Gulf Coast Consortium Innovative Drug Discovery and Development Conference

New Drug Modalities

May 7-8, 2024

Houston, Texas

Gulf Coast Consortia

QUANTITATIVE BIOMEDICAL SCIENCES

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QUANTITATIVE BIOMEDICAL SCIENCES

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 Omics, and Translational Pain Research. GCC training programs focus on Biomedical Informatics, Computational Cancer Biology, Molecular Biophysics, Pharmacological Sciences, Precision Environmental Health Sciences, and Antimicrobial Resistance. 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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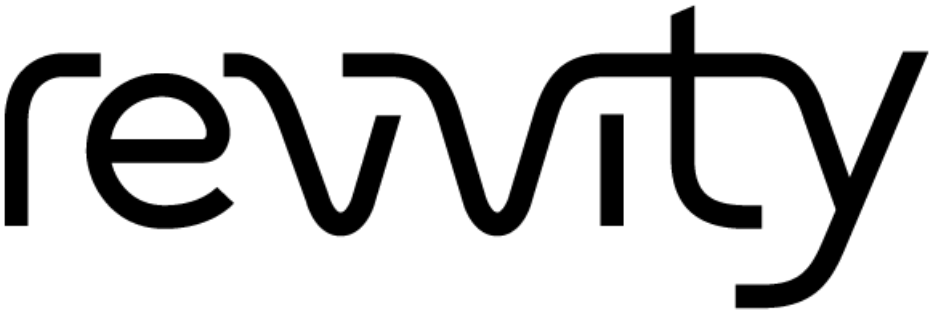


Please be sure to stop by and thank them for their support during the breaks!

May 7, 2024

Day 1

8:00-8:30	Registration, light breakfast and coffee
8:30	**Welcome:** Suzanne Tomlinson, Gulf Coast Consortia
Convenor	Wenshi Liu, Institute of Bioscience and Technology, Texas A&M Univ.
8:40-9:20	Keynote Presentation *Therapeutic Potentials of Pseudo-Natural Peptides, Therapeutic Potentials of Pseudo-Natural Peptides, Products, and Neobiologics* **Hiroaki Suga**, Univ. of Tokyo
Session 1	**Pharma and State of the Field**
Convenor	Mary Geck Do, MD Anderson Cancer Center
9:20-9:45	*Intriguing Therapies in 2024 and Beyond: An Insider's Perspective* **Elaine Lea-Chou**, ELC Consulting
9:45-10:10	*Beyond the Needle: Novel Approaches to Peptide Administration* **Mohamed ElSayed,** RVAC Medicines
10:10-10:35	*NexGen Modeling, from Ideation to the Clinic* **Jose Duca**, Novartis
10:35-10:40	Core Highlight: GCC REACH **Dillon Fritz**, Gulf Coast Consortia
10:40-11:15	Networking Break
Session 2	**Next-Generation Immune-Modulator Approaches**
Convenors	Zhiqiang An, Univ. of Texas Health Science Center Houston Qingyun Liu, Univ. of Texas Health Science Center Houston
11:15-11:40	*LILRBs - Myeloid Checkpoint Targets for Cancer Treatment* **Alec Zhang**, Univ. of Texas Southwestern
11:40-12:05	*Immunotherapies Targeting Myeloid Cell Receptors* **Charlene Liao**, Immune-Onc Therapeutics
12:05-12:30	*Simultaneous Targeting of Multiple Receptors with Ligand-Drug Conjugate for Cancer Treatment* **Jim Liu**, Univ. of Texas Health Science Center Houston
12:30-12:35	Core highlight: Accelerator for Cancer Therapeutics **Deepa Chakravarti**, TMC Innovation
12:35-1:30	Lunch-Event hall
Session 3	**Leading-Edge Biologic and (Cyclo)Peptide Technologies**

Convenors	Diane Chow, Univ. of Houston Dong Liang, Texas Southern Univ.
1:30-1:55	*DA's Approach to Approve the Therapeutic Biologics in Cancer Therapy – Clinical Pharmacology Aspect* **Hong Zhao**, FDA
1:55-2:20	*Superhigh-Capacity Polymeric Micelles for Chemo/Immunotherapy of Cancer* **Alexander Kabanov**, Univ. of North Carolina
2:20-2:45	*Lipid Nanoparticles for Overcoming Biological Barriers to mRNA Delivery* **Michael Mitchell**, Univ. of Pennsylvania
2:45-3:10	Panel Discussion
3:10-3:15	Core Highlight: Advanced Cancer Antibody Drug Modalities Core **Zhiqiang An**, Univ. of Texas Health Science Center Houston
3:15-3:25	Networking Break
Session 4 Convenors	**The Promise and Challenges of Cell Therapies** Jason Cross, MD Anderson Cancer Center Vinay Nair, MD Anderson Cancer Center
3:25-3:50	**Cassian Yee**, MD Anderson Cancer Center and MongooseBio
3:50-4:15	*The Promise and Challenges of Cell Therapies* **Jason Bock**, CTMC+
4:15-4:40	*TIL Therapy in Melanoma* **Rodabe Amaria,** MD Anderson Cancer Center
4:40-5:00	Panel Discussion
5:00-5:05	Core Highlight: Preclinical Development Core for Large Molecule Therapeutics **Jim Liu**, Univ. of Texas Health Science Center
5:05-6:15 pm	Poster Session-odd numbered posters & Networking Reception-Event hall

May 8, 2024

<u>Day 2</u>

8:00-8:30	Registration, light breakfast and coffee
8:30	Welcome: Suzanne Tomlinson, Gulf Coast Consortia
Session 5 Conveners	**Gene Editing and Viral Therapies** Pete Davies, Institute of Bioscience and Technology, Texas A&M Clifford Stephan, Institute of Bioscience and Technology, Texas A&M

8:35-9:00 *Refueled CAR T Cell Therapy to Cure Solid Tumor*
Xiaotong Song, Institute of Bioscience and Technology, Texas A&M Univ.

9:00-9:25 *Engineered Biomolecular Condensation to Augment CRISPR/Cas-Based Epigenome Editing and Transcriptional Regulation*
Jing Li, Rice Univ.

9:25-9:50 *Deliver Therapeutics, Inc. and Ponce Therapeutics, Inc. – The Bellicum Phoenix Rises*
Kevin Slawin, Ponce Therapeutics

9:50-9:55 Core highlight: Combinatorial Drug Discovery Core, MLOTS, and HTF
Clifford Stephan, Institute of Bioscience and Technology, Texas A&M Univ.

9:55-10:00 Core Highlight: Advanced Microscopy and Image Informatics
Michael Bolt, Baylor College of Medicine

10:00-10:30 Networking Break

Session 6 **Can We Ensure Equitable Access to Next-Generation Drugs?**
Convenor Suzanne Tomlinson, Gulf Coast Consortia

10:30-10:40 **Amanda Onwuka**, RTI International

10:40-10:50 **Veronica Ajewole**, Texas Southern Univ.

10:50-11:00 **Rosalia Guerrero**, Texas Epidemic Public Health Institute

11:00-11:30 Panel Discussion

11:30-11:35 Core highlight: Center for Comprehensive PK/PD and Formulation
Dong Liang, Texas Southern Univ.

11:35-1:30 **Lunch and Poster Session**-even numbered posters
11:35 Lunch
12:30 Poster Session-even numbered posters

Session 7 **What's Next for Nucleic Acid-Based Drugs**
Conveners Trinh Tat, Houston Methodist Research Institute
John Cooke, Houston Methodist Research Institute

1:30-1:55 *Next-Generation mRNA Design – Increasing mRNA Potency with a New Cap Analog*
Kate Broderick, Maravai Life Sciences

1:55-2:20 *AI-Assisted Directed Evolution of Immunogens*
Jimmy Gollihar, Houston Methodist Research Institute

2:20-2:25 Core highlight: RNA Biology Core
John Cooke, Houston Methodist Research Institute

Closing Keynote

Conveners Jason Cross, MD Anderson Cancer Center

2:25-3:05 **Future Directions Keynote**
The History, Current State, and Future of Artificial Intelligence in Drug Discovery and Development
Naheed Kurji, Recursion Canada

3:05 Closing Remarks
Suzanne Tomlinson, Gulf Coast Consortia

Veronica B. Ajewole, PharmD, BCOP
Associate Professor, Pharmacy Practice
Texas Southern University
Clinical Pharmacist Specialist, Oncology
Houston Methodist Hospital

Can We Ensure Equitable Access to Next-Generation Drugs?

Dr. Ajewole serves as Associate Professor in the Department of Pharmacy Practice at Texas Southern University (TSU) and as a Clinical Pharmacist and an Adjunct Assistant Professor of Oncology at Houston Methodist Hospital. She received her Doctorate of Pharmacy from TSU and completed her oncology pharmacy residency at Houston Methodist Hospital. Dr. Ajewole is a Board-Certified Oncology Pharmacist with clinical practice in oral chemotherapy at Houston Methodist Hospital Cancer Center.

She is the principal investigator and program director of the Cancer Prevention and Research Institute of Texas Funded Breast Cancer Screening and Prevention Center at TSU. This program provides no-cost breast cancer screening and diagnostic services, patient navigation, and education for ethnic minority women. Recently, she led her team at TSU in collaboration with Baylor College of Medicine in receiving the P20 NCI grant (only one funded in the nation in FY24 cycle) titled Collaborative Union for Cancer Research, Education, and Disparities. She is the founding Director of the National Institutes of Health-Research Centers in Minority Institutions Center for Biomedical and Minority Health Research—Community Engagement Core, the founding director of CDC/Houston Health Department funded Advance Health Equity program and also the Principal Investigator of a Centers for Medicare & Medicaid Services-funded grant on prostate cancer in African American men.

Dr. Ajewole's passion is anchored in advancing health equity among ethnic minority population as reflected in her dedication and service to her patients, students, community, and church. She enjoys serving and spending quality time with her husband and four wonderful children.

Rodabe Amaria, MD

Director, Clinical Research within Melanoma Medical Oncology
MD Anderson Cancer Center.
TIL Therapy in Melanoma

Since joining the Department of Melanoma Medical Oncology at MD Anderson Cancer Center in July 2013, Dr. Amaria has worked to establish herself as a clinical and translational researcher. She has been the Principal Investigator of numerous clinical trials including a mix of industry-sponsored trials and investigator-initiated where she had the key role in design and implementation. Dr. Amaria's research interests have coalesced around three major subjects; neoadjuvant therapy, trials for NRAS mutated melanoma and adoptive cell therapy in metastatic melanoma. Dr Amaria leads the MD Anderson Adoptive Cell Therapy with Tumor Infiltrating Lymphocyte (TIL) program and has extensive experience designing and implementing studies using both un-engineered and engineered TIL. She is also managing TIL therapy in other solid tumors including various forms of gynecologic and gastrointestinal cancers and sarcomas. She is also the leader of the MD Anderson Standard of Care TIL Therapy program and has been instrumental in designing workflows to support standard of care TIL. Additionally, Dr. Amaria has established a busy clinical practice and has extensive experience treating melanoma patients on and off clinical trial protocols. She is also the Director of Clinical Research within Melanoma Medical Oncology at MD Anderson Cancer Center.

Jason Bock, MD, PhD
CEO, CTMC
The Promise and Challenges of Cell Therapies

Jason Bock, PhD, is CEO of CTMC, a joint venture between Resilience + MD Anderson Cancer Center. Formed in May 2022 to accelerate patient access to impactful cell therapies by bridging cell therapy development and manufacturing with MD Anderson's clinical trial capabilities. In 2019, Jason was recruited by MD Anderson from Teva Pharmaceuticals to build the Biologics Development group. The group purchased a 60,000 SF facility in the Texas Medical Center and has since formed multiple partnerships with both MD Anderson faculty and early-stage biotech firms to bring their products through the IND process. Previously, Jason was Site Head and VP of Global CMC Biologics in the Specialty R&D Division of Teva Pharmaceuticals. He joined Teva through the acquisition of CoGenesys, a private biotech firm as a spinoff from Human Genome Sciences (HGS), where he worked after completing a PhD at Stanford University in Molecular & Cellular Physiology.

Kate Broderick, PhD
Chief Innovation Officer
Maravai LifeSciences
Next-Generation mRNA Design – Increasing mRNA Potency with a New Cap Analog

Dr. Kate Broderick, the Chief Innovation Officer at Maravai LifeSciences, has more than 20 years of experience in the life science industry. A recognized vaccine expert, Dr. Broderick has a broad background in device and product development in the DNA therapeutic and drug delivery field. She also actively works with teams at TriLink BioTechnologies, a Maravai company, to advance its global reagents and manufacturing services. Prior to joining Maravai in 2022, Dr. Broderick held roles of increasing responsibility at Inovio Pharmaceuticals, most recently as Senior Vice President, R&D. Dr. Broderick has served as a principal investigator for a variety of grants and awards from government agencies and non-profits, including the National Institutes of Health. She received her Ph.D. from the University of Glasgow in Scotland and completed her post-doctoral research at the University of California, San Diego.

José Duca, PhD
Global Head of Computer-Aided Drug Discovery
Novartis
NexGen Modeling, from Ideation to the Clinic

José is the Global Head of Computer-Aided Drug Discovery. He joined Novartis in 2010, after 10 years with the Schering-Plough Research Institute and Merck Research Laboratories in Kenilworth, NJ, USA.

With expertise in computational medicinal chemistry, molecular thinking, novel modes of action to drug the undruggable, José constantly pushes the frontiers of drug discovery and computational. His extensive drug discovery experience informs his innovative approaches to challenging projects. He has pioneered several novel modalities that later became widely adopted.

Driven by a vision of a fully integrated computational drug discovery team, he combines drug discovery knowledge with first principles and physics. Leveraging the rapid evolution of computational techniques, José has assembled an exceptional global team.

Beyond his professional pursuits, José is passionate about innovation, servant leadership, music, sports, and wine.

His mission is to revolutionize drug discovery seeking the fastest path to impact human medicine.

Mohamed ElSayed, PhD

EVP & Chief Technology Officer RVAC Medicines

Beyond the Needle: Novel Approaches to Peptide Administration

Dr. Mohamed ElSayed is a seasoned drug hunter with +25 years of leadership experience spanning pharmaceutical companies, biotech organizations, and academic institutions. Throughout his professional career, he led the development of transformative medicines spanning small molecules, biologics, genetic medicines, and precision therapies for multiple therapeutic indications.

Presently, as the EVP & Chief Technology Officer of a biotech firm, he is leading a global R&D organization at Waltham/MA, Shanghai/China, and Singapore focused on development of mRNA-based vaccines for the emerging markets. Before this role, Dr. ElSayed was a VP of Biotechnology at Eli Lilly where he built the Oral Biologics Platform, played a critical role in shaping Lilly's Genetic Medicines Strategy, and spearheaded multiple strategic partnerships with direct investment totaling +$400M. Dr. ElSayed had multiple advisory and operational roles with increasing responsibilities in other biopharmaceutical companies including Abbvie, Samyang Research Corporation, and Guilford Pharmaceuticals.

Earlier in his career, Dr. ElSayed was a tenured professor at the University of Michigan where he established an internationally recognized program focused on the development of investigational therapeutics for cancer and autoimmunity. During his academic career, he received multiple honors/awards including the US National Science Foundation CAREER Award, Coulter Foundation Translational Research Partnership in Biomedical Engineering Award, and US Department of Defense Award. He co-authored +180 research articles and conference proceedings, delivered +80 invited talks, and he is an inventor of 8 patents.

