results in downregulation of both. These results exhibit regulation of ER, AR, and HER2 through LXR ligands, thereby suggesting molecular crosstalk between these mechanisms. Thus, our results highlight the potential utility of targeting LXR for endocrine resistance in breast cancer.

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Poster 17

The Promise of Multi-targeted ADC Therapy in Colorectal Cancer: Epiregulin and Amphiregulin.

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Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States with a 14% five-year survival rate when metastasized. Current treatment options for metastatic CRC (mCRC) can be limited by toxic side effects and drug resistance, so new targeted therapies are necessary to improve mCRC patient outcomes. Antibody-drug-conjugates (ADCs) act as guided missiles where a monoclonal antibody (mAb) conjugated to cytotoxic payloads binds its tumor-specific target, internalizes, and traffics to lysosomes for payload release, inducing tumor cell death while sparing normal tissues. Previous studies and our analyses of RNA-seq expression data from The Cancer Genome Atlas (TCGA) colorectal adenocarcinoma cohort show that the epidermal growth factor receptor (EGFR) ligand epiregulin (EREG) is frequently overexpressed in CRC tumors compared to normal tissues. Thus, we developed EREG-targeted ADCs that reduced CRC patient-derived xenograft tumor growth, yet regrowth was observed after treatment termination. Importantly, ADC efficacy depends, in part, on tumor cell-surface levels of the target antigen. Our TCGA analyses and previous studies show EGFR ligand amphiregulin (AREG) is often co-overexpressed with EREG in CRC patients. Therefore, we hypothesize that co-targeting EREG and AREG will enhance ADC efficacy by increasing the number of target antigens for ADC binding and internalization. We have cloned and purified human AREG-targeted mAbs to develop an AREG-targeted ADC as well as generated AREG overexpression cell lines for mAb characterization. Our preliminary data demonstrate AREG mAb specificity and binding, which promotes internalization and lysosomal trafficking in CRC cells. These data suggest AREG to be a suitable ADC target, and future work will test whether co-targeting EREG and AREG provides additional therapeutic benefit.

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Poster 18

A Phenotypic Screen Identifies Xanthohumol and Other Flavonoids as Killers of Bladder Cancer

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Bladder cancer accounts for 4% of cancer diagnoses in the US. Current treatments primarily involve trans-urethral resection of bladder tumors (TURBT) and immunotherapy with Bacille Calmette-Guerin (BCG). Despite the efficacy of TURBT, issues with residual tumors persist. We chose to utilize Cell Painting to screen a set of 244 flavonoid compounds for bladder cancer cell toxicity. Using multiparametric high content analysis termed SPACe, we discover promising candidates underscoring the potential of flavonoids in targeting bladder cancer cells and elucidating their mechanisms of action. Notably, compounds such as xanthohumol show promise in reducing cancer cell viability by altering lipid metabolism. We further show the effectiveness of hit compounds in subsequent spheroid and chorioallantoic membrane systems. Overall, this research emphasizes the role of innovative screening methods in drug discovery and potential synergistic effects of combining flavonoids with existing therapies like BCG for improved bladder cancer treatment outcomes.

Acknowledgements

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Poster 19

Developing Novel Allosteric Integrin a3 Targeting Antibodies for Podocyte-Specific Delivery of Nanoparticles for Treatment of Proteinuric Kidney Disease

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Podocytes are specialized epithelial cells that surround the glomerular capillaries, forming foot processes (FPs) that are vital for maintaining the structural integrity and proper function of the kidney. Focal segmental glomerulosclerosis (FSGS) is a leading cause of chronic kidney disease (CKD) and a primary glomerular disorder that often progresses to end-stage renal disease (ESRD). In the United States, it contributes to 7–20% of idiopathic nephrotic syndrome cases in children and around 40% in adults. FSGS is characterized by podocyte damage, resulting in foot process effacement, loss of the slit diaphragm, and the onset of proteinuria. Integrin α3β1, the most abundant integrin in the kidney, is crucial for maintaining podocyte integrity. Loss of the α3 subunit or associated protein CD151 disrupts podocyte adhesion, leading to detachment and severe proteinuria. In children with homozygous deletion or missense mutations, a3 integrin plays a pivotal role in the development of FSGS, driving glomerular damage and disease progression. Despite advances in understanding FSGS, effective targeted therapies remain limited. Current treatments, primarily glucocorticoids, have significant side effects and limited efficacy. To address this, we are developing antibody-conjugated lipid nanoparticles (ALNPs) designed to selectively target podocytes and deliver therapeutic agents via podocyte expressed integrin α3β1, offering a promising approach for improving treatment outcomes in FSGS.

Using a naive human phage display library, conformation-based screening and cell–based high–throughput screening assays, we developed novel allosteric agonist antibodies targeting integrin α3β1. These allosteric agonist antibodies exhibit high binding to α3β1 on podocytes *in vitro* and in human and mouse tissues. They selectively target active conformation of α3β1. Our ongoing studies are exploring conjugation strategies and antibody formats (scFvs vs full antibodies) targeting α3β1 to determine their suitability for LNP functionalization and targeted delivery in FSGS treatment. Our findings underscore the potential of α3β1 activation as a precise therapeutic strategy to effectively target glomerular dysfunction and proteinuric diseases.

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Poster 20

Pomegranate Extract Mitigated MMF-Induced Diarrhea

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Purpose: Mycophenolate mofetil (MMF) is a widely used immunosuppressant in organ transplantation and autoimmune diseases. However, its clinical utility is often limited by gastrointestinal (GI) toxicity, particularly diarrhea, which compromises patient adherence and therapeutic efficacy. *Punica granatum* (pomegranate) contains bioactive polyphenols, flavonoids, and tannins with known anti-inflammatory and mucosal-protective properties. This study investigates whether *P. granatum* components can mitigate MMF-induced GI toxicity in a rat model. **Methods:** Female Wistar rats were used in this study to establish the MMF-induced diarrhea model and to determine the anti-diarrhea efficacy of pomegranate. MMF was administered to rats for 5 consecutive days to induce diarrhea. Pomegranate extract was continuously administered starting from day 0 to day 9, after stopping MMF dosing on day 7 to determine diarrhea prevention efficacy. Body weight and fecal conditions were monitored to determine the diarrhea severity and antidiarrhea efficacy. Different doses of MMF and pomegranate extract were tested. Additionally, the quality of the pomegranate extract was evaluated by UPLC analysis. **Results:** MMF administration caused mild diarrhea starting from Day 5 and in 40 % of the control group, significantly reduced body weight, and increased diarrhea incidence, with severe cases observed. In the control group, which was dosed with oral gavage vehicle, 90 % of the rats experienced severe diarrhea (grade > 3). In the pomegranate treated group, 80% experienced severe diarrhea on day 8. However, continuous co-administration of *P. granatum* extract in the treatment group improved stool consistency to 100% and preserved body weight. The dosing level of *P. granatum* extract plays an important role in preventing diarrhea. **Conclusion:** This study has successfully developed an MMF-induced diarrhea in a healthy rat model. Our findings suggest that *P. granatum* components effectively mitigated MMF-induced diarrhea, likely through anti-inflammatory and antioxidant mechanisms that preserve intestinal integrity. This study highlights a potential adjunctive strategy to enhance MMF tolerability in patients requiring long-term immunosuppressive therapy.

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Poster 21

Machine Learning-Based Rational Design of Inorganic Engineered Nanoparticles for Improved Safety in Biomedical Applications

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Though engineered nanoparticles (NPs) show promise for targeted drug delivery, their clinical use remains limited, primarily due to nano-bio interactions in systemic circulation. These interactions lead to unintended NP capture by the mononuclear phagocytic system, causing off-target toxicity and reduced delivery to intended tissues. NP physicochemical properties modulate nano-bio interactions; thus, effective nanomedicine delivery requires rational NP design for improved safety. To this end, we present an experimentally validated ML-based binary classifier to predict organ-specific toxicity *in vitro* and *in vivo* based on NP design and experimental factors. To guide rational design, explainability analysis is used to elucidate critical parameters influencing toxicity.

Through rigorous meta-analysis, an extensive *in vitro* toxicity dataset was curated, standardized, and split 80/20 to train and validate 22 binary classification models (linear, clustering, and tree-based), where 10-fold nested cross-validation optimized hyperparameters and ensured generalizability. The top five performing models were selected for explainability analysis via SHapley Additive exPlanations (SHAP) and Partial Dependence Plots (PDPs) to quantify structure-toxicity relationships. SHAP-ranked features guided *in vivo* dataset attribute selection, which was enhanced with a seven-compartment PBPK model to quantify average organ exposure up to the time when toxicity was measured.

The *in vitro* dataset (N=8752) was characterized by ten attributes, with cytotoxicity defined via cell viability at a 70% threshold. Model validation yielded excellent performance for tree-based models (AUC>0.9, CatBoost AUC=0.944). SHAP ranked concentration, composition, size, exposure time, organ, surface coating, and Zeta potential (**ζ)** as most influential in toxicity outcome. PDP quantified how the probability of NP toxicity prediction changes with variations in a single feature. For instance, larger NP sizes suggested decreased toxic effects, while highly positive **ζ** increased toxicity likelihood. Retraining the top five models with only the seven SHAP-selected features led to negligible performance changes.

The in vivo dataset (N=410) was characterized by the same SHAP features. Organ exposure, analogous to *in vitro* concentration, was derived from the simplified PBPK model. Tree-based models provided exceptional performance (RF AUC=0.964), with concentration, **ζ**, and composition ranked as critical. Our work provides a strategy for predicting and explaining the toxicity of engineered NPs, thereby supporting the pursuit of rational design of NPs.

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Poster 22

Extending the Alchemical Transfer Method (AToM) to Predict Intrinsic Aqueous Solubility During Lead Optimization

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During late-stage lead optimization in small molecule drug discovery, aqueous solubility remains a critical property to optimize as it directly influences bioavailability, metabolism, and even formulation. While higher throughput data-driven methods are effective and commonly employed early in drug discovery to predict different types of solubility, they become less reliable for intrinsic thermodynamic solubility, which is critical as a compound progresses to the lead stage. Here, we introduce an extension of the Alchemical Transfer Method (AToM) to predict thermodynamic solubility in water. Unlike traditional free energy perturbation (FEP) methods, AToM bypasses the need to simulate both sublimation and hydration processes, enabling a direct evaluation of the dissolution process and significantly enhancing computational efficiency. This is achieved by displacing a molecule from its crystal surface into bulk water within a single simulation box. AToM was benchmarked in this context against 100 molecules from the Cambridge Structural Database (CSD) with experimental thermodynamic solubility data. This framework is a valuable and cost-effective tool for accurate intrinsic solubility prediction.

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Poster 23

Repaid Discovery of a Novel Acetylation Targeting Chimera (AceTAC) for Acetylation of P53 Via High-throughput Direct-To-Biology (DTB) Platform

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Lysine acetylation is a fundamental post-translational modification (PTM) that plays a pivotal role in controlling gene transcription, DNA repair, cell cycle progression, and apoptosis. Recent advances in chemically induced proximity technologies—such as PROTACs and molecular glues—have revolutionized targeted protein degradation and stabilization. Extending this concept, Acetylation Targeting Chimeras (AceTACs) represent a novel class of bifunctional molecules designed to recruit acetyltransferases to specific protein such as tumor-suppressor proteins then induce the pharmacologic activation.

Here, we report a potent AceTAC L3C4-AB006-1 which recruits the acetyltransferase P300 to the tumor suppressor P53, inducing robust acetylation of P53 at concentrations as low as 200 nM. This modification leads to the transcriptional upregulation of downstream targets such as P21, highlighting its potential utility in cancer therapy. Acetylation of P53 has been associated with enhanced transcriptional activity, improved DNA-binding capacity, and elevated tumor suppressor functions, making it a strategic target for anticancer therapies.

To accelerate the development of AceTACs, we developed a Direct-to-Biology (D2B) screening platform. This approach enables nanomole-scale synthesis coupled with immediate functional testing, dramatically reducing both the cost and time required for high-throughput candidate evaluation. Using D2B, we rapidly established a library of bifunctional molecules by combinatorially assembling diverse warheads and linkers. The successful identification of L3C4-AB006-1 validates D2B as a powerful and efficient tool for the rapid discovery of functional proximity-inducing molecules.

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Poster 24

Formulation of Tunable PLGA/PEG Nanoparticles for Drug IV Delivery: Correlation Between Drug Solubility and Encapsulation Efficiency

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Limited aqueous solubility of many novel chemical entities poses a significant challenge to the development of intravenous formulations and the accurate determination of absolute bioavailability. To address this limitation, we developed a microfluidic-based method for rapidly generating PLGA/PEG mixture encapsulated nanoparticles, thereby enhancing the solubility of poorly soluble small-molecule drugs for intravenous administration.

Expanding on prior work that established control over nanoparticle size, polydispersity, and zeta potential through design of experiments (DoE)-based parameter optimization, we investigated how drug-specific physicochemical properties influence encapsulation efficiency. Under standardized conditions, PLGA/PEG nanoparticles were synthesized through a microfluidic nanoprecipitation process on an Unchained Labs Sunshine system to encapsulate a range of marketed drugs, including afatinib, capecitabine, paclitaxel, itraconazole, ibuprofen, chrysin, and wogonin. Ultra-performance liquid chromatography (UPLC) methods were developed to quantify encapsulation efficiency of entrapped drugs. Mathematical modeling revealed a linear, negative correlation between the aqueous solubility of a drug and its encapsulation efficiency in PLGA/PEG NPs.

Intravenous injections in Sprague Dawley rats confirmed that these nanoparticles are biocompatible, with no adverse effects observed. This microfluidic nanoprecipitation strategy thus offers a robust platform for formulating poorly soluble compounds into intravenous dosage forms, with drug solubility serving as a rapid indicator of encapsulation potential. Ultimately, this strategy has the potential to enhance preclinical pharmacokinetic assessments and support the advancement of new small-molecule drug candidates.

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Poster 25

Mapping the Determinants of TCR Recognition in HER2-mutant NSCLC

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HER2 hotspot mutations occur in 2–4% of non-small cell lung cancers (NSCLC) and are typically resistant to immune checkpoint inhibitors due to low PD-L1 expression and tumor mutational burden. However, their essential oncogenic role makes them promising targets for T cell receptor (TCR)-based immunotherapies. We previously identified immunogenic epitopes from prevalent HER2 mutations that elicit cytotoxic T cell responses, identified and validated their TCRs. Here, we applied alanine scanning to dissect the contribution of individual peptide residues to TCR recognition and T cell activation, aiming to refine epitope selection for therapeutic TCR design. We focused on HLA-A*02:01-restricted epitopes derived from common HER2 mutations, including Y772dupYVMA, G776delinsVC, and S310F. Alanine-substituted peptide libraries were generated, and the impact of each residue on TCR binding and T cell activation was assessed using peptide-pulsed target cells and TCR-engineered T cells. Single-cell RNA sequencing (scRNAseq) was used to profile TCR sequences and associated transcriptomes, providing insights into T cell heterogeneity, clonality, and function. Epitopes derived from the human proteome and presenting potential for cross-recognition were also identified for further testing. Multiple HER2-derived epitopes were immunogenic, driving antigen-dependent T cell expansion and cytotoxicity. Single-cell TCR sequencing identified cognate receptors for each epitope. Alanine scanning experiments are currently underway to assess how specific residue substitutions affect T cell activation, cytokine production and cytotoxicity, with the goal of identifying positions critical for peptide immunogenicity. These studies are expected to provide structural and functional insights to inform epitope prioritization, determine potential toxicities, and guide future TCR design and affinity optimization. In summary, this study supports the feasibility of targeting HER2-mutant NSCLC with TCR-engineered T cells. The data for alanine scanning is expected to effectively identify key determinants of immunogenicity, enhancing understanding of TCR–peptide–MHC interactions, highlighting potentially cross-recognized epitopes and informing precision TCR-based immunotherapy development.

