3RD ANNUAL GCC IDDD CONFERENCE:

ACCELERATING DRUG DEVELOPMENT – LEARNING FROM SUCCESS & FAILURE

MAY 3-4, 2022
HOUSTON, TEXAS

Gulf Coast Consortia
QUANTITATIVE BIOMEDICAL SCIENCES

Gulf Coast Consortia
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 AI in Healthcare, Antimicrobial Resistance, Cellular and Molecular Biophysics, Innovative Drug Discovery and Development, Immunology, Mental Health Research, Regenerative Medicine, Single Cell Omics, Theoretical and Computational Neuroscience, Translational Imaging and Translational Pain Research. GCC training programs currently 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, and the Institute of Biosciences and Technology of Texas A&M Health Science Center.

GCCIDDD Executive Steering Committee

Stanley Watowich
UTMB, Ridgeline Therapeutics
Chair

Clifford Stephan
IBT TAMU
Co-*Chair*

Zhiqiang An, UT Health
Diana Chow, Univ. of Houston
John Cooke, HMRI
Jason Cross, MDACC, IACS
Mary K Geck Do, MDACC, IACS
Scott Gilbertson, Univ. of Houston
Phil Jones,, MDACC, IACS
Dong Liang, TSU

Qingyun "Jim" Liu, UT Health
Michael Mancini, BCM
Margie Moczygemba, IBT TAMU
Suzanne Tomlinson, Gulf Coast Consortia
Stephen T.C. Wong, HMRI
Damian Young, BCM

For today's conference use hashtag:

#gcciddd22

Follow us on LinkedIn:

Gulf Coast Consortia - Research

Agenda

Day 1 – May 3

8:30 Welcome

8:40 Keynote Presentation
mRNA Technology: From Vaccines to Future Medicines
Andrea Carfi, Moderna

Session 1: Learning from Clinical Trials - Early Decision Making in the Clinic, Leveraging Proof-of-biology Readouts
Convener: Phil Jones, MD Anderson Cancer Center

9:20 *Potential Pitfalls in Precision Oncology – A Biotech Viewpoint*
Klaus Hoeflich, Versant Newco

9:45 *Pioneering the Discovery and Development of PARP7 and PARP14 Inhibitors as New Therapeutics*
Melissa Vasbinder, Ribon Therapeutics

10:15 Panel discussion

10:45 Break

11:00 *The HLA-E Program from Conception to Acquisition*
Jon Weidanz, UT Arlington

11:25 *Developing a Robust Drug Discovery Engine for Protein Modulation and Beyond*
Gwen Hansenn, Nurix Therapeutics

11:50 *Discovery of Inhibitors of 15-Prostaglandin Dehydrogenase for Tissue Repair and Regeneration*
Joseph Ready, UT Southwestern

12:20 Lunch and Cores
12:20 Lunch
1:15 Core Overview and Showcase

Session 2: Fail Early Lead Optimization
Conveners: Cliff Stephan, Institute of Biosciences and Technology, Texas A&M
Pete Davies, Institute of Biosciences and Technology, Texas A&M

2:30 *Targeting the AAA ATPase p97 for Cancer - Opportunities and Challenges*
Donna Huryn, Univ. of Penn

3:00 *Why 90% of Clinical Drug Development Fails and How to Improve It?*
Duxin Sun, Univ. of Michigan

3:30 Break

Session 3: Metabolic Stability and Pre-formulation

Conveners: Diana Chow, University of Houston
Dong Liang, Texas Southern University

3:45 *Impact of ADME/PK on the Discovery of IACS-6274, A Potent GLS-1 Inhibitor in Clinical Development*
Yongying Jiang, MD Anderson Cancer Center

4:15 *Application of Metabolite Identification Experiments in Drug Discovery*
Catalina Suarez, Repare Therapeutics

4:45 *Understanding and Identifying Immunogenicity of Biological Drug Products*
Kristina Howard, FDA

5:15 Wrap up and Reception (pre-function)

Day 2 – May 4

8:30 Keynote Presentation
Drug Discovery: Lessons from Failures and the Occasional Success
Nigel Liverton, Tri-Institutional Therapeutics Discover Institute

Session 4: AI in Drug Discovery and Development
Convener: Stan Watowich, Univ. of Texas Medical Branch at Galveston

9:15 *Machine Learning for Drug Discovery: Challenges and Opportunities*
Regina Barzilay, Massachusetts Institute of Technology

9:45 *AI for Therapeutics, Where We Are and Where We Are Going*
Bissan Al-Lazikani, MD Anderson Cancer Center

10:15 Break

Session 5: What Pharma and Investors Want
Convener: Suzanne Tomlinson, Gulf Coast Consortia

10:30 **Shamina Rangwala**, Pfizer

10:45 **Nicola La Monica,** JNJ Innovation

11:00 **Rima Chakrabarti**, KdT Venture

11:15 **Jay Parrish**, Arch Ventures

11:30 **Rez Halse**, RA Capital Management

11:45 Panel Q&A

12:15 Lunch and Poster Session
12:15 Lunch
12:45 Poster session

Session 6: RNA Therapeutics
Convener: John Cooke, Houston Methodist Research Institute

1:45 *mRNA-Based Approach for Treating Ischemic Heart Disease*
Lior Zangi, Icahn School of Medicine Mount Sinai

2:10 *RNA-based Interventions for the Treatment of Aging and Aging-associated Disorders*
Vittorio Sebastiano, Stanford Univ.

Session 7: Future Trends
Convener: Jim Liu, University of Texas Health Science Center

2:35 *Drug Discovery in the Shadow of COVID-19: A Reflection on the Roles of "Big Pharma", "Biotech", the Academic Biomedical Research Community and the Economics, and Politics of Healthcare*
Barry Morgan, HitGen

3:00 *Leveraging Targeted Protein Degradation to Overcome Resistance in Cancer Immunotherapies*
Jin Wang, Baylor College of Medicine

3:25 Closing remarks

In alphabetical order of presenter

Bissan Al-Lazikani, PhD
Professor
Genomic Medicine

AI for Therapeutics, Where We Are and Where We Are Going

Bissan Al-Lazikani FRSB MBCS is a data scientist and drug discoverer with experience in academia and industry. She is Professor, Genomic Medicine; Director of Discovery Data Science and founding faculty of the Data Science Institute at MD Anderson Cancer Center. Prior to this, she was Head of Data Science at the Institute of Cancer Research, London. She is formally trained in biology and computer science: BSc Molecular Biology from University College, London; MSc Computer Science from Imperial College, London; PhD Computational Biology from the University of Cambridge, and Howard Hughes postdoctoral fellowship Biophysics, Columbia University, NY. She co-led the creation of the groundbreaking ChEMBL database. Then she led the creation of the world's largest public drug discovery knowledgebase, canSAR, integrating vast multidisciplinary data; and leading suite of AI-driven drug discovery analysis algorithms. She applies these to discovery novel drugs and optimize therapy for adult and pediatric cancers.

Abstract: The use of Artificial Intelligence is becoming a mainstay of drug discovery and development. In some areas, such as target discovery and prioritization, and drug design, the use of AI is maturing and already impacting drug discovery. In others, the capitalizing on Big Data and artificial intelligence remains in its infancy. I will illustrate, with examples, these different stages and explore key emerging areas to power drug discovery in the near future.

Regina Barzilay, PhD
Engineering Distinguished Professor for AI and Health, Electrical Engineering and Computer Science

Machine Learning for Drug Discovery: Challenges and Opportunities

Regina Barzilay is a School of Engineering Distinguished Professor for AI and Health in the Department of Electrical Engineering and Computer Science and a member of the Computer Science and Artificial Intelligence Laboratory at the Massachusetts Institute of Technology. She is an AI faculty lead for Jameel Clinic, an MIT center for Machine Learning in Health. Her research interests are in natural language processing and applications of deep learning to chemistry and oncology. She is a recipient of various awards including the NSF Career Award, the MIT Technology Review TR-35 Award, Microsoft Faculty Fellowship and several Best Paper Awards at NAACL and ACL. In 2017, she received a MacArthur fellowship, an ACL fellowship and an AAAI fellowship. In 2021, she was awarded the AAAI Squirrel AI Award for Artificial Intelligence for the Benefit of Humanity, the AACC Wallace H. Coulter Lectureship Award, and the UNESCO/Netexplo Award. She received her PhD in Computer Science from Columbia University and spent a year as a postdoc at Cornell University. Prof. Barzilay received her undergraduate degree from Ben-Gurion University of the Negev, Israel.

Andrea Carfi MSc, PhD
Chief Scientific Officer
mRNA Technology: From Vaccines to Future Medicines

Andrea Carfi is the CSO for Infectious Disease at Moderna. Moderna Infectious Disease focuses on the discovery and development of vaccines as well as other therapeutic and prophylactic approaches against infectious disease targets using Moderna proprietary mRNA technology. Andrea joined Moderna in 2017 as Head of Antigen Design and Selection and Project Leader. Since January 2019 he is leading a team now close to hundred scientists working in Infectious Disease Research.