Jimmy Gollihar, PhD
Professor, Pathology & Genomic Medicine
Head of the Laboratory of Antibody Discovery &
Accelerated Protein Therapeutics (ADAPT)
Houston Methodist Research Institute
AI-Assisted Directed Evolution of Immunogens

Dr. Gollihar is a Professor of Pathology & Genomic Medicine and Head of the Laboratory of Antibody Discovery & Accelerated Protein Therapeutics (ADAPT) at the Houston Methodist Research Institute (HMRI). His work encompasses a broad range of engineering biology, from the design of simple genetic “parts” and circuits to protein engineering and industrial biomanufacturing. He uses a foundation in synthetic biology to domesticate non-model organisms and then employs these tools and chasses to engineer proteins or biosynthetic pathways with therapeutic and industrial potential. He adopts a holistic approach to protein engineering by employing concepts in directed evolution, rational design, and artificial intelligence to create biological countermeasures, diagnostics, and vaccine candidates. He is a Professor of Pathology & Genomic Medicine and Head of the Laboratory of Antibody Discovery & Accelerated Protein Therapeutics (ADAPT) at the Houston Methodist Research Institute (HMRI). His work encompasses a broad range of engineering biology, from the design of simple genetic “parts” and circuits to protein engineering and industrial biomanufacturing. He uses a foundation in synthetic biology to domesticate non-model organisms and then use s these tools and chasses to engineer proteins or biosynthetic pathways with therapeutic and industrial potential. He uses a holistic approach to protein engineering by employing concepts in directed evolution, rational design, and artificial intelligence to create biological countermeasures, diagnostics, and vaccine candidates.

Rosalia Guerrero, MBA
Director
Vulnerable Populations
UTHealth School of Public Health
Connecting Latino Populations to Clinical Trials through Partnerships with Community Health Workers

Rosalia Guerrero currently serves as the Director of Vulnerable Populations for the Texas Epidemic Public Health Institute (TEPHI) and manages the Community Health Worker Training Program at the UTHealth, School of Public Health (UTSPH) in Houston. She has over 15 years of experience working with frontline public health workers and low-resourced communities. Rosalia's interests focus on community engagement and community-based participatory research around various health, environment, and social justice issues. She has worked with urban, rural, and border communities including colonia communities along the Texas-Mexico border. Rosalia has a B.S. in Psychology and Pre-Medicine from Texas A&M, College Station, an MBA from the University of Houston Downtown, and is pursuing her DrPH from UTSPH.

Alexander Kabanov, PhD, DrSci
Mescal S. Ferguson Distinguished Professor
Director, Center for Nanotechnology in Drug Delivery
University of North Carolina
Superhigh-Capacity Polymeric Micelles for Chemo/Immunotherapy of Cancer

Alexander Kabanov is a Distinguished Professor at the Eshelman School of Pharmacy, UNC-Chapel Hill, where he also directs the UNC Center for Nanotechnology in Drug Delivery, the Carolina Institute for Nanomedicine, and NCI's T32 training program in Cancer Nanotechnology. He earned his Ph.D. and D.Sc. in Chemical Sciences from Moscow State University in 1987 and 1990, respectively.

Kabanov has made significant contributions to nanomedicine, pioneering the use of polymeric micelles, polyelectrolyte complexes, nanogels, and exosomes for delivering small drugs, nucleic acids, and proteins therapeutically. His work resulted in the first clinical trial involving a polymeric micelle drug. He is a highly cited researcher in Pharmacology and Toxicology, with over 340 scientific papers (>52,000 citations, Google h-index >117), 36 US patents, and co-founding several pharmaceutical companies.

He has mentored over 80 graduate students and postdocs, with a strong commitment to diversity. Kabanov also established symposium series in nanomedicine and drug delivery www.nanodds.org, chaired Gordon Research Conferences, and received numerous honors and awards, including the Lenin Komsomol Prize, NSF Career award, George Gamow award, and Controlled Release Society (CRS) Founders award.

He is an elected member or fellow of prestigious academies and organizations, including Academia Europaea, Russian Academy of Sciences, National Academy of Inventors, American Association for the Advancement of Science, American Institute for Medical and Biological Engineering, and CRS. He has served as the past President and current CEO of the Russian American Science Association, director-at-large for CRS (2019-2022), and chair of the CRS College of Fellows sub-committee (2022-2023).

Abstract: The lecture focuses on the use of Poly(2-oxazoline) (POx) based polymeric micelles (PMs), which have the unique ability to carry a high load of water-insoluble drugs. This capability enhances the solubility, stability, efficacy, and safety of these drugs. The shape of the micelle influences the drug's performance.

For instance, spherical micelles accumulate rapidly in tumors and demonstrate more potent anti-tumor effects compared to worm-like micelles. The latter accumulate at a slower rate and release the drug into the bloodstream. Micelles loaded with two drugs exhibit superior anti-tumor activity compared to micelles carrying a single drug or a combination of drugs, as well as a combination of free drugs. This strategy, termed “drug design by co-formulation”, holds promise for cancer immunotherapy. The presentation will discuss the relationship between drug loading, the critical micelle concentration, the partitioning of micelles and serum proteins, pharmacokinetic and toxicokinetic profiles, and efficacy. These innovative approaches hasten the application of novel PMs for therapeutic uses in cancer and other diseases. The research was funded by NIH grants CA198999 and CA264488. The conflict-of-interest statement indicates an affiliation with DelAQUA Pharmaceuticals.

Key words: polymeric micelles, poly(2-oxazoline), cancer, paclitaxel, TLR7/8, CSF1R

Keynote presenter

Naheed Kurji, MBA
President
Recursion Canada
The History, Current State and Future of Artificial Intelligence in Drug Discovery and Development

Naheed is the President of Recursion Canada, the Canadian wholly-owned subsidiary of Recursion Pharmaceuticals (NASDAQ: RXRX). Prior to joining Recursion, Naheed was the Co-founder, President and CEO of Cyclica, a Toronto-based biotech company (acquired by Recursion in May 2023). At Cyclica, Naheed had the distinct privilege of working with an incredibly talented and dedicated team that was considered one of the pioneers of what is now the increasingly hot space of AI for Drug Discovery and Development. Naheed was also a co-founder and Board Member of EntheogeniX Biosciences, a psychedelic inspired biotech company for mental health, is co-founder of the Alliance for Artificial Intelligence in Healthcare (AAIH) for which he served as Chair until May 2023, a Board Member of the Ontario Bioscience Innovation Organization (OBIO), and Board Member at Life Sciences of Ontario (LSO).

Elaine Lea-Chou, PhD
CEO, FounderCEO, Founder
ELC Private Consulting
Intriguing Therapies in 2024 and Beyond: An Insider's Perspective

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.

Jing Li, PhD
Research Scientist
Rice University

Engineered Biomolecular Condensation to Augment CRISPR/Cas-Based Epigenome Editing and Transcriptional Regulation

Dr. Jing Li is a research scientist in the lab of Isaac Hilton at Rice University. She is dedicated to developing and applying new cutting-edge CRISPR/Cas-based epigenome editing tools. She is particularly interested in deciphering the pathology of human diseases using these new technologies. In this talk, she will describe a new class of gene regulatory and epigenome editing tools that leverage biomolecular condensation in live human cell nuclei.

Charlene Liao, PhD
Founder, CEO and Chair of the Board
Immune-Onc Therapeutics
Immunotherapies Targeting Myeloid Cell Receptors

Charlene Liao, PhD, co-founded Immune-Onc Therapeutics and has served as President and Chief Executive Officer and as a member of the board of directors since May 2016. Charlene has 25 years of industry experience in drug development and business leadership. From 2002-2016, Charlene held global drug development roles at Genentech where she was instrumental in leading development efforts across the product lifecycle for ten new molecular entities (NMEs) in a variety of therapeutic areas including: hematology-oncology, oncology, immunology, infectious diseases, and metabolic disorders. Her first drug at Genentech is called Ocrevus® (for MS) and is now the best-selling medicine in the entire Roche and Genentech pipeline. Prior to joining Genentech, Charlene was a Director of Business Development at Rigel. She began her career in biotech as a scientist at Tularik, before its acquisition by Amgen.

Charlene received her Ph.D. from Brandeis University in the laboratory of famed biologist Dr. Michael Rosbash, who was awarded the 2017 Nobel Prize in Physiology or Medicine. Charlene completed her postdoctoral research in immunology at UCSF where she was a Fellow of the Damon Runyon Cancer Research Fund in the laboratory of Dr. Dan Littman and a Special Fellow of the Leukemia and Lymphoma Society (LLS) in the laboratory of Dr. Art Weiss.

Qingyun (Jim) Liu, PhD
Professor and Director, IMM-Center for Translational Cancer Research
Janice Davis Gordon Chair for Bowel Cancer Research
University of Texas Health Science Center Houston
Simultaneous Targeting of Multiple Receptors with Ligand-Drug Conjugate for Cancer Treatment

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. He led multiple groups successfully in delineating the function and mechanism of many orphan receptors, developing HTS assays, identifying and optimizing drug leads, and delivering clinical candidates. In particular, he led and championed the drug discovery project of tryptophan hydroxylase 1 (TPH1) at Lexicon Pharmaceuticals that led to the discovery and development of a first-in-class, orally active inhibitor of TPH1 (Xermelo®) that was approved by FDA for patients from carcinoid syndrome diarrhea. Since coming to academia, he has led his group to the discovery of R-spondins (RSPO) as ligands of LGR4/5/6 and delineation of signaling mechanisms of LGR4/5/6. Dr. Liu's 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.

Michael J. Mitchell, PhD
Associate Professor, Bioengineering
School of Engineering and Applied Science
University of Pennsylvania
Lipid Nanoparticles for Overcoming Biological Barriers to mRNA Delivery

Michael J. Mitchell is an Associate Professor of Bioengineering at the University of Pennsylvania, and the Lipid Nanoparticle Delivery Systems Group Leader at the Penn Institute for RNA Innovation. He received a BE in Biomedical Engineering from Stevens Institute of Technology in 2009, a PhD in Biomedical Engineering with Prof. Michael King from Cornell University in 2014. He was a Postdoctoral Fellow in Chemical Engineering with Prof. Robert Langer at MIT from 2014-2017, prior to pursuing his independent career at University of Pennsylvania in 2018. The Mitchell lab's research broadly lies at the interface of biomaterials science, drug delivery, and cellular and molecular bioengineering to fundamentally understand and therapeutically target biological barriers. Specifically, his lab engineers new lipid and polymeric nanoparticle platforms for the delivery of different nucleic acid modalities to target cells and tissues across the body. His lab applies their research findings and the technologies developed to a range of human health applications, including the engineering of CAR T cells for cancer immunotherapy, mRNA vaccines, genome editing, cardiovascular disease, and in utero therapeutics to treat disease before birth.

Mitchell has received numerous awards as an independent investigator, including the National Institutes of Health Director's New Innovator Award, the Rising Star Award from the Biomedical Engineering Society, the Career Award at the Scientific Interface from the Burroughs Wellcome Fund, and the Research Scholar Award from the American Cancer Society. In 2022 Mitchell was named "Emerging Inventor for the Year" by Penn's for Innovation in recognition for his lipid nanoparticle technologies and received the Young Investigator Award from the Society for Biomaterials, the T. Nagai Award from the Controlled Release Society, the National Science Foundation CAREER Award, and was named a 2023 Young Innovator in Cellular and Molecular Bioengineering. He is a co-founder of Liberate Bio, a biotechnology company focused on developing non-viral delivery technologies for genetic medicines, and serves on Scientific Advisory Board of numerous biotechnology companies.

Kevin Slawin, MD
Founder and Managing Partner
Rapha Capital Management, LLC
Deliver Therapeutics, Inc. and Ponce Therapeutics, Inc. – The Bellicum Phoenix Rises

Kevin Slawin, M.D. is the Founder and Managing Partner of Rapha Capital Management, LLC. Formerly a robotic oncologic surgeon, he is now a biotech investor and founder focusing on disruptive healthcare technologies. He was the co-founder of Bellicum Pharmaceuticals, Inc., leading Bellicum to a successful $161 million IPO in December 2014.

He is also the founder and CEO of Ponce Therapeutics, Inc. (https://poncetherapeutics.com), which reunites the team that founded Bellicum Pharmaceuticals and that is using advanced technologies to develop novel therapeutics targeting the fundamental mechanisms of aging, and DELiver Therapeutics, Inc. (https://delivertherapeutics.com), which is applying high throughput DNA encoded library (DEL) drug screening combined with other advanced technologies in novel ways to deliver small molecule and peptide therapeutics that address some of the most challenging and, some previously termed “undruggable”, targets in clinical medicine. Both have R&D facilities located at K2Bio in Houston (https://www.k2-biolabs.com/), a coworking research facility for biotech and pharma startups recently opened in Houston, where he is a co-founder, investor, and board member. He is also the Founder, Chairman and CEO of PrintBio, Inc. (https://printbio.com), a commercial stage company with products powered by advanced bio-printing technologies.

Slawin joined the Baylor College of Medicine as Director of The Baylor Prostate Center in 1994 and was appointed the Dan Duncan Family Professor in Prostate Cancer and Prostatic Diseases in 2003, established by the well-known Houston oil man and philanthropist of the same name. He currently lives in Miami, FL where he is Founder and CEO of Miami Medicos (https://miamimedicos.com), a membership organization of physicians, founders, executives, and investors catalyzing the healthcare entrepreneurial ecosystem in Miami and worldwide.

Xiaotong Song, PhD
Associate Professor
Center for Infectious and Inflammatory Diseases
Texas A&M Univ. Institute of Biosciences & Technology
Refueled CAR T Cell Therapy to Cure Solid Tumor

Dr. Xiaotong Song is an Associate Professor at the Institute of Biosciences & Technology (IBT), Department of Translational Medical Sciences, with the Texas A&M School of Medicine. He obtained his MD from Peking University Health Science Center in 1993 and completed his PhD in Immunology at Nanjing Medical University in 2002. Following this, Dr. Song pursued postdoctoral training at the Center for Cell and Gene Therapy (CAGT) at BCM in 2003. In 2010, Dr. Song was appointed as a Tenure-track Assistant Professor at CAGT, where he led a group focused on adoptive cell therapies, vaccines, and oncolytic viral therapies. His research at CAGT/BCM received funding through NIH R01 and DOD awards.

In 2016, Dr. Song founded Icell Kealex Therapeutics and served as the full-time CEO. Under his leadership, the company conducted IND enabling studies for oncolytic vaccinia virus targeting solid tumors, securing a multimillion-dollar investment from the Cancer Prevention and & Research Institute of Texas (CPRIT) and NIH SBIR, leading to a successful exit in 2020. Dr. Song is a serial entrepreneur, having co-founded several startups (4 VC-backed, >$43M raised, 1 exited). Currently, Dr. Song is dedicated to developing a unique and disruptive CAR T cell platform for solid tumor by addressing the limitations of current CAR T cell therapies.