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Poster 26

Investigating Novel Small Molecules for Selective Cytotoxicity Against Acute Myeloid Leukemia

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Acute myeloid leukemia (AML) is an aggressive hematological malignancy that has poor prognosis and high relapse rates with cytotoxic chemotherapeutics. Current chemotherapies are often poorly tolerated in older patients or those with comorbidities, significantly limiting clinical options. New, better treatments are needed to overcome resistance and improve outcomes for AML patients. Heavy reliance on oxidative phosphorylation for ATP production and increased sensitivity to mitochondrial damage are common features for AML cells, making these organelles a prime target for therapeutic intervention. Previous studies identified compounds that initiate mitochondrial turnover through PINK-1 stabilization (PS-compounds) and selectively kill AML cells. The most promising compounds were derived from an original hit named PS127. These PS127-family molecules impaired mitochondrial bioenergetics by upregulating reactive oxygen species (ROS), reducing respiration, and inducing apoptosis and ferroptosis in AML cells.

We utilized Prediction of Activity Spectra for Substances (PASS) to identify likely biochemical functions: apoptosis agonist, thioredoxin/glutathione reductase inhibitor (T/GRi), and autophagy inducer. We screened ~4.2 million molecules *in silico* for these functions and identified 93 hits molecules, 81 of which were closely related to PS127-family molecules. Four of the 14 tested molecules had a sub-micromolar CC50 in MOLM-13 (AML cell line). Evaluation of these hits in a broader range showed that they had low CC50 values in multiple AML cell lines and >15-fold higher CC50 in healthy peripheral blood mononuclear cells, indicating specificity against leukemic cells. These molecules were synergistic with existing AML treatments, indicating their promise for combinatorial therapy. To elucidate their mechanisms of action, we evaluated predicted PASS activities. We found that PS-treated cells induced high levels of apoptosis in AML cells, as shown by Annexin-V staining. Additionally, co-treating PS-treated cells with an autophagy inhibitor prevented cell death, indicating functional autophagy is required to induce cytotoxicity. Surprisingly, we found that the PS-molecules did not interfere with thioredoxin reductase (TrxR) activity, but decreased the reduced glutathione (GSH) to oxidized glutathione (GSSG) ratio, suggesting specificity against glutathione reductase (GSR). Supplementation with GSH or its precursor but not other ROS scavengers increased cell viability, supporting glutathione metabolism as a target. Further experiments using differential scanning fluorimetry (DSF) confirmed binding of active PS127-family compounds to GSR. Current research involves assessing the effect of prioritized hits on mitochondrial bioenergetics and function (ROS production, ATP-production, membrane depolarization). This will lay the foundation for future evaluation of these compounds (and their combinations with current treatments) in preclinical murine AML PDX models.

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Poster 27

Targeting Breast Cancer-Specific Enhancer RNA1-BCOE1 Inhibits Breast Cancer Progression

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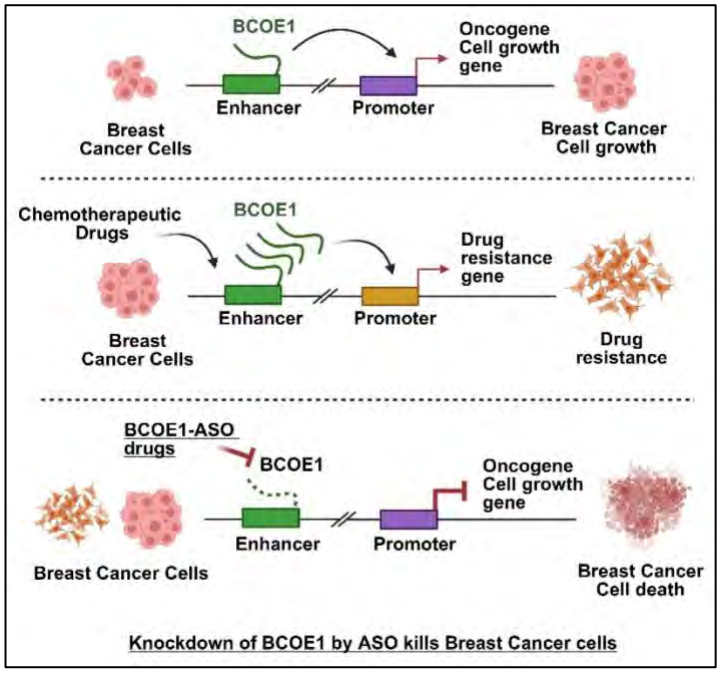
Abstract: Large-scale genomics studies have discovered that noncoding RNAs (ncRNAs) drive a striking number of diverse roles in the development and diseases including cancer by regulating transcription, RNA processing, and translation. Emerging evidences reveal that enhancer-RNAs (eRNAs), a class of long ncRNA transcribed from enhancer regions of the genome play important roles in enhancer activation and enhancer-driven gene regulation in human cancers. However, knowledge gaps remain in terms of the fundamental mechanisms of eRNA in cancer progression and how to therapeutically target the oncogenic eRNAs in a tumor-specific manner. This study aims to identify the driver eRNA in human breast cancer (BRCA) and explore its mode of action and therapeutic potential. In this study, we used high throughput Omics analysis, invitro and invivo assays. By analyzing the genome-wide transcript profiles in breast cancer cells, we identified a significantly upregulated eRNA, which we named Breast Cancer Overexpressed eRNA 1 (BCOE1). Knockdown of BCOE1 by transfecting antisense oligonucleotides (ASO) inhibits BRCA cell growth, whereas it has no impact on normal/BCOE1-null cells. Our RNA-seq and CHIP-seq data showed that BCOE1 regulates the expression of key genes and transcription factors which modulates cell cycle and proliferation through RNA PolII recruitment. This study revealed that BCOE1 is a key driver eRNA in BRCA and a potential therapeutic target. This study will offer a critical understanding of mechanisms behind eRNA-driven cancer progression and guide to develop promising 'eRNA targeted therapy' for breast cancer.



Keywords: Enhancer RNA, Breast Cancer, Targeted therapy, Antisense oligonucleotides.

Acknowledgements: This study is supported by CPRIT Grant RP210043, National Institute of Health (NIH), and UTHealth Houston.

Poster 28

Absolute Quantification of Rat Uridine-Diphosphate-Glucuronosyl Transferase Isoforms using LC-MS/MS

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Abstract: Uridine5′-diphosphate-glucuronosyltransferase (UGT) is the major phase II metabolism enzyme responsible for glucuronidation of drugs and endogenous compounds. However, the absolute protein expression levels of difference Ugt isoforms in rodents, which are commonly used in biomedical research, has not been determined. The purpose of this study was to determine the absolute protein expression level of different Ugt isoforms in rat liver and intestine using LC-MS/MS. Seven UGT isoforms, namely Ugt1a1, Ugt1a2, Ugt1a3, Ugt1a5, Ugt1a6, Ugt1a7, Ugt2b6 in rat liver and intestine were tested. A Sciex 6500 triple quadrupole LC-MS system was used for this analysis. The rat liver and intestine S9 were digested with trypsin, two signature peptides for each isoform were employed by positive ion multiple reaction monitoring (MRM) mode. Standard addition method was used to validate the assay to account for the matrix effect. The validated method has a linear range of 500–0.2 4ng/ml for the signature peptides. The precision, accuracy, and matrix effect were in acceptable ranges. The absolute expression levels of seven Ugt isoforms in the intestine and liver of rats were quantified. The isotope label-free absolute quantification method used here had good accuracy, sensitivity, linear range, and reproducibility, and were used successfully for the accurate determination of Ugts from tissues. This method can be used for rats Ugt isoform quantification in tissues.

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Poster 29

Clay Attenuates Fat-Induced Diarrhea via Fat Adsorption and Bile Acid Modulation in Mice

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Abstract:

Fat-induced diarrhea is a prevalent gastrointestinal disorder associated with excessive dietary fat intake, elevated pancreatic lipase activity, and disrupted bile acid metabolism. Current treatment options are limited, often targeting symptoms rather than the underlying biochemical imbalances. This study aims to develop a reproducible mouse model of fat-induced diarrhea using Glyceryl-trioleate (GTO) and to evaluate the anti-diarrheal therapeutic of clay as a low-cost intervention to attenuate fat-induced diarrhea.

GTO was administered at increasing doses (100, 200, 1000, and 2000 mg/kg/day) to induce diarrhea and establish the model. Clay (Montmorillonite K10) was administered orally at two doses (2g/kg/day and 4g/kg/day), and a control group received GTO only to assess dose-dependent efficacy. Diarrheal symptoms were monitored, and fecal samples were collected for gross analysis and quantification of free oil spots as an indicator of undigested fat. Intestinal tissues were subjected to histological examination to assess structural integrity. Fecal bile acid profiles were evaluated using liquid chromatography-mass spectrometry (LC-MS), including both total and primary bile acids such as Cholic acid (CA), Glyco-cholic Acid (GCA), Deoxycholic acid (DCA), Lithocholic acid (LCA), chenodeoxycholic acid (CDCA), and Tauro-cholic acid (TCA).

Diarrhea incidence rose dose-dependently at 0.5% at 100 mg/kg, 1.0% at 200 mg/kg, 1.5% at 1000 mg/kg, and 2.5% at 2000 mg/kg. The 2000 mg/kg/day dose was selected for subsequent studies due to its consistent and moderate diarrhea-inducing effect with low variability. Clay treatment resulted in a dose-dependent decrease in diarrhea severity in mice subjected to glyceryl trioleate-induced fat malabsorption. Compared to the control group receiving glyceryl trioleate alone, clay co-administration at 2 g/kg reduced diarrhea scores by approximately 48%, while the higher dose of 4 g/kg achieved an 83% reduction. These effects were supported by reduced free oil spots in feces revealed by microscopic examination, indicating efficient adsorption of dietary fats. Histological analysis showed preserved mucosal architecture, indicating no tissue damage in both treatment and control groups. Total bile acid profiling and LC-MS analysis revealed a substantial reduction in primary fecal bile acids, with specific decreases in CA, LCA, GCA, DCA, CDCA, and TCA levels, suggesting a modulatory effect of clay on bile acid metabolism.

Clay effectively alleviates fat-induced diarrhea through two primary mechanisms: adsorption of dietary fats and modulation of fecal bile acid composition. These findings highlight clay's potential as a safe, cost-effective therapeutic strategy for managing fat malabsorption-related gastrointestinal disorders.

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Poster 30

Blockade CHI3L1 Enhances Hepatocellular Carcinoma Response to Anti-PD1 Antibody

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Hepatocellular carcinoma (HCC) is an aggressive cancer with poor prognosis and limited systemic treatment options. Up to 80% of HCC patients are present with long-term liver inflammation and cirrhosis, creating an immunosuppressive microenvironment that promotes tumor progression. However, despite the approval of immune checkpoint inhibitors (ICIs), such as anti-PD1 monoclonal antibody (mAb), response rates remain low. This highlights the need to identify additional immunosuppressive factors as combinatory therapy targets. Clinical studies have linked elevated chitinase-3-like-1 (CHI3L1) levels to poorer prognosis in HCC, but its role in ICI resistance remains unknown.

Our data showed that *Chi3l1*$^{-/-}$ mice developed significantly smaller tumors after anti-PD1mAb treatment. Further mechanistic studies revealed that Chi3l1 deficiency led to increased CD8^{+} T cell infiltration and enhanced activation of CD8^{+} T cell. Single-cell RNA sequencing data revealed that tumor infiltrated neutrophils (TANs) are the predominant source of Chi3l1, and TANs in WT mice exhibited higher hypoxia-inducible factor 1-alpha (HIF1A) activation compared to *Chi3l1*$^{-/-}$ mice. Taken together, our findings may uncover a previously unrecognized role of neutrophil-derived CHI3L1 in activates HIF1A in an autocrine manner, driving TANs toward a pro-tumor phenotype that suppresses anti-tumor immunity and induces resistance to anti-PD1mAb therapy.

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Poster 31

On-tissue Spatial Profiling with Quantitative Mass Spectrometry Discovers Isomeric Lipid Alternations in Patient-derived orthotopic Medulloblastoma Mouse Models

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Medulloblastoma (MB) is the most common malignant pediatric brain tumor with the propensity to metastasis at both initial diagnosis and recurrence. Lipid metabolism is increasingly recognized as a critical role in cancer metastasis and therapeutic resistance, yet the structural diversity and spatial heterogeneity of lipid isomers in biological tissues limited our understanding of lipid reprogramming during these processes. To address this, we developed a novel platform that integrates aziridination-based isobaric mass tagging strategy with mass spectrometry imaging (MSI) techniques to achieve spatially resolved, C=C positional isomer-specific, and quantitative lipid profiling on tissues sections. Using patient-derived orthotopic medulloblastoma mouse models, we discovered distinct lipid isomer distributions between tumor cores and metastatic sites. We found that n-9 fatty acids and phosphatidylcholines were more abundant in tumor cores, whereas n-7 lipids were less rich, indicating a differential preference for lipid biosynthetic pathways. Specifically, tumor cores favor elongation by fatty acid elongase (Elovl) followed by stearoyl-CoA desaturase (SCD), while metastatic sites prefer the desaturation-first pathway. Notably, n-10 fatty acids and phosphatidylcholines were significantly enriched in metastatic regions. Unlike common unsaturated lipids formed via SCD, n-10 lipids arise from an alternative desaturation pathway that involves fatty acid desaturase 2 (FADS2), which has recently been reported to be abnormally expressed in cancer cells and is potential therapeutic target for treatment. Our results suggest aberrant FADS2 activity in metastatic MB. Additionally, we observed significant lipid accumulation in post-radiotherapy PDOX mouse models through quantitative lipid profiling, highlighting enhanced fatty acid synthesis and lipid droplet formation as adaptive responses to therapeutic stress. Our findings highlight the complexity of lipid reprogramming in MB and underscore the importance of analyzing isomeric lipids to gain deeper insight into tumor biology, biomarkers discovery and therapeutic strategies.

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Poster 32

In Silico Design of Novel *Artocarpus altilis* Derived Compounds Targeting the C-Myc/Max Heterodimer.

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The c-MYC proto-oncogene is a key driver of cancer progression, yet effective inhibitors remain elusive due to challenges such as low potency and poor pharmacokinetics. This study explores *Artocarpus altilis*-derived compounds as novel c-MYC inhibitors using Insilico techniques. From 81 bioactive compounds screened, Ellagic acid, Artonin M, Cycloaltilisin 7, and Broussoflavonol F demonstrated superior binding affinities to c-MYC compared to the reference drug Alisertib. Molecular dynamics simulations revealed exceptional stability for Broussoflavonol F, which also exhibited the most favorable MM-PBSA binding energy. Pharmacokinetic analysis indicated promising drug-like properties, though some toxicity concerns were noted. These findings highlight the potential of *Artocarpus altilis*-derived compounds, particularly Broussoflavonol F, as potent c-MYC inhibitors. This study provides a foundation for further experimental validation and optimization, offering a promising strategy for targeting c-MYC-driven cancers.

Poster 33

Decoding p53 (R249S)- Mutated Liver Cancer: From Developmental Origins to Targeted Therapies

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Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer globally and the second leading cause of cancer-related mortality. Unlike other cancers such as prostate or lung, HCC incidence has tripled since 1980, with a five-year survival rate remaining under 20%. For early-stage disease, current clinical interventions such as surgical resection, local ablation, and liver transplantation have demonstrated limited efficacy. Systemic therapies for advanced HCC, including FDA-approved multi-kinase inhibitors like sorafenib and regorafenib, extend overall survival by less than three months and are associated with low response rates and significant toxicity, underscoring the need for more effective and targeted therapies.

Recent advancements in high-throughput sequencing and multi-omics approaches have identified p53 mutations (particularly p53(R249S)) as key drivers of HCC development and progression. However, most research has been conducted in cancer cell lines with extensive genomic instability and multiple concurrent genomic mutations, clouding our understanding of the cellular malfunctions directly triggered by mutant p53. Additionally, there exists an unmet clinical imperative to explore whether the HCC-relevant p53(R249S) mutation can be leveraged as a therapeutic vulnerability for the treatment of HCC. Hence, our human pluripotent stem cell (hPSC) platform featuring the p53(R249S) mutation, devoid of secondary mutations yet preserving a robust functional connection between the p53(R249S) mutation and HCC, offers an ideal cellular framework for delving into the oncogenic role of mutant p53 in HCC.