Andrea has almost 20 years of experience in drug discovery and vaccine development at Moderna, GSK, Novartis Vaccines and IRBM / Merck. Over the years he has held roles of increasing responsibility with a focus on structural biology, antigen design, small molecule antivirals discovery and vaccines development. Prior to joining Moderna Andrea was at GSK and Novartis Vaccines for seven years. During this time he led the US based Protein Biochemistry team which was responsible for the design, selection, characterization and early development of novel vaccine targets against viral infectious disease. Some of these vaccine candidates are now in late stage clinical trials. Andrea was also leading the Novartis Vaccines Antigen Design platform across the research sites of Cambridge, US and Siena, Italy. During his time at Moderna Andrea has led the early development of the CMV mRNA vaccine, now in a Phase 3 efficacy study, and has built both a large portfolio of mRNA vaccines against Infectious Disease targets and grown a large and productive team. Most recently Andrea was closely involved in the development of Spikevax, the Moderna mRNA vaccine against COVID-19.

Andrea holds a Master of Science in Physics for University of Canterbury in UK, a Master of Science in Chemistry from Pavia University, Italy, and a PhD in Biophysics from the Université Joseph Fourier in Grenoble, France. He also trained as postdoctoral fellow in the laboratories of Prof. Stephen Harrison and Prof. Don Wiley at Children's Hospital, Boston US. Andrea is co-author of more than 100 publication in peer-reviewed scientific.

Rima Chakrabarti, MD
Partner

Rima Chakrabarti MD, is a partner at KdT Ventures. She grew up in Scranton, Pennsylvania and went to Brown University for college, where she studied Neuroscience and Bioengineering. She graduated with honors after completing a research thesis focused on the use of functional MRI to characterize the effects of psychoactive substances on visual perception.

She grew up in Scranton, Pennsylvania, studied Neuroscience and Bioengineering at Brown University and attended medical school at UT Southwestern Medical Center, the academic home of Drs. Joe Goldstein, Michael Brown, and Helen Hobbs, all pioneers in lipid metabolism who became Rima's research mentors. Under their guidance, she was awarded a Howard Hughes Medical Institute (HHMI) Research fellowship for two consecutive years to design and build a microbial-based probe for tracking lipid and cholesterol bioactivity in the body. Her work led to the characterization of dynamic pools of bioactive lipids on cell membranes and suggested that lipid-based signaling plays an important role in cardiovascular disease. She published her work in the journal Elife, was a featured speaker at multiple national conferences, and graduated with honors in basic science research. She went on to do her residency in Neurology at the University of Pennsylvania.

More recently, Rima moved to Houston, Texas to join the venture creation studio Fannin Innovation Studio, first as an Entrepreneurship fellow then as Associate Principal. Here, Rima identified and in-licensed therapeutic assets from academic institutions with commercial potential into the Fannin portfolio. Rima helped move these technologies through early preclinical development with the use of grant funding and worked on clinical development with spin out company Pulmotect, an inhaled broad-spectrum therapeutic for preventing lung infections in immunocompromised patients that is currently in phase 2 clinical trials.

She joined KdT Ventures in March of 2020, first as a principal on the investment team. Since joining, she has led investments in Remedy Robotics, Faeth

Therapeutics, Dimension Inx, and Modulus Therapeutics. Currently, she also maintains an adjunct professorship in Neuroscience at the Geisinger School of Medicine and is a visiting lecturer at the Rice University Jones School of Business and Brown University School of Medicine.

Rez Halse, PhD
President

Rez Halse is President of RAVen, also known as RA Ventures, RA Capital's company creation incubator. Rez's primary responsibility is to lead early-stage private investments in, and oversee the creation of, new companies developing therapeutics and other medical technologies. Rez brings to RA over 20 years of experience working in the life-science industry. Prior to RA, he served in a dual role at Merck Research Laboratories (MRL). He was Vice President of Merck business development and licensing where he led BD activities in the US (West Coast), Europe, and Asia Pacific region, as well as President of MRL Ventures where he led equity investing in early-stage therapeutics companies. Prior to Merck, he was a Partner with the Partners Innovation Fund, the corporate venture arm of Mass General Brigham hospital (formerly Partners HealthCare), where he invested in Seed/Series A therapeutics-focused companies. Rez has also held roles at Novartis, a virtual R&D company (BVD), and Xcellsyz Ltd, a UK-based start-up. Rez holds a BSc in biochemistry and PhD in cell biology from Newcastle University, UK

Gwenn M. Hansen, PhD
Chief Scientific Officer

Developing a Robust Drug Discovery Engine for Protein Modulation and Beyond

Gwenn M. Hansen, Ph.D. currently serves as Chief Scientific Officer of Nurix Therapeutics, a biotechnology company focused on discovering and developing protein modulation therapies for the treatment of cancer and other serious diseases. Since joining Nurix in January of 2016, Gwenn has focused on developing a robust pipeline for early stage discovery by developing a platform based on DNA encoded chemistry technology and leveraging it across a range of target classes, particularly E3 ubiquitin ligases. Prior to joining Nurix, Gwenn was an Associate Professor in the Center for Drug Discovery at Baylor College of Medicine and prior to that she served as Senior Director of Drug Discovery Technologies at Lexicon Pharmaceuticals. Dr. Hansen obtained a Ph.D. in Biomedical Sciences from the University of Tennessee/Oak Ridge National Laboratory and completed post-doctoral study at Baylor College of Medicine and M.D. Anderson Cancer Center.

Klaus Hoeflich, PhD
Chief Scientific Officer

Potential Pitfalls in Precision Oncology – A Biotech Viewpoint

Klaus serves as Chief Scientific Officer at Nested Therapeutics, a new biotech company focused on discovering the next generation of precision oncology medicines. Prior to his current role, Klaus was senior vice president and head of biological sciences at Blueprint Medicines, and senior scientist and program leader at Genentech. Klaus has 20 years of experience in R&D, contributed to the development of four FDA-approved cancer medicines, and authored more than 70 scientific articles. He obtained his PhD degree in medical biophysics from the University of Toronto and has been awarded a Medical Research Council of Canada's Next Generation Award.

Abstract: The formula for successfully testing a novel precision medicine in the clinic requires the combination of an inhibitor with sufficient selectivity and potency to optimally engage the target, clear biomarkers to enrich for patient response, and a robust therapeutic hypothesis substantiated by preclinical data. When done correctly these criteria can result in rapid clinical proof-of-concept (cPOC). For small biotech, cPOC is essential to de-risk decision making, open investment of resources, and identify potential accelerated approval paths. However, despite these possible benefits, it remains a challenge to achieve consistently in drug discovery and development. In this seminar, we will discuss lessons learned from recent, novel approaches targeting FGFR and RAS/MAPK signaling pathways in the biotech setting.

Kristina E. Howard, DVM, PhD
Research Veterinary Medical Officer, Division of Applied Regulatory Science (DARS), OCP/OTS/CDER/FDA

Understanding and Identifying Immunogenicity of Biological Drug Products

Kristina Howard received her veterinary degree from the Virginia-Maryland Regional College of Veterinary Medicine and her Doctorate in immunology from North Carolina State University. She joined the FDA in 2010 and is currently a principal investigator in the Division of Applied Regulatory Science, Center for Drug Evaluation and Research of the United States Food and Drug Administration. Her research focuses on developing and improving in vitro and in vivo models to better predict adverse events and immunogenicity for biological drug products in humans. Her laboratory has been actively making bone marrow-liver-thymus (BLT) humanized mice and using them to evaluate biological drug products since 2012.

Donna M. Huryn, PhD
Professor
Pharmaceutical Sciences

Targeting the AAA ATPase p97 for Cancer - Opportunities and Challenges

Donna M. Huryn began her career as a medicinal chemist in the pharmaceutical industry (Hoffmann-La Roche & Wyeth Research), and contributed to drug discovery efforts for HIV, cancer, asthma, and CNS disorders with increasing levels of responsibility. In 2004, she joined academia, and is now Professor at the University of Pittsburgh's School of Pharmacy, and holds an adjunct appointment in the Chemistry Department at the University of Pennsylvania. She is a Fellow of the American Chemical Society, recipient of the ACS Philadelphia Local Section Award and Philip S. Portoghese Lectureship, and has held a number of elected positions within the American Chemical Society and the AAAS. She is Associate Editor of ACS Medicinal Chemistry Letters and co-author of the textbook Medicinal Chemistry (CRC Press). Professor Huryn's research focuses on the design and synthesis of small molecule probes and drugs to treat cancer, acute kidney injury, neurodegenerative and muscular disorders.