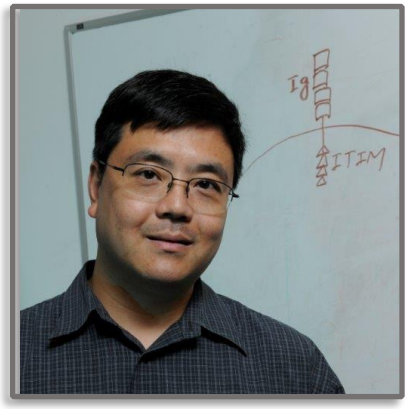
Keynote presenter

Hiroaki Suga, PhD
Chemistry, Graduate School of Science
University of Tokyo
Therapeutic Potentials of Pseudo-Natural Peptides, Products and Neobiologics

Hiroaki Suga obtained his Ph. D. in Chemistry (1994) from the Massachusetts Institute of Technology; post-doctoral fellow in Massachusetts General Hospital/Harvard Med School (94–97); a tenure-track Assistant Professor in the Department of Chemistry in the State University of New York at Buffalo (1997); the tenured Associate Professor (2002); Research Center for Advanced Science and Technology in the University of Tokyo, Associate Professor (2003–2005), Full Professor (2005–2010); Department of Chemistry, Graduate School of Science in the University of Tokyo (2010–current). He is the recipient of Akabori Memorial Award 2014 of Japanese Peptide Society; Max-Bergmann Gold Medal 2016; Nagoya Medal Silver 2017; Vincent du Vigneaud Award 2019; Research Award of the Alexander von Humboldt Foundation 2020; MIT T.Y. Shen Lectureship 2022; ETHZ Prelog Medal Lecture 2022; Wolf Prize in Chemistry 2023; Nelson J. Leonard Distinguished Lecture of the University of Illinois at Urbana-Champaign; Van't Hoff Award Lectureship of the Royal Netherlands Academy of Science. He is also an academic founder of and the Board of Directors of PeptiDream Inc. Tokyo (2006–2018), a publicly traded company in the Tokyo Premier Stock Exchange Market, which has many partnerships with pharmaceutical companies in worldwide. He is also an academic co-founder of MiraBiologics Inc. and the Board of Directors since 2017.

The genetic code is the law of translation, where genetic information encoded in RNA is translated to amino acid sequence. The code consists of tri-nucleotides, so-called codons, assigning to particular amino acids. In cells or in ordinary cell-free translation systems originating from prokaryotes or eukaryotes, the usage of amino acids is generally restricted to 20 proteinogenic (standard) kinds, and thus the expressed peptides are composed of only such monomers. However, we recently devised a new means to reprogram the genetic code, which allows us to express non-standard peptides containing multiple non-proteinogenic amino acids in vitro. This lecture will describe the most recent development in the genetic code

reprogramming approach that enables us to express natural product-like non-standard peptides. The technology involves (1) efficient macrocyclization of peptides, (2) incorporation of non-standard amino acids, such as N-methyl amino acids and beta/gamma-amino acids, and (3) reliable synthesis of libraries with the complexity of more than a trillion members. When the technology is coupled with an in vitro display system, referred to as RaPID (Random Peptide Integrated Discovery) system, the non-standard cyclic peptide libraries with various ring sizes can be screened (selected) against various drug targets inexpensively, less laboriously, and very rapidly. Moreover, this technology was integrated with post-translational modifying enzymes to display pseudo-natural products. This lecture discusses therapeutic potentials using such pseudo-natural macrocyclic peptides and products, and more recent advance in generating neobiologics by means of LassoGraft technology.



Chengcheng (Alec) Zhang, PhD
Morton H. Sanger Professorship in Oncology and
Michael L. Rosenberg Scholar for Biomedical Research
University of Texas Southwestern Medical Center
LILRBs - Myeloid Checkpoint Targets for Cancer Treatment

Dr. Chengcheng (Alec) Zhang, Morton H. Sanger Professorship in Oncology and Michael L. Rosenberg Scholar for Biomedical Research at University of Texas Southwestern Medical Center, earned his B.S. degree from University of Science and Technology of China in 1992 and his Ph.D. in Biochemistry from the University of Illinois at Urbana-Champaign in 1999. He received his postdoctoral training under the mentorship of Dr. Harvey Lodish at Whitehead Institute/MIT, where he initiated several projects on hematopoietic stem cells and cancer research. Dr. Zhang established his independent lab at UT Southwestern Medical Center in 2007. His laboratory research focuses on the biology of immune inhibitory receptors including leukocyte Ig-like receptor subfamily B (LILRB) in cancer immunology and hematopoietic cells. He is also accustomed to working at the intersection of basic research and its clinical applications; anti-LILRB2 and anti-LILRB4 blocking antibodies discovered through his collaboration with Drs. Zhiqiang An and Charlene Liao are in clinical trials for treatment of myeloid leukemia and solid cancers. He published 119 peer-reviewed publications in hematopoietic and cancer research fields. He was a recipient of several awards, including American Society of Hematology Junior Faculty Scholar Award, Leukemia & Lymphoma Society Scholar Award, and Royan International Research Award. He has trained 8 graduate students and 27 post-doctoral researchers. Most of his former postdoc trainees acquired positions as PIs in research institutions or in biopharmaceutical industry.

Hong Zhao, PhD
Master Pharmacokineticist
FDA

FDA's Approach to Approve the Therapeutic Biologics in Cancer Therapy – Clinical Pharmacology Aspect

Dr. Hong Zhao earned her PhD in Pharmaceutical Sciences from the School of Pharmacy, University of Connecticut. She has been with the FDA over past 25 years as Clinical Pharmacology Reviewer, Team Leader, Master Reviewer and now Master Pharmacokineticist. She has developed her expertise in therapeutic biologics during her early years in the Center for Biologics Evaluation and Research (CBER) and later became team leader covering clinical pharmacology review of all biologics submitted to the Center for Drug Evaluation and Research (CDER). During this period, she conducted many regulatory projects addressing biologics review issues such as biologics comparability assessment, immunogenicity testing, drug-drug interaction potential, QT interval prolongation potential, specific populations including hepatic and renal impairment as well as biosimilar development. She presented the results of these regulatory projects within the FDA and at the National Technology Conference and at other scientific conferences, and contributed to the FDA biologics guidance development. In her later years, she has been mainly working on review of oncology drugs and biologics and has accumulated rich regulatory review experience and institutional knowledges. She is very passionate about the review work she has been doing as it directly impacts America people's health.

Poster 1

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Sadhna Aggarwal[1*], Ye Rui[1], Steven Lin[1]

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a kground Esophageal adenocarcinoma (EAC) remains a formidable challenge, particularly in the context of radiation therapy. Esophageal adenocarcinoma is the most common subtype of esophageal cancer in the United States. The 5-year survival rate for esophageal adenocarcinoma in the United States is extremely low, hovering around 5%. This statistic reflects the challenges associated with early detection, aggressive tumor behavior, and limited treatment options. Radiation therapy plays a crucial role in the treatment of esophageal adenocarcinoma (EAC). Understanding the mechanisms of radiation resistance is essential for improving the outcomes. Therefore, it underscores the importance of continued research, and identifying predictive markers associated with treatment response is crucial for optimizing patient outcomes.

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The importance of immune profiling in tailoring treatment approaches for EAC patients undergoing radiation therapy

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Poster 1

Exploring Immune Marker Prevalence in Esophageal Adenocarcinoma Patients: Insights from Opal-Multiplex Immunofluorescence

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Background: Esophageal adenocarcinoma (EAC) remains a formidable challenge, particularly in the context of radiation therapy. Esophageal adenocarcinoma is the most common subtype of esophageal cancer in the United States. The 5-year survival rate for esophageal adenocarcinoma in the United States is extremely low, hovering around 5%. This statistic reflects the challenges associated with early detection, aggressive tumor behavior, and limited treatment options. Radiation therapy plays a crucial role in the treatment of esophageal adenocarcinoma (EAC). Understanding the mechanisms of radiation resistance is essential for improving the outcomes. Therefore, it underscores the importance of continued research, and identifying predictive markers associated with treatment response is crucial for optimizing patient outcomes.

Methods: We conducted an in-depth analysis of immune markers within EAC tumor samples (n=16), focusing specifically on patients who exhibited distinct responses to radiation therapy. To validate our findings, we employed Opal-Multiplex immunofluorescence, enabling simultaneous visualization of multiple immune markers (CD4, CD8, CXCL13, GzmB, and PD1).

Results: Our study revealed an altered expression subset of several immune cells (especially CXCL13+ T cells) that demonstrated elevated expression ($p<0.05$) in the good responders group compared to non-responders. These cells may play pivotal roles in modulating the tumor microenvironment and influencing treatment efficacy.

Conclusion: Understanding the immune landscape in EAC and its association with radiation response could guide personalized therapeutic strategies. Further investigations are warranted to elucidate the functional significance of these immune markers and their potential impact on treatment outcomes.

The importance of immune profiling in tailoring treatment approaches for EAC patients undergoing radiation therapy

Poster 2

Androgen Deprivation Therapy and the Risk of Rheumatic Autoimmune Diseases in Men with Prostate Cancer

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Prostate cancer is the second most common cause of cancer death among men. Most men with prostate cancer are diagnosed at localized stages and treated with standard options including radiation, hormonal therapy, or surgery. Androgen Deprivation Therapy (ADT) is one of the mainstay treatments for prostate cancer patients, but it carries a range of possible adverse effects, including cardiovascular and autoimmune diseases. The mechanistic and biological pathways of androgens in regulating the immune cells and the physiological balance of autoimmunity are altered through ADT by increasing the number of regulatory T-cells, cytokines, and pro-inflammatory markers. Rheumatic autoimmune diseases (RAD) include rheumatoid arthritis, lupus, ankylosing spondylitis, and Sjogren's syndrome. Objective: To examine whether ADT increases the risk of RAD in men with prostate cancer. **Methods:** A cohort of patients aged >=66 years who were first diagnosed with stages (Ⅰ-Ⅲ) prostate cancer between 2010 – 2019 was identified, using the Texas Cancer Registry linked to Medicare data. The exposure to ADT was defined by the receipt of a GnRH agonist/antagonist, or orchiectomy. All patients were followed until the *diagnosis of RAD* or censored by the end of the study follow-up period or death. The patients with non-ADT were matched (1:1) to those with ADT exposure. The Kaplan-Meier method was used to produce unadjusted estimates of survival free of any RAD among the groups that did or did not receive ADT. The Cox proportional hazard analyses were used to estimate hazard ratios (HRs) with 95% CI of RAD associated with the two groups. Both models were adjusted for potential confounders in the cohort as age, race, education, marital status, poverty, metro residence, grade, stage, comorbidity index, and concomitant medications. **Results:** A total of 10,100 matched patients were included in the analysis. The failure rates of RAD over time calculated using the Kaplan-Meier curves showed that patients receiving ADT had higher rates of RAD of 11%(95% CI: 0.10 - 0.12), while men who received non-ADT had lower rates of RAD of 9%(95% CI: 0.08 - 0.10). In the Cox proportional regression model, ADT use was significantly associated with an increased risk of RAD, HR = 1.29(95% CI: 1.17-1.56).

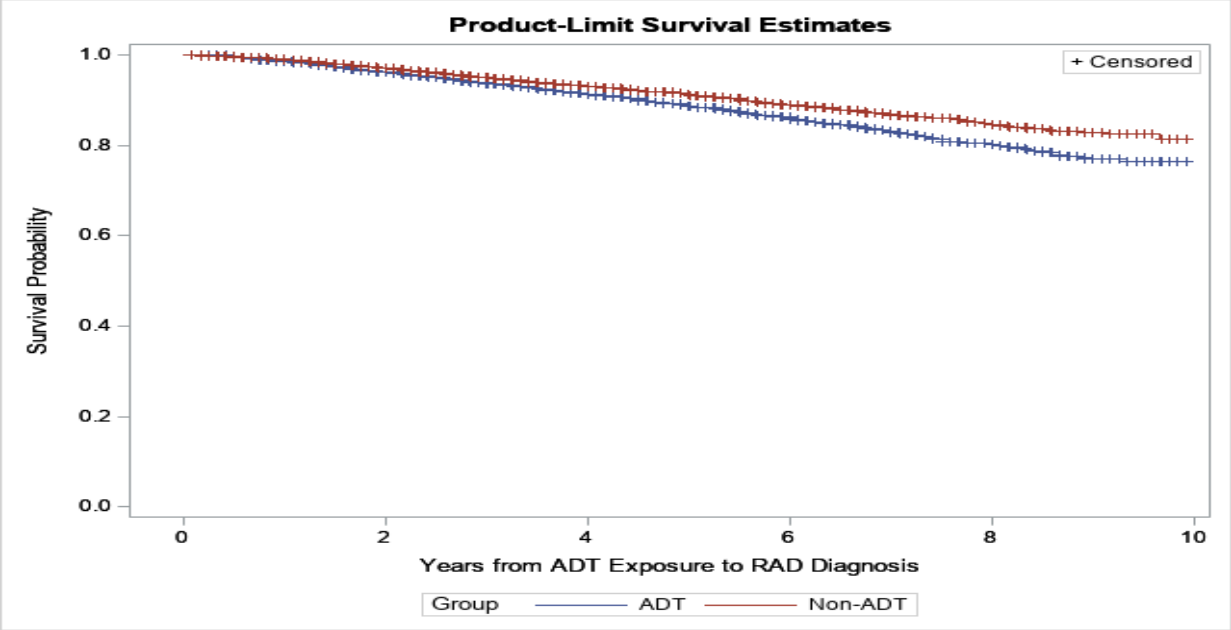

Figure 1: Kaplan-Meier shows the survival probability of free RAD

Conclusion: Our analyses showed that patients who received ADT had a 29% increased risk of being diagnosed with RAD. Linking ADT to an increased risk of RAD adds to the broad list of known adverse effects, which have a significant clinical and public health impact. Our investigation is consistent with two large population-based studies both of which showed an increased risk of RAD in prostate cancer patients who received ADT. Hence, it is imperative for clinicians to assess the care patterns and engage in discussions regarding potential adverse effects prior to initiating ADT.

Acknowledgments: This research project is supported by the Cancer Prevention and Research Institute of Texas (CPRIT) grant ID# RP210130 and National Institutes of Health (NIH), AHRQ grant ID# T32 HS 26133-5.

Poster 3

Regulation of Liver X Receptor Protein Stability by Novel Ligands in Pancreatic Cancer Cells

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Abstract

Liver X Receptors (LXRs) are nuclear receptors that act as ligand-modulated transcription factors. LXRs are overexpressed in various cancers, including pancreatic cancer, and targeting LXR with small molecule ligands has emerged as a promising therapeutic strategy in cancer. Current small molecule LXR ligands were originally developed for the treatment of atherosclerosis and other metabolic diseases. To identify ligands specifically targeting cancer cells, we screened a focused library of drug-like molecules predicted to bind to LXR using molecular docking. In the screen, novel LXR ligand GAC0001E5 (1E5) exhibited significant anti-proliferative effects in human pancreatic ductal adenocarcinoma (PDAC) cell lines. Functionally, 1E5 is an LXR inverse agonist which decreases LXR target gene expression and a “degrader” of LXR proteins following prolonged treatment. We posit that this novel ligand inhibits PDAC cells by downregulating the expression of LXR target genes. To test this hypothesis, we treated cancer cells with the previously described LXR inverse agonist SR9238 and examined its effect on cancer cell proliferation. Interestingly, treatments with SR9238 had no effect on pancreatic cancer cell prolifreatoin as compared to the novel ligand 1E5 and the 1E5 derivative KD-95, suggesting that LXR inverse agonism was insufficient to inhibit cell proliferation. To determine whether SR9238 has similar effects on LXR protein levels as novel ligands, we performed western analysis of protein expression following ligand treatment. In contrast to the novel ligands 1E5 and KD-95, treatments with SR9238 increased LXR protein levels. Furthermore, time-course studies in cycloheximide treated cells indicated that novel ligands decreased protein stability whereas SR9238 had the opposite effect. Inhibition of proteasomal degradation and autophagy abolished the effects of 1E5 and KD-95 in a cell line-dependent manner. Related to these observations, previously published data revealed that knockdown of LXR expression greatly diminished PDAC cell proliferation. Taken together, these findings indicate that LXR expression is essential in pancreatic cancer cells and suggest that the novel ligands may disrupt its involvement in protein-protein interactions and non-genomic mechanisms.