Using this platform, we integrated machine learning-guided hepatic differentiation, single-cell transcriptomics, and pathway enrichment analyses to uncover downstream effectors of p53(R249S). Our studies identified FOXM1, a transcription factor known to promote cell cycle progression and genomic instability, as a key downstream target of mutant p53. High FOXM1 expression correlates with a poor prognosis in HCC patients, suggesting it may represent a tractable therapeutic vulnerability.

To evaluate this, we investigated thiostrepton, a thiazole antibiotic and known FOXM1 inhibitor, as a potential therapeutic agent. Preliminary results demonstrate that thiostrepton significantly reduces cell viability in HCC cell lines, supporting its potential as a targeted therapy. Mechanistically, thiostrepton treatment leads to downregulation of FOXM1 transcriptional targets involved in mitotic progression and DNA repair. Our findings support a model in which p53(R249S) exerts oncogenic activity through upregulation of FOXM1, and highlights thiostrepton as a promising targeted agent for FOXM1-driven HCC. This work reveals a novel p53-FOXM1 axis in liver cancer and underscores the utility of stem cell-based models in preclinical drug development.

Poster 33

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Poster 3

Novel Protein Interactor of Voltage-Gated Sodium Channel 1.6 Modulates Medium Spiny Neurons Excitability: Impact on Neuropsychiatric Disorders Drug Discovery

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Neuropsychiatric disorders (NDs) significantly impact the well-being of individuals by negatively affecting their overall health and productivity. Despite evidence pointing to genetic, environmental, and epigenetic factors as common key factors in the etiology, progression, and treatment of NDs, there is still inadequate knowledge on the molecular mechanisms that confer resilience to these disorders. In previous studies, we identified the voltage-gated Na+ channel Nav1.6 as a mediator of neuroplasticity induced by environmentally enriched (EC) or isolated (IC) conditions which are used as models for resilience and vulnerability. Protein-protein interactions are essential mediators of Nav1.6 channel function and the impact of EC/IC conditions on the relative composition of the Nav1.6 interactome is not known. Based on this, we recently investigated the Nav1.6 protein interactome under EC and IC conditions to identify auxiliary proteins that may confer resilience or vulnerability to NDs in the hippocampus and striatum. We identified 88 and 32 differentially expressed protein interactors of Nav1.6 in the striatum and hippocampus respectively of EC/IC rats. Following this, we selected one of the top 5 differentially expressed interactors (Protein X) for further investigation. Using immunoprecipitation and confocal imaging, we validated the interaction between Nav 1 6 and protein X, and functional studies implicate this protein as a modulator of Nav1.6 activity and medium spiny neuron excitability. The results of this study offer valuable information on a new molecular target with potential for the development of novel neurotherapeutics.

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Poster 35

A Glycine-based Tripeptide Linker for Maximizing the Therapeutic Index of Antibody–Drug Conjugates

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Abstract

Valine-citrulline (VCit) is an industrial-standard protease-cleavable linker used in antibody-drug conjugates (ADCs) for cancer therapy. However, its in vivo linker instability can cause various clinical adverse effects, including neutropenia and hepatotoxicity, leading to dose delay or treatment discontinuation. Here, we report that a glycine-based tripeptide linker sequence, glutamic acid-glycine-citrulline (EGCit), has the potential to solve these clinical issues without compromising the ability of traceless drug release and ADC therapeutic efficacy.[1] We demonstrate that our EGCit ADC resists human neutrophil protease-mediated degradation and spares differentiating human neutrophils. Notably, our anti-HER2 ADC shows almost no sign of blood and liver toxicity in healthy mice at 80 mg kg^{-1}. Our EGCit ADCs also exert greater antitumor efficacy in multiple xenograft tumor models compared to the FDA-approved ADCs, including Kadcyla® and Enhertu®. Because of the linker's simplicity, desirable physicochemical properties, and independence from conjugation modality and payload type, the EGCit linker is transferable to a wide range of ADC designs and other drug delivery agents. We believe that the EGCit linker technology will help expand the repertoire of effective, safe, targeted drug delivery systems. This may provide clinicians and patients with cancer with access to otherwise unrealistic treatment options, such as high-dose ADC therapy.

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and Research Institute of Texas (RP210043, postdoctoral fellowship to S. Y. Y. Ha). We gratefully acknowledge the following researchers for providing the cell lines used in this study: U87ΔEGFR from Prof. Balveen Kaur (UTHealth) and KPL-4 from Dr. Junichi Kurebayashi (Kawasaki Medical School). We thank Prof. Momoko Yoshimoto (UTHealth) for providing scientific advice on studies using human HSPCs, and Dr. Yoshihiro Otani and Dr. Kyotaro Ohno (Okayama University) for providing a clinical opinion for MRI and liver tissue analysis.

Poster 36

Characterization and Development of Human Cell Line-Derived Extracellular Vesicles Loaded with IL-10 to Mitigate Inflammation at the Fetal-Maternal Interface

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OBJECTIVE: Preterm birth (PTB; birth before 37 weeks of gestation) contributes to increased neonatal morbidity and mortality. PTB is a complex obstetrical syndrome where > 50% of PTB cases are associated with intrauterine infections and fetal inflammatory response. Anti-inflammatory cytokine IL-10 has been shown to reduce inflammation-induced uterine contractions in animal models; however, intra-amniotic administration of recombinant IL-10 (rIL-10) is not clinically feasible in pregnant subjects. We previously reported using extracellular vesicles (EVs) electroporated with IL-10 (eIL-10), which addresses these limitations and enhances bioavailability; however, eIL-10 is costly to produce. To overcome this limitation, we transfected the IL-10 plasmid into cells, allowing EVs to load IL-10 during their biogenesis.

METHODS: Using an IL-10 lentiviral construct, HEK293 T/SF cells were transfected, and the media collected. EVs were isolated via tangential flow filtration and ultracentrifugation. HEK293 T/SF WT and IL-10 EVs (tIL-10) were characterized by size (ZetaView), EV-specific tetraspanin markers (western blotting and NanoView). An IL-10 ELISA measured the concentration of IL-10 in tIL-10. To evaluate tIL-10 functionality, a HEK Blue reporter cell line was exposed to either native (from non-transfected HEK293T/SF) EVs or various tIL-10 concentrations. Maternal decidual cells were then exposed to either PBS, 100 ng/mL of lipopolysaccharide (LPS) to induce inflammation, and LPS + rIL-10 or tIL-10 at dosages of 5, 50, and 500 ng. After 24 hours, an Almar Blue assay evaluated cell metabolism, and pro-inflammatory cytokine IL-6 concentrations in the supernatant were measured via ELISA.

RESULTS: The EV sizes of WT and tIL-10 samples at diameters of 125 ± 83.6 nm and 127.8 ± 60.6 nm, respectively, were not significantly different and fell within the established size range of 30-2000nm. Additionally, the presence of EV markers and the absence of cellular markers were established, and no difference was seen between WT and tIL-10 samples in their presence or intensity. tIL-10 also showed significant activation ($p \leq 0.0001$) of IL-10 receptors in HEK Blue cells compared to WT EVs. Moreover, tIL-10 significantly reduced ($p \leq 0.001$) IL-6 production in LPS-treated cells compared to LPS alone, and this effect was enhanced compared to LPS + rIL-10. tIL-10 neither impacted cellular metabolism nor was cytotoxic.

CONCLUSIONS: These results established the utility of using transfected IL-10 HEK293 T/SF cells to naturally and effectively produce IL-10 EVs through biogenesis. tIL-10, like rIL-10, is also effective, in activating IL-10 receptors to exert anti-inflammatory downstream effects. Our approaches have generated functionally active exosomal IL-10 that can be used for preclinical and future clinical trials to reduce the risk of PTB.

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Poster 37

Accelerating Discovery in a Rare Neurodevelopmental Disorder: The Power of Patient-Driven Research in FAM177A1 Deficiency

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1. FAM177A1 Research Fund
2. Source Biologics
3. SomaLogic
4. KAL Research Initiatives

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FAM177A1-Related Neurodevelopmental Disorder is a newly characterized, autosomal recessive condition initially described in a 2024 publication following a 2020 scientific poster presentation. The disorder presents with early-onset neurodevelopmental delay and progresses to severe neurodegeneration, marked by intractable seizures, motor regression, behavioral disturbances, and potential neuroinflammatory features. Affected individuals require comprehensive, multidisciplinary care involving genetics, neurology, rheumatology, and neuroimmunology. Currently, no disease-specific therapies are available.

In response to this critical unmet need, a patient-led initiative catalyzed a coordinated research effort to accelerate the discovery of potential treatments. Leveraging early insights from the Undiagnosed Diseases Network and supported by philanthropic contributions and partner funding, this initiative established disease models in zebrafish, Drosophila, and mice; generated and characterized human cell lines; and executed an unbiased high-throughput drug screen. Promising compounds have been prioritized and shared with clinicians for potential repurposing. Additional efforts include the development of a frog model and the initiation of a gene therapy program.

This collaborative framework—driven by affected families—has compressed traditional research timelines, enabling substantial progress in under five years. Transparent communication and sustained engagement across scientific, clinical, and patient communities have produced rapid scientific advancements while maintaining patient-centered priorities.

We report on clinical phenotypes, metabolomic analyses from plasma, fibroblasts, and whole zebrafish, and identify convergent protein targets across individuals. Key research gaps are highlighted, and collaboration is invited from experts in neurodegeneration, neuroinflammation, and drug development.

This model of urgency-driven, patient-centered research offers a replicable strategy for expediting therapeutic discovery in newly identified rare diseases with significant unmet clinical needs.

Poster 38

Evaluation of EGFR and LGR5 Dual-Targeting Therapeutic Strategies for the Improved Treatment of Colorectal Cancer

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Despite extensive efforts to develop novel therapies, colorectal cancer (CRC) remains the second-leading cause of cancer-associated death in the United States. One of the primary challenges in treating CRC is therapy resistance mediated by cancer stem cells (CSCs), a subpopulation of cancer cells with infinite replicative potential that can differentiate to drive tumorigenesis and relapse. Thus, targeting CSCs has become an attractive therapeutic strategy.

Antibody-drug conjugates (ADCs) are a rapidly expanding class of anticancer drugs that utilize monoclonal antibody (mAb) specificity to hone cytotoxic payloads to cancer cells. We previously generated ADCs targeting leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5), a CSC biomarker that is highly overexpressed in CRC. LGR5 ADCs demonstrated high specificity and efficacy in CRC cells and xenograft models without notable toxicity, although tumors eventually relapsed following treatment cessation. Interestingly, FDA-approved therapies targeting epidermal growth factor receptor (EGFR) have been shown to increase LGR5 expression in patient-derived models of CRC. This study aims to determine the mechanisms of EGFR-mediated regulation of LGR5 expression and evaluate the therapeutic efficacy of EGFR-targeting therapies in combination with LGR5 ADCs for the improved treatment of CRC.

We have demonstrated that cetuximab (CTX), an EGFR-targeting mAb approved for *KRAS*^{WT} metastatic CRC (mCRC), increases LGR5 protein levels independent of *KRAS*/*PIK3CA* mutational status in CRC cell lines, tumor organoids, and cell line-derived xenografts. Additionally, we identified a novel EGFR-LGR5 interaction that is enhanced by CTX treatment. Furthermore, we have generated a camptothecin-based LGR5 ADC (8E11-CPT2) utilizing site-specific conjugation technology that demonstrates target- and dose-dependent cytotoxicity in CRC cells and was well-tolerated up to 20 mg/kg. Importantly, combination treatment of 8E11-CPT2 with CTX significantly reduced tumor burden with notable regression in some mice and extended survival compared to LGR5 ADC and CTX monotherapies in two *RAS*^{MUT} CRC patient-derived xenograft models. To evaluate alternative EGFR and LGR5 dual-targeting therapeutic strategies, we generated an EGFR:LGR5 bispecific antibody (bsAb) that binds its cognate receptors, internalizes to the lysosome, and promotes EGFR and LGR5 degradation. Future work will involve the development of an EGFR:LGR5 bsADC that will be evaluated in vivo against LGR5 ADC combination therapy with CTX. Taken together, these results demonstrate that dual-targeting of EGFR and LGR5 may prove more effective than LGR5- and EGFR-monotargeted approaches in treating CRC, providing an improved treatment option for *RAS*^{MUT} and *PIK3CA*^{MUT} mCRCs.

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Poster 39

Dissecting 3D Chromatin Dynamics in Li-Fraumeni Syndrome

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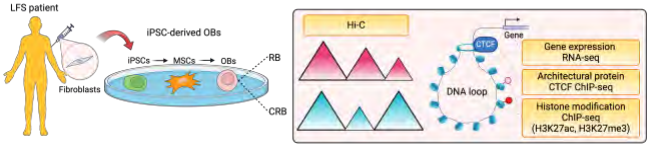
The advancement of induced pluripotent stem cell (iPSC) technology has empowered the in vitro modeling of human diseases, particularly in cancer predisposition disorders like Li-Fraumeni syndrome (LFS) marked by germline p53 mutations. LFS patients are at an increased risk of developing multiple cancers throughout their lifetime, with a particular susceptibility to breast cancer, gliomas, sarcoma, and osteosarcoma. In this study, we utilized LFS iPSC-derived osteoblasts, the cells of origin for osteosarcoma, as a unique platform to delve into the intricate role of mutant p53 in osteosarcoma development, focusing specifically on 3D chromatin architecture.

Application of chromosome conformation capture (3C) and its derivative High-throughput chromosome conformation capture (Hi-C) have emerged as invaluable tools, offering researchers insights into the spatial organization of the genome within the nucleus. This technological progress enhances our comprehension of vital biological processes, including gene transcription regulation through physical chromatin interaction and chromatin 3D structure reshaping. The tumor suppressor p53, a key player in maintaining genomic stability, orchestrates cellular responses to genotoxic stress by controlling cell-cycle checkpoints and apoptosis. However, the full understanding of how a p53 mutation potentiates osteosarcoma progression, particularly the oncogenic property (gain-of-function) of mutant p53, is not yet complete. Therefore, we employed LFS iPSC-osteoblasts as a distinctive model to explore the complex involvement of mutant p53 in osteosarcoma formation, with a particular emphasis on the 3D chromatin structure. We investigated changes in A/B compartments, topologically associated domains (TADs), and chromatin loops in LFS and healthy family iPSC-derived osteoblasts and integrated with mRNA-seq as well as ChIP-seq for comprehensive investigation of functional oncogenes during osteosarcomagenesis. Among the 40 oncogene-associated genes modulated by 3D chromatin structure alterations, ARID1A is significantly downregulated in LFS osteoblasts and is correlated with improved overall survival in osteosarcoma patients. This finding highlights its potential as a therapeutic target. Notably, ARID1A loss has been implicated in defective DNA damage repair and mismatch repair during cancer progression, rendering tumors more susceptible to targeted therapies, including EZH2 inhibitors and ATR inhibitors.

In summary, our findings provide insights into the potential role of mutant p53 in modulating 3D chromatin structure, including compartment switching, dynamics of TAD borders, and rewiring of loops, ultimately influencing aberrant oncogenic gene expression in LFS patients.



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Poster 40

Immunologically Targeting U1 Mutant Shh Medulloblastoma

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Objectives

Medulloblastoma (***MB***) is the most common malignant pediatric brain tumor and represents a significant burden of morbidity and mortality in the US. MB is comprised of four subgroups: Wnt, Shh, Group 3, and Group 4. Shh tumors represent 25% of cases and subdivides into Shh-b and Shh-**γ**, Shh-a, and Shh- d[1]. A portion of the Shh-a patients have either germline or somatic mutations of *TP53* conferring an aggressive phenotype with nearly 100% mortality. Half of Shh MB carry an identical somatic point mutation in a non-coding small nuclear RNA (**s*nRNA***) called U1 (r.3A>G) which is found in 97% of Shh-d tumors, and in most Shh-a tumors with *TP53* mutations[2]. Current therapies for patients with *TP53* and U1 mutant Shh-a MB observe rare survivors, and adult Shh-d patients continue to experience significant morbidity and mortality calling for urgent prioritization of these tumors for targeted therapy. Here we identify a novel intron derived epitopes in U1 mutant MB to develop targets for selective immunotherapies.