Yongying Jiang, PhD
Principal Scientist
ADME/PK

Impact of ADME/PK on the Discovery of IACS-6274, A Potent GLS-1 Inhibitor in Clinical Development

Dr. Yongying Jiang leads the ADME/PK group at the Institute for Applied Cancer Science at the University of Texas MD Anderson cancer center. He received his bachelor's degree in Pharmaceutical Chemistry from Beijing Medical University, his master's degree in Medicinal Chemistry from Peking Union Medical College, and his PhD in Medicinal Chemistry from Rutgers university, New Jersey, in 2004. Following his postdoctoral research into the mechanism of cytochrome P450-catalyzed carbon hydroxylation at the University of California San Francisco, he joined the DMPK group at Roche Nutley, New Jersey, in 2008. In 2013 he joined the Institute for Applied Cancer Science at the University of Texas MD Anderson cancer center. Over the past nine years he has built an ADME/PK team to support the progression of several programs from discovery to the clinical development, using an integrated ADME/PK approach to support drug discovery and development.

Abstract: ADME (Absorption, Distribution, Metabolism, and Excretion) are the processes that determine the pharmacokinetic (PK) profile of a drug in animal or human body. Optimization of ADME/PK properties of novel therapeutics is essential for them to be effective in humans.

IACS-6274 is a potent glutaminase-1 (GLS-1) inhibitor developed at MD Anderson's Institute for Applied Cancer Science (IACS), a team of closely collaborating chemists, biologists, pharmacologists and ADME/PK scientists. This presentation will show the impact of various ADME/PK studies during the lead optimization phase of our GLS-1 program, the preclinical PK properties of IACS-6274, human PK projection, and clinical PK and pharmacodynamics (PD) analysis. IACS-6274 is currently in Phase I clinical development for the treatment of specific subsets of lung and ovarian cancers. The initial clinical results will also be described.

Nicola La Monica, PhD
Senior Director of the Infectious Diseases & Vaccines Therapeutic Area

Nicola La Monica joined Janssen, Pharmaceutical Companies of Johnson and Johnson as Senior Director of the Infectious Diseases & Vaccines Therapeutic Area at the Boston Innovation Center. In this role, he works with external collaborators to drive innovation around novel approaches to infectious disease and vaccine research and development. A biologist with more than 25 years of experience in large pharmaceutical and biotech companies, Nicola has successfully led drug discovery efforts for the treatment of Hepatitis C virus infections and oncology, as well as development programs for cancer immunotherapy.

Prior to joining Janssen, Nicola was Vice President at Idera Pharmaceuticals from 2009 to 2012 where he led research programs for the biology group, including developing strategies to evaluate its proprietary oligonucleotides as therapeutic agents for the treatment of hematological malignancies, autoimmune diseases and as vaccine adjuvants. From 1991 to 2009, he worked at the Istituto di Ricerche di Biologia Molecolare (IRBM), Rome, Italy, a research site of Merck Research Laboratories. His most recent position was Director of Antiviral. Prior to that, he held the positions of Director of Oncology and Director of Cancer Immunology and Genomics. Nicola earned his BA degree in Biology from the University of Rochester in 1982. His graduate studies were completed at Columbia University, where he earned a PhD in Microbiology in 1988.

Nigel Liverton, PhD
VP of Chemistry
Drug Discovery: Lessons from Failures and the Occasional Succes

Nigel Liverton obtained his PhD at Southampton University in the U.K. and following postdoctoral research with Prof. Amos B Smith at the University of Pennsylvania, spent 28 years at UK and US sites for Merck Research Laboratories, where he led multidisciplinary drug discovery teams targeting diseases in the CNS, cardiovascular, immunology and infectious diseases areas. His group was responsible for advancing multiple drug candidates into clinical development. Contributions to the discovery of the HCV protease inhibitor grazoprevir were recognized with a “Heroes of Chemistry” award presented by the American Chemical Society. He subsequently joined WuXi AppTec as Executive Director in the International Discovery Service Unit working with a wide range of clients to advance their small molecule discovery efforts. Currently, as VP of Chemistry at the Tri-Institutional Therapeutics Discovery Institute, Nigel provides scientific leadership across the portfolio of small molecule drug discovery projects to advance research at Weill Cornell Medicine, Memorial Sloan Kettering Cancer Center and The Rockefeller University towards small molecule clinical candidates for novel targets.

Abstract: Excerpts of drug discovery programs undertaken at Merck Research Laboratories over the course of 30 years, with a focus on medicinal chemistry decision making. Projects encompass a range of therapeutic areas including CNS, cardiovascular and antiviral via activity against ion channels, enzymes and receptors. Part of the presentation will cover the discovery of first and second generation HCV NS3/4A protease inhibitors vaniprevir and grazoprevir, including the computational chemistry study leading to identification of a novel structural entry point in a highly competitive field.

Barry A. Morgan, PhD
Chief Scientific Officer

Drug Discovery in the Shadow of COVID-19: A Reflection on the Roles of "Big Pharma", "Biotech", the Academic Biomedical Research Community and the Economics, and Politics of Healthcare

Barry A. Morgan, Ph.D. is currently Chief Scientific Officer for HitGen Inc., where he focuses on developing and applying DNA-encoded chemistry technology to early stage small-molecule drug discovery. Barry has over 40 years of experience in R&D in the Pharmaceutical and Biotechnology industries in the UK, France, the USA and now China. He was Vice President, Molecular Discovery, and Site and Business Head at GlaxoSmithKline, Boston 2007-2012. He was previously Senior Vice President for Chemistry and Discovery Sciences at PRAECIS PHARMACEUTICALS Inc., where he was a primary inventor of DNA Encoded Library (DEL) Technology. Barry has presented invited seminars at over 100 Academic and Industry Symposia in Europe, the USA and China, has authored over 100 publications, and is an inventor on more than 40 patents in the area of drug discovery. He has contributed to over twenty drug development candidates in a range of therapeutic areas, of which more than ten have advanced to clinical study. In his capacity as a manager, he has recruited, managed and mentored hundreds of scientists from the Americas, Europe, Asia, Africa and Australia in a range of disciplines.

Barry is Adjunct Professor at the Institute for Molecular Medicine, University of Texas Health Sciences, Houston TX, where he focuses on collaborations applying DEL technology to novel drug targets in academia, and the economics of drug discovery and development.

Abstract: A common metric of the quality of healthcare is life expectancy. We will review life expectancy in the USA over the past hundred and sixty years and examine how scientific endeavor, with a focus on drug discovery has reacted to healthcare crises during that period. Although we will place considerable emphasis on the recent discovery of drugs to mitigate the consequences of SARS-CoV-2 infection, we will also examine the discovery of other agents that have the capacity to improve quality of life and survival rate. We will attempt to draw summary conclusions from these discoveries that may provide guidance to the next generation of drug hunters.

Jay Parrish, PhD
Venture Partner at ARCH Venture Partners
Chairman of Pretzel Therapeutics

Jay Parrish, Ph.D. is a Venture Partner at ARCH Venture Partners and Chairman of Pretzel Therapeutics, a company focused on developing first-in-class therapeutics addressing mitochondrial dysfunction. Previously, he was co-founder and Chief Business Officer of Vir Biotechnology, a company focused on infectious disease. As Vir's first employee, he helped lead the company through its IPO and first drug approval. At ARCH, Dr. Parrish is a board member of Interline Therapeutics, co-founder and board member of Rome Therapeutics, and advises companies throughout the portfolio.

Dr. Parrish is an accomplished scientist who began his career at Gilead Sciences, Inc. in the Medicinal Chemistry group where his research focused on the discovery of small molecule anti-virals for the treatment of HIV, hepatitis C, and respiratory syncytial viruses. In this role, he was involved with several successful discovery campaigns, including being a co-inventor of ledipasvir (Harvoni®), approved as a cure for hepatitis C genotypes 1, 4–6, and remdesivir (Veklury®), approved for COVID-19. Dr. Parrish has authored over 25 peer-reviewed scientific publications and holds over 30 issued patents.

After nearly a decade in research, Dr. Parrish joined Gilead's Corporate Development team, where he was involved in building Gilead's oncology and infectious disease portfolio, ultimately leading infectious disease business development for the company.

Dr. Parrish holds a B.S. in Chemistry from Emory University and a Ph.D. in Synthetic Organic Chemistry from the University of South Florida. He completed a Postdoctoral Fellowship at the Scripps Research Institute and received an M.B.A. from U.C. Berkeley's Haas School of Business.

Shamina Rangwala, PhD
Global Lead
Internal Medicine in the Emerging Science & Innovation group

Shamina Rangwala is the Global Lead for Internal Medicine in the Emerging Science & Innovation group at Pfizer. In this role, she uses her extensive expertise and network in drug discovery and development to identify novel therapies and technologies for the treatment of cardiovascular and metabolic disease.

Shamina received her Ph.D. in Pharmacology at The Ohio State University and completed her post-doctoral fellowship with Dr. Mitch Lazar at the University of Pennsylvania, where her research interests focused on the role of PPARs and adipokines on body weight and insulin resistance. Since leaving Penn, Shamina has worked in drug discovery at several large pharmaceutical companies in positions of increasing responsibility, including Novartis and Novo Nordisk. Prior to joining Pfizer, she worked at Janssen/JNJ – initially as a team leader in Cardiovascular and Metabolic Research, where she led two programs into early clinical development, and subsequently at the JNJ Innovation Center in London, where she led efforts in identifying external opportunities in cardiometabolic and retinal diseases in Europe.