Acknowledgements: This study was supported by a grant from Golfers Against Cancer awarded to Dr. Chin-Yo Lin.

Poster 4

A Peptide Derived from Scorpion Venom Having Immunomodulating Properties

Jennifer Rivera, Carolina Rivera, and Hugo A. Barrera-Saldaña.

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The modulation of T cells activated by targeting the Kv1.3 potassium channel has emerged as a promising step for the treatment of autoimmune diseases and chronic inflammatory conditions. By selectively blocking these channels, it is possible to suppress the aberrant immune response while sparing the normal functions of the immune system. For this reason, the development of selective Kv1.3 inhibitors remains a complex and challenging task. We present a novel pharmacological property of Vm24, a natural peptide that was identified as part of the proteomic analysis of venom collected from the Mexican scorpion *Vaejovis mexicanus smithi*. Subsequent studies have demonstrated that Vm24, when added to TCR-activated human T cells, suppresses CD25 expression, inhibits cell proliferation, and mitigates delayed-type hypersensitivity reactions in a chronic inflammation model. This suggests that Vm24 functions similarly to a toxin, specifically blocking Kv1.3 on human CD4+ TEM cells, which play a crucial role in inflammation and autoimmune diseases. Finally, sequence analyses identified Vm24 as the first example of a new subfamily of α-type K+ channel blockers (systematic number α-KTx 23.1). Comparative analysis with other Kv1.3 blockers isolated from scorpions has revealed structural features that likely contribute to Vm24's high affinity and specificity towards Kv1.3 channels. Since its discovery, different studies have been carried out that have positioned this compound as a powerful and selective candidate for use as a therapeutic agent in the clinic.

Poster 5

Liver X Receptor Ligand GAC0001E5 Disrupts ER Signaling in Luminal Breast Cancer

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Estrogen receptor α (ERα) is a major contributor to carcinogenesis in ER-positive breast cancer. Endocrine therapy (e.g., tamoxifen) is commonly utilized as first-line therapy for ER-positive patients as it can disrupt ER-dependent tumorigenesis. However, the development of endocrine resistance in a subset of patients is a major concern. This substantiates the need for investigation into alternative therapeutic approaches. Liver X Receptors (LXRs) are members of the nuclear receptor superfamily of ligand-dependent transcription factors. LXRs are involved in lipid and fatty acid metabolism, and cholesterol homeostasis. LXR upregulation in cancerous tissue is associated with the cancer hallmark of metabolic reprogramming. Thus, targeting LXR with ligands could be a potential avenue for future research in therapeutics. In the pursuit of developing cancer-specific LXR ligands, our lab conducted a focused library screening of putative LXR ligands in pancreatic cancer cell lines. The novel ligand GAC0001E5 (1E5) demonstrated strong anti-proliferative properties in pancreatic cancer and later, in endocrine-sensitive and resistant breast cancer. We observed that 1E5 functions as an inverse agonist, recruiting corepressors to downregulate LXR and target gene expression. Since ERα is the prime driver of breast carcinogenesis in ER-positive luminal breast cancer, we hypothesize that the anti-tumor properties of 1E5 are due to the disruption of ER signaling. To test this hypothesis, we conducted protein and gene expression studies of estrogen receptor upon 1E5 treatment. We find that 1E5 treatment results in downregulation of ESR1 gene and western blot studies show downregulation of ERα protein as well. Furthermore, we also observe downregulation of ER-target genes. This exhibits regulation of ER through LXR ligands, thus suggesting the possibility of molecular crosstalk between ER and LXR signaling. The development of endocrine resistance is complex and multifactorial, thus further studies will be performed to determine other potential target mechanisms regulated by small molecule 1E5 in ER-positive breast cancer.

Acknowledgments: This research is supported by a grant from Golfers Against Cancer awarded to Chin-Yo Lin.

Poster 6

Pharmacologically Targeting the Nav1.6:GSK3β Complex to Mitigate Hyperexcitability in Early-Stage Alzheimer's Disease

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Abstract

Despite recent technological advancements and global initiatives to elucidate the pathophysiology of Alzheimer's disease (AD), there remains a deficiency in disease-modifying therapeutic interventions. Multiple studies indicate that aberrant hippocampal hyperexcitability is one of the first pathological features observed in early-stage AD. Voltage-gated Na+ (Nav) channels are the principal regulators of the action potential, with Nav channel isoform 1.6 (Nav1.6) serving as a primary mediator of neuronal excitability in the adult brain. Glycogen Synthase Kinase 3β (GSK3β) regulates Nav1.6 channel activity through direct binding to and phosphorylation of the Nav1.6 channel intracellular C-terminal domain. Notably, increased expression and dysregulation of both Nav1.6 and GSK3β are observed in the hippocampus of AD brains. Thus, pharmacological modulation of the GSK3β:Nav1.6 protein-protein interaction interface represents a promising strategy to regulate aberrant hyperexcitability in early AD. Using the split-luciferase complementation assay, we have identified a small molecule ligand (1063) that significantly inhibits Nav1.6/GSK3β complex assembly and binds appreciably to GSK3β without inhibiting its intrinsic kinase activity. Functionally, 1063 reduces Nav1.6-mediated sodium currents in heterologous cells in a manner reminiscent of GSK3β knockdown. Using *ex vivo* patch clamp electrophysiology we show that hyperexcitability in the CA1 region of the hippocampus is effectively mitigated following shRNA-mediated knockdown of GSK3β, and that the effects of 1063 in this region are GSK3β-dependent. Finally, *in vivo* studies show that 1063 is able to dose-dependently decrease epileptiform activity in a mouse model of AD neuropathology. Taken together, these results illustrate a novel, druggable interface between Nav1.6 and GSK3β and demonstrate the potential of pharmacologically modulating this complex to mitigate hyperexcitability in early-stage AD and other disorders.

Acknowledgements: This research is supported by the following sources: NIH Grant No. T32AG0679 (TB); Houston Area Molecular Biophysics Program (NIH Grant No. T32 GM008280; NMD); NIH/NIMH Grant R01MH111107 (FL); NIH/NIMH Grant R01MH095995 (FL); John Sealy Memorial Endowment Funds (FL)

Poster 7

AKR1C3 inhibitors induce allosteric changes in ligand binding interactions - implications for androgen receptor coactivation

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In the United States, prostate cancer is a prevalent disease among men. While androgen deprivation therapy has shown effectiveness, many patients progress to castration-resistant prostate cancer (CRPC), which has a poor prognosis and limited therapeutic options. This highlights the urgent need for new drug targets to block the androgen signaling pathway. One such potential target is Aldoketoreductase 1C3 (AKR1C3), found to be highly expressed in CRPC tumors, where it plays a critical role in activating the androgen receptor both by converting androgens enzymatically and through direct receptor coactivation. GTx-560 was found to be a compound capable of inhibiting both these activation pathways of the androgen receptor, though its action mechanism remains unclear. We propose that GTx-560 uniquely induces structural changes in AKR1C3, preventing its coactivation capability, differently from other enzymatic inhibitors like indomethacin, which do not block coactivation. Using solution NMR, we investigated the allosteric impacts of ligand binding on AKR1C3. Our findings demonstrate that both GTx560 and indomethacin suppress slow exchange in HNCO spectra, implying a conformational selection upon ligand interaction. Additionally, chemical shift perturbations (CSPs) in the HNCO spectra caused by ligand association highlight several significant CSPs away from the ligand's site of attachment, suggesting these compounds' role as allosteric modulators altering the structure of AKR1C3. Preliminary data on residual dipolar coupling suggest that AKR1C3 adopts a dynamic range of conformations when not inhibited, with ligand binding potentially favoring specific conformations within this range.

Acknowledgements: Supported by a Cancer Therapeutics Training Program fellowship (CTTP), (CPRIT Grant No. RP210043).

Poster 8

Characterization of Activity and Mechanism of Action of the *Enterococcus faecalis* Bacteriocin EntV on Fungal Pathogens

Giuseppe Buda De Cesare[1], Shantanu Guha[1], Melissa R. Cruz[1], Shane A. Cristy[1], Antonino Zito[2], David R. Andes[4], Peter J. Stogios[3], Michael C. Lorenz[1], and Danielle A. Garsin[1]

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Candida albicans, an opportunistic fungal pathogen, causes systemic and superficial infections, especially in immunocompromised patients. Treatment of fungal infections is complicated by limited antifungal options and the development of drug resistance. Previous work from our group demonstrated that the bacterium *Enterococcus faecalis*, a normal constituent of the oral and gut microbiome that is often co-isolated with *C. albicans*, antagonizes hyphal morphogenesis, biofilm formation, and virulence in *C. albicans*. These effects are mediated by EntV, a 68aa bacteriocin produced by *E. faecalis*. Based on structural data, we identified a 12aa fragment of EntV that was fully active in both *in vitro* and *in vivo* experiments, including mouse oropharyngeal candidiasis and disseminated infection models. Given the promising results, we are currently investigating the mechanism of action of the EntV peptides using several approaches. The 12mer localizes to the cell surface, with a greater binding of the peptide to hyphae compared to yeast cells, indicative of a higher amount of the peptide target in hyphae. The binding of the peptide to extracellular vesicles in *C. albicans* and *Cryptococcus neoformans*, another opportunistic fungal pathogen, suggests a connection with the antivirulence activity of EntV. In fact, the EVs are involved in virulence and biofilm formation in multiple fungal species and the similar localization of EntV in both species highlights the potential for this peptide as a broad-spectrum antifungal. Lastly the transcriptome changes induced by the 12mer indicate a possible mechanism of action associated with the Rim101 pathway, important for filamentation and virulence. Together these approaches are working to identify the molecular mechanism of EntV and enhancing its activity, both important step in its further development as a potential therapeutic.

Acknowledgements: This work is supported by the National Institute of Health (NIH).

Poster 9

Investigating Nebivolol, an Anti-hypertensive Drug, for Treating Triple Negative Breast Cancer

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Breast cancer (BC) is the most common cancer in women in the U.S. Among various types of BCs, triple negative BC (TNBC) has a high-risk of recurrence and poorer prognosis. Chemotherapy, which is associated with many acute and chronic toxicities, remains the primary treatment for TNBC. Despite aggressive therapy, within 5 years of diagnosis, about one-third of patients with early-stage TNBC progress to develop metastasis, which has a median survival of only 12 months. Therefore, there is an unmet need to identify novel drugs that are safe and effective for treating TNBC. Our group has reported the repurposing potential of nebivolol in TNBC using two cell line models (MDA-MB-231& MDA-MB-468). Here, we aimed to test the effects of nebivolol using a panel of TNBC cell lines and identify its mechanism of action. A concentration-dependent effect of nebivolol (1 nM-30 μM) and the half-maximal inhibitory concentration (IC50) were determined. We then conducted RNA-seq and reverse phase protein array (RPPA) analysis to determine the potential downstream pathways impacted by nebivolol in MDA-MB-231 and SUM159 cells. Nebivolol inhibited the growth of multiple TNBC cell lines in a concentration-dependent manner. The IC50 (μM) of nebivolol were 8.4 for MDA-MB-231, 9.0 for BT549, 13.5 for BT20, 11.6 for SUM159, 8.5 for HCC1937, and 12.7 for HCC70. RNA-seq analysis suggested autophagy and lysosomes pathways to be significantly upregulated. RPPA analysis nominated DNMT3B and pTRAP220/MED1(T1457) as significantly downregulated proteins upon nebivolol treatment in both cell lines. Integrative bioinformatic analysis of RNA-seq and RPPA data is ongoing to identify critical pathways regulated by nebivolol. Testing of additional cell line models will allow selection of the best model for the *in vivo* therapeutic studies. Ongoing cell-based effects of nebivolol will guide pharmacokinetic studies to determine the plasma concentration required for the effective tumor growth inhibition.

Acknowledgements: This research was funded by BC230597(Department of Defense, Breast Cancer Research Program) Meghana Trivedi (PI) 01/01/2024-12/31/2026

Poster 10

Implementation of a Screening Funnel for the Discovery of Potent and Selective HRI Inhibitors

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The heme-regulated inhibitor (HRI) kinase has been recently identified as a novel therapeutic target acting through distinct mechanisms to overcome inefficient erythropoiesis associated with (1) SF3B1-mutant myelodysplastic syndrome with ringed sideroblasts ($SF3B1^{mutant}$ MDS-RS)[a] and (2) Sickle Cell Disease (SCD)[b]. Patients with MDS-RS or SCD often experience anemia that requires frequent red blood cell transfusions, and even though novel agents are approved to treat these conditions, challenges remain. Luspatercept showed ~40% efficacy for MDS-RS patients, and the CRISPR-Cas9 based therapy CTX001 for SCD is currently unavailable for most patients due to its excessive costs. The potential benefits of inhibiting the HRI pathway for the treatment of anemia has led us to initiate a drug discovery campaign to identify potent and selective HRI small molecule inhibitors.

HRI belongs to the EIF2AK kinase family regulating the Integrated Stress Response pathway. EIF2AK family members respond to various stress signals such as heme deprivation (HRI; EIF2AK1), viral infection (PKR; EIF2AK2), ER stress (PERK; EIF2AK3), and amino acid deprivation (GCN2; EIF2AK4). Upon activation, all family members phosphorylate serine 51 on eIF2a, leading to translation of ATF4, transcriptional modulation of target genes, and subsequent phenotypic response to mitigate cellular stress. Here, we present our efforts to develop and implement robust biochemical/enzymatic and cellular assays to screen and prioritize compounds following a framework for evidence-based decision-making during drug discovery and development.

[a]Blood Cancer Discov. 2022; 3(6):554-567

[b]Blood Adv. 2020; 4(18):4560-4572

Poster 11

Peptide-drug Conjugates Against CAFs and Metastatic Cancer Cells

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During carcinoma progression, mesenchymal stromal cells (MSCs) become recruited to tumors and contribute to the pool of cancer-associated fibroblasts (CAFs). Adipose stromal cells (ASCs), the MSCs from fat tissue increasingly recruited by carcinomas in the context of obesity, have been shown to support cancer progression. On the other hand, metastasis of cancer cells to distant organs from primary tumors endows cancer cells with therapy resistance properties. We developed an *in vivo* screening of a combinatorial cyclic peptide library to discover peptides that target CAFs and metastatic cancer cells. We identified a peptide we named WAT7 that binds to a non-glycanated decorin (ngDCN) on the surface of ASCs. We constructed a hunter-killer peptide composed of WAT7 conjugated to a proapoptotic peptide (D-CAN) to deplete ngDCN+ CAFs in various mouse models. We found that D-CAN treatment suppressed macrophage M2 polarization and increased infiltration of cytotoxic T-lymphocytes. We assessed the effect of D-CAN on the efficacy of anti-PD-L1 antibody. Compared to D-CAN or anti-PD-L1 antibody alone, combination treatment had a synergistic effect on tumor regression. We propose that improved approaches to target mesenchymal stroma in tumors may be effective in combination with immunotherapy.

Based on the same screening approach, we have isolated a panel of breast-lung metastasis cyclic peptides (BLMPs) with tropism for murine and human cancer cells disseminated to the lung. Two of these peptides, BLMP5 and BLMP6, have been used for targeted delivery of imaging probes and experimental therapeutics *in vivo.* We have also performed *in vivo* radioactive studies for imaging and biodistribution analysis in human BCa xenograft models. We are further developing BLPMP peptides as tools that will advance approaches to timely detection and intervention of metastatic cancer.