Methods

Cryptic exons (CryEx) were identified in both Shh-d U1 snRNA mutant samples and Shh-d U1 wildtype (WT) samples using CryEx pipeline[3]. In-house scripts were utilized for selecting for cryptic exons that are uniquely expressed in Shh-d U1 snRNA mutant samples compared to Shh-d U1 WT samples. By overlapping genes containing U1 snRNA mutation induced cryptic exons in Shh-d samples with cell surface protein, we identified candidate U1 mutation induced neo-antigens at the cell surface in Shh-d samples.

Results

Analyzing 180 Shh MB RNA-seq samples, we identified 23% Shh-a, no Shh-b, 97% of Shh-d and 3% Shh-γ harbored the U1 mutation. The splicing landscape was then interrogated comparing Shh-d U1 snRNA mutant samples to WT samples. Gencode unannotated junctions provided us with preliminary data to show 941 misspliced transcripts in short reads RNA-seq. To further validate, 6 primary patient samples were prepared for longread single nuclei RNA sequencing employing the Parse combinatory barcoding followed by Oxford Nanopore Technology (ONT) sequencing. The processed data was then interrogated for a non-sense mediated decay pipeline to inform downstream proteomic assays and analysis. In parallel, Shh U1 mut and WT patient derived xenograft models in immunodeficient mice were generated to *in vivo* passage cells for biotinylation and mass spectroscopy in order to identify a surface antigen for targeted discovery. From the short read RNAseq data, PTCH1 neoantigen formed from the CryEx insertion translates a protein that is unique to the tumor cells (i.e., not in normal tissue) was

identified as a juxtamembrane but intracellular as a potential diagnostic marker used to identify patients with U1 mutation for subsequent drug discovery .

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Poster 41

Development and Preclinical Evaluation of Novel CAR-T Cell Therapy for Prostate Cancer

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ABSTRACT

Prostate cancer (PCa) remains to be the second leading cause of cancer death. And as the late stage of PCa, metastatic castration-resistant prostate cancer (mCRPC) remains a formidable challenge with no cure available to date. Despite that recent progress of immunotherapy, especially chimeric antigen receptor T (CAR-T) cell therapy, gain momentum in hematological malignancies, the advances of these technique have not yet translated into clinical benefits for mCRPC partially due to the unfavorable tumor microenvironment (TME) to immune cells. The preclinical data for CAR-T therapies based on prostate-specific membrane antigen (PSMA) have not provide compelling evidence to overcome the immunosuppressive TME. This limits its potential for the clinical translation and underscores the critical need for developing novel therapies against mCRPC that can enhance CAR-T efficacy. Herein, we aim to develop a novel CAR-T system towards mCRPC via combining fibroblast growth factor signaling with CAR-T to boost the immunotherapy against prostate cancer cells with multiple purposes. The proposed strategy can not only improve CAR-T cell proliferation and survival but serves as a chemoattractant system to facilitate CAR-T cells extravasation and infiltration into tumors. And the novel system holds the potential to be expended to other solid tumors in the future.

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Poster 42

A Novel, Pleiotropic Nanozyme for Targeting Mitochondrial Deficits in Rare and Ultra Diseases exemplified by Friedreich's Ataxia

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Abstract:

Mitochondrial dysfunction plays a central role in many rare diseases due to its critical involvement in cellular energy production and metabolism. These disorders are often complex and variable, influenced by both genetic and environmental factors. Although new therapies and diagnostic tools are emerging, continued collaboration is essential, particularly in the rare disease field to drive progress. Here, we present a novel therapeutic approach for mitochondrial dysfunction using a synthetic nanoparticle, or "nanozyme," with versatile enzymatic properties, which we term *Pleozyme*. *Pleozymes* catalytically dismutate superoxide, facilitate electron transfer within mitochondrial components, and convert hydrogen sulfide into protective polysulfides. They localize to the mitochondria, cross the blood-brain barrier, and have shown therapeutic benefit in models of acute brain injury and chronic metabolic disease. In Friedreich's Ataxia (FRDA), mitochondrial dysfunction results from GAA repeat expansions in the FXN gene, leading to frataxin deficiency and disrupted iron-sulfur cluster formation, critical for electron transport and iron homeostasis. FRDA-associated cardiomyopathy, a major cause of early mortality, is characterized by left ventricular hypertrophy and fibrosis, ultimately leading to heart failure. We evaluated *Pleozymes* efficacy in human FRDA iPSC-derived cardiomyocytes and sensory neurons, both alone and in combination with the FDA-approved drug SKYCLARYS® (Omaveloxolone), which activates the Nrf2 antioxidant pathway. Despite its approval, disease progression remains a concern. To address iron overload in FRDA, we developed a deferoxamine-conjugated *Pleozyme* variant (PLZ002) for targeted iron chelation. Using FRDA patient-derived iPSCs and isogenic controls differentiated into cardiomyocytes, we assessed mitochondrial function via Extracellular Flux Assay (Agilent Seahorse), lipid peroxidation using the Click-IT assay, Nrf2 activation through immunofluorescence, and cardiomyocyte contractility using the IonOptix CytoMotion Lite System. FRDA cardiomyocytes exhibited a 74.5% reduction in maximal respiration and a 53% decline in contractility compared to controls ($p < 0.000001$). Treatment with DEF-PEG-OAC improved maximal respiration by 16% and fully restored contractility ($p < 0.0001$). *Pleozymes* also increased nuclear Nrf2 localization by 52%, with an

additive effect observed when combined with Omaveloxolone ($p < 0.05$), likely via Keap1 oxidation.

These findings highlight *Pleozyme's* potential to enhance mitochondrial bioenergetics, reduce oxidative stress, and restore cardiomyocyte function. Our study provides strong preclinical evidence supporting *in vivo* evaluation and potential clinical translation of *Pleozyme* as a novel therapy for FRDA and other mitochondrial disorders.

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Poster 43

3D Printed Tablets of Dual Anti-HIV Drugs: A Step Toward Dose-Flexible Pediatric Therapy

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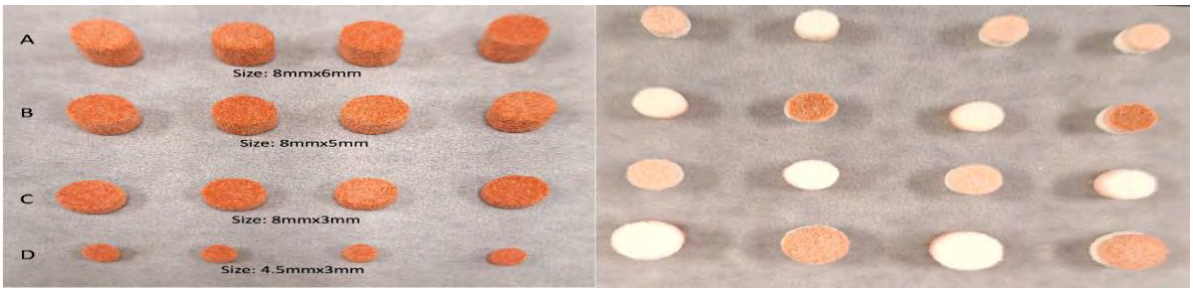
This study aimed to develop orally dissolving drug delivery systems, known as printlets, incorporating the dual antiviral agents lamivudine (LMV) and tenofovir disoproxil fumarate (TNF) to address flexible pediatric dosing needs. These printlets were designed for personalized antiviral treatments, particularly in hospital settings requiring patient-specific therapies. Binder jet 3D printing was chosen due to its ability to produce multi-layered dosage forms without heat, making it suitable for thermolabile drugs. A challenge was ensuring consistent product quality, including desirable physical, mechanical, and dissolution characteristics. The study explored critical quality attributes (CQAs) and their relationships with formulation variables and process parameters. A factorial design of experiments (DoE) was used to optimize the printing process by varying independent factors such as excipient concentration and printing conditions, identifying the optimal formulation and settings. The final printlet design was a bilayer system. The first layer contained TNF (50% w/w), hydroxypropyl methylcellulose (HPMC, 10-20% w/w), and lactose (30-40% w/w). The second layer included LMV (50% w/w), HPMC (10-20% w/w), and lactose (30-40% w/w). Printlets were manufactured in different sizes, with diameters of 8 mm, 6 mm, and 5 mm, and a fixed height of 3 mm, and 8mm of fixed diameter with varying heights of 6 mm, 5 mm, 3 mm etc. allowing flexible dosing for patient needs.
Key printing parameters included the number of binder sprays per layer: 2-3 for the first layer and 4-6 for the second layer. A fixed layer thickness of 0.36 mm was used, and the drying phase took place at 50°C to remove solvents while maintaining the stability of the APIs.
The printlets were comprehensively characterized for mechanical strength, disintegration time, drug dissolution profiles, and physicochemical stability. The DoE showed that the number of binder sprays and HPMC concentration significantly influenced the mechanical properties and disintegration behavior. All optimized formulations met dissolution requirements for both APIs, though slight variations in dissolution rates were observed depending on the formulation and conditions. Further analysis using Fourier Transform Infrared Spectroscopy (FTIR) confirmed no physical or chemical interactions between the APIs and excipients, ensuring the chemical integrity of the formulations. X-Ray Powder Diffraction (XRPD) showed no significant amorphization in the APIs, indicating they retained their crystalline state and stability. In conclusion, the study successfully developed 3D-printed bilayer printlets incorporating LMV and TNF, demonstrating dose flexibility, stability, and compliance with dissolution standards.

Acknowledgements: This research received funding from the National Institutes of Health



Poster 44

Development of Selective CDK5 Inhibitor for the Treatment of Idiopathic Pulmonary Hypertension.

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Idiopathic pulmonary arterial hypertension (IPAH) is a rare severe disorder characterized by progressive vascular remodeling and increased pulmonary artery pressure, leading to right heart failure. Despite the availability of vasodilator-based therapies, there is no current treatment that directly addresses the underlying cellular and molecular drivers of IPAH pathogenesis. One of the key cellular features of IPAH is the persistence of apoptosis-resistant, hyperproliferative smooth muscle cells, which contribute to vessel narrowing and fibrosis. Recent research has identified cyclin-dependent kinase 5 (CDK5) as a critical player in IPAH, driving the endothelial-to-mesenchymal transition (EndMT) and pathological vascular remodeling.

Our work focuses on the development of selective, reversible, non-covalent CDK5 inhibitors as a novel therapeutic approach for IPAH. We used a structure-based drug design strategy targeting the ATP-binding site of CDK5. From this effort, we identified a promising lead compound, TK-22, which exhibited potent inhibitory activity against CDK5 *in vitro* with an IC_{50} of 33.3 nM using a bioluminescent kinase assay. Molecular docking and dynamic simulations showed strong interactions of TK-22 with key residues within the CDK5 active site.

To validate its functional effects, TK-22 was tested in an *in vitro* EndMT model using GFP-tagged mouse pulmonary artery endothelial cells (MPAECs). Cells treated with the peroxynitrite donor SIN-1 to induce EndMT showed increased expression of mesenchymal markers such as α-SMA, SM22α, and N-cadherin. TK-22 treatment significantly reduced these markers in a dose-dependent manner, demonstrating its efficacy in inhibiting CDK5 mediated pathological signaling. These results suggest that TK-22 can effectively suppress EndMT and potentially reverse key features of IPAH pathology.

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Poster 45

Expression and Production of Malaria CSP(Circumsporozoite) Recombinant Protein as a Vaccine Candidate in *Pichia pastoris*

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Abstract:

Malaria and hookworm infections are two major global health problems that contribute significantly to the rise of anemia, particularly in developing countries. The Center for Vaccine Development is exploring the production of a recombinant malaria vaccine to be combined with an existing vaccine for hookworm infection, with the ultimate goal of creating an effective anti-anemia vaccine. The Circumsporozoite Protein (CSP) of *Plasmodium falciparum* has been a key target for malaria vaccine development. This study aimed to evaluate the expression of four recombinant CSP-derived proteins in *Pichia pastoris* to determine their potential as malaria vaccine candidates. The DNA sequence encoding four CSP variants (PfaCSP0001-00004) was optimized for yeast codon usage and cloned into the pPINKα-HC expression vector. The constructs were transformed into *P. pastoris* PichiaPink Strain #4. After selection using Pichia Adenine Dropout (PAD), 15 colonies were cultured and induced with 0.5% methanol. The expressed recombinant protein was identified by SDS-PAGE and Western blotting using Anti-CSP Rabbit IgG monoclonal antibody. The clones with the highest expression yield were selected to make seed stocks for subsequent production. All four constructs were successfully expressed in *P. pastoris* but displayed a higher molecular weight than theoretically expected, likely due to post-translational modifications. Based on these results, PfaCSP0002 (similar to the CSP region of the R21 vaccine) and PfaCSP0004 (the full-length protein) were selected for further development. Fermentation using 1L bioreactor was performed, yielding 399±48 mg of PfaCSP0002 per L of fermentation supernatant (FS) and 198±11 mg/L for PfaCSP0004. Ion exchange and size exclusion chromatography were employed to purify the proteins. A panel of assays, including SDS-PAGE, dynamic light scattering and HPLC, have also been applied to examine the size, purity, and integrity of the two purified PfaCSP proteins. Collectively, our study shows that the *P. pastoris* PichiaPink-expressed PfaCSP proteins could be produced in a scalable process for further vaccine development.

Poster 12

COOKIE-Pro: Covalent Inhibitor Binding Kinetics Profiling on the Proteome Scale

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Covalent inhibitors are an emerging class of therapeutics, but methods to comprehensively profile their binding kinetics and selectivity across the proteome have been limited. Here we introduce COOKIE-Pro (COvalent Occupancy KInetic Enrichment via Proteomics), an unbiased method for quantifying covalent inhibitor binding kinetics on a proteome-wide scale. Leveraging a covalent inhibitor derived desthiobiotin (DTB) probe, COOKIE-Pro uses a two-step incubation process with mass spectrometry-based proteomics to determine k_{inact} and K_I values for covalent inhibitors against both on-target and off-target proteins. We validated COOKIE-Pro using the BTK inhibitors spebrutinib and ibrutinib, accurately reproducing known kinetic parameters and identifying both expected and novel off-targets. The method revealed that spebrutinib has over 10-fold higher potency for TEC kinase compared to its intended target BTK. We further demonstrate that COOKIE-Pro is compatible with streamlined cysteine activity-based protein profiling (SLC-ABPP) datasets, enabling efficient conversion of competition ratios to meaningful kinetic parameters. By providing a comprehensive view of covalent inhibitor binding across the proteome, COOKIE-Pro represents a powerful new tool for optimizing the potency and selectivity of covalent drugs during preclinical development.

Furthermore, we enhanced the COOKIE-Pro workflow to accommodate covalent fragment screens. While the SLC-ABPP workflow requires only a desthiobiotin iodoacetamide (DBIA) probe, the COOKIE-Pro workflow necessitates a corresponding DTB probe for each covalent fragment. To address the challenge of probe availability, we implemented a direct-to-biology (D2B) synthesis strategy. This approach involves synthesizing both covalent fragments and their corresponding DTB probes in 384-well plates, which are then utilized directly in the COOKIE-Pro workflow without purification. The integration of D2B synthesis with the COOKIE-Pro workflow enables us to screen hundreds of fragments within a week. In contrast to the SLC-ABPP workflow, which often yields numerous false-positive results, our methodology generates high-confidence covalent fragment hits that serve as suitable starting points for subsequent medicinal chemistry optimization.

Poster 46

The Tilting Motion of the Central Core Reveals the Transport Mechanism of the Sarco/endoplasmic Reticulum Ca^{2+}-ATPase.