Joseph Ready, PhD
Estabrook Distinguished Chair in Biochemistry
Director of the Medicinal Chemistry Facility

Discovery of Inhibitors of 15-Prostaglandin Dehydrogenase for Tissue Repair and Regeneration

Joseph Ready completed his undergraduate studies in chemistry at the University of North Carolina at Chapel Hill in 1996. He then moved to Harvard and received his Ph.D. working with Eric Jacobsen. In 2001 he joined John Wood's group at Yale University for postdoctoral studies. He established his independent research career at the University of Texas Southwestern Medical Center in Dallas in 2003 where his group is interested in the synthesis of biologically active small molecules. He is currently holds the Estabrook Distinguished Chair in Biochemistry and is the director of the Medicinal Chemistry Facility.

Abstract: The enzyme 15-prostaglandin dehydrogenase (15-PGDH) catalyzes the first step in the degradation of prostaglandins including PGE2. It is a negative regulator of tissue repair and regeneration in multiple organs. Accordingly, inhibitors of 15-PGDH are anticipated to elevate in vivo levels of PGE2 and to promote healing and tissue regeneration. The small molecule SW033291 inhibits 15-PGDH with Ki = 0.1 nM in vitro, doubles PGE2 levels in vivo, and shows efficacy in mouse models of recovery from bone marrow transplantation, ulcerative colitis, and partial hepatectomy. Optimized variants of SW033291 with improved solubility, drug-like properties and in vivo activity will be described.

Vittorio Sebastiano, PhD
Associate Professor
Obstetrics and Gynecology

RNA-based Interventions for the Treatment of Aging and Aging-associated Disorders

Dr. Vittorio Sebastiano is an Associate Professor in the Department of Obstetrics and Gynecology at Stanford School of Medicine. His lab has established a new technology named ERA (Epigenetic Reprogramming of Aging), which repurposes the conceptual idea of reprogramming, with the goal to promote epigenetic rejuvenation of adult cells leaving their identity untouched. This new technology was patented and is being implemented by Turn Biotechnologies, of which Dr. Sebastiano is co-founder, Head of Research, and Chair of the Scientific Advisory Board.

In 2009, Dr. Sebastiano completed a postdoctoral fellowship at the laboratory of Dr. Marius Wernig at Stanford University, where he implemented the newly discovered iPSC technology and was among the first to demonstrate that iPSCs can be efficiently derived, genetically modified, and implemented for cell therapy in genetic diseases (Sebastiano et al., 2014, Science Translational Medicine).
Dr. Sebastiano completed his undergraduate and graduate studies at the University of Pavia, Italy, where he studied murine germ cells and preimplantation development and where he pioneered cellular reprogramming by Somatic Cell Nuclear Transfer. He joined the Max Planck Institute for Molecular Biomedicine as a postdoctoral fellow under the mentorship of Dr. Hans Robert Schöler, where he continued his research on cellular reprograming, germ cells biology, and embryonic development.

Stanford University

Catalina Suarez
Research Scientist II

Application of Metabolite Identification Experiments in Drug Discovery

Catalina Suarez is a Research Scientist II at Repare Therapeutics. She is part of the DMPK group and supports different discovery programs as the DMPK representative. Her main focus is the application and development of Metabolite Identification (MetID) experiments to advance discovery programs. Prior to joining Repare Therapeutics, Catalina worked at MD Anderson's Institute for Applied Cancer Science (IACS), solving metabolic pathways and tackling DMPK challenges. Catalina holds a B.S. in Chemistry from Universidad ICESI, Colombia and a M.S in Chemistry from the University of Texas at El Paso.

Abstract: In the past years, metabolite identification (MetID) studies have evolved from a development role to a discovery role where we actively use MetID in the different phases of drug discovery. Depending on the stage of the project, MetID is used to understand clearance mechanisms, modulate metabolism to improve metabolic stability, find reactive or active metabolites, help in the selection of species for toxicological studies and address questions of metabolites in safety testing.

During the presentation we will discuss the advantages and disadvantages of the most common biological systems used to do MetID experiments, the different instrumentation that can be used and some of the available software for data analysis. The presentation will show examples where MetID experiments helped answer questions about the difference in clearance pathways across species, GSH reactive metabolites, metabolites formed by Aldehyde oxidase (AO), N-oxide metabolites formation, and modulation of clearance.

Repare Therapeutics

Duxin Sun, PhD
Charles Walgreen Jr. Professor, Pharmacy
Professor, Pharmaceutical Sciences
College of Pharmacy

Why 90% of Clinical Drug Development Fails and How to Improve It?

Dr. Duxin Sun is the Charles Walgreen Jr. Professor of Pharmacy and Professor of Pharmaceutical Sciences in the College of Pharmacy at the University of Michigan. Dr. Sun serves as the Director of Pharmacokinetics (PK) Core. Dr. Sun also has joint appointment in the Chemical Biology program, the Interdisciplinary Medicinal Chemistry program, and University of Michigan's Comprehensive Cancer Center. Dr. Sun received broad training in Pharmaceutical Sciences (PhD), Molecular Biology (visiting scientist), Pharmacology (MS) and Pharmacy (BS).

Dr. Sun's research interests focus on drug discovery, nanomedicine and pharmacokinetics. Dr. Sun has published more than 240 papers (H-index 63), mentored 37 PhD students and 70 postdoctoral fellows/ visiting scientists. Dr. Sun is a Fellow of American Association of Pharmaceutical Scientists (AAPS) and has served as chair of the PPB (Physical Pharmacy and Biopharmaceutics) in AAPS. Dr. Sun served on FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee (2017-2020). Dr. Sun served on study section for NIH and FDA.

Abstract: It takes 10 to 15 years and around US$1 billion to develop one successful drug. Despite these significant investments in time and money, 90% of drug candidates failed during phase I-III clinical trials and drug approval despite implementation of many successful strategies, which is due to four possible reasons: lack of clinical efficacy (30-40%), unmanageable toxicity (30%), poor drug-like properties (15-20%), and lack of commercial needs and poor strategic planning (10%).

The continued high failure of clinical drug development raises a question of whether there are other aspects of drug development that are being overlooked? On the one hand, it is challenging to truly confirm the molecular target that is the cause of human disease and drug's intended target. On the other hand, current drug optimization process may not be ideal that may have misled drug candidate selection and impacted the balance clinical dose/efficacy/safety. This presentation will discuss the reasons why 90% drug development fails and how to improve it.

Melissa Vasbinder
Vice President, Drug Discovery and Development

Pioneering the Discovery and Development of PARP7 and PARP14 Inhibitors as New Therapeutics

Melissa Vasbinder is a drug discovery and development leader with eighteen years of experience in the pharmaceutical and biotechnology industry and is currently Vice President of Drug Discovery and Development at Ribon Therapeutics, a clinical stage biotechnology company developing therapeutics targeting stress support pathways in cancer and inflammation. As an early member of the Ribon team, Melissa helped to create the company's proprietary BEACON+ platform and was one of the project leaders for the PARP7 program leading the discovery of Ribon's first clinical development candidate RBN-2397 from hit to lead through candidate selection and IND-enabling studies into early clinical development. Prior to joining Ribon in 2016, Melissa worked at AstraZeneca in the Oncology Chemistry group on numerous projects and was part of the project team that delivered clinical candidates AZD4573 (CDK9 inhibitor) and AZD4205 (JAK1 inhibitor). Melissa has served within the AACR organization as Chairperson of the Chemistry in Cancer Research (CICR) group and as a previous co-chair for the AACR Annual Meeting Program Committee. Melissa received her Ph.D. from Boston College and her B.S. from Trinity University in San Antonio, Texas.

Jin Wang, PhD
Professor
Pharmacology and Chemical Biology

Leveraging Targeted Protein Degradation to Overcome Resistance in Cancer Immunotherapies

Dr. Wang received his B.S. degree in chemistry from Peking University and Ph.D. in organic chemistry from the Ohio State University. As a postdoc at the University of North Carolina at Chapel Hill, he worked in the field of drug delivery and nanomedicine. In 2011, he started his independent career as an assistant professor and CPRIT scholar in Cancer Research in the Department of Pharmacology and Chemical Biology at Baylor College of Medicine. He is currently the Michael E. DeBakey, M.D., Professor in Pharmacology in the same department. His research centers on chemistry and serves biology, spanning from chemical biology tool and method development to rational design of therapeutics, including small molecule inhibitors, protein degraders, and antibody-drug conjugates.