Poster 12

Sterically Confined Rearrangements of SARS-CoV-2 Spike Protein Control Cell Invasion

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Abstract

The pandemic due to the SARS-COV-2 virus has taken a great toll on humanity, costing economic and life losses. Along with this current crisis, a great scientific push to dissect and understand the way this virus operates has revealed key information to reduce the overall impact on humans, such as the development of vaccines. Nevertheless, the molecular mechanisms used by this virus are highly unexplored. Implementing a Structure-Based Modeling (SBM), we were able to uncover the pathway used by the virus' Spike protein to merge both host and invader membranes allowing the insertion of the virus contents into the host. Also, the discovered pathway elucidates how the presence of post-translational modifications of the protein enhances the probability of virus-host contact. Further, the proposed viral entry mechanism serves as a base to probe new medically relevant configurations of the Spike protein. These configurations may allow the identification of new epitopes or sites of interest for better treatment of COVID. Following that, future steps delve into the methods to block the transition midway, this may be achievable by introducing small peptides or binding antibodies. That potentially will inhibit the transformation of the Spike protein, therefore, reducing the entry probability of the virus to human cells.

Acknowledgements: Work at the Center for Theoretical Biological Physics was supported by the NSF (Grant PHY-2019745). JNO was supported by the National Science Foundation (NSF) grants CHE-1614101 and PHY-1522550 and by the Welch Foundation (Grant C-1792). PCW was supported by NSF grant MCB-1915843. JNO is a Cancer Prevention Research in Texas Scholar in Cancer Research.

Poster 13

A Genetically Encoded Phage Display Technique Targeting Bromodomain Protein 9 (BRD9) for Discovery of Peptide Inhibitors

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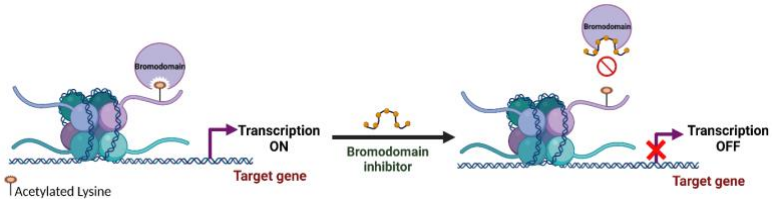
Acetylation is the most dynamic protein translational modification often associated with increased DNA accessibility and transcription. These acetylated histones recruit transcription and remodeling factors, and their deregulation could result in aberrant expression of survival and growth-promoting genes. Recognition of acetylated lysine is principally mediated by bromodomains (BRDs). Recent studies have shown that BRD9 is preferentially used by cancers that harbor SMARCB1 abnormalities such as malignant rhabdoid tumors and sarcomas. BRD9 is an essential component of the SWI/SNF chromatin remodeling complex, and a critical target required in acute myeloid leukemia. As the biological function of BRD9 in tumorigenesis becomes clear, bromodomain of BRD9 has become a new hot target for effective tumor treatment method. BRD9 has a different architecture than other bromodomains. Due to larger hydrophobic cavity of BRD9, it can recognize longer propionyl and butyryl marks on lysine. Thus, N□-butyryl-lysine (BuK) can selectively bind to BRD9. Our group is specialized in the amber suppression-based noncanonical amino acid (ncAA) mutagenesis technique. Herein (Fig 1), we propose to extend this technique using phage-displayed ncAA-containing peptide libraries for the identification of high-affinity and highly selective BRD9 inhibitors.



Phage display is a technique for rapid screening of potential ligands. It is facilitated through the creation of a genetic fusion between a randomized peptide sequence and pIII, a phage coat protein. This direct link between genotype and phenotype allows for peptide screening. We utilized Phage-assisted, Active site Directed Ligand Evolution (PADLE) approach to target BRD9. To identify the binders, we choose 7mer phagemid library which generates $1.5x10^{10}$ randomized possible peptides displayed on PIII of bacteriophages. The peptides screened were tested for binding using Bio-Layer Interferometry and inhibition by Alpha Screen assay. Based on Structure Activity Relationship studies second-generation focused selection was done to screen for more potent peptides.

Conclusion: Selected peptides successfully bind and inhibit BRD9, and we aim to further optimize its cellular target engagement and on-target effects in inhibiting leukemia cell growth and suppressing the expression of BRD9 target genes.

Acknowledgement: This work was supported by the Welch Foundation grant A-1715, National Institutes of Health awards R01CA161158 and R35GM145351, Texas A&M X-Grants mechanism, Texas A&M Chancellor EDGES Fellowship and Cancer Prevention and Research Institute of Texas grant RP170797.

Poster 14

Remodeling DNA Methylation Landscapes to Prolong CAR T-cell Activity to Overcome Cancer Relapse

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Although chimeric antigen receptor (CAR) T-cell based immunotherapy has achieved promising outcomes in patients with lymphoma and leukemia over the past five years, antigen escape and gradual reduction of T cell activity led to cancer relapse in nearly 50% of patients after initial treatment. Recent studies uncovered the critical role of DNA methylation in boosting CAR T activity, hence pointing to the possibility of overcoming cancer relapse through precise control over the DNA methylation regulatory pathways in therapeutic T cells. DNA methylation landscape is tightly controlled by DNA methyltransferases (DNMTs) and methylcytosine dioxygenases (TETs). We identified two classes of small molecules which might have inhibitory effects on DNMT1 enzyme. In vitro enzymatic activity assay indicated that several candidate compounds had strong DNMT1 inhibition. The inhibitory effect of these candidates was further tested in a co-culture system composed of CD19-positive Raji lymphoma cells and engineered CAR T-cells. Luciferase assay showed that some candidates could significantly increase luciferase level and enhance CAR T-cell activity. To modulate TET activity, we developed more than 15 nanobodies against TET2. Immunofluorescence staining and immunoprecipitation experiments showed that two nanobodies showed strong colocalization with TET2, suggesting that they can recognize TET2 efficiently. In parallel, the nanobodies against TET2 were fused with various proteasomal degradation systems to modulate intracellular TET2 protein levels and we are currently using this tool to modulate TET2 activity in CAR T-cells. The CAR T-cell modulating activities of both DNMT1 inhibitors and TET2 nanobodies will be tested in mouse models of CD19-positive tumor, thereby establishing the preclinical rationale of manipulating the DNA methylation landscapes to benefit CAR T-cell therapy.

Acknowledgement: Shaohai Fang is the Cancer Therapeutics Training Program fellow (supported by CPRIT Grant No: RP210043).

Poster 15

In Situ Accurate Quantitative Mass Spectrometry Profiling of Isomeric Lipids via Aziridine-based Isobaric Tags Reveals Distinct Spatial Lipids Change in Medulloblastoma Mice

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Lipids are biomolecules with a high potential value in disease diagnosis and therapeutics. Unraveling lipid content, level, and distribution is crucial to understanding physiological processes, boosting biomarker discovery, and eventually developing treatment. However, in situ accurate quantitative mapping of lipids on tissue remains an unsolved challenge. Lipids often exist as isomers which exacerbates the difficulty of isomeric quantitation. Herein, we developed a strategy using aziridination-based isobaric tag labeling to enable accurate relative quantitation of unsaturated lipids at the isomer level. Unsaturated Lipids are derivatized on tissue via aziridination to convert C=C bonds to aziridines followed by isobaric mass tag labeling on the nitrogen atoms. Lipid mapping at the isomer level was achieved by desorption electrospray ionization (DESI)-mass spectrometry imaging (MSI) after aziridination that produces diagnostic ions of C=C positions via collision-induced dissociation (CID). Accurate relative quantitation of lipids from different tissues was achieved by releasing the unique mass reporter ions from isobaric tags in Higher-energy collisional dissociation (HCD) after extraction, mixing, and analysis of tagged lipids from different sample by liquid extraction surface analysis (LESA)-MS. The quantitation capability has been demonstrated using FA 18:1 and PC 34:1, showing good linearity with the slope of 0.98 and 1.1.

We applied this method to investigate the change of lipid isomers in the progression, invasion, and metastasis of medulloblastoma. Many different lipids categories on brain tissue such as fatty acids, cholesterols and phospholipids were successfully derivatized with high reaction yield which could achieve 90% and above. Tandem DESI-MSI revealed the distinct distribution of lipid isomers in tumors as compared with surrounding normal brain tissues. FA 18:1 (n-7) and FA 18:1 (n-10) were highly expressed in tumors, while FA 18:1 (n-8) and FA 18:1 (n-9) had lower expression in tumors. PC18:0/18:1 (n-7) showed lower expression in tumors while PC18:0/18:1 (n-9) was highly expressed in tumors. Derivatized lipids from tumor and normal tissue were in situ labeled by different isobaric mass tags separately, ensuring high labeling efficiency while preserving spatial information. The results indicated a significant increase in the lipids contents within the tumor. Specifically, FA 18:2 and PC 32:1, exhibited a remarkable increase, with concentrations approximately four-fold higher compared to those found in surrounding normal tissues. Furthermore, concentration changes varied across lipid isomers. For example, FA 18:1 (n-10) increased more compared to other isomers, which is consistent with the latest biological findings that n-10 fatty acid pathway was activated in cancer cells.

Poster 16

Exploring the Age Dependency of Breast Cancer Driven by Mutant p53

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Breast cancer (BC) is an age-related disease. Its incidence increases in women after age 40, yet it is more aggressive in younger women. How age impacts BC remains unknown. Genetic alterations in BC most frequently occur in *p53*, with most mutations occurring somatically at arginine 248 (R248; R245 in mice). This study aims to compare $p53^{R245W}$ driven mammary tumors initiated at 2 months (corresponding to human age of ~20 years old) and 10 months old (corresponding to human age of ~50 years old) mice.

Utilizing previously generated conditional mouse $p53^{wm\text{-}R245W}$ allele, mutant p53 was induced in the epithelial cells of the mammary gland by delivering the adenovirus expressing Cre into the mammary ducts of $p53^{wm\text{-}R245W/+}$ mice. Following injection, the mice were monitored by palpation three times per week for breast tumor development. Palpable tumors were measured with a digital caliber three times per week. Animals were sacrificed when the dimension of primary tumor reached 2 cm and the tumors as well as lungs, livers and brain, the organs that mutant p53 driven mouse breast tumors would metastasize were collected into formalin, -80^0C and the tumor cells were cultured. Paraffin embedding and sectioning, as well as hematoxylin and eosin staining was carried out for examination of tumor histology and metastasis. At the same time, DNAs and RNAs were extracted from the frozen tissues. The expression of breast cancer molecular subtype markers, Esr1, Pgr and Erbb2, will be examined by quantitative Reverse Transcriptase Polymerase Chain Reaction (qRT-PCR). Tumor incidence, latency and growth rate, animal survival, metastasis, and the spectra of histological and molecular subtypes of tumors will be compared between mice injected with Ad-Cre at the age of 2 or 10 months.

The tumors initiated at the 2- and 10-months in mice driven by p53R245W were compared and the results showed that tumor latency period between the two groups was 7- to 12- months. The tumor growth rate in 2-month mice was more aggressive and progressed faster than the 10-month-old mice. The tumors collected in formalin were sectioned and analyzed by histopathologist to identify the metastasized and non-metastasized tumors. Furthermore, the DNA and RNA were extracted from the non-metastasized tumors and the samples that confirmed recombination through PCR were sequenced to determine the alterations in gene expression. The results from sequencing will show us the signaling pathways that are either up- or down-regulated due to mutant p53 in both the mice groups. The molecular sub-types and loss of heterozygosity were also determined using PCR.

This study furthered our understanding of age dependence and may allow the tailoring of therapeutic strategies to breast tumors.

Acknowledgements: NIGMS grant award 1SC2GM135111-01, NIMHD grant award U54MD007605, CPRIT grant RP180748 and RCMI – CBMHR.

Poster 17

Exploring Nav1.6 Protein-Protein Interactions in Resilience to Neuropsychiatric Disorders: Impact on 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. The results of this study offer valuable information on a new molecular target with potential for the development of novel neurotherapeutics.

Acknowledgements: We acknowledge our funding sources as follows: NIH R01MH124351 (FL), NIH 1R01MH132226 (FL).

Poster 18

The Development of Small Molecule Inhibitors Selectively Targeting the ENL YEATS Domain for Treating Acute Myeloid Leukemia

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Abstract: Acute myeloid leukemia (AML) ranks the second most frequently diagnosed and the most lethal subtype of leukemia. Recent genetic loss-of-function studies have highlighted the critical role of a YEATS domain-containing protein, known as eleven-nineteen-leukemia (ENL), in AML. ENL operates as a transcriptional coactivator and is pivotal for the growth of AML cells with oncogenic multiple lineage leukemia (MLL) rearrangements. Our prior research led to the discovery of a series of small molecule inhibitors (**1**, **7**-**9**, **11-15** and **24**) that showed pronounced and specific inhibitory effects against the ENL YEAST domain. In our latest work, we introduced an innovative NanoBRET system that facilitated the evaluation of cellular permeability, potency, selectivity, and stability of these ENL inhibitors and thereby positioned them for subsequent in-depth studies. Through *in vitro* metabolic stability and cell growth inhibition evaluations, we identified the standout ENL YEATS domain inhibitor **13**. This inhibitor demonstrated exceptional *in vitro* metabolic stability and potent anti-proliferation effects on MLL-fusion leukemia cell lines. Mouse pharmacokinetic (PK) studies revealed that, when administered orally at 20 mg/kg, inhibitor **13** achieved 60.9% bioavailability and maintained 2.6-h mean residence time. With these advantageous PK attributes, inhibitor **13** showcased impressive anti-AML efficacy, leading to extended survival for AML-xenografted mice. In summary, our research underscores the potential of inhibitor **13** as a leading drug candidate to counteract ENL's deleterious effects in AML and its based further optimization for improved characteristics.

Acknowledgement

This work was supported by NIH-R21CA267512 and CPRIT Grant RP210043.

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Poster 19

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 commonly 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. In phase II and III studies of Adcetris (VCit-based ADC), neutropenia and hepatotoxicity were observed in 16%–22% and 7% of patients respectively, 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. 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.

Acknowledgments

This work was partly supported by the National Institute of General Medical Sciences (R35GM138264 to K. Tsuchikama), the Department of Defense Breast Cancer Research Program (W81XWH-19-1-0598, to K. Tsuchikama), the Cancer Prevention and Research Institute of Texas (RP150551 and RP190561, to Z. An), the Welch Foundation (AU-0042-20030616, to Z. An), the Japan Society for the Promotion of Science (postdoctoral fellowship to Y. Anami), and the Cancer Therapeutics Training Program funded by the Cancer Prevention and Research Institute of Texas (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 20

Insights into the Divergence of Structural Functions in the iFGF/Nav Channel Protein-Protein Interface for Therapeutic Targeting

Haghighijoo Z, Gurtu A, Laezza F

Voltage-gated Na+ (Nav; Nav1.1-1.9) channels are the molecular determinants of the action potential in excitable cells, and their involvement in diverse pathologies, such as epilepsy, neurodegeneration, schizophrenia, and bipolar disorder, has spurred a significant interest in targeting these channels for drug development.

Although X-ray crystallography and CryoEM have provided significant structural insights, the sequence homology among the various Nav channel isoforms presents challenges for selective drug targeting. Consequently, there is a need for alternative strategies that can provide finer control over each Nav isoform with increased specificity. The intracellular fibroblast growth factors (iFGFs; FGF11-14) are a family of accessory proteins of Nav channels shown to bind the Nav channel C-terminal tail domain (CTD) through protein-protein interaction (PPI). While studies have identified unique determinants and druggable pockets in some of these PPI interfaces, the overall structural similarities among all iFGF/Nav channel complexes and their potential application for drug development remain largely uncharacterized.