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Abstract

The sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) transports two Ca^{2+} ions per ATP hydrolyzed from the cytoplasm to the lumen. However, how the ATP hydrolysis remotely drives the Ca^{2+} transport is unclear. In the SERCA1a crystal structures, the ATP hydrolysis is accompanied by the notably increasing tilting angle of the central core (CC) and the Ca^{2+} transport, and the CC tilting angle dramatically decreases in the E2 to E1 transition. We demonstrated that the significantly increasing tilting motion of the CC drove the Ca^{2+} release in the molecular dynamics simulation of the R836A variant, and the dramatic spontaneous decrease in the CC tilting angle of the E2 state drives the transition from E2 to E1 states. The repulsion between the phosphorylated D351 and the phosphate groups in ADP triggers the release of ADP from the SERCA1a headpiece. We proposed a novel SERCA transport mechanism in which ATP hydrolysis drives a significant tilting motion of the CC, which drives Ca^{2+} transport and the A domain rotational motion in the E1P-ADP-$2Ca^{2+}$ to E2P transition. The dramatic spontaneous decrease in the CC tilting angle of the E2 state drives the restart of the transport cycle.

Poster 47

Biodegradable Nanofluidic Drug-Eluting Seed for Durable Intratumoral Drug Delivery and Potent Immune Activation

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Intratumoral immunotherapy offers a promising strategy to improve cancer treatment; however, heterogeneous drug distribution within the tumor and rapid drug linkage limits its therapeutic potential. To address these challenges, we developed the biodegradable Nanofluidic Drug-Eluting Seed (b-NDES), an implantable device designed to improve intratumoral immunotherapy delivery, minimize systemic dissemination, and biodegrade over time, eliminating the need for surgical removal. Four different formulations containing varying ratios of polycaprolactone (PCL), poly(lactic-co-glycolic acid) PLGA and barium sulfate were electrospun to fabricate the devices. The resulting devices feature a hollow cylindrical drug reservoir with a nanofibrous wall to control release. To identify the optimal formulation for device fabrication, we evaluated the morphology, in vitro release of CD40 agonist antibody and degradation profile. The formulation 1:4 PCL:PLGA + barium sulfate showed the most sustained and constant release in vitro; thus, it was selected for further in vivo studies. In the 4T1 Triple Negative Breast Cancer (TNBC) murine model, b-NDES was implanted intratumorally using a minimally invasive clinical trocar-based procedure. The b-NDES enabled sustained localized delivery of CD40 agonist antibody, which remained confined to the tumor. Complete 4T1 tumor eradication was achieved with b-NDES delivered CD40 agonist antibody and STING agonist combination coupled with radiotherapy, without inducing systemic toxicity. These results support b-NDES as a minimally invasive, intratumoral platform for localized, controlled, and sustained drug delivery, well-suited for combination therapies in the treatment of aggressive tumors, such as TNBC.

Acknowledgements: This work is supported by Nancy Owen Breast Cancer Foundation, Golfers Against Cancer, and Houston Methodist Research Institute (A.G., C.Y.X.C.).

Poster 5

Intratumoral biodegradable-Nanofluidic Platform for Localized Multimodal Immunotherapy Enhances Tumor Eradication and Immune Memory

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Tumor-infiltrating lymphocytes (TILs) are key regulators of the tumor immune microenvironment (TIME), with higher TIL levels associated with improved prognosis across various cancers. Although immunotherapy shows promise, its efficacy is often compromised by cancer cell resistance, especially in single- or dual-drug regimens. Multi-drug approaches targeting diverse immune pathways could improve outcomes, but systemic delivery is limited by severe toxicities. To overcome this, we developed a biodegradable nanofluidic drug-eluting seed (b-NDES) platform for sustained, localized release of multiple immunotherapeutic agents. We loaded these implants with immune checkpoint inhibitors (α-CTLA4), immune adjuvants (STING agonist, resiquimod), IL-12, and agonist antibodies (α-CD40), and delivered them intratumorally in mouse models of 4T1 triple-negative breast cancer (TNBC), KPC pancreatic cancer, and KLN205 lung cancer. In the 4T1 model, we explored three-, four-, and five-drug combinations to assess their ability to eradicate tumors. The b-NDES platform markedly improved tumor control, with the five-drug regimen standing out as the most effective—achieving complete tumor clearance in three out of six mice. This five-drug effect was consistent across KPC and KLN205 models, demonstrating robust efficacy across diverse tumor types. Rechallenge experiments in the 4T1 model further revealed durable immune memory, with mice rejecting subsequent tumor inoculation and T cells recognizing tumor cells via IFN-γ secretion. In KPC abscopal models, the five-drug regimen induced systemic immune activation, leading to regression of untreated distant tumors. Serum cytokine and chemokine profiling via Olink platform identified a strong pro-inflammatory signature with the five-drug regimen, correlating with enhanced anti-tumor immunity. Compared to systemic intraperitoneal injections, which triggered a cytokine storm, b-NDES delivery minimized toxicity, maintaining stable body weight and temperature with fewer liver changes. This b-NDES platform provides an innovative, localized approach to multimodal immunotherapy, achieving potent tumor eradication, systemic immunity, and long-term immune memory with reduced toxicity. These findings underscore its potential to advance safer, more effective treatments for aggressive cancers.

Acknowledgement: This work is supported by Nancy Owens Breast Cancer Foundation, Golfers Against Cancer, and Houston Methodist Research Institute (A.G., C.Y.X.C.).

Poster 48

Development and Validation of a UPLC Assay for Quantification of a Novel Anti-CRPC Agent PC257 in Preformulation and Formulation Studies

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Purpose: PC257 is a first-in-class novel compound specifically targets the FKBP52 cochaperone for the treatment of castration-resistant prostate cancer (CRPC). The promise of treatment capability by PC257 is exhibited through the behaviors of inhibition observed towards androgen, glucocorticoid, and progesterone receptors (AR, GR, PR). Our preliminary studies showed that PC257 was insoluble in aqueous solution and showed sparse solubility in organic solvents. Thus, we have developed a simple, reproducible, and specific assay to quantitate PC257 potency to facilitate preformulation and formulation development of the drug by using Waters Acquity H-Class Ultra Performance Liquid Chromatography (UPLC) system. **Methods:** PC257 was separated from the commonly used dosage formulation inactive ingredients on a Waters Acquity BEH C_{18} column (2.1 x 50 mm, 1.7 µm) under a gradient mobile phase of water (A) and acetonitrile (B) at 0.5 mL/min. Prednisone was used as an internal standard (IS) and the compounds were monitored at 252 and 283 nm with a run time of 5 mins. The retention times for PC257 and prednisone (IS) were 2.38 mins and 1.97 mins, respectively. UPLC method was validated according to *U.S. Food and Drug Administration (FDA) Bioanalytical Guidelines for Industry (May 2018)* to prove repeatability and dependability by establishing linearity, accuracy, precision, and stability. Buffer solutions for pH Solubility and Stability studies were prepared to USP standards and the selected pH points were 2.0, 4.0, 5.0, 6.8, 7.4, 9.0, 10.0, and 11.0. Between 1.5 and 2.0 mg of PC257 was dissolved in 500 µL of buffer solution and placed on a shaker at room temperature for 120 hrs for solubility study. PC257 stock solutions were prepared at a concentration of 150 µg/mL. 150 µL of stock solution was added to 350 µL of selected buffer solutions and placed on a shaker for 120 hours at room temperature. Solubility and stability time point samples were retrieved, processed for analysis and stored at -20°C. Upon the last sample retrieval, samples were analyzed via UPLC. **Results:** The assay was linear for PC257 concentrations which ranged from 0.5208 µg/mL to 200 µg/mL (R^2 = 0.999). Intra-day and inter-day accuracy and precision fell within the ±15% allowance outlined by the FDA guidance. pH solubility study showed ≤ 250 µg/mL solubility of PC257 across the entire range of buffer solutions up to 120 hrs. The most stable environments were pH 4.0 and 5.0 buffers, where ≤10% degradation occurred over 120 hours at 7.6 ug/mL. Stability was maintained in acidic and neutral environments for at least 48 hours. The basic pH buffer solutions (9.0,10.0,11.0) showed approximately 40% degradation after 24 hours. The developed UPLC method provided the ability to expound initial preformulation assays through pH solubility and stability studies. This method also assists in optimizing the drug delivery system by quantifying the drug loading and encapsulation efficiency.

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Poster 49

Utilizing GST-Affinity Tag In Site-Selective Labelling Of Proteins

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Chemical probes play a crucial role in biomedical and biological research by enabling the study of protein functions and interactions. These probes feature reactive groups that covalently react to specific sites on target proteins. Site-specific labeling offers significant advantages by reducing sample heterogeneity and preserving protein structure and function. However, traditional methods such as SNAP/CLIP tags, cysteine-specific labeling, and unnatural amino acid incorporation require genetic modifications, which can be expensive, time-intensive, and sometimes incompatible with the target protein.

To address these challenges, this study focuses on developing a chemical probe capable of covalently labeling protein with GST-tag. While probes are developed to bind GST, none have been used in this manner. To evaluate the labelling process and optimize reaction conditions, a series of experiments were conducted as outlined below. An equimolar mixture of GST-tag and pyrimidine-based BODIPY probe were incubated to determine the time required to achieve 90% labeling. The reaction was monitored for 24 hours, with samples collected at various time points and analyzed via SDS-PAGE. Fluorescence imaging was employed to evaluate labeling efficiency. The next phase of this research is to evaluate the probe's binding site via LCMS/MS and asses its functional applicability through FRET.

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Poster 50

Developing *In Vitro* Models of Head and Neck Cancer Tumor Microenvironments using 3D Droplet-Based Bioprinting

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Background: Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer, encompassing nearly all cancers arising from the epithelial linings of the oral cavity, throat, larynx, and nasal cavity. HNSCC progressively resists conventional chemotherapies and is understudied in biomedical research. HNSCC is a disease of several causes, but currently that caused by human papillomavirus (HPV) infection is on the rise.

The tumor microenvironment (TME) enables cancer progression, and the extracellular matrix (ECM) plays a crucial role. Models for studying cancer pathways and testing drugs range from 2D monolayers on plastic to *in vivo* tumor studies in mice. 3D hydrogel systems offer advantages over other models: they enable cell organization, migration, and interaction with a surrounding hydrogel-based ECM, while preserving a compact *in vitro* format.

High-throughput drug screening (HTS) is conducted primarily in 2D multi-well plates, due to restrictions in automated dispensing, liquid handling, and imaging. Although dispensers enable bulk deposition of cells and hydrogel solutions across multi-well plates, such instruments do not have the requisite spatial or volume resolution to print organized patterns *within* each well. Here we describe the use of a novel droplet-based bioprinter (DB-BP) to create spatially organized arrays of HNSCC within hydrogels with varying moduli and bioactive peptide epitopes.

Methods: A benchtop DB-BP (RASTRUM, Inventia Life Sciences) was used to bioprint two HNSCC cell lines: FaDu (HPV^-) and 2A3 (HPV^+). Cell identity was assayed with short tandem repeat (STR) profiling and immunostaining for E7 protein in the HPV^+ line. Separate orthogonal solutions were printed rapidly as coincident 1 µL droplets: a bioink (4-arm maleimide-functional poly(ethylene glycol) (PEG)) and an activator (cells and bis-thiol linear PEG in aqueous solution). Upon contact, droplets instantly crosslink and encapsulate the cells of interest as microgel voxels < 500µm in diameter. The bioprinted 3D cell arrays were cultured in media and assayed for viability and phenotype.

Results: Cells retained high viability in hydrogels across 10 days. Immunostaining confirmed high proliferative capacity and epithelial phenotype. Cells developed into asymmetric multicellular clusters, which varied inversely in size as a function of gel modulus. No quantitative difference was recorded in growth rate between FaDu and 2A3 cells.

Conclusions: These early studies demonstrated the feasibility of the platform for encapsulation of both HNSCC lines. Fluorescent viability assays demonstrated high cell survival through day 10 and progressive growth of multicellular clusters, confirming that the 3D printed hydrogel models can support cell growth and proliferation. In future work, these models can be assayed with anti-cancer therapeutics to further compare the platform against other 2D or 3D *in vitro* models.

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Poster 51

Development of a Sensitive LC-MS/MS Method for Quantifying DNA Methylation and Hydroxymethylation

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Abstract

Purpose: DNA methylation and hydroxymethylation are important epigenetic modifications that regulate gene expression and genome stability that are closely related to cancer development and prognosis. The bisulfite conversion-based assay or antibody-based enzyme-linked immunosorbent assay for methylation detection has low specificity, is labor-intensive, and/or does not differentiate methylation from hydroxymethylation. To address these issues, we developed a sensitive, reproducible, and specific LC-MS/MS method for simultaneous quantification of 2'-deoxycytidine (2-dC), 5-methyl-2'-deoxycytidine (5-mdC), and 5-hydroxymethyl-2'-deoxycytidine (5-hmdC) in enzymatically digested DNA preparations. **Methods**: A SCIEX Triple Quad™ 6500 mass spectrometry equipped with a UPLC system was used to simultaneously separate 2-dC, 5-mdC, and 5-hmdC on a reverse-phase C18 Waters column (Atlantis T3, 3 µm, 2.1 × 100 mm) in a gradient mobile phase. The analytes were enzymatically hydrolyzed from genomic DNA purified from cell culture. MS detection was in positive electrospray ionization mode using MRM transitions that had been optimized for each compound. **Results**: The study compounds exhibited MRM transitions at m/z 228.082→ 112.1 for 2-dC; 242.110→ 126.1 for 5-mdC, and 258.139→ 142.1 for 5-hmdC. The standard curve concentrations for 5-hmdC ranged from 0.025 ng/mL to 10 ng/mL, while those for 2-dC, and 5-mdC ranged from 0.25 ng/mL to 50 ng/mL. The total assay run time was 6 minutes. All compounds were found to exhibit excellent stability under the sample extraction and analytical conditions, confirming accurate and reproducible quantification of all compounds. The methods for all 3 compounds were linear in the standard curve ranges ($R^2 > 0.999$). The intra-day and inter-day precision and accuracy were acceptable with deviations less than 10%. The developed assay is being applied for the quantification of DNA methylation in various cell culture media. **Conclusion**: We have developed a sensitive, specific, and reproducible LC-MS/MS method for quantification of 2-dC, 5-mdC, and 5-hmdC, for evaluation of DNA (hydroxy)methylation in cell culture. This assay may be used in tissue samples and applied to clinical biomarker studies.

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In Vitro Metabolic Stability Studies of B4-007, a Novel Peptide for Triple-Negative Breast Cancer Treatment

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Purpose: B4-007 is a novel Ephrin agonist peptide comprised of 15 amino acids. This peptide has a high nano-molar binding affinity for the receptor EphB4 and thus is being developed as first-in-class therapy for the treatment of triple-negative breast cancer (TNBC). This study aims to evaluate the metabolic stability of B4-007 in various matrices in order to optimize chemical structure modification and predict in vivo disposition of the peptide. **Methods**: B4-007 was tested in the following matrices: mice plasma, human plasma, human cell line (A2780) with fetal bovine serum (FBS), non-cell media without FBS, and cell-conditioned media without FBS. Prepared triplicates of each were incubated in a water bath at 37ºC with a beginning B4-007 concentration of 10 µg/mL. Serial samples were collected at multiple time points up to 6-hour or 24-hour period. Protein precipitation with acetonitrile was used to extract B4-007 from samples. The analysis was conducted on a SCIEX 4000 LC-MS/MS System with chromatographic separation performed by a Kinetic HILIC column (50 x 2.1 mm, 2.6 µm, 100 Å). Using gradient elution and L-Proline as the internal standard (IS), the mobile phases consisted of 0.25% formic acid in water and 0.25% formic acid in acetonitrile. In positive ionization mode, the Multiple Reaction Monitoring transitions were at m/z 854→1215 for B4-007 and m/z 122→75 for IS. Metabolite identification was conducted on SCIEX X500B accurate LC-MS/MS instrument. **Results**: A difference in degradation patterns was observed between mice and human plasma. In the 24-hour stability study, B4-007 degraded more rapidly in mouse plasma with an initial half-life of 1.29 hours. The concentration declined quickly, leaving 20% of B4-007 after 6 hours and 4% after 22 hours. In contrast, B4-007 was more stable in human plasma, revealing slower degradation with an initial half-life of 29.7 hours. After 6 hours, about 80% of B4-007 remained, and by 22 hours, 65% remained. Additionally, for the three cell culture media, the presence of cellular byproducts and FBS correlated with increased degradation of B4-007, suggesting the potential influence of enzymatic or protein factors. In 6-hour stability studies, B4-007 demonstrated the greatest stability in non-cell media without FBS, moderate stability in cell-conditioned media without FBS, and the least stability in A2780 media with FBS. Then using SCIEX X500B accurate LC-MS/MS instrument, two major metabolites were predicted and identified for B4-007 in mouse plasma. **Conclusion**: These studies provide insights into the stability of B4-007 across various matrices and establish initial degradation profiles. These preliminary results will be helpful in exploring the degradation pathways of the peptide and investigating the key enzymes impacting its stability. Moreover, this knowledge can be used to guide the synthesis of more stable analogs of B4-007, optimizing its potential as a therapeutic agent.