Abstract: PROTACs are a novel therapeutic modality to inhibit the scaffolding functions of proteins. I will present our recent work on a novel PROTAC to boost antitumor immunities of cancer immunotherapies. One common feature for immune checkpoint blockades (ICBs), activated cytotoxic T cells, CAR-T and CAR NK cells is that they all kill cancer cells through granule exocytosis and death ligands to activate programmed cell death. However, cancer cells that are insensitive to these programed death mechanisms will evade killing mediated by the antitumor immunity. We developed a novel PROTAC that can synergize with anti-PD1 to trigger immunogenic cell death and significantly inhibit tumor growth in an immunotherapy insensitive B16F10 mouse melanoma mouse model.

Jon Weidanz, MPH, PhD
Associate Vice President for Research
The HLA-E Program from Conception to Acquisition

Jon Weidanz, MPH, Ph.D. is an Associate Vice President for Research and a Professor with tenure, in the Department of Kinesiology, College of Nursing and Health Innovation, and a member of the Multi-Professional Center for Health Informatics at the University of Texas at Arlington (UTA). He also holds a courtesy faculty appointment in the Department of Bioengineering at UTA. He founded the North Texas Genome Center at UTA in 2018 and served as its director until 2022. Dr. Weidanz has broad experience and interest in biotechnology with particular knowledge and expertise in immunology, immuno-engineering, and immunotherapy research and product development. He has more than 60 peer-reviewed articles, book chapters and published conference proceedings and has been an invited speaker at more than 50 conferences, universities and companies. While at Texas Tech University Health Sciences Center (TTUHSC), he was named as a Distinguished Professor and recognized for his teaching accomplishments, receiving the prestigious President's Excellence in Teaching Award and the Chancellor's Council Distinguished Teaching Award. While at TTUHSC, he established the Department of Immunotherapeutics and Biotechnology and served as its first Chair. Prior to becoming Chair, he was the founding director of the Center for Immunotherapeutics Development. Additionally, he served as Associate Dean of the Graduate School and director of the Biotechnology graduate program.

His research has been funded by various agencies including the NIH, over many years to identify tumor-specific peptides presented by the human leukocyte antigen (HLA) system for use as potential targets for immunotherapy. As part of this focus, his laboratory developed methods to discover antibodies that recognize specific peptide/HLA complexes that his laboratory dubbed as T-cell receptor mimicking (TCRm) antibodies. TCRm molecules share the binding selectivity traits of T-cell receptors while retaining the positive attributes of antibodies. TCRms are highly valued as research tools and his group has used them extensively to study antigen presentation in tumor cells. Furthermore, his laboratory has been active in research and development of other immunotherapeutic agents including soluble T-cell receptors, and multifunctional/multispecific protein-based molecules. His earlier interests led to the laboratory's most recent exciting project, the discovery of a TCRm, EXX-1, to Qa-1b/Qdm peptide complex, the ligand for NKG2A/CD94 inhibitory receptor.

The NKG2A axis is a newly discovered immune checkpoint that suppresses the cytolytic function of Natural Killer cells and CD8+ T-cells in the tumor microenvironment. His laboratory has shown that EXX-1 TCRm can enhance anti-tumor immunity against tumors in mice. Translation of these recent basic research findings to immunotherapies for treating human cancers is being pursued by his former company, Abexxa Biologics that was recently acquired by Boehringer Ingelheim (https://www.boehringer-ingelheim.us/press-release/boehringer-ingelheim-acquires-abexxa-biologics-further-expand-its-research-efforts).

Additionally, Dr. Weidanz is a seasoned entrepreneur with more than 25 years of relevant corporate biotechnology accomplishments, experience in the transformation of early-stage university technology into companies, directly involved as a founder or co-founder in the formation of four biotech start-up companies with two exits to pharma companies. He holds more than 40 issued, pending, and provisional patents (US and international) with 6 patents having been out-licensed to 3rd parties for commercial development. Recently, he was elected to the National Academy of Inventors for his outstanding contributions as an innovator.

Abstract: Targeted immunotherapy strategies such as bispecific T-cell engagers and chimeric antigen receptor T-cells (CAR-T) have improved patient treatment outcomes for some cancer indications. However, many cancer patients do not qualify for treatment with targeted immunotherapies because the target recognized by the therapeutic agent is not present on tumor cells. For example, ~25% of breast cancer patients have tumors that overexpress Her2 receptor meaning a majority of breast cancer patients do not qualify for immune therapies to Her2. Discovering new tumor associated-antigens and tumor neo-antigens is an area of intense investigation. Antigens presented on the cell surface as Human Leukocyte Antigen (HLA) complexes could theoretically permit access to potentially the entire proteome for developing targeted cancer immunotherapies. However, the polymorphic nature of classical HLA class I proteins limits use of promising HLA-targeting agents. To broaden population coverage, Abexxa Biologics was formed to develop ways to target non-classical HLA-E-peptide complexes expressed on cancer cells. Contrary to classical HLA class I, HLA-E is monomorphic with expression generally being induced or upregulated on cancer cells. Moreover, HLA-E presents peptides, some which could be tumor-specific. Abexxa was formed on the idea that novel cancer-specific HLA-E-peptide targets could be identified and that high affinity, antigen-specific T-cell receptor mimetic (TCRm) antibodies could be made to recognize presented HLA-E-peptide targets on the surface of cancer cells. Here we describe generation, characterization, and application of TCRm antibodies targeting HLA-E/peptide complexes and demonstrate the proof-of-concept that led to the acquisition of Abexxa by Boehringer Ingelheim in late 2021.

Lior Zangi, PhD
Associate Professor
Cardiovascular Research Institute and Genetics & Genomic Sciences

mRNA-Based Approach for Treating Ischemic Heart Disease

Lior Zangi, PhD, is an Associate Professor with Tenure at the Icahn School of Medicine at Mount Sinai, New York. He completed his education and training at the Weizmann Institute of Science, and Harvard University. He has established a new method, mRNA based, for gene delivery into skeletal and cardiac muscle. In the last year, these mRNA delivery methods have been used for COVID19 vaccinations and promoting cardiovascular regeneration in ischemic heart disease. Currently, Prof. Zangi's laboratory investigates mRNA delivery method into healthy or unhealthy specific cell types and organs, to fight different diseases such as heart failure and cancer.

Abstract: Modified mRNA is an attractive and novel in vivo gene delivery method that allows high gene expression in variety of organs, including the heart. Expression is seen within 10 minutes following delivery and can last from several days and up to a week. The strength of Modified mRNA as a gene delivery therapy is in its safety, transiently, and high expressivity. It does not require nuclear localization or transcription or integrate into the host genome. Most important, the modifications made to the mRNA allows it to avoid the innate immune system, specifically TLR activation, and reduce mRNA cleavage due to its lack of recognition by RNase. Our main goal is to unravel regenerative genes that can enhance cardiac regeneration after injury. For that, we are using modified mRNA as a novel gene delivery system to locally up-regulate or downregulate selected genes after myocardial infarction in small and large animal models. We recently optimized our modified mRNA delivery methods to the heart and identify a novel system that allows translation specifically in cardiomyocytes or non-cardiomyocytes (specific modified mRNA translation system (SMRTs)). We also discover several novel therapeutic target genes that enable cardiovascular regeneration, cardiac protection or cardiac regeneration post ischemic injury.

Poster numbers In alphabetical order of presenter

First Name	Last name	institution	Abstract Title	Poster #
Fernando	Alvarez	MDA	Structure-Guided Discovery of Potent, Selective, and Brain-Penetrating Inhibitors of RIP1	2
Parsa	Arman	UTMB	iFGF14 Peptide Derivative Differentially Regulates Nav1.2 and Nav1.6 Function	3
Priyanka	Banerjee	TAMU	Conjugated Bile Acids Mediated Oxidative Stress Induces Lymphangiogenesis Via The	4
Tim	Baumgartner	UTMB	Targeting the Nav1.6:GSK3β Protein:Protein Interaction Complex to Mitigate Hippocampal Hyperexcitability in Neuropsychiatric Disorders	5
Christopher	Carroll	MDA	Potent and Selective Tetrhydropyrido[4,3-d]pyrimidine ATR Inhibitor with Robust In Vivo Efficacy	6
Harmannus	de Kraker	UTSA	Protein Kinase C Epsilon (PKCε) Inhibitors for Non-opioid Pain Management	8
Nolan	Dvorak	UTMB	Expanding the Druggable Genome: Targeting Protein:Protein Interaction Interfaces for Neuropsychopharmacological	9
Madeline	Galbraith	RU	Identifying Phenotypes Associated with Coupling the Epithelial-to-Mesenchymal Transition and	10
Rayane	Ghoteimi	BCM	Targeting PKMYT1 Member of the Wee Kinase Family in Cancer Treatment	11
Jyotsna	Godavarthi	TSU	An Ongoing Study Of DND1 Function In Somatic Cancers	12
Nana	Goode	UTMB	Kinase Regulation of Voltage-gated Na+ Channels Cell Surface Expression	1
Ritu	Gupta	TSU	Optimization of PLGA Nanoparticles of AC1LPSGZ using	13