To identify unique structural patterns among iFGF/Nav PPI complexes, we constructed 36 AF2-multimers corresponding to experimentally validated and theoretical iFGF/Nav channel complexes using available crystal structures. We then defined the structural determinants of their PPI interfaces and assessed ligand docking within identified druggable pockets using the Glide ligand docking method. Ligands included iFGF-derived peptidomimetics and small molecules with known functional effects on Na+ currents and neuronal excitability.

Our study revealed crucial amino acid residues at the N-terminus and within the β-12 strands of all iFGFs as key determinants of the PPI interface, exhibiting unique contact map patterns defined by their Nav channel isoform binding partner. Thus, despite some degree of structural conservation of key iFGF residues within the 36 PPI complexes, unique druggable pockets suitable for drug development were identified.

In conclusion, the iFGF/Nav channel complexes represent an unprecedented opportunity for drug development targeting Nav channels.

Funding: We acknowledge our funding sources as follows: NIH Grant R01MH124351 (FL), R01MH132226 (F.L.), R01 MH111107 (F.L.) U18DA052504 (F.L.).

Poster 21

Investigation of 2-Cyanopyrimidines as Macrocyclic Peptide Linkers for Phage Display

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Sitting on the interface between small molecules and large biologics, cyclic peptides show promise as a therapeutic agent for the identification of ligands for extracellular membrane proteins. Alongside this, phage display has emerged as a powerful technique that can screen billions of peptides for binding a desired target within a matter of weeks. Although there have been methods previously developed to identify cyclic peptide ligands through phage display, the majority of techniques are hindered by the necessity to use small molecule linkers that react nonspecifically with phage residues. In this work, five different 2-cyanopyrimidine scaffolds or derivatives were investigated for their selective reactivity with N-terminal cysteines. Of these, two novel linkers, pCAmCP and mCAmCP, were identified as efficient organic linkers for phage libraries containing two cysteines. Using both linkers to generate macrocyclic 12mer peptide libraries, peptide ligands were identified for ZNRF3, a membrane bound E3 Ligase that shows promise in degrading membrane proteins. One of the identified peptides (Z27S1) afforded high affinity for ZNRF3 with a K_D of 360 nM. These results validate the development of two novel small molecule linkers for phage display that can be used to identify potentially therapeutic cyclic peptides, while also highlighting the advantages of having multiple different linkers during phage selections. In future experiments, Z27S1 will be used to promote proteolytic degradation of therapeutically relevant membrane proteins by the creation of proteolysis-targeting chimeras (PROTACs) for a variety of proteins.

Acknowledgements: This project is supported by the National Institutes of Health (R35GM145351 to WL) and the Welch Foundation (A-1715 to WL).

Poster 22

EGFR Inhibitors Increase LGR5 Expression and Enhance Potency of LGR5 Antibody-Drug Conjugates Targeting Colorectal Cancer Stem Cells

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Colorectal cancer (CRC) is the second leading cause of cancer-associated death in the United States. One of the primary challenges in treating CRC is therapy resistance thought to be 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 among the fastest growing classes of anticancer drugs and utilize monoclonal antibodies (mAbs) to hone cytotoxic payloads to cancer cells. We generated ADCs targeting leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5), a biomarker of CSCs highly overexpressed in CRC. LGR5 ADCs demonstrated specificity and efficacy in CRC cells and xenograft models, though relapse after treatment withdrawal was a major obstacle. Interestingly, FDA-approved therapy targeting epidermal growth factor receptor (EGFR) has been shown to increase *LGR5* mRNA levels in patient-derived CRC models. This study aims to determine the mechanism of EGFR regulation of LGR5 expression and evaluate the efficacy of combination treatments targeting EGFR and LGR5 for the treatment of CRC.

To analyze the effect of EGFR inhibition on LGR5 expression, a panel of CRC cell lines of different *KRAS* and *PI3CKA* mutation statuses were treated with FDA-approved EGFR- and HER2-targeted mAbs or small molecule inhibitors. LGR5 protein levels were increased independent of mutation status. We also observed increases in LGR5 protein levels in patient-derived CRC tumor organoids treated with EGFR-targeting mAb cetuximab (CTX) and in LoVo CRC cell line xenografts treated either with CTX or HER2-targeting mAb trastuzumab (TTZ). Notably, treatment of CRC cells with EGF, MEK1/2 inhibitor trametinib, and EGFR-directed siRNA all resulted in concomitant reduction in EGFR and LGR5 protein levels, suggesting EGFR and LGR5 are co-degraded. Co-immunoprecipitation and immunocytochemistry experiments identified a novel EGFR-LGR5 interaction and co-internalization mechanism in CRC cells, respectively. Furthermore, we showed EGFR-LGR5 interaction is enhanced by treatment with CTX. To evaluate the efficacy of combination therapies targeting EGFR and LGR5, CRC cells and a patient-derived CRC xenograft model were treated with LGR5 ADCs with or without CTX. Importantly, CTX significantly enhanced the potency of LGR5 ADCs incorporating different classes of cytotoxic payloads in vitro and in vivo. These results suggest combining LGR5 ADCs with EGFR inhibitors may be a more effective approach for the treatment of CRC and eliminating CSCs to overcome resistance and relapse.

Acknowledgments: This work is supported by the National Institutes of Health (NCI, R01CA226894, R21CA270716, and R21CA282378), the Cancer Prevention Research Institute of Texas (RP210092), the Gulf Coast Consortia Training Interdisciplinary Pharmacology Scientists fellowship (T32GM139801-03), and The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences (GSBS).

Poster 23

Nano-approaches for Combined Radiation and Immunotherapy of Cancer Based on STING Activation

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Pancreatic cancer is a common malignancy, however it is difficult to diagnose at an early stage when most curable. Developing combined approaches to pancreatic cancer treatment would lead to more patient-specific treatment and consequently greater treatment outcomes. This work assesses the use of hollow gold nanoparticles (HGNs) as nano-delivery systems for stimulating the cyclic GMP-AMP synthase (cGAS) - stimulator of interferon genes (STING) pathway in pancreatic cancer cells while also acting as radiosensitising agents for simultaneous radiation therapy. This approach would thereby combine nanotechnology, protected drug delivery, targeted immunotherapy and enhanced radiation therapy for treatment of intractable cancers.

Radiation therapy is a common treatment across all types of cancer, including pancreatic cancer. However, due to the low doses that must be administered to prevent healthy tissue damage, courses of radiation treatment can be long with poor outcomes. Consequently, radiation therapy is an ideal candidate for combination with radiosensitisation agents, such as gold nanoparticles, or with immunotherapy to improve the dose effect. New immunotherapy approaches include targeting the cGAS-STING pathway in the tumour. Activation of this pathway stimulates type I interferon responses which are needed for priming tumour-specific cytotoxic T cells. However, STING agonists are limited due to poor cytosolic entry, serum stability and systemic toxicity. Additionally non-specific activation of STING can cause widespread inflammatory responses which may lead to difficulties translating this approach to the clinic. This highlights the need for protected and targeted STING agonist delivery. HGNs have been shown to be useful in cancer therapy due to a number of unique properties, including drug loading capabilities, ability to be functionalised for tumour targeting and radiation enhancement capacity. Yet, HGNs have not previously been used for drug delivery of immunotherapy agents, like STING agonists. HGNs show particular promise for STING agonist delivery because their unique shape could be exploited for drug loading, protected drug delivery and controlled release at the target site, thus addressing the poor stability and systemic toxicity.

The main aims of this research are to investigate the use of HGN as targeted drug delivery systems for STING activation with controlled release in pancreatic cancer cells. We will also assess the radiosensitisation properties of HGNs in pancreatic cancer cells. Finally, we will evaluate the subsequent immune and radiation responses in cancer cells following this combined treatment. Our preliminary studies have shown great radiosensitising effects when combining HGNs with external beam radiation. Furthermore, our work has suggested that these HGNs can be loaded with therapeutic agents and controlled release can be triggered upon X-ray radiation of the particles. We aim to further adapt this work to assess HGNs as carriers of STING agonists. Overall, utilising HGNs as both targeted drug delivery systems and radiosensitising agents would allow a novel combination approach to tackling difficult to treat cancers, such as pancreatic cancer.

Poster 24

Deep Learning to Predict Protein-Protein Interactions

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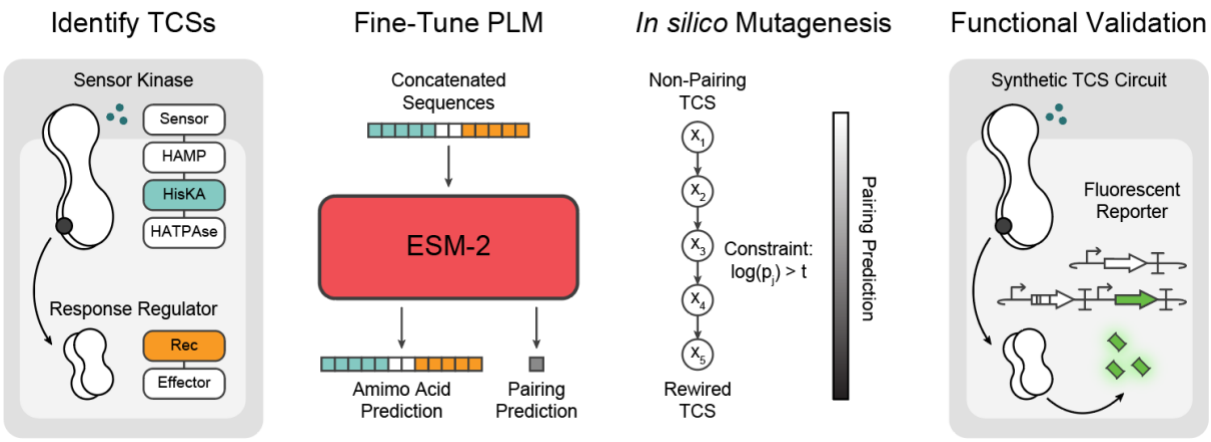
Accurate prediction of protein-protein interactions is a vital unsolved problem in computational biology. Previous methods utilizing sequence alignments and/or homology models of protein structure have proven unsuccessful for engineering purposes. We explored the ability of large language models to predict protein-protein interactions using bacterial two-component systems (TCSs) as a test case. We fine-tuned ESM-2 on a masked-language modeling task to predict amino acid residues for paired TCS sequences. The model accurately identifies covarying residues in the interfacial space, along with previously unidentified residues important in pairing specificity. We found that sequence embeddings alone contained significant pairing information when compared with the null data set and performed better than DCA in naïve pairing prediction. We then fine-tuned the model for sequence classification. Using this method, we explore the model's ability to predict orphan TCSs in six well-characterized model organisms, as well as our ability to engineer novel protein-protein interactions *in vivo* using an E. coli expression system.



Poster 24

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 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. All expressed exons were filtered to exclude known exons to further examine novel or cryptic exons. To select for Shh-d U1 snRNA mutant induced cryptic exons, a few more filtering parameters were applied, such as keeping cryptic exons arise from introns, ones that are not identified in Shh-d U1 WT and included >10% of their inclusion rates measured by percent spliced in (***PSI***) in Shh-d U1 snRNA mutant samples. These cryptic exons can be further subdivided into first, middle, and last based on where the cryptic sequence located in the novel isoform . Of the middle CryEx, we identified 43188 that were U1 mutant induced. Filtering for <0.1 PSI values, 75% were in more than 50% of the U1 mutant samples. Further filtering for cell surface Middle CryEx, three of the 75 middle CryEx overlapped. The 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 for therapeutic drug discovery.

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Acknowledgements
Dr. Michelle Kameda-Smith's fellowship is supported by the Gulf Coast Consortia (GCC) Cancer Prevention and Research Institute of Texas (CPRIT) Cancer Therapeutics Trainee Program (CTTP) CPRIT Grant No. RP201003. Dr. Nabil Ahmed is supported by the National Cancer Institute (NCI) U54 CA232568. Dr. Michael Taylor is supported by the Canadian Institute for Health Research (CIHR), Genome Canada, Cancer Research UK (CRUK) (C9685/A228598), National Institute of Health (NIH) R01NS106155 and R01CA255369 and the Cancer Prevention and Research Institute of Texas (CPRIT) RR220051.

Poster 26

4M Therapeutics is a Biotechnology Startup Uniquely Poised to Develop Innovative Therapies for Central Nervous System Disorders

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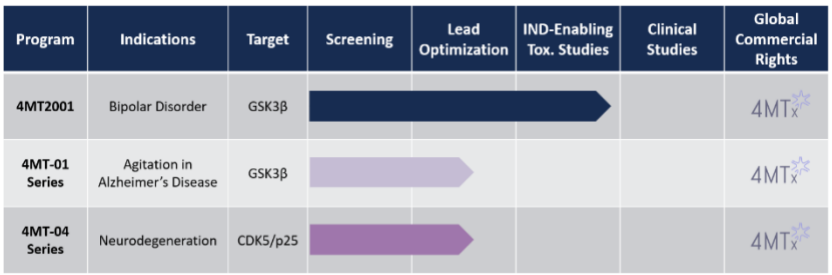
4M Therapeutics (4MTx) is a biotechnology startup developing therapies for central nervous system disorders with blockbuster potential. 4MTx applies unique insights from its living human brain cell platform, which was developed through a collaborative effort between Harvard, MIT, and the University of Washington, to identify and design more effective and safer therapeutics. The company's founders were the first to identify hyperactive Glycogen Synthase Kinase-3 Beta (GSK3β) in living human brain cells derived from induced pluripotent stem cells (iPSCs) of patients with bipolar disorder and Alzheimer's disease. 4MTx's lead compound, 4MT2001, a GSK3β inhibitor, has demonstrated safety and efficacy data that support its potential as a best-in-class treatment for bipolar disorder. Eli Lilly initially developed ruboxistaurin, the parent compound of 4MT2001, as a treatment for diabetic retinopathy. Although ruboxistaurin did not gain approval for this indication, it demonstrated good tolerability in more than 2,000 elderly patients, most of whom were treated for more than a year. 4M Therapeutics discovered that both ruboxistaurin and its primary metabolite, 4MT2001, inhibited GSK3β but 4MT2001 provided enhanced potency and selectivity for GSK3β and a superior pharmacokinetic and pharmacodynamic profile. 4MT2001 reduced mania-like behavior in animals, showing efficacy similar to lithium, but at 1/1000th the molar concentration. The data suggest that 4MT2001 could be an effective, safer alternative to lithium in the treatment of bipolar disorder. The FDA provided feedback on the 4MT2001 program, and a Phase 1 clinical trial is planned for 2025. The company's pipeline also includes some of the most potent and specific GSK3β inhibitors ever developed. The 4MT-01 series is being developed for the treatment of agitation in Alzheimer's disease. The 4MT-04 series inhibits the CDK5/p25 complex and has shown efficacy in rescuing learning and memory deficits and reducing microgliosis and neuronal loss in an aged animal model of tau pathology. It may provide breakthrough potential in neurodegenerative diseases. Thus far, 4MTx has raised over $5 million to date with all founders and board members participating.

4MTx Pipeline



Acknowledgements: The organization's work has been funded by seed investors.