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Poster 53

Dual-Platform Fluorescent Probes: Advancing RIPK1 Target Engagement with NanoBRET and TR-FRET Assays

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Target engagement assays are critical for drug discovery, with Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) and Nano Bioluminescence Resonance Energy Transfer (NanoBRET) representing two complementary approaches for biochemical and cellular evaluation. Traditionally, these platforms demand distinct fluorescent tracers tailored to their unique detection systems, requiring separate probe development for comprehensive target characterization. Despite their widespread adoption, the development of platform-specific fluorescent tracers often leads to increased costs and experimental complexity. In this study, two fluorescent tracers, T2- BODIPY -FL and T2-BODIPY-589, initially developed for receptor-interacting protein kinase 1 (RIPK1) target engagement studies in TR-FRET and NanoBRET applications respectively, were systematically evaluated for their performance across both platforms under various detection parameters. By evaluating their performance across both assay systems, we demonstrate that both tracers can effectively bridge biochemical and cellular assays, delivering reliable measurements. T2- BODIPY-589, with its red-shifted spectral properties, exhibits superior performance in NanoBRET assays (Z' up to 0.80) while maintaining acceptable functionality in TR-FRET systems (Z'=0.53). In contrast, T2-BODIPY -FL provides optimal performance for TR-FRET (Z'=0.57) but also demonstrates potential for use in NanoBRET (Z' up to 0.72), albeit with reduced efficiency. Competition assays with an unlabeled inhibitor yielded consistent binding constants across all tracer-platform combinations, validating their reliability for quantitative measurements. Our findings highlight the potential for integrating a single tracer across diverse assay platforms, reducing the need for separate probe development and enhancing experimental consistency. This approach has broad implications for streamlining assay development, improving data comparability, and enables more direct comparisons between biochemical and cellular data, with broader implications for integrated drug discovery programs across diverse target classes.

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Poster 54

Leading RNA Therapeutics: Houston Methodist RNACore

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The RNAcore at the Houston Methodist Research Institute is staffed by experienced scientists, who produce high-fidelity research- and clinical-grade RNA, including mRNA, modified mRNA (mmRNA), self-amplifying RNA, circular RNA and long noncoding RNA, for the support of fundamental research and clinical applications. The RNAcore is an emerging leader in RNA synthesis, generating RNA constructs for the scientific and medical communities in the Texas Medical Center and across the world.

We are an academic group centered in the largest medical center in the U.S., driven by our passion for mRNA therapeutics, and working with a corporate discipline to help academic groups and small companies transform their great RNA ideas into clinical reality. The RNAcore is equipped with all the necessary tools to perform plasmid development, template DNA production, RNA synthesis, and RNA quality assessment. We have developed our proprietary processes for synthesizing, purifying, lyophilizing, encapsulating, and validating clinical-grade mRNA drugs. The Center is enriched by scientists with skills in RNA construct design, synthesis, purification, and validation; a GLP program to generate pre-clinical data for IND submissions; a cGMP team with clean rooms to manufacture clinical-grade RNA therapeutics; a first-in-man clinical trials unit; and faculty collaborators in the Department of Nanomedicine who devise customized solutions for RNA delivery.

The RNAcore provides services for developing and generating high-fidelity RNA for any gene/loci of interest. With efficient and fast construct generation, we can provide a wide range of generic or personalized RNA molecules for any desired species, with specified modifications that can be tailored to produce the optimal expected experimental outcomes. We specialize in helping our clients from the initial stages of construct design and work with them throughout the project to maximize the potential of taking their therapies all the way to the clinic. In addition, we introduce a new concept of hospital-based RNA therapeutics, which include vaccines, preventives, and therapies that target diseases such as cancer, parasitic and viral infections, Alzheimer's, aging, cardiac regeneration, cholesterol, and more.

Contact us today if you are looking for a personalized approach that takes your research to the next level by using mRNA therapeutics. We are accepting new clients and offer a variety of mRNA services and analytical assays to help you achieve your concept to commercialization goals. We can help you to establish proof-of-concept, and work with you all the way to the clinic. We are also open to collaborations, and sponsored research agreements, where industry typically only offers a fee-for-service option.

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Poster 55

Investigating the Immune Effects of Radiation Dose Enhancement using Internalized Gold Nanoparticles

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Unrepaired DNA damage may lead to mis-segregation of chromosomes during cell division and formation of smaller immature nuclei called micronuclei[1]. The poorly formed nuclear envelope around these micronuclei exposes DNA to cytoplasmic sensors[1,2]. Cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS), a DNA sensor, produces the second messenger cyclic GMP-AMP (cGAMP)[1]. cGAMP binds and activates the adaptor protein STING (stimulator of interferon genes), triggering a type-I interferon response, leading to innate immune cell-mediated clearance of the damaged cell[2]. We hypothesize that radiation-induced genomic DNA damage, amplified by gold nanoparticles (GNP), leads to cGAS activation and stimulation of an inflammatory response.

We propose to test this using cetuximab-conjugated gold nanorods (GNRs), our prototype GNP, that enhance receptor-mediated internalization into colorectal cancer cells overexpressing epidermal growth factor receptor (EGFR). Firstly, we evaluated GNRs conjugated with polyethylene glycol (PEG), control antibody (IgG), or cetuximab in two murine colorectal cancer cell lines, CT26 and MC38. The cell lines were transduced to overexpress human EGFR. Preliminary immunofluorescence results suggest that irradiation of cells with internalized cetuximab-conjugated GNRs significantly increases micronuclei formation compared to irradiation of cells treated with PEGylated or IgG-conjugated GNRs. This observation suggests potential activation of the cGAS-STING pathway, which may trigger an antitumor immune response. cGAS-STING activation and co-culture phagocytosis assays will assess immune consequences of GNP-mediated radiosensitization *in vitro*. To further confirm additive effects of our conjugated GNRs, they will be evaluated for the ability to modulate clonogenic survival after irradiation. Lastly, C57Bl/6 mice bearing bilateral ovalbumin-expressing MC38 and CT26 thigh tumors will be utilized to investigate the potential of immune activation and abscopal effect. The studies are currently in progress to establish definitive conclusions regarding these mechanistic relationships. This investigation advances our understanding of nanomaterial-biological interactions, revealing novel opportunities for therapeutic development in nanomedicine and immunotherapy.

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Poster 34

Targeting RNase H2: A Dual Mechanism Strategy to Elevate Replication Stress, DNA Damage, and Antitumor Immunity in Triple-Negative Breast Cancer

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Triple-negative breast cancer (TNBC) remains one of the most aggressive breast cancer subtypes due to the absence of targeted therapies and poor clinical outcomes. Our study reveals that TNBC cells rely on overexpression of Ribonuclease H2 (RNase H2) particularly its catalytic subunit RNASEH2A to overcome oncogene-induced senescence and cope with elevated replication stress. Elevated RNASEH2A expression in TNBC highlights RNase H2 as a promising therapeutic target. We assessed the impact of RNASEH2A silencing and pharmacologic inhibition of RNase H2 using R14, a selective small-molecule antagonist. Both genetic and pharmacological disruption of RNase H2 increased replication stress markers phosphorylated RPA32 and γH2AX, leading to suppressed tumor growth and prolonged survival in TNBC models, with minimal impact on normal mammary epithelial cells. Enzymatic assays confirmed R14 as a potent and specific inhibitor of RNase H2. In vivo, R14 demonstrated favorable safety and tolerability in mouse models. RNase H2 inhibition also sensitized TNBC cells to ATR and PARP inhibitors, showing strong potential for combination therapy. Notably, RNase H2 inhibition triggered immune activation through accumulation of cytosolic single-stranded DNA, enhancing chemokine expression CCL5, CXCL10 and immune cell infiltration. This immune activation synergized with immune checkpoint blockade, further amplifying antitumor responses. Together, our findings identify RNase H2 as a novel, dual-function therapeutic target in TNBC- capable of both intensifying replication stress and potentiating antitumor immunity. The selectivity and safety of R14 support its potential in combination therapies involving DNA damage response inhibitors and immunotherapies.

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Poster 56

Sustained Release of Polymer-Antiretroviral Conjugates with Enhanced Solubility and Stability from Nanofluidic Drug Delivery Implant for HIV Pre-Exposure Prophylaxis

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The development of innovative drug delivery systems is crucial for improving the efficacy and patient compliance of HIV pre-exposure prophylaxis (PrEP) drugs. This study investigates a refillable subcutaneous nanofluidic drug delivery implant (NanoDDI) designed for the sustained release of hydrophobic antiretroviral drugs, dolutegravir (DTG) and bictegravir (BIC). The NanoDDI technology utilizes Si/SiC nanochannel membranes to achieve sustained drug release via diffusion; however, the extremely low water solubility and poor aqueous stability of DTG and BIC limit the diffusion and release of the drugs. To address these limitations, we synthesized conjugates of the drugs and a hydrophilic polymer (HP) to enhance solubility and stability. The conjugates (HP-DTG and HP-BIC) exhibited significantly improved solubility in PBS compared to the free drugs (39 mg/mL for HP-DTG and 170 mg/mL for HP-BIC). Stability studies conducted at 37°C and 60°C showed that while the free drugs were unstable in PBS, HP-DTG and HP-BIC remained stable over three months. In vitro release studies demonstrated sustained-release profiles, with 44.2% of HP-DTG and 33.7% of HP-BIC released over three months. Preliminary pharmacokinetic data in rats indicated that DTG and BIC released from NanoDDI were maintained in rat plasma for up to two months, suggesting a promising approach for prolonged PrEP drug administration. Additionally, the refillability of the NanoDDI benefits patients by avoiding the need for repeated surgical interventions to replace implants. This key advantage, coupled with the improved stability and solubility of the antiretroviral drugs, will contribute to reduced healthcare costs, improved patient adherence, and overall effectiveness of HIV PrEP.

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Quantification of Isoniazid and its Metabolites in Human Plasma for PK/PD Analysis

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Introduction: Tuberculosis (TB) is commonly found in immunocompromised individuals, such as those with HIV, who often experience comorbid conditions like atherosclerosis and diabetes. Isoniazid (INH) is a commonly used medication in multidrug therapy for TB. Preliminary studies have shown alterations in patients' risk of diabetes and cardiovascular diseases following the usage of isoniazid. Our goal is to establish a correlation between isoniazid pharmacokinetics (PK) and its pharmacodynamic (PD) outcomes. Previously published methods for the quantification of isoniazid and its metabolites require multiple column separations and have narrow linear curve ranges. Thus, it is important to design a simple analytical method that can quantify concentrations of isoniazid and its metabolites simultaneously.
Purpose: Develop and validate a simple, sensitive, specific, and reproducible LC-MS/MS method for quantification of isoniazid (IH), N-acetyl isoniazid (AcIH), Isonicotinic Acid (INA), hydrazine (HZ), and acetylhydrazine (AcHZ) in human plasma.
Method: Isoniazid, acetyl isoniazid, and isonicotinic acid were analyzed directly, while hydrazine and acetyl hydrazine were examined after undergoing derivatization with p-tolualdehyde. Chromatographic separation utilized a normal-phase HILIC column with gradient elution consisting of mobile phase A (an aqueous solution of 10 mM ammonium formate, pH 6.96) and mobile phase B (pure acetonitrile). MS/MS detection was performed in multiple reaction monitoring mode (MRM) with ion-pairs (m/z) of 138→121.10, 180→120.90, 124→80, 237→120.10, 177.10→118.20 for IH, AcIH, INA, HZ, and AcHZ, respectively. A single-step protein precipitation extraction method was employed before LC-MS/MS quantification.
Results and Discussion: The calibration curves for Isoniazid, acetyl isoniazid, and isonicotinic acid ranged from 80 ng/mL to 10,000 ng/mL; for hydrazine, 10–1,000 ng/mL; and for acetylhydrazine, 100–10,000 ng/mL. The variation in calibration ranges for hydrazine and acetylhydrazine was attributed to the 1:10 ratio used during their derivatization process. The calibration curves for all analytes exhibited linearity, with correlation coefficients (r) exceeding 0.993. Currently, validation studies are underway to evaluate parameters including intra-day and inter-day precision and accuracy, stability under various conditions (i.e. autosampler, bench-top, freeze-thaw cycles, and long-term), matrix effects, and recovery. So far, the method has proven that it is possible to analyze all five compounds in a single normal-phase HILIC column with a broader concentration span suitable for clinical sample analysis.
Conclusion: A robust, sensitive, specific, and reproducible LC-MS/MS method has been developed to facilitate the accurate quantification of isoniazid and its metabolites in clinical plasma samples for PK/PD analysis.

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Imaging Microglia Activation by TREM2-ImmunoPET

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Neuroinflammation, an inflammatory response in the central nervous system, is seen in many neurological diseases and can be evaluated by examining immune-associated glial cells like microglia. TREM2 (triggering receptor expressed on myeloid cells-2) is a key target for developing treatments for diseases such as Alzheimer's, due to its role in microglial activation, neuroinflammatory and neurodegenerative pathways, and tumor progression. This study aims to detect neuroinflammation using ImmunoPET (Positron Emission Tomography), a non-invasive imaging technique based on antibodies. We engineered and analyzed ^{89}Zr labeled TREM2 antibody for its specificity toward TREM2 in cell models and its uptake in a mouse model of neuroinflammation.

Zirconium-89 (^{89}Zr) was used to radiolabel a TREM2 bispecific agonist antibody (TREM2-Tfr_BsAb), which also targets the transferrin receptor (TfR) to help it cross the blood-brain barrier. The TREM2 antibody and a control antibody (IgG) were conjugated with deferoxamine isothiocyanate (DFO-CNS) in DMSO for 2 hours at 37°C. The reaction's completion and purity were verified through radio-iTLC analysis. The specificity of TREM2 binding was tested using wild-type (WT) and TREM2-overexpressing (TREM-2 OE) HEK 293 cell lines. In vivo biodistribution of the tracer was evaluated by PET/CT imaging at 4-, 24- and 48-hours post-injection in healthy mice. Neuroinflammation was induced by administering lipopolysaccharide (LPS) at a dose of 2 mg/kg before PET tracer injection.

^{89}Zr-TREM2-Tfr_BsAb and the IgG control achieved activity yields of 74±3% (n=6) and 76±3% (n=6), respectively. Both showed radiochemical purity higher than 99% and remained stable in PBS at 4°C for up to 48 hours. TREM-2 OE cells showed 3.3- and 3.6-fold higher uptake of ^{89}Zr-TREM2-Tfr_BsAb compared to WT cells at 30 and 60 minutes. Compared to the control antibody, ^{89}Zr-IgG, ^{89}Zr-TREM2-Tfr_BsAb had more than 6-fold higher uptake in TREM-2 OE cells at both time points. In healthy animals, PET imaging showed more brain uptake of ^{89}Zr-TREM2-Tfr_BsAb compared to ^{89}Zr-IgG at 48 hours post-injection. In the LPS-neuroinflammation model, ^{89}Zr-TREM2-Tfr_BsAb uptake was 2-fold higher in the brains of LPS-inflamed mice compared to the control at 24- and 48-hours post-injection.

In conclusion, we developed a TREM2-specific imaging agent, ^{89}Zr-TREM2-Tfr_BsAb, for ImmunoPET of microglial activation in a neuroinflammation model. Our study showed TREM2-mediated uptake in cells and higher brain uptake in LPS-inflamed mice, indicating its potential as a valuable tool for neuroinflammatory screening.