Poster numbers

In alphabetical order of presenter

First Name	Last name	institution	Abstract Title	Poster #
Zahra	Haghighijoo	UTMB	Probing the FGF:Nav Channel Protein:Protein Interface with Short Peptidomimetics	14
Matthew	Hamilton	MDA	The Discovery of IACS-9779 and IACS-70465 as Potent Inhibitors Targeting Indoleamine 2,3-	15
Kehinde	Idowu	TSU	The Design and Development of GMC1 Analogues: Targeting the Regulation of FKBP52 and Hormonal Receptors in Prostate Cancer Cells	16
Danielle	Jamison	UTMB	Screening of FGF12 Ligands for Modulation of Nav1.2 Activity	17
Chung-Fan	Kuo	UH	In Vitro Assessment of An Anti-tumor Pharmaceutical loaded Nano-	18
Kang	Le	MDA	IACS-8300 - A Novel DLK Inhibitor For CIPN	19
Hanyue	Liao	UH	Clinical 3-D PK/PD Correlations of Atorvastatin and Simvastatin in	20
Hanfeng	Lin	BCM	E3 Ligase Complex Structure-Based Rational Design Accelerating the Lead Optimization of PROTACs	21
Dai	Lu	UH	Evaluation of Combination Therapy of Paclitaxel and Cyclopamine for the Treatment of Hepatocellular Carcinoma (HCC)	7
Ryan	Murphy	UTMB	Discovery of Balanced and Novel G Protein Biased Agonists for the Orphan Receptor GPR52	22
Karinel	Nieves-Merced	UTSA	Design and Synthesis of Novel Menin PROTACs for Pediatric Leukemia	23
Junghwa	Park	UH	Therapeutic Implications of Riluzole in Patients with Spinal Cord Injury	24
Marie	Rincon Nigro	TSU	The Effect of Gastric Acid Secretion Blockade on the Oral Bioavailability of OJT007	25

Poster numbers In alphabetical order of presenter

First Name	Last name	institution	Abstract Title	Poster #
Arthur	Sefiani	A&MHCS	Novel Adult Brain Processing Method Reveals Age-, Sex-, and Species-dependent Effects of Pharmaceutical Compounds on Neuron Survival And Neuritogenesis	26
Nyma	Siddiqui	TSU	Impact of Host Physiological and Pathological Conditions on the Activity of Gut Microbial Beta-glucuronidases Towards Hydrolysis of Baicalin	27
Aditya	Singh	UTMB	FGF13 Ligand Prevents Mechanical Hypersensitivity and Nociceptive Behavior by Selectively Blocking Hyperactive Nav1.7 Channels	28
Pankaj	Singh	TAMU	The GCC CPRIT Center for Advanced Microscopy and Image Informatics	29
Shraddha	Subramanian	UTH	Development of a Novel Combination Therapy Targeting MET and LGR5 to Overcome Resistance in Colorectal Cancer	30
Michael	Tidwell	UTSA	Design, Synthesis and Structure-Activity Relationship of CNS Penetrant Small Molecule ER-Beta Agonists for Glioblastoma (GBM) Therapies	31
Elissa	Tjahjono	Ru	Novel Mitochondria-Targeting Compounds Selectively Kill Human Leukemia Cells	32
Jun	Yan	MDA	Targeting Intracellular Oncogene Cyclin E (CCNE) With Peptide-HLA-Specific CAR-T Cells	33
Kai	Yang	TAMU	Drug Repurposing and Development for Main Protease of SARS-CoV-2	34
Muhammad Saad	Yousuf	UT Dallas	Modulating the Sigma2 Receptor (TMEM97) is an Effective Strategy for Treating Neuropathic Pain	35
Xin	Yu	BCM	Pharmacologic Degradation of RIPK1 Enhances Anti-cancer Immunity	36

Structure-Guided Discovery of Potent, Selective, and Brain-Penetrating Inhibitors of RIP1 Kinase

Alvarez FG[1], Ramaswamy V[1], Hamilton MM[1], Reyna NJ[1], P Bardenhagen JP[1], Shepard H[1], Goodwani S[2], Kendra A[2], Bianca F[2], Acton P[2], Lightfoot Y[2], Hamby M[2], Xu QA[1], Jiang Y[1], Geck Do M[1], Cross JB[1], Jones P[1], Ray WJ[2], Lewis RT[1]

1. Institute for Applied Cancer Science (IACS), Therapeutics Discovery Division, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States.
2. The Neurodegeneration Consortium, Therapeutics Discovery Division, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States.

Corresponding Author: Fernando G. Alvarez Email fgalvarez@mdanderson.org

Background Receptor-interacting serine/threonine-protein kinase 1 (RIPK1) is a key mediator of cell death and inflammation and has been implicated in the pathogenesis of Alzheimer's disease. Inhibition of RIPK1 activity has been shown to protect against necroptosis in multiple animal models. Thus, it presents a viable target for developing drugs for a range of human degenerative and inflammatory diseases.

Hypothesis/Goals We hypothesized that small molecule brain-penetrant RIPK1 inhibitors would useful in inhibiting or preventing neuroinflammation induced by hyper-active microglia. To this end, we sought to identify proprietary, brain-penetrant, and selective RIPK1 inhibitors.

Methods We embarked on a parallel screening strategy for identifying novel hits that allosterically inhibit RIPK1. Three different hit-finding strategies were conducted in parallel to obtain hits. All three hit-finding methods delivered multiple chemical series and were subsequently evaluated and progressed in parallel by our chemistry team. In this poster, we will focus on a chemical series discovered using the information-based approach and optimized for potency, metabolic stability and brain penetration.

Results Exploration of novel modifications of a literature compound led to the identification of 5-benzyl-N-(3-chloro-2-fluorophenyl)-1H-1,2,4-triazole-3-carboxamide as an unoptimized hit compound selective for inhibition of RIPK1. A crystal structure of this hit bound to RIPK1 indicated that it binds to an allosteric pocket as a "type III" inhibitor. Through structure-based drug design (SBDD), we optimized this hit to lead compound IACS-52584, a potent, selective, and brain-penetrant RIPK1 inhibitor. In mouse BV2 microglial cell line, IACS-52584 dose-dependently inhibited pSer166 RIPK1 with IC_{50} an of ~1.1μM. In mouse primary microglia, IACS-52584 significantly attenuated transcriptional changes as well as cytokine release induced by TNFα+zVAD+BV6 (necroptosis) stimuli. Furthermore, administering IACS-52584 (100mg/kg, PO) to mice injected with LPS (1mg/kg, IP) resulted in significant reduction of brain and plasma cytokine levels as compared to vehicle-treated mice.

Conclusions We identified an N-benzyl-1,2,4-triazole-3-carboxamide series with reasonable potency and good physiochemical properties. Optimization of this series by our chemistry team led to the discovery of IACS-52584, which showed good potency, brain penetration, and exclusive kinase selectivity for RIPK1. *In vitro* and *in vivo studies* showed IACS-52584 attenuates transcriptional and cytokine levels relevant to neuroinflammation and neurodegenerative diseases.

Acknowledgements We would like to thank the Oskar Fischer Project, the Bowes Foundation, and the Belfer Family Foundation for funding this project and The Neurodegeneration Consortium.

Poster 3

iFGF14 Peptide Derivative Differentially Regulates $Na_v1.2$ and $Na_v1.6$ Function

Arman P, Haghighijoo Z, Xue Y, Wang P, Chen H, Zhou J, Laezza F

Department of Pharmacology & Toxicology, University of Texas Medical Branch

Corresponding Author: Dr. Fernanda Laezza, Department of Pharmacology & Toxicology, University of Texas Medical Branch, 301 University Blvd. Galveston, TX, E-mail: felaezza@utmb.edu

Background: Voltage-gated Na^+ channels (Na_v) are the molecular determinates of action potential initiation and propagation because of their role in mediating ionic flow (Na^+). Out of the nine voltage-gated Na^+ channels ($Na_v1.1$-$Na_v1.9$), $Na_v1.2$ and $Na_v1.6$ are of particular interest to neuroscientists because of their expression and distribution throughout the central nervous system (CNS). Although the α-subunit can sufficiently confer transient Na^+ currents (I_{Na}), *in vivo* these channels exist alongside β-subunits and in addition are modulated by auxiliary proteins like intracellular fibroblast growth factor 14 (FGF14) through protein:protein interactions (PPI). Previous studies have identified ZL0177, a peptidomimetic derived from a short peptide sequence thought to mediate the FGF14:$Na_v1.6$ PPI interface, as a functionally active modulator of $Na_v1.6$ mediated I_{Na}. In this report, ZL0177 was chosen for selectivity studies against the α-subunit of $Na_v1.2$ and $Na_v1.6$ for further evaluation. To that end, we assessed the isoform selectivity and mechanism of action of ZL0177 in heterologous cells stably expressing the α-subunit of either $Na_v1.2$ or $Na_v1.6$. Lastly, we complemented our electrophysiology studies with *in silico* docking of ZL0177 to $Na_v1.2$ and $Na_v1.6$ homology models.