Poster 27

Generation of Highly Selective Monoclonal Antibodies Inhibiting Matrix Metalloproteinases

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As a group of zinc-dependent endopeptidases, matrix metalloproteinases (MMPs) are crucial in controlling several physiological and pathological procedures. Among them, MMP-2/-9/-14 are promising pharmacological targets and their inhibitory antibodies have great potential as valuable drugs in neuropathic pain and cancer. Because the catalytic domain fold and reaction mechanism are highly conserved among the MMP family members, the available MMP small molecule inhibitors target multiple proteinases resulting in off-target side effects. In addition, single MMP has both detrimental and beneficial effects through the cleavage of different substrates. Consequently, there is a requirement to develop target/substrate specific monoclonal antibodies. However, existing mAbs selection/screening methods are mainly based on binding affinities but not inhibitory function, therefore few or none of the selected binders have required target/substrate specific inhibition. To facilitate substrate specific mAbs discovery, a negative selection method is highly required for isolating mAbs that do not impede MMP-14-catalyzed degradation of nontarget substrate. Levansucrase hydrolyzes sucrose and leads to accumulation of levan in periplasm of gram-negative bacteria, resulting in cell death. Therefore, levansucrase was modified by inserting a cleavable peptide, and we demonstrated that modified levansucrase can be applied for negative selection. By combining convex paratope antibody library and function-based periplasmic genetic selections, MMP-2/-9/-14 inhibitory mAbs were successfully isolated. In the case of MMP-9 inhibitory mAbs, isolated mAbs effectively inhibited activated MMP-9 proteolytic activity from cleaving peptide and physiological/macromolecular substrates including collagen type IV, gelatin and interleukin-1β (IL-1β). Importantly, isolated mAbs were highly selective toward MMP-9 over (cd)MMP-2/-12/-14/-24. In diabetic neuropathy mouse models, systemic administration of MMP-9 inhibitory IgGs promoted nerve fiber regeneration, and attenuated neuropathic pain in the STZ, PTX, db/db and CCI models as well as improved wound healing. As regards MMP-14 inhibitory mAbs, isolated mAbs showed nanomolar potency toward cdMMP-14 with high selectivity over (cd)MMP-2/-12/-14/-24. More importantly, isolated mAbs inhibited the cleavage of target syndecan-1 by MMP-14 not nontarget MCP3. In addition, MMP-2 inhibitory mAbs showed nanomolar binding affinity and potency. Technological developments within this study allow us to discover target/substrate specific mAbs inhibiting MMP-2/-9/-14 of biomedical importance, and novel MMP-2/-9/-14 mAbs will be of great therapeutic potential for the management of diabetic neuropathy and cancer treatment.

Acknowledgements: This study was supported by NIH R35GM141089 and CTTP traineeship from CPRIT Grant No. RP210043.

Poster 28

Thyroid Hormone Metabolites as Therapeutics for Cardiac Repair in Female Rats

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Women are prone to endocrine deficiencies as well as a loss of estrogen (E2) due to menopause. Thyroid hormone deficiency correlates with diminished cardiac health, and post-menopausal status increases cardiovascular disease risk. The effects of this double reduction of thyroid hormone and E2 on the heart is important to evaluate to create sex-specific approaches for heart failure treatment. This study evaluates the impacts of hypothyroidism and menopause on cardiac function in a female rodent heart failure model to evaluate differences in individuals with and without hormone replacement therapy. We examined the impact of triiodothyronine (T3), 3,3'-diiodothyronine (T2), and E2 on cardiac repair in hypothyroid, post-menopausal rats with surgically induced myocardial infarctions (MIs). Hypothyroidism was generated through oral administration of propylthiouracil (1 mg/mL) and menopause via ovariectomy. Over 9 weeks, weight, blood pressure, hormone levels, and temperature were measured, and heart function evaluated pre- and post-MI with echocardiograms and electrocardiograms. Heart and thyroid tissues (histopathology) and serum T3, T4, and TSH were assessed for the impact of hormone replacement therapy on cardiac repair. Blood pressure analyses revealed a significant decrease in pulse in hypothyroid rats versus euthyroid controls. Post-MI, both groups showed comparable declines in cardiac function. Oral T3 treatment led to reduced left ventricular ejection fraction (LVEF) in euthyroid rats but increased LVEF in hypothyroid rats, compared to saline and 3,3’-T2 treatments. T3 treated hypothyroid rats also exhibited enhanced cardiac output relative to saline or 3,3’-T2. Current heart failure treatments (e.g., beta-blockers) decrease cardiac workload and oxygen demand, aiding regeneration. We demonstrate T3's opposing effects: detrimental (reducing LVEF) in the euthyroid state, but beneficial (increasing LVEF) in the hypothyroid state. Thus, thyroid hormone therapy in hypothyroid patients may be effective for heart failure treatment, despite current contraindications.

Acknowledgements: This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs through the Congressionally Directed Medical Research Program under Award No. W81XWH-22-1-0007 (CSF).

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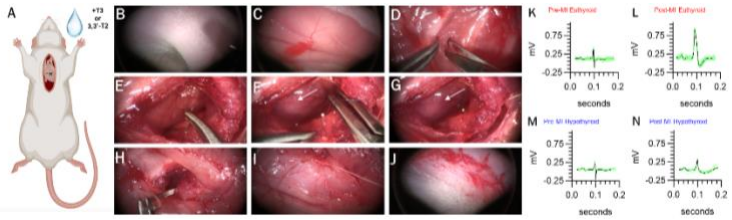

Fig. 1. Photographs of various stages of the left anterior descending artery (LAD) ligation surgical method and representative EGC traces.

Poster 29

Investigating Mitochondria-targeting Compounds for Selective Cytotoxicity in Leukemia

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Acute myeloid leukemia (AML) is an aggressive hematological malignancy that has a poor prognosis with cytotoxic chemotherapies, low remission rates, and a high incidence of relapse. Current chemotherapies are often poorly tolerated by older patients or those with comorbidities, significantly limiting clinical options. Additionally, leukemic cells develop resistance mechanisms to current therapies. New and better treatments are needed for patients with this diagnosis.

Heavy reliance on oxidative phosphorylation for ATP production and increased sensitivity to mitochondrial damage are common features of AML cells, making these organelles a prime target for therapeutic intervention. Previous studies have identified compounds that initiate mitochondrial turnover (mitophagy) and selectively kill AML cells. The most promising compounds to date, derived from an original hit named PS127, impaired mitochondrial bioenergetics by upregulating reactive oxygen species (ROS), reducing basal and ATP-linked respiration, and activating apoptosis and ferroptosis in AML cells.

To explore additional chemical space, we utilized PASS (Prediction of Activity Spectra for Substances) cheminformatic software to identify the likely biochemical functions of PS127-family molecules. We screened ~4.2 M molecules *in silico* for these functions and identified 213 hits, 93 of which were closely related to PS127-family molecules based on ChemMine clustering. Thirteen out of 93 molecules, representing different structural groups, were tested for their ability to kill AML cells, with 5 molecules exhibiting $CC50_{AML}$ in sub-micromolar levels in the MOLM-13 AML cell line.

Evaluation of these 5 hits in a broader range of cells showed that they had low CC50 values in multiple AML and ALL (acute lymphoblastic leukemia) cell lines. Interestingly, there was a strong correlation between $CC50_{AML}$ and $CC50_{ALL}$ for these molecules. These compounds were much less active against CML (chronic myeloid leukemia) cells, consistent with different metabolic adaptations in acute and chronic hematological cancers. Furthermore, these molecules showed synergy with two existing AML and ALL treatments (doxorubicin and midostaurin), but not with cytarabine, suggesting specific interactions between drugs.

Our current research involves assessing additional synergistic combinations, examining the effect of prioritized hits on mitochondrial bioenergetics, and exploring their molecular mechanisms predicted by cheminformatic analysis. This will lay the foundation for future evaluation of these compounds (and their combinations with current treatments) in preclinical AML and ALL patient-derived xenograft murine models.

Acknowledgements: This research was supported by National Institutes of Health (NIH) National Institute of General Medical Sciences (NIGMS) 2R35GM129294 and NIH National Cancer Institute (NCI) 1R21CA280500. Thank you to all current and past lab members who set the foundation for this project.

Poster 30

Viral Condensates as An Innovative Drug Screening Platform

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The recent pandemic has shown how ill-prepared we are for emergent infectious diseases. In a large part this is because of a lack of pharmaceutical interest in infectious disease and the difficulty of safely studying such contagious pathogens in the lab. Especially high-content drug screening of infected cells remains challenging given the need to grow copious amounts of live virus. Creating pathogen-free cell-based models that reliably recapitulate specific steps of the viral life cycle could provide a powerful platform to speed up the discovery of novel viral targets and drug classes.

Upon infection, several human viruses form so-called viral factories—biomolecular condensates consisting of viral and host proteins that are essential to viral replication. Given their importance, these organelles are excellent drug targets yet remain largely untargeted as they are only observed in cells infected with live viruses. Our lab has leveraged our expertise in studying biomolecular condensates to reconstitute these viral factories from minimal components. In other words, by identifying the critical viral proteins responsible for viral factory formation we can simply overexpress these in human cells to create a cell-based model that mimics infection. We call these viral factory mimics (VFMs) and they are compatible with BSL-2 culturing and therefore perfectly suited for high-content image-based screens.

As a proof of concept, we have pursued this approach for the classic example of a BSL-4 virus: Ebola. We have successfully generated and characterized an Ebola VFM and have initiated high-content image-based drug screens to identify small compounds that alter these viral condensates. In doing so, we already identified several promising compounds that could perturb viral replication. We are currently exploring a larger drug space to find additional lead compounds and are setting up preclinical experiments aimed at testing the therapeutic potential of our lead compounds. In all, by expanding these efforts to other human viruses of high unmet need we hope to democratize global access to treatment options for infectious disease and provide a rapid and adaptable platform to prepare us for future pandemics.

Acknowledgements: This project is supported by the Cancer Prevention and Research Institute of Texas, (CPRIT).

Poster 31

Evaluating Novel Circular RNAs as a Possible Gene Replacement Therapy in CLN3 Batten Disease

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There are 13 known types of Batten disease (also known as neuronal ceroid lipofuscinosis), a genetic neurodegenerative lysosomal disease. Each type has different gene variants, severity, age of onset, symptoms, and rates of progression. The most common type of Batten disease ceroid lipofuscinosis, neuronal 3 (CLN3), also known as juvenile Batten disease, is caused by mutations in the *CLN3* gene that encodes a lysosomal transmembrane protein. There currently is no cure or approved treatment to slow the progression of CLN3 Batten disease (which is ultimately fatal).

Recent advancements in RNA therapeutics including the COVID mRNA vaccines and antisense oligonucleotides are presenting options to treat diseases or to target aberrant proteins that were previously thought to be “undruggable”. One major obstacle to expanding mRNA therapies to genetic diseases is their short half-life in vivo. Since circular RNAs are protected from both 5’ and 3’ exoribonucleases, their stability in vivo is greatly improved over linear mRNAs. To this end, we design and produce circular RNAs to be used as vaccines and therapies. We have made circular CLN3 RNA and validated that the circRNA expressed CLN3 protein in vitro. Finally, we are using animal models to test whether circular CLN3 RNA shows promise as a possible treatment for CLN3 Batten disease.

Acknowledgements: This work was supported by a Career Cornerstone Award from the Houston Methodist Research Institute and additional funding from the Houston Methodist Foundation (both to DLK).

Poster 32

LXR Inverse Agonist 1E5 Disrupts HER2/ERBB2 and Induces Oxidative Stress in HER2-positive Breast Cancers

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The HER2-positive subtype represents approximately 20% of all breast cancer cases. Insensitivity and development of acquired resistance to targeted therapies in some patients lead to their poor prognosis. HER2-overexpressed tumors demonstrate upregulation in metabolic reprogramming, a major hallmark of cancer that promotes cell proliferation and survival. Liver X receptors (LXRs) belong to the nuclear receptor superfamily and function as metabolic regulators modulating lipid, cholesterol, and glucose metabolism. In our previous work, a novel LXR inverse agonist, GAC0001E5 (1E5), was discovered and characterized to inhibit cancer cell proliferation by disrupting glutaminolysis and inducing oxidative stress. In this study, HER2-positive breast cancer cells were treated with 1E5 to investigate potential inhibitory effects and mechanisms of action. 1E5 inhibited LXR function and cancer cell proliferation, resembling the published work in other cancer types. Expression of *de novo* lipogenesis (DNL) genes, including crucial enzyme fatty acid synthase (*FASN*), were downregulated after 1E5 treatment, and results from co-treatment experiments with FASN inhibitor C75 suggest that the same pathway is triggered by 1E5. Treatments with 1E5 increased oxidative stress as a result of disrupting glutaminolysis. Markedly, HER2 transcript and protein levels were both significantly downregulated by 1E5. Collectively, knowledge obtained from these findings highlights the therapeutic potential of targeting HER2 overexpression and associated metabolic reprogramming via the modulation of LXR in HER2-positive breast cancer.

Acknowledgments: The studies described in this poster were funded by a grant from Golfers Against Cancer awarded to Chin-Yo Lin.

Poster 33

Enhancing Tacrolimus (FK506) Pharmacokinetics for Systemic Management of Psoriasis: A Computational Modeling Approach

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Tacrolimus, also known as FK506, is an immunosuppressant used to prevent the rejection of transplanted organs and for the short-term management of severe or treatment-resistant psoriasis. While oral tacrolimus at a dose of 0.1 mg/kg has shown effectiveness, its systemic dermatological use has not been approved yet but has been offered off-label. Moreover, real-world clinical observations suggest that psoriasis patients with specific area involvement may not always reflect the severity of their skin condition, and many patients treated with topicals still have significant area involvement, highlighting a potential discrepancy between treatment practices and guidelines, and indicating an unmet medical need for systemic treatment in psoriasis patients. This research focuses on enhancing the pharmacokinetics of oral tacrolimus for treating psoriasis. By applying a fragment-based approach, a fragment from FK506 was selected and further screened to develop nine molecule analogs with improved biological activity and binding to the target protein FKBP12. The efficacy of these New Chemical Entities (NCEs) in binding to the target protein was assessed through a hit-to-lead optimization process for increased potency and selectivity while reducing off-target effects. Among the discovered NCEs, FK6024, which was also a bivalent ligand, stood out as a candidate due to its characteristics such as lower binding energy, high gastrointestinal absorption, and decreased off-target toxicity. Computational simulations revealed that FK6024 exhibits approximately 26.06% binding energy than FK506 indicating it is a final compound, with improved pharmacokinetic properties. Computational modeling was performed using free web tools including SwissTargetPrediction, SwissDock, and SwissADME for fragment screening, molecular docking, and ADME predictions. Future work will focus on further optimization and application of these methods using comprehensive software packages like ACD/Labs to enhance the potency and minimize off-target toxicity of targeted NCEs, contributing to the improvement of oral FK506 pharmacokinetic properties for treatments of severe or treatment-resistant psoriasis.

Acknowledgments: I extend my gratitude to Dr. Dong Liang, Dr. Ilnaz Raeisi, Dr. Selvam Chelliah, Dr. Yuan Chen, Dr. Kehinde Idowu, and Dr. Evgeny Vulfson for their guidance and support throughout the research process. Their expertise and mentorship have been instrumental in shaping the development of this work.