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Poster 59

4-(heptyloxy)phenol Induces Unfolded Protein Response, Leading to Programed Cell Death in Ewing Sarcoma Cells

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Ewing sarcoma is a rare and aggressive cancer of the bones and soft tissues, predominantly affecting children and adolescents, and presents significant therapeutic challenges. We identified 4-(heptyloxy)phenol (AC-45594) as a potential therapeutic agent capable of inducing cell death in Ewing sarcoma (ES) cells. We used multiple assays, including cytotoxic assay, RT-qPCR, RPPA, mass spectrometry, and immunoblotting, etc., to investigate the mechanisms of AC-45594 in inhibiting the growth of ES cells. Cell viability assays revealed that AC-45594 specifically inhibited the growth of ES cells among fifteen tested cell lines from eight cancer types/origins. The study of the chemical structure-activity relationship showed that phenol's hydroxyl group and the alkoxy chain's length are crucial for inhibiting cell growth, with an optimal alkyl chain length of seven to nine carbon atoms. Further analyses through gene expression, proteomics, and immunoblotting indicated that AC-45594 activated the unfolded protein response (UPR) and apoptosis in ES cells. These findings suggest that AC-45594 could be a promising agent for treating ES tumors by specifically targeting and killing cancer cells through the induction of ER stress and the activation of UPR and apoptosis pathways.

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Poster 4

Investigating the Role of SSRIs' as a Potential Therapeutic for Neurodegenerative Diseases

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Neurodegenerative diseases (NDDs) are prevalent in the U.S., with chronic neurodegenerative conditions predicted to double in the next two decades. Many of these diseases share similar characteristics, including aggregate-related pathologies and mitochondrial dysfunction. Proper mitochondrial recycling via mitophagy is crucial for maintaining mitochondrial homeostasis and overall neuronal health. Initiation of mitophagy requires the stabilization of PINK1 on the outer mitochondrial membrane. Previously, the Kirienko Lab screened 45,000 compounds for PINK-1 (worm ortholog of PINK1) stabilizers in *C. elegans* and identified sertraline as a promising candidate. Sertraline is an FDA-approved selective serotonin reuptake inhibitor (SSRI) commonly prescribed to treat depression. It has also been shown to increase survival and neurogenesis in mammalian Huntington's and Parkinson's disease models.

Our follow-up experiments showed that sertraline increased motility, average distance traveled, and rotation index in *C. elegans* expressing β-amyloid in body wall muscle cells. Moreover, it decreased protein aggregation in Alzheimer's, Huntington's, and Parkinson's disease models, as well as age-dependent aggregation of non-pathogenic LBP-2 protein. Testing additional SSRIs showed that some, but not all, had these neuroprotective effectives. Supplementation with serotonin did not affect phenotypes, but inhibition of mitophagy abolished the rescue, suggesting these molecules are moonlighting, with some function in mitochondrial metabolism. Treatment with cobalamin (vitamin B12), a critical cofactor in mitochondrial branched-chain fatty acid metabolism, or metformin, a compound known to improve mitochondrial function, alleviated paralysis in the Alzheimer's disease model, corroborating the relationship between improved mitochondrial health and alleviation of NDD symptoms. Our results reveal the potential of repurposing SSRIs as a therapeutic for NDDs.

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ABSTRACT:

Structural and Functional Investigation of Antiviral Mitochondrial Drug Toxicity

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RNA viruses such as SARS, influenza, and hepatitis C virus pose a significant pathogenic risk to global populations and are responsible for 44% of all emerging human infectious diseases. One approach to inhibit RNA viruses is by targeting the viral RNA polymerase with antiviral drugs known as nucleotide inhibitors (NIs), which act as chain terminators. However, many of these NI compounds fail late-stage human clinical trials due to severe drug toxicity caused by off-target effects on host mitochondrial replication machineries. The human mitochondrial RNA polymerase POLRMT is a major off-target of NIs, but the molecular mechanisms of POLRMT-NI interactions are not well-understood and pose a major liability to drug development. We utilize a gel-based approach to determine the kinetics parameters and inhibitory effects of select NIs as they are differentiated by or incorporated by POLRMT.

We observed that certain NI compounds interacting with POLRMT resulted in a cleaved product rather than the anticipated incorporation activity. There is no clear evidence of POLRMT showing exoribonuclease activity in the presence of an NI compound. We are currently exploring the effect of certain NI compounds on potential POLRMT excision activity stimulation. This research will contribute to understanding the mechanisms of POLRMT incorporation of NIs for future design of antivirals with high specificity, increased therapeutic index, and low risk of emergent viral resistance.

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Comprehensive Evaluation of Physicochemical, Metabolic and *in vivo* Characteristics of GT-14, a Novel Inhibitor of $G\alpha_i2$ Protein

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Prostate cancer affects millions of men globally and is second most frequent cause of cancer among males. A substantial proportion of these patients develop metastatic castration-resistant prostate cancer (mCRPC) that progresses irrespective of castration levels of serum testosterone. Despite significant advancements in therapies, mCRPC remains incurable and can cause considerable disease burden. $G\alpha_i2$ protein has been identified as a key molecular driver of metastasis and plays a crucial role in facilitating cell migration and invasion in prostate cancer cells, positioning it as a valuable target for treating mCRPC. To validate $G\alpha_i2$ protein as a therapeutic target, novel small molecule inhibitors were identified and synthesized by Dr. Oyelere's group at Georgia Tech Institute of Technology. GT-14, identified as [(E)-4-((1-(1-methyl-1H-indol-2-yl) ethylidene) amino) phenol], was selected as the lead prototype compound based on its inhibition of $G\alpha_i2$ intracellular activity and cell migration assays. In this study, we performed a comprehensive evaluation of physicochemical properties (solubility, stability, lipophilicity), Caco-2 cell permeability, hepatic microsomal metabolic stability and biotransformation, and *in vivo* PK behavior of GT-14 to assess its potential as a drug candidate for mCRPC.

The results showed that GT-14 exhibits limited water solubility at room temperature (0.11 mg/mL) but shows good solubility in solvents including dimethyl sulfoxide and dimethyl acetamide (>80 mg/mL), and limited solubility in cosolvents such as PEG 300, PEG 400, Labrasol, propylene glycol, and Labrafac (5.3-17.2 mg/mL). A stable co-solvent formulation was developed to enable intravenous administration for pharmacokinetic studies. GT-14 has a log P value of 2.38 ± 0.04, indicating notable lipophilicity. The compound achieves maximum solubility at a pH of approximately 4.6, with reduced solubility at higher pH values. It remains stable across a broad pH range (1.2–7.4) but degrades in strongly basic conditions (pH > 9). GT-14 exhibits high permeability (1.3×10^{-5} cm/s) in Caco-2 cell culture models. Metabolic studies reveal that GT-14 undergoes Phase I metabolism. The pharmacokinetic and tissue distribution study was performed in male Sprague-Dawley rats following an intravenous administration of GT-14. The concentration-time profile is characterized by a rapid distribution phase (distribution half-life ~ 16 min) followed by a slower elimination phase from plasma (elimination half-life ~4.5 hr). Also, GT-14 exhibits large apparent volume of distribution (~ 25 L/kg) implying wide distribution to different organs from the central compartment. Tissue distribution analysis indicated the highest concentration in the prostate, followed by the kidneys, lungs, heart, and liver. These findings highlight GT-14's promising characteristics, reinforcing its potential as a new chemical entity for therapeutic development.

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Developing GPR56-Targeted Antibody-Drug Conjugates for Triple-Negative Breast Cancer Treatment

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Triple-negative breast cancer (TNBC) poses a significant challenge in oncology, comprising 10-15% of all breast cancer cases. Its aggressive nature, high metastatic potential, and lack of targetable receptors result in limited treatment options and poor prognosis. The emergence of chemotherapy resistance further complicates TNBC management, underscoring the urgent need for novel therapeutic strategies. Antibody-drug conjugates (ADCs) have emerged as a promising approach for targeted cancer therapy. These innovative drugs combine monoclonal antibodies (mAbs) specificity with potent cytotoxic payloads, enabling precise delivery of chemotherapy drugs to cancer cells. This targeted approach potentially enhances efficacy while minimizing damage to healthy tissues, making ADCs an attractive option for developing more effective TNBC treatments.

Our research identified G protein-coupled receptor 56 (GPR56) as a promising target for ADC development in TNBC. Analysis of The Cancer Genome Atlas data revealed that high GPR56 expression correlates with poor overall survival in breast cancer patients and is significantly elevated in TNBC compared to non-TNBC. Notably, GPR56 demonstrated a higher tumor-to-normal tissue expression ratio than TROP2, an approved ADC target. Therefore, we hypothesize that GPR56 is a potential target for treating TNBC. We previously developed an anti-GPR56 ADC (10C7-Duo) by conjugating duocarmycin payload to a GPR56-specific mAb, 10C7, which had significant antitumor efficacy in colorectal cancer models. Importantly, 10C7-Duo showed high potency in TNBC cell lines with high GPR56 expression, exhibiting target-dependent cytotoxicity. Though 10C7-Duo has robust antitumor efficacy, 10C7 mAb showed agonist activity that may have long-term tumor-promoting capabilities. Therefore, we are currently developing new and improved ADCs incorporating different drug payloads and an anti-GPR56 mAb, 9E3, which does not exhibit agonist activity. Future work will focus on both ADC single-agent and combination therapies using TNBC cell lines, patient-derived samples, and xenograft mouse models.

This study aims to develop novel GPR56-targeted ADCs for TNBC, potentially enhancing efficacy, reducing side effects, and overcoming therapy resistance. By addressing the urgent need for effective TNBC treatments, this approach could significantly improve outcomes for TNBC patients.

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Poster 65

Nuclear Factor kappa-B Inhibitor IKK2 Regulates Nav1.7 CHANNEL FUNCTIONS in the hIPSC-Derived Sensory Neurons

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Nuclear factor-kappa B (NF-kB), a family of transcription factor proteins, is considerably conserved from insect to human and plays crucial roles in a large variety of cell physiological and pathological processes, including neurodegenerative diseases, memory storage, immunity and cancer, and chronic pain. IKK consists of two homologous catalytic subunits IKKα (IKK1) and IKKβ (IKK2), and a regulatory subunit IKKγ (NEMO). Among the nine subunits of Nav channels, the tetrodotoxin-sensitive (TTX-S) Nav1.7 channel has proved critical for the excitability and chronic pain highly expressed in dorsal root ganglion (DRG) neurons. The active form of NF-kB reversibly interacted with Nav1.7 channels and TNF-α/NF-kB signaling escorts to chronic hyperexcitability of DRG neurons. NF-kB regulates Nav1.7 channel functions in a non-transcriptional manner, which is critically implicated in various neurophysiological and diseases. Based on this information, we hypothesize that pharmacological inhibition of the IKK2/Nav1.7 complex could counteract the IKK2-dependent modulation of Nav1.7 functions. To that end, we combined in-cell split-luciferase assay (LCA), pharmacological interrogation, and whole-cell patch-clamp electrophysiology in hiPSC-derived sensory neurons, as well as viral vector-based knockdown of IKK2 was implemented for discovery and functional validation of Nav1.7 channel. Bay-11-7082 (IKK inhibitor) was found to significantly inhibit IKK2/Nav1.7 complex assembly using the LCA with an EC_{50} value of 347 nM. In addition, whole-cell patch-clamp recordings in the presence of Nav1.8 blocker (A-803467) of hiPSC-derived sensory neuronal cells expressing Nav1.7 showed that Bay-11-7082 selectively regulates peak current density, tau (τ) fast inactivation, voltage-dependent activation, steady-state inactivation, long-term inactivation curves as well as cumulative use dependency of Nav1.7. Further, employing AAV-shIKK2-mediated knockdown of IKK2 abolished all the Nav1.7 functionality compared to AAV-shControl expressing sensory neurons. These findings reveal a novel interaction between IKK2 and Nav1.7, providing insights into NF-κB signaling and a potential therapeutic target for neuropathic conditions.

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Poster 2

Two-Pronged Precision: Evaluating a novel dual-targeting antibody-drug-conjugate based therapy to combat colorectal cancer.

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A significant hurdle in colorectal cancer (CRC) treatment is the relapse of residual disease, which can be attributed to cancer stem cells (CSCs). CSCs potentiate metastatic progression by exploiting their capacity to self-renew and differentiate. Furthermore, this immortal cell population exhibits plasticity, allowing cells to alter their phenotype in response to environmental cues that bolster inherent drug resistance. As a bona fide CSC marker, LGR5 is a promising drug target. We generated anti-LGR5 antibody-drug conjugates (ADCs) that inhibited tumor growth yet failed to prevent relapse following treatment completion. Follow-up studies indicate recurrent tumors evade therapy by converting into a drug-resistant LGR5-negative ($LGR5^-$) state and, at least in part, depend on MET-STAT3 cascade activation for survival. To eliminate drug-resistant $LGR5^-$ cells, we generated MET-targeted ADCs by conjugating a highly selective MET monoclonal antibody (mAb) backbone to the DNA-crosslinking payload pyrrolobenzodiazepine via a site-specific conjugation methodology. The MET ADC was evaluated for cancer cell-killing efficacy in parallel with MET mAb, non-targeting control mAb (cmAb), and control ADC (cADC). MET ADC demonstrated high efficacy and potency in MET-expressing CRC cells in vitro, while unconjugated MET mAb, cmAb, and cADC exhibited minimal effects. Additionally, MET ADC had no impact on MET KD CRC cells, demonstrating its specificity. Safety studies in immunocompetent mice showed the MET ADC was well-tolerated with minimal toxicity. Moreover, when evaluated in CRC cell line xenografts, the MET ADC induced significant tumor regression and prolonged overall survival. However, MET ADC monotherapy alone did not effectively prevent tumor relapse. Thus, an ADC combination strategy dual-targeting $LGR5^-$ and $LGR5^+$ cells is a more promising approach to eliminating heterogeneous tumors. Pilot cytotoxicity assays evaluating the combination of MET ADCs with next-generation LGR5 ADCs showed moderate synergistic effects *in vitro.* The improved iteration of our LGR5 ADC was produced by attaching a topoisomerase I inhibitor derivative to a previously characterized LGR5 mAb backbone in a site-specific manner. Currently, we are investigating the efficacy of combining MET ADCs and LGR5 ADCs in patient-derived xenograft (PDX) models of CRC. These findings present a novel mechanism underpinning CRC plasticity and a rationale for an ADC-based treatment strategy to overcome colorectal tumor resistance and heterogeneity.

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A High Content Phenotypic and Reverse Proteomics Platform for Rapid Discovery of Cell-Specific Antibodies for Drug Conjugate Development

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Targeted drug conjugates (TDCs) represent a promising therapeutic strategy, enabling selective delivery of cytotoxic agents to diseased cells. However, the development of highly specific antibodies remains a critical challenge, particularly for diseases characterized by cellular heterogeneity. We present a generalizable platform that integrates high content imaging, single-cell analysis, and reverse proteomics to guide the discovery of monoclonal antibodies (mAbs) with cell-type specificity. First, we profiled a panel of bladder cancer cell lines using automated immunofluorescence imaging to capture key features such as protein expression levels, localization, and heterogeneity in signaling pathways. These phenotypic signatures were used to select two target cancer cell lines that likely represent distinct surface antigen profiles. Mice were subsequently immunized with whole cells or enriched membrane fractions from each cell line. Over 2,000 hybridoma clones were generated and screened within 24 hours using an image-based high-throughput assay to assess binding specificity and subcellular localization. This approach identified a panel of mAbs with minimal cross-reactivity and strong binding to live target cells, highlighting their potential utility in TDC applications. Our findings demonstrate that combining phenotypic profiling with reverse proteomics offers a powerful, scalable strategy for discovering cell-specific antibodies. This platform can accelerate the development of targeted biologics across a range of cancers and other disease models.