Methods: Automated planar-patch electrophysiology was utilized to study the selectivity of ZL0177 against HEK-293 cells stably expressing either $Na_v1.2$ or $Na_v1.6$ Na^+ channels. *In silico* docking was used to predict ZL0177 ligand binding site.

Results: Upon testing the pharmacological effects of ZL0177 on $Na_v1.2$ and $Na_v1.6$ in HEK-293 cells, we observed statistically significant changes in peak I_{Na} density as well as depolarizing shifts in both $V_{1/2}$ of activation and steady-state inactivation that were isoform specific. While ZL0177 effectively decreased $Na_v1.6$ mediated peak I_{Na} density at 1 μM, it was ineffective at this concentration against $Na_v1.2$ mediated I_{Na}. However, at 1 μM ZL0177 caused a statistically significant depolarizing shift in $V_{1/2}$ of activation for both $Na_v1.2$ and $Na_v1.6$ when compared to their corresponding controls. In addition, ZL0177 (1 μM) caused a selective depolarizing shift in $V_{1/2}$ of steady-state inactivation for $Na_v1.2$, with no effect on the same parameter in $Na_v1.6$. Docking revealed that ZL0177 binds strongly to residues Glu^{1884} in $Na_v1.2$ and Met^{1869} in $Na_v1.6$ via H-bonds. Subsequently, there are various hydrophobic and π-π interactions with Lys^{1891}, Tyr^{1883}, and Thr^{1887} for $Na_v1.2$ and Arg^{1891}, Tyr^{1883}, and Thr^{1887} for $Na_v1.6$.

Conclusions: ZL0177 produced a larger reduction in $Na_v1.6$ mediated peak I_{Na} when compared to $Na_v1.2$ mediated peak I_{Na}, but exhibited either no selectivity or opposite selectivity towards voltage-sensitivity of activation and steady-state inactivation. These ZL0177 isoform-specific modulations of $Na_v1.2$ and $Na_v1.6$ might be driven by the ligand interacting with Glu^{1884} ($Na_v1.2$) and Met^{1869} ($Na_v1.6$) residues. This study could provide useful information for the development of novel isoform-specific probes and future neurotherapeutics against Na_v channels.

Acknowledgements: We acknowledge our funding sources as follows: We acknowledge our funding sources as follows: NIH Grant R01MH12435101 (FL), R01ES031823 (FL); U18DA052504 (FL); Technology Commercialization Program (FL).

Poster 3

Keywords: Voltage-Gated Na+ (Na_v) Channels; Automated Planar Electrophysiology; Protein:Protein Interaction (PPI); Na_v1.6:FGF14 Complex; Drug Discovery; Central Nervous System (CNS); Auxiliary Protein; Accessory Protein; Peptidomimetics; ZL0177;

Poster 4

Conjugated Bile Acids Mediated Oxidative Stress Induces Lymphangiogenesis Via The Activation of -p90RSK-Vascular Endothelial Growth Factor Receptor 3 Signaling Axis

Priyanka B[1], Kumaravel S[1], Roy S[1], O'Brien A[1], Bayless K[1], Alpini G[2], Glaser SG[1], Chakraborty S[1]*.

1. Department of Medical Physiology, Texas A&M Health Science Center College of Medicine.
2. Indiana University and Richard L. Roudebush VA Medical Center Gastroenterology, Medicine.
* Dr. Sanjukta Chakraborty, Department of Medical Physiology, Texas A&M Health Science Center College of Medicine, Medical Research and Education Building, 8447 Riverside Parkway, Bryan 77807, USA. Email: schakraborty@tamu

Background and aim: Conjugated bile acids (BA), taurochenodeoxycholic acid (TCDCA) and taurocholic acid (TCA) levels are significantly elevated in several liver pathologies, including but not limited to chronic inflammatory liver diseases, cholestatic liver diseases and also found in the metastatic lymph node (LN). There are also reports of increase level of lymphangiogenesis in those diseases. However, it is not known whether there is biological connections between the elevated level of pathological BAs and increased level of lymphangiogenesis. In this current study we aimed to delineate the specific effects of BAs on lymphangiogenesis and establish specific molecular pathways mediating this signaling axis. **Methods and results:** We measured BA levels LN and serum of MDR2$^{-/-}$ mice compared to wild type (WT) and found that BA levels were significantly high in both the serum and LN of MDR2$^{-/-}$ mice. By the immunohistochemical staining of liver tissue sections we found that there was increase level of lymphangiogenesis in the MDR2$^{-/-}$ mice compared to WT. We also found that human LECs (hLECs) which express the BA receptors TGR5, FXR can be directly affected by the TCDCA and TCA. Both the TCDCA (100 μM) and TCA (100 μM) increased the proliferation, invasion, migration, tube formation of hLECs which were inhibited by the specific BA receptor inhibitor (small molecule TGR5 antagonist (SBI-115)). These two BAs also increased cellular metabolism as measured by the Seahorse assay and it was associated with a significant increase in maximal glycolytic capacity and ATP productionenhanced expression of glycolytic Phosphofructokinase, platelet (PFKP), Hexokinase 2 (HK2) and Fatty Acid Synthase (FASN). Interestingly, we also found that BAs induced the oxidative stress in hLECs with the production of reactive oxygen species (ROS) via the activation of the redox genes, namely, RAC1, Nox4 which were also highly expressed in the MDR2$^{-/-}$ mice. Further, BAs phosphorylated the redox sensitive kinase p90RSK (S380), an important regulator of endothelial cell dysfunction. This BA mediated p90RSK activation was significantly abrogated in the presence of TGR5 inhibitor, p90RSK specific inhibitor BI-D1870 and Reactive Oxygen Species (ROS) inhibitor N-acetyl cysteine (NAC). The BA induced p90RSK activation increased the SUMOylation of the downstream molecule Prox1 which is a well known trascriton factor for VEGFR3 in the context of lymphangiogenesis. Inhibition of BA induced p90RSK activation inhibited the BA induced VEGFR3 transcription, hLEC invasion and lymphangiogenesis.

Conclusion: We have established a novel mechanism of BA-induced oxidative stress in hLEC as a potential regulator of lymphangiogenesis mediated by pp90RSK via TGR5. Thus, the role of p90RSK inhibitor in the BA induced lymphangiogensis needs further investigation and could be considered as potential therapeutic target to control the BA mediated pathological lymphangiogenesis.

Acknowledgement: CPRIT HIHR RP210213 grant and American Heart Association grant 17SDG33670306 to S.C. We also thank CTTP training program and Gulf Coast Consortia for the traineeship.

Poster 5

Targeting the Nav1.6:GSK3β Protein:Protein Interaction Complex to Mitigate Hippocampal Hyperexcitability in Neuropsychiatric Disorders

Baumgartner TB, Singh AK, Dvorak NM, Wadsworth PA, Laezza F

Department of Pharmacology & Toxicology, University of Texas Medical Branch

Corresponding Author: Dr. Fernanda Laezza, Department of Pharmacology & Toxicology, University of Texas Medical Branch, 301 University Blvd. Galveston, TX, E-mail: felaezza@utmb.edu

Background: Dysfunction of the hippocampus and related neural circuitry is implicated in a diverse array of neuropsychiatric disorders. Located deep in the temporal lobe, this brain region plays a critical role in learning, memory formation, social cognition, and emotional processing. Multiple lines of evidence show a causal relationship between hippocampal hyperexcitability and memory impairment, cognitive deficits, and epileptiform activity. Voltage-gated Na^+ channels (Nav channels) are transmembrane proteins with critical regulatory roles in synaptic function and neuronal firing. Nav1.6 is the most densely expressed Nav channel isoform in the adult human brain. Importantly, Nav1.6 plays a critical role in action potential initiation due to its localization at the axon initial segment, and therefore serves as the primary target for modulation of neuronal excitability. The Nav1.6 channel is regulated through its interactions with various key auxiliary proteins and signaling molecules. Recent studies from our laboratory have revealed that glycogen synthase kinase 3β (GSK3β) binds the Nav1.6 C-terminal tail and phosphorylates the T1938 residue of its C-terminal domain, indicating that GSK3β regulates the Nav1.6 channel via a dual-function mechanism including phosphorylation and complex formation. Functionally, genetic silencing of GSK3β suppresses Nav1.6-encoded currents, while increased phosphorylation of T1938 via GSK3β promotes maladaptive firing of neurons under vulnerable conditions. This evidence suggests that dysregulated GSK3β-mediated phosphorylation of Nav1.6 is a biomarker of neuronal vulnerability and facilitates neuropathological phenotypes associated with the cognitive deficits.

Hypothesis/Goals: The goals of this study are to map the interaction sites mediating Nav1.6:GSK3β complex formation, optimize lead compounds identified to inhibit the PPI complex, and evaluate selected compounds for functional modulation of Nav1.6-mediated hyperexcitability and other disease-related phenotypes in hippocampal neurons. We hypothesize that pathological hippocampal hyperexcitability can be diminished through pharmacological modulation of the Nav1.6:GSK3β complex.

Methods: Split-luciferase complementation assay (LCA), surface plasmon resonance (SPR), and whole-cell patch clamp electrophysiology

Results: Using the LCA, a class of 43 compounds with ideal drug-like properties was selected for their ability to selectively inhibit Nav1.6:GSK3β complex formation in a dose-dependent manner. Additional screenings were performed specifically against the GSK3β:Nav1.6 complex, yielding five structurally diverse compounds that substantially inhibit complex formation at low micromolar concentrations. Additionally, a mutation screen of GSK3β and the Nav1.6 CTD has revealed binding "hot spots" of the PPI interface that serve as potential targets for small-molecule functional modulation.

Conclusions: The Nav1.6:GSK3β PPI complex is a critical mediator of neuronal excitability and deeper understanding of this interaction will guide optimization of lead compounds targeting the Nav1.6:GSK3β complex interface into potential neurotherapeutics.

Acknowledgements: We acknowledge our funding sources as follows: NIH Grant R01MH12435101 (FL), R01ES031823 (FL); U18DA052504 (FL); Technology Commercialization Program, HAMBP training grant no. T32GM008280 (NMD), NIH Grant no. T32AG0679 (TB), PhRMA Foundation (PAW).

Poster 6

Potent and Selective Tetrhydropyrido[4,3-d]pyrimidine ATR Inhibitor with Robust In Vivo Efficacy

Carroll CL, Ramaswamy VSK, Bardenhager JP, Cross JB, Di Francesco ME, Geck Do M, Giuliani V, Heffernan TP, Jiang Y, Jones P, Kang Z, Liu CY, Ma Y, Pang J, Shepard H, Yau A
1. Therapeutics Discovery Division, UT MD Anderson Cancer Center

Johnson MG, Lively S, Lapointe D, Adler M
2. Department of Chemistry, ChemPartner Corporation

Ding Y, Cao J, Jia W, Du M, Li W, Niu X, Wang K, Zhao X, Yan M, Liang H, Maoshan C, Liping Z, Yuzhuang Y, Cao Q, Zhang Z, Lan P, Guo Z,
3. Department of Chemistry, Shanghai ChemPartner

Chen M, Fang C, Lv X, Li M, Chen H, Wen J, Liu M, Gu Y, Hao J
4. Department of Protein Science/In Vitro Biology/In Vivo Biology, Shanghai ChemPartner

Lu Y, Huang J, Yan L, Xu L, Xu L
5. Department of DMPK, Shanghai ChemPartner

Corresponding author: Christopher L. Carroll, Therapeutics Discovery Division, UT MD Anderson Cancer Center, 1881 East Rd, Houston, TX, E-mail: clcarroll@mdanderson.org

Background: Ataxia telangiectasia and Rad3 related protein (ATR) is a serine/threonine protein kinase member of the phosphatidylinositol 3-kinase-related (PIKK) protein family. ATR is a critical regulator of the DNA damage response pathway (DDR) sensing DNA single-strand breaks and arresting the cell cycle to allow for nucleotide excision or homologous recombination DNA repair mechanisms. Inhibition of ATR is expected to afford therapeutic benefit for the treatment of cancer in combination with DNA-damaging chemotherapies by sensitizing cells to the genotoxic agents and as a single agent in synthetic lethal context such as in tumor types with ATM-/- genotype.

Goals: Identify novel inhibitors of ATR kinase with *in vivo* efficacy for drug candidate development

Methods: Using a published tetrahydropyrazolo[1,5-*a*]pyridine ATRi as a prototypical small molecule inhibitor and a computationally generated homology model of ATR we developed a binding model for inhibition of ATR. From this binding pose we generated a short list of replacement scaffolds for the core tetrahydropyrazolo[1,5-a]pyridine and synthesized representative leads in each scaffold to assess biochemical activity and selectivity.

Results: Tractable SAR and feasible synthetic chemistry favored lead optimization for the tetrahydropyrido[4,3-*d*]pyrimidine series. Series-related time-dependent CYP inhibition liabilities were mitigated by fluorine substitution of the core. Potency and selectivity improvements ultimately led to the identification of IACS-008738 which demonstrated ATR inhibition *in vivo* and robust efficacy in tumor growth inhibition models.

Conclusions: Advanced lead IACS-008738 demonstrated excellent cell-based inhibition of ATR, very good selectivity against related PIKK family of targets and good DMPK properties. IACS-008738 showed complete suppression of pChk1 *in vivo* at 50 mpk and efficacy in tumor growth inhibition at 75 mpk. Time-dependent CYP inhibition for the tetrahydropyrido[4,3-*d*]pyrimidine series could be mitigated by monofluorination of the 6-methyl substitution.

Poster 8

Protein Kinase C Epsilon (PKCε) Inhibitors for Non-opioid Pain Management

De Kraker, HC[1], Wang, HY[1], Fleischer CN[3], Hart M[2], Li G[2], Levine J[4], Parker P[5], Messing RO3, McHardy SF[1]

1. Center for Innovative Drug Discovery, Medicinal Chemistry Core Facility, Department of Chemistry, University of Texas San Antonio
2. High-throughput Screening Core Facility, Department of Biochemistry, UT Health San Antonio.
3. Department of Neurology, University of Texas at Austin.
4. Department of Medicine, University of California San Francisco.
5. The Francis Crick Institute, London, UK

Corresponding author: Stanton F. McHardy, Department of Chemistry, University of Texas San Antonio, 1 UTSA Circle, San Antonio, Texas, E-mail: Stanton.mchardy@utsa.edu

Background
Pain, both chronic and acute, is one of the primary reasons for people to seek medical care. In a CDC report from 2018 it was estimated that 1 in every 5 US citizens suffer from chronic pain. This has been linked to other health problems such as opioid addiction, restricted mobility and depression. Thus, the development of drugs with novel targets that avoid opioid receptors is in high demand. PKCε was identified as a druggable target that is closely involved in signal transduction pathways leading to pain response. Early *in vivo* results showed an off-target effect of reduced locomotor activity in mice.

Hypothesis/Goals
Our initial goal is to identify drug-like lead compounds with high efficacy in *in vivo* pain models. Furthermore, inhibition of the closely related Rho associated coiled-coil forming protein kinase (ROCK) was hypothesized to cause the undesired off-target effect. Thus, we sought to increase selectivity of our inhibitors over ROCK.

Methods
Guided by the first known crystal structure of a PKCε inhibitor bound to PKCε recently established by our program, we will present structure-activity relationship (SAR) studies to optimize and advance lead series through an iterative SAR process. Parallel analysis of physicochemical properties such as MW, LogD, tPSA and hydrogen bond donors/acceptors aided new compound design.

Results
A novel and highly enantioselective synthetic route, conducive to our SAR studies was designed and optimized. Several new lead compounds were identified with increased potency and selectivity for PKCε and significantly reduced CYP450-2D6 activity. Lead compounds have shown robust *in vivo* activity in Paclitaxel-induced hyperalgesia animal models.

Conclusions
Our SAR studies have produced several analogs as potential clinical candidates with increased PKCε potency and improved selectivity, as well as improved in vitro ADME characteristics. In vivo dosing studies are planned to evaluate the impact of increased selectivity over ROCK on the previously observed adverse effects.

Acknowledgements

Funding: DOD Grant CDMRP Award# W81XWH1810389

Poster 9

Expanding the Druggable Genome: Targeting Protein:Protein Interaction Interfaces for Neuropsychopharmacological Probe Development

Dvorak NM,[1] Wadsworth PA,[1] Engelke DS,[2] Singh AK,[1] Nguyen N,[3] Tapia CM,[1] Wang P,[1] Chen H,[1] Powell RT,[3] Stephan C,[3] Do Monte FHM,[2] Zhou J[1], Laezza F[1]

1. Department of Pharmacology and Toxicology, University of Texas Medical Branch
2. Department of Neurobiology and Anatomy, University of Texas Health Science Center
3. Institute of Biosciences and Technology, Texas A&M Health Science Center

Background: Perturbations of neuronal excitability cause neuropsychiatric disorders. Current therapeutics target receptors, enzymes, and transporters to ameliorate the aberrant neuronal activity; however, these approaches are associated with intolerability and delayed therapeutic onset. Thus, there is a need to identify new surfaces to target to develop improved neuropsychopharmacological agents. Whereas protein:protein interaction (PPI) interfaces have been successfully targeted in the oncology field to develop antineoplastic agents with lessened side effects, these surfaces have not yet been explored in central nervous system (CNS) drug discovery. Therefore, to actualize the potential of PPI interfaces as targets for the development of improved neuropsychopharmacological agents, the development of probes to interrogate PPIs of therapeutic interest is a necessary prerequisite.

Hypothesis/Goals: On account of its profound regulation of the output of medium spiny neurons (MSN) of the nucleus accumbens