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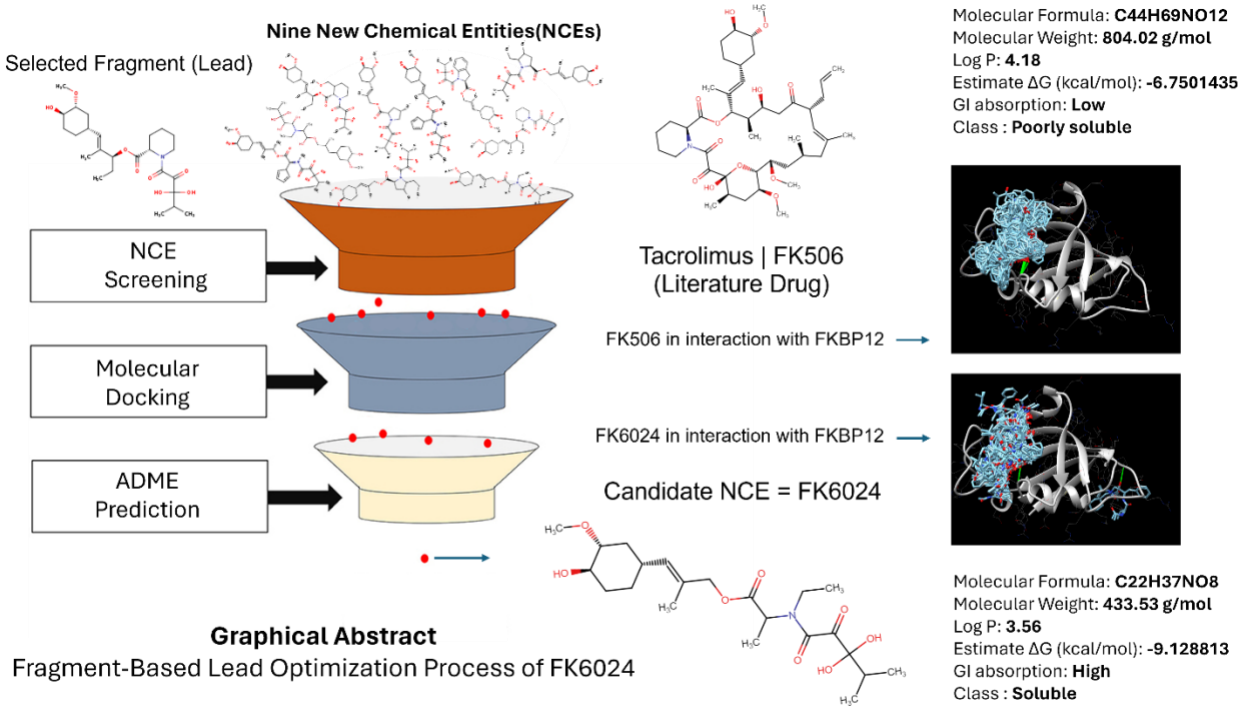

Graphical Abstract

Fragment-Based Lead Optimization Process of FK6024

Poster 34

Structural and Functional Investigation of Antiviral Mitochondrial Drug Toxicity

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RNA viruses such as SARS, Dengue, and hepatitis C virus pose a significant pathogenic risk to global populations and are responsible for 44% of all emerging human infectious diseases. These RNA viruses utilize a viral RNA-dependent RNA polymerase to replicate their genomes by exploiting host cell machinery. A class of antiviral drugs known as nucleoside/nucleotide inhibitors (NNIs) competitively inhibit the viral RNA polymerase by chain termination of viral replication. However, a large number of these NNIs have failed during clinical trials due to severe off-target interactions, primarily with the human mitochondrial RNA polymerase (POLRMT). The off-target interactions effect of NNIs on POLRMT during mitochondrial replication and transcription are not well-characterized, and a more comprehensive understanding of POLRMT inhibition by NNIs is essential for future design of antivirals with high specificity, increased therapeutic index, and low risk of emergent viral resistance. Our ***central hypothesis*** is that drug toxicity of NNIs is correlated with their frequency of incorporation and chain termination of human POLRMT RNA transcription. To test our central hypothesis, we will perform functional and structural studies to evaluate the off-target effects of novel antiviral drugs on POLRMT. Steady-state kinetic analyses of single-nucleotide incorporation of 12 novel NNIs will be used to determine kinetics parameters such as K_M and V_{max} for each NNI. Utilizing this data, we will use cryo-EM to determine structural components of novel antiviral drugs in complex with POLRMT during incorporation events, revealing mechanisms related to chain termination and inhibition of PORLMT.

Acknowledgements: This project is supported by the National Institutes of Health (NIH), the Gulf Coast Consortia Houston Area Molecular Biophysics Training Program (HAMBP), and the UTMB-Novartis Alliance for Pandemic Preparedness (UNAPP).

Poster 35

GSK3β Scaffolding in the Nav1.6 Channel Complex Modulates Neuronal Excitability in Medium Spiny Neurons

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Kinase signaling pathways regulating ion channel macromolecular complexes play a crucial role in fine-tuning neuronal activity and remodeling synapses. However, the molecular mechanisms underlying the regulation of these molecular complexes are still poorly understood. In recent studies, we have shown that the interaction between glycogen synthase kinase 3β (GSK3β) and the C-terminal domain (CTD) of the voltage-gated Na+ channel Nav1.6 is critical in mediating maladaptive plasticity of medium spiny neurons (MSNs) in the nucleus accumbens (NAc), a key brain area in the reward circuit. Building on these findings, we hypothesized that inhibition of GSK3β/Nav1.6 complex formation could counteract MSN maladaptive plasticity. Here, we developed a library of peptide-based probes to modulate the scaffolding function of GSK3β in the Nav1.6 channel complex. Using structure-guided in-cell assays and surface plasmon resonance, we discovered that probe ZL141 efficiently inhibits the formation of the GSK3β/Nav1.6 complex and binds to GSK3β. Whole-cell patch-clamp recordings in HEK293 cells stably expressing Nav1.6 demonstrated that ZL141 regulates peak current density, voltage-dependent activation, steady-state inactivation curves, and long-term inactivation of Nav1.6 in a GSK3β-dependent manner. In line with its impact on Nav1.6 currents, ZL141 demonstrated a protective effect on MSN maladaptive plasticity, mimicking the effect seen with in vivo silencing of GSK3β. These results provide evidence for a novel mechanism regulating the Nav channel and neuronal excitability via a functionally relevant GSK3β/Nav1.6 complex.

Funding: We acknowledge our funding sources as follows: NIH Grant NIH R01MH124351 (FL), R01MH132226 (F.L.), R01 MH111107 (F.L., J.Z.), R01 DA038446 (JZ), U18DA052504 (FL), and HAMBP training grant no. T32GM008280 (N.M.D.), the training program funded by the National Institute of Aging, NIH grant no. T32AG067952-01 (T.J.B.).

Poster 36

IACS-16559, A CBP/P300 Bromodomain Inhibitor for the Treatment of Specific AML Subsets

Ciro Zanca[1], Michael Soth[2], Guang Gao[1], Jason Gay[1], Ningping Feng[1], Christopher Bristow[1], Kang Le[2], Quanyun Xu[2], Phuong Nguyen[2], Yongying Jiang[2], Teresa Perry[2], Faika Mseeh[2], Paul Leonard[2], Jason Cross[2], Virginia Giuliani[1], Joe Marszalek[1], Philip Jones[2], Tim Heffernan[1]

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Block in differentiation and accumulation of undifferentiated blasts are hallmarks of Acute Myeloid Leukemia (AML), and epigenetic processes have been shown to play a critical role in hematological malignancies. Paralogs CREBBP (CBP) and EP300 (P300), in association with co-factors, are hijacked during leukemogenesis by aberrant transcriptional factors, thus driving blast proliferation and maintaining an undifferentiated phenotype. We developed IACS-16599, a highly selective CBP/P300 bromodomain inhibitor with good cross-species and predicted human pharmacokinetics, and explored the effects of this compound in AML *in vitro* and *in vivo* models. We found that IACS-16559 mediates an antiproliferative response in specific AML subsets, with synergistic effects observed when combined with an MLL-Menin inhibitor. Mechanistic studies suggest that results are driven by an induced myeloid differentiation phenotype. Collectively, our findings provide a compelling basis for further exploring the use of CBP/P300 bromodomain inhibitors in combination with MLL-Menin inhibition in specific subsets of AML patients.

Acknowledgement: Development of IACS-16559 was funded by The Mark Foundation for Cancer Research.

Poster 37

Unveiling Patient-Specific Neuronal Activity Landscape in MECP2 Duplication Syndrome Using Human Brain Organoids

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Abstract

Neurological disorders affect over 3 billion people worldwide, and ~15% of these patients are children in whom the disorder is often attributed to neurodevelopmental origin. There is no cure for developmental disorders, and current treatments focus on symptom management through medications, behavioral therapy, and psychological counseling. However, due to patient heterogeneity, every individual responds to therapy differently, underscoring the need for personalized medicine approaches. Human brain organoids have emerged as a transformational platform for advancing personalized medicine, offering unique insights into the pathophysiology of neurological diseases and facilitating the development of tailored therapeutic interventions. Brain organoids are derived from human pluripotent stem cells and they replicate the structure, organization, and function of the human brain. In this study, we used this model to investigate the electrophysiological properties of neurons in MECP2 Duplication Syndrome, a severe genetic neurodevelopmental syndrome affecting boys. MECP2 duplication impairs brain function and leads to seizures, generalized somatic and autonomic hypotonia, and intellectual disability. Previous studies in mouse models of MECP2 duplication have suggested aberrant gamma-aminobutyric acid (GABA) pathway, impairing the inhibitory activity and disrupting the delicate balance between excitation and inhibition in the brain. Therefore, our objective was to examine the GABAergic activity in human brain organoids from MECP2 Duplication patients during early development, to better understand the neuronal activity in this syndrome and lay the groundwork for future drug discovery efforts to normalize it. We performed multiplexed electrophysiological recordings over seven weeks in culture, using multielectrode arrays (MEA), and evaluated the effects of picrotoxin, a GABA-A receptors blocker, on neuronal activity. Our results revealed distinct GABAergic populations with unique electrophysiological responses in MECP2 Duplication organoids compared to organoids from healthy controls. These data enhance our understanding of GABAergic mechanisms in MECP2 Duplication Syndrome and provide a platform for the development of new therapeutic interventions targeting these circuits. As we strive towards addressing the unmet medical needs of over 3 billion individuals worldwide affected by neurological disorders, the utilization of innovative tools like human brain organoids holds promise for the development of more effective and personalized treatments, ultimately improving the lives of patients and their families.

Poster 38

A Novel MET Antibody-Drug Conjugate Based Combination Therapy to Overcome Colorectal Cancer Plasticity and Drug Resistance

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Despite therapeutic advancements, colorectal cancer (CRC) remains the second deadliest malignancy in the United States. Challenges encountered in CRC treatment may be attributed to cancer stem cells (CSC), an immortal tumor cell population. CSCs potentiate tumor relapse by exploiting its infinite replicative potential and inherent drug resistance. Moreover, CSCs exhibit plasticity, allowing them to transition between differentiated and undifferentiated states in response to environmental cues to evade therapy and drive metastatic progression. MET is a receptor tyrosine kinase frequently upregulated in CRCs. We previously showed that treatment with chemotherapies or antibody-drug conjugates (ADCs) targeting the CSC marker LGR5 led to the loss of LGR5 expression with concomitant MET-STAT3 pathway activation in therapy-resistant CRC cells. Further, we showed that LGR5 couples to the scaffold protein IQGAP1, which correlates with poor prognosis in several cancer types. Interestingly, our new data shows that LGR5 knockdown enhances IQGAP1 interaction with MET and STAT3 via co-immunoprecipitation assays, suggesting a role for IQGAP1 in mediating MET-STAT3 activation and plasticity of $LGR5^+$ CRC cells. To overcome therapy-induced plasticity, we generated MET-targeting ADCs conjugated to DNA-crosslinking payloads. First, we cloned and produced MET monoclonal antibodies (mAbs) and evaluated them for specificity and binding in a panel of CRC cell lines expressing different MET protein levels. MET mAbs demonstrated high selectivity for MET-expressing CRC cells and internalized to lysosomes, which is necessary for ADC payload release. To generate MET ADCs, we employed a site-specific conjugation methodology to attach cleavable peptide linker-drug moieties to the highest affinity MET mAb. MET ADCs were evaluated for cancer cell-killing efficacy *in vitro* in parallel with MET mAb, non-targeting control mAb (cmAb), and control ADC (cADC). MET ADC demonstrated high potency and efficacy in MET-expressing CRC cells, whereas MET mAb, cmAb, and cADC had minimal effects. MET ADCs were then tested in combination with chemotherapies or other targeted therapies. The combination of MET ADCs with 5-fluorouracil and SN38 showed a synergistic effect *in vitro*. Future work involves investigating the safety and efficacy of MET ADCs alone and combined with chemotherapies in xenograft models of CRC. These findings present a mechanism underpinning CRC plasticity and the rationale for a novel treatment modality to potentially overcome CRC resistance and relapse.

Acknowledgements: This work was supported by the National Institutes of Health (NCI, R01CA226894, R21CA270716, and R21CA282378), the Cancer Prevention Research Institute of Texas (RP210092 and RP210045), and The University of Texas MD Anderson Cancer Center UTHealth Houston Graduate School of Biomedical Sciences (GSBS).

Poster 39

Combining a Novel Dual-Specific PD-L1/PD-L2 Antibody with HER2 Antibody Drug Conjugates

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Checkpoint blockade therapies, especially those targeting the programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) axis, have revolutionized cancer treatments, leading to unprecedented results in progression free survival (PFS) as well as overall survival (OS). Despite these advances, numerous patients fail to respond or relapse following an initial period of response. Poor detection reagents and substantial differences between mouse and human function has fostered a lack of appreciation for the significant role of programmed death-ligand 2 (PD-L2) in tumor immune suppression. Using a fully human yeast display library, we set out to create a next generation PD-L1/PD-L2 dual-specific antibody (IMGS-001), engineered with enhanced antibody dependent cellular cytotoxicity (ADCC) and cellular phagocytosis (ADCP) effector functions. IMGS-001 showed extensive binding to human PD-L1 and PD-L2, as well as to the murine orthologs. Treatments with IMGS-001 enhanced infiltration of immune cells within syngeneic tumor models and led to improved survival across both immune “hot” and immune “cold” tumors when compared to anti-PD-1 and anti-PD-L1 treatment arms. Moreover, we explore the option of combining the newly discovered antibody with a human epidermal growth factor receptor 2 (HER2) targeting antibody-drug conjugates (ADCs). Subsequent upregulation of PD-L1 and PD-L2 post-HER2 targeted therapies contributes to the lack of efficacy for some patients, and we aim to combine IMGS-001 with frontline HER2 ADCs to explore their potential synergy.

Acknowledgements: This research is supported in part through a grant award from the Cancer Prevention & Research Institute of Texas (“CPRIT”). Grant number and title are DP200094: Cytoreductive Bispecific PD-L1/PD-L2 Antibodies Active Across Immune "Hot" and "Cold" Cancers.

Poster 40

Development of ADAR1 Inhibitors to Improve Cancer Immunotherapy

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Cancer immunotherapy has achieved unprecedented clinical responses and is fundamentally transforming cancer treatment. Recent genetic screenings have identified ADAR1 as a promising target for improving immunotherapy. ADAR1 catalyzes the conversion of adenosine to inosine in double-stranded RNA (dsRNA), with elevated levels of dsRNA editing observed in most tumor types relative 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 medicinal chemistry optimization. Secondly, the lack of structural information for ADAR1's deaminase or RNA binding domains has impeded structure-based drug design.

We are currently developing a high-throughput ADAR1 activity assay based on fluorescence quenching and TR FRET techniques. Leveraging the High Throughput Research and Screening Center at TAMU-IBT, we aim to perform drug screening to identify potential inhibitors. Additionally, we conducted high throughput docking studies using the structure of ADAR1's deaminase domain, leading to the identification of 24 initial hits. Furthermore, molecular potency evaluation was conducted using ADAR1 editing assays and TR FRET binding assays, revealing three molecules with IC50 values in the micromolar range. By effectively integrating wet and dry lab experiments, we anticipate rapid optimization of effective inhibitors and subsequent medicinal chemistry studies.

Acknowledgments: We are grateful for the generous support from Cancer Prevention and Research Institute of Texas funded Cancer Therapeutics Training Program CPRIT Grant No: RP210043

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