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Estimation of *in vivo* RNA Lifespan and Codon Optimality Effects on Circular mRNA Translation

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The remarkable achievement of highly effective COVID-19 mRNA vaccines has demonstrated the potential of mRNA medicines to combat diseases. Recently, synthetic circular RNAs (circRNAs) have been engineered and proved to offer advantages over their linear counterparts. The covalently closed structure of circRNAs prevent their degradation by exonucleases, thereby extending the duration they express protein. However, the direct measurement of *in vivo* synthetic RNA lifespan is still lacking. In this work, we created RNAs encoding double degron (CL1/PEST)-tagged reporter proteins to estimate the lifespan of different RNAs. The addition of two mechanistically independent C-terminal degron motifs decreased the half-life of reporter proteins to ~1-2 hours, thereby decoupling RNA lifespan from the lifespan of the translated protein. With double degron-tagged reporters, we observed that circRNAs have extended half-life compared to linear RNAs when transfected in HEK293 and U2OS cell lines. These data demonstrate that these reporter RNAs will be a useful tool to estimate *in vivo* RNA half-life. Furthermore, there have been no reports demonstrating the of effects of codon optimality on circRNA translation. We developed and used a proprietary codon optimality matrix to re-engineer the coding sequence of firefly luciferase (FLuc). Our data show that linear and circular mRNAs encoding optimal FLuc elicited dramatic increases in luciferase activity compared to the non-optimal FLuc when transfected in HEK293, U2OS, and ARPE-19 cell lines. Together, these results suggest that circRNAs could serve as superior mRNA technology for disease prevention and therapy. This work also highlights the potential of modulating translation from different RNA platforms by modulating codon usage.

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Identifying Microbial Patterns and Respiratory Disease Incidence Across Seasons in a Metropolitan Area

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Respiratory diseases such as COVID-19 and influenza have caused significant morbidity and mortality worldwide. Therefore, surveillance of pathogens such as SARS-CoV-2 and influenza is crucial for tracking disease spread and determining circulating microorganisms. In addition, examining how environmental factors such as location, seasonality, and air pollution contribute to adverse respiratory health outcomes would improve our ability to prevent disease. Understanding how these various determinants of health lead to disease would enable us to identify biomarkers as potential medical countermeasures as well. The objective of this study is to characterize microbial and respiratory disease patterns in a metropolitan area in the United States. Air filter samples were collected over a one-year period, then shipped to our laboratory. Afterwards, we extracted DNA and RNA from air filter samples using the ZymoBIOMICS DNA/RNA Miniprep Kit. DNA was then prepared for sequencing using the Oxford Nanopore Technologies (ONT) Rapid PCR Barcoding Kit. PromethION flow cells were utilized on an ONT P2Solo instrument, and results were analyzed through bioinformatics programs. The cases of selected respiratory diseases during each season were assessed through public datasets. Our preliminary results show that microorganisms such as bacteria, eukaryotes, viruses, and archaea were identified during each season. Microbial patterns differed in relation to levels of COVID-19 and influenza. Our next steps are to further analyze the interaction between pathogens and seasonality and their effects on respiratory health outcomes. Through this work, we aim to mine health outcomes and metagenomic data to identify biomarkers related to differences in infectious and chronic disease incidence. We are planning to include air pollution data as well. Our long-term goal is to prevent and control future outbreaks through aerosol surveillance to mitigate morbidity and mortality from respiratory diseases.

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Poster 69

Therapeutic Potential of EntV P4D Peptide Against Fungal Infections

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Estimates are that fungal infections kill 1.5-3.5 million people per year. Presently, there are only three broadly used classes of antifungals available, namely polyenes, azoles and echinocandins. Antifungal-resistant isolates of both common and emergent pathogens, including various *Candida* species (e.g. *albicans*, *auris, krusei, parapsilosis, tropicalis* and *glabrata*), are increasingly associated with life-threatening disease, particularly among immunocompromised patients. Increasingly widespread resistance to commonly used antifungals is of great public health concern, particularly given the paucity in development of novel classes of antifungals. Our labs have characterized a peptide produced by *Enterococcus faecalis*, EntV, that rather than act as a fungicidal, inhibits *Candida albicans* pathogenicity. Over the course of our studies we have developed a 10 residue D-amino acid variant of the EntV peptide, referred to as P4D (patent# PCT/US2023/065708), that not only retains the full anti-infective capability of the active form of EntV, but exhibits enhanced stability under physiological conditions (e.g. in serum). In this study we have preliminarily tested the therapeutic capability of P4D in the *C. elegans* worm infection model as well as in mouse models of oropharyngeal and systemic candidiasis. In these models, P4D peptide showed significant efficacy in reducing infectious fungal burden and enhancing survival of the infected host. Moreover, our mouse model data shows that orally administered P4D peptide is effective against multiple *Candida* species (i.e. *albicans, glabrata,* and *auris*) in either immunocompetent or immunocompromised hosts. Future experimentation will further test the anti-infective potential of P4D against other fungal genera in various dosing regimens, its efficacy in combinatorial therapy with existing antifungals, and define the mechanisms by which P4D both inhibits *Candida* virulence and promotes host immunity. These discoveries have great potential to advance development of novel and better therapeutic approaches against antimicrobial resistant fungal infections.

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Pharmacokinetic Analysis of a Novel Peptide for Triple-Negative Breast Cancer via Different Routes of Administration in Mice

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Purpose: B4-007 is a novel, high-affinity bi-directional ephrin agonist peptide that simultaneously activates EphB4-initiated Abl/Crk1 tumor-suppressive signaling in tumor cells and inhibits EFNB2-regulated angiogenic signaling in endothelial cells. It is being developed as a first-in-class therapeutic for the treatment of triple-negative breast cancer (TNBC). This study aimed to evaluate the pharmacokinetic profiles of B4-007 following intravenous (IV), intraperitoneal (IP), or subcutaneous (SC) administration in mice. The findings will support the optimization of dosing strategies for B4-007 in preclinical development and future clinical applications. **Methods**: B4-007 was administered as a single dose (20 mg/kg) via IV, IP, or SC routes to female BALB/c mice. Serial blood samples (10 µL each) were collected from the tail using heparin-coated tips at the following time points: 2, 5, 15, 30, and 45 minutes, and 1.0, 2.0, 4.0, and 6.0 hours post-dose. Concentrations of B4-007 and its primary metabolite M1 in blood were quantified using LC-MS/MS. Blood samples were processed via protein precipitation with acetonitrile. Analysis was conducted on a SCIEX 6500+ LC-MS/MS system, using a Synergi Fusion-RP column (4 µm, 150 × 2 mm, 80 Å; Phenomenex) with gradient elution. 4-Hydroxybenzophenone was used as the internal standard (IS). Multiple Reaction Monitoring data were collected in positive mode by detecting the specific precursor to product ion transitions, m/z 854.0 →1215.4 for B4-007, m/z 725.4 → 958.5 for M1, and m/z 199.1 →121.1 for the IS. **Results**: Following IV administration of B4-007, the peptide distributed rapidly with an observed mean blood concentration of 4853 ng/mL at 2 minutes post-dose, followed by a slower terminal elimination half-life ($T_{1/2}$) of 2.45 hours. The estimated mean clearance and volume of distribution were 1.9 L/h and 7.1 L, respectively. After IP administration, B4-007 was gradually absorbed, achieving a mean maximum blood concentration (C_{max}) of 104.3 ng/mL at 52 minutes (T_{max}). The absolute bioavailability of B4-007 via the IP route achieved 73.3%. Interestingly, following SC administration B4-007 reached a similar mean C_{max} of 102.5 ng/mL as compared to the IP group but at a much earlier time (5 minutes post-dose). However, the absolute bioavailability of SC administration was 27%. B4-007 was primarily and rapidly hydrolyzed in circulation to its major metabolite M1 after all administration routes. Following IV administration of B4-007, the mean C_{max} of M1 was 10,328 ng/mL at 2 minutes post-dose with a mean $T_{1/2}$ of 10.8 minutes. **Conclusion**: Different pharmacokinetic behaviors were observed for the peptide drug B4-007 following various routes of administration in the female mouse model. Unlike conventional small molecules, the unique metabolism and disposition pharmacokinetic characteristics of peptides would be critical in guiding further development of the new class of peptide drugs as novel clinical therapeutics.

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AI-Enhanced Discovery and Development of Novel Inhibitors for Endocrine-Resistant Breast Cancer

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Resistance to endocrine therapy (ET) in hormone receptor-positive (HR+) breast cancer (BC) poses a continuing clinical challenge, especially in advanced stages. The most common cause of acquired resistance is activating mutations in the ligand-binding domain of estrogen receptor alpha (ERα), with Y537S and D538G mutations leading to constitutive activation and rendering standard-of-care therapeutics—Tamoxifen, Fulvestrant, and aromatase inhibitors—ineffective. While recent therapeutics such as Elacestrant have received FDA approval, clinical outcomes remain modest, underscoring the urgent need for novel targeted therapies against mutant ERα. We recently developed a cutting-edge computational drug discovery pipeline utilizing machine learning (ML) and molecular dynamics simulations to screen ultra-large compound libraries for novel modulators of Y537S and D538G ERα. The pipeline will be applied to the lead-like subset of the ZINC22 chemical library, consisting of approximately 16 billion molecules after enumeration of stereoisomers, tautomers and protomers. The top candidates are filtered based on binding free energy (ΔG), lipophilicity (logP), molecular weight, and structural diversity. Following computational analyses, experimental validation and preclinical development of the most promising lead compounds will be performed. Experimental validation will include primary efficacy screens in T-47D HR+ BC cell lines harboring Y537S and D538G mutations at 100 μM concentrations. IC_{50} values will be determined for active compounds across a 0.1 nM–100 μM range, while selectivity is assessed using non-tumorigenic MCF 10A cells. Target validation will include fluorescence polarization-based competitive binding assays using recombinant mutant Erα, siRNA-mediated knockdown of ERα, overexpression of mutant ERα, western blotting to examine protein stability, and RT-qPCR for downstream gene expression analysis. Tamoxifen, Fulvestrant, and Elacestrant will serve as clinical benchmarks in all assays. Lead compounds with favorable *in vitro* profiles will undergo pharmaceutical optimization. Co-solvent formulations will be developed to enhance solubility and stability and will be evaluated using LC-MS/MS and various surfactant/emulsifier systems. Stability testing under diverse conditions will guide formulation selection for *in vivo* studies. Preclinical efficacy testing is planned in orthotopic xenograft models using T-47D cells expressing Y537S and D538G mutant ERα in female SCID mice. Pharmacokinetic (PK), pharmacodynamic (PD), and toxicokinetic (TK) analyses will be conducted using optimized formulations. Blood and tumor samples will be evaluated for compound distribution and ERα modulation using LC-MS/MS and western blotting. Organ-level toxicology studies will assess compound accumulation and systemic safety. This comprehensive approach aims to develop novel inhibitors with meaningful clinical benefits for ET-resistant HR+ BC, thereby addressing a critical unmet need in breast cancer therapy.

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E-Slices with Intact TME for Empirical Response Measurements for Immunotherapies and Other Drugs from Human Tumors

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To overcome known challenges associated with other functional precision assays in oncology, such as organoids and PDX models, EMPIRI developed a proprietary 3D *ex vivo* tumor culture method called E-slices that enables rapid, personalized drug sensitivity testing in a clinically actionable time frame. This platform technology can also transform drug discovery and development efforts in oncology by providing clinically relevant preclinical and clinical assays using fresh human tissues with rapid turn around and flexible downstream analyses options.

E-slice is a faithful model of individual cancer patient's tumor, including the TME. It is a proprietary 3D tissue culture platform that is generated by making thin sections of **intact, fresh tumor tissues** from cancer patients. Importantly, the E-slice method has been shown to accurately predict individual patient treatment responses to chemotherapies and targeted therapies in two small retrospective clinical studies. In addition, because E-slices retain tumor infiltrating immune cells and spatial topography of all cell types in their native TME, E-slices sustain immune cell survival and cellular phenotypes, enabling immunotherapy response measurements and biomarker discoveries ex vivo.

Specifically for immunotherapy response measurements, key differentiators of the E-slice platform from other ex vivo systems are: 1) E-slice is generated from fresh patient tumor tissues with **tumor-trained and -resident immune cells** and not artificially introduced PBMCs used in most other systems; 2) E-slices are cultured **serum-free, chemically defined medium** that does not artificially activate or suppress the immune system; 3) E-slice has been **validated by single cell RNA-sequencing to maintain immune cells in their native states** up to 8 days ex vivo; 4) E-slices can be used to detect secreted protein and metabolic biomarkers in the conditioned media pre- and post- treatment for biomarker discovery; and 5) E-slice can **measure human-specific immunotherapy responses ex vivo in 8-12 days**.

To determine immunotherapy responses from patients samples, E-slice assays were used to test Nivolumab in lung cancer patient samples and its efficacy was validated with increased INFG levels in the conditioned media of responders. In another ongoing study, E-slice assay is used to measure Pembrolizumab responses in triple negative breast cancer patients. Thus far, the responder frequency measured by E-slice matches those from KEYNOTE-522. In summary, we present a novel ex vivo 3D human tumor tissue culture platform that faithfully replicates and retains each patient tumor's TME and can enhance immunotherapy development pipelines and clinical deployment.

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Development of ADAR1 Inhibitors to Improve Cancer Immunotherapy

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Cancer immunotherapy has achieved unprecedented clinical responses and is fundamentally transforming the landscape of cancer treatment. Recent genetic screenings have identified ADAR1 as a promising target for enhancing immunotherapy efficacy. ADAR1 catalyzes the conversion of adenosine to inosine in double-stranded RNA (dsRNA), with elevated levels of dsRNA editing observed in most tumor types compared to normal tissue. However, two major challenges have hindered the development of specific inhibitors targeting ADAR1. Firstly, existing assays for ADAR1 activity have low throughput, limiting high-throughput drug screening and hindering optimization through medicinal chemistry. Secondly, the lack of structural information for ADAR1's deaminase and RNA-binding domains has hampered structure-based drug design efforts.

To address these challenges, we are currently developing a high-throughput ADAR1 activity assay based on fluorescence quenching and TR-FRET techniques. Utilizing the High Throughput Research and Screening Center at TAMU-IBT, we aim to conduct drug screening to identify potential inhibitors. Additionally, we performed high-throughput docking studies using the structure of ADAR1's deaminase domain, which led to the identification of 24 initial hits. Molecular potency evaluation was carried out using ADAR1 editing assays and TR-FRET binding assays, revealing three compounds with IC50 values in the micromolar range. By effectively integrating both wet and dry lab approaches, we anticipate the rapid optimization of effective inhibitors followed by subsequent medicinal chemistry studies.

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AlphaFold3 in Drug Discovery: A Comprehensive Assessment of Capabilities, Limitations, and Applications

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Accurate prediction of protein-ligand interactions remains a cornerstone challenge in drug discovery. AlphaFold3 (AF3), a recent breakthrough Diffusion Transformer model, holds significant promise for structural biology, but its performance across diverse pharmaceutical applications requires systematic evaluation. In this study, we comprehensively benchmark AF3's capabilities using carefully curated datasets, examining its performance in binary protein-ligand complexes, apo/holo structural variations, GPCR-ligand conformations, ternary systems, and inhibitor affinity prediction.

Our analysis reveals that AF3 excels at predicting static protein-ligand interactions with minimal conformational changes, significantly outperforming traditional docking methods in side-chain orientation accuracy. However, we identify critical limitations: AF3 struggles with protein-ligand complexes involving significant conformational changes (>5Å RMSD), demonstrates a persistent bias toward active GPCR conformations regardless of ligand type, performs poorly on ternary complex prediction, and lacks reliable affinity ranking capability. Notably, AF3's performance declined significantly on structures released after its training cutoff date, suggesting potential memorization rather than physical understanding of molecular interactions.

We explored AF3's practical utility through applications in chemoproteomics data interpretation, drug resistance mutation prediction, and kinome profiling simulation. AF3 demonstrated value as a "true-hit binary interaction modeler," capable of generating reliable structural models for experimentally validated binding pairs. However, its ranking metrics showed minimal correlation with experimental binding affinities and limited ability to differentiate across the kinome, highlighting the need for integration with physics-based scoring methods.

Our findings indicate that while AF3 represents a significant advancement in protein-ligand structure prediction, it requires complementary approaches to address its limitations in conformational sampling, affinity ranking, and complex system modeling. Recent developments like YDS Ternoplex suggest that enhanced sampling techniques can overcome some of these limitations. The optimal strategy for leveraging AF3 in drug discovery likely involves its integration into hybrid computational pipelines that combine AI-based prediction with physics-based refinement and experimental validation.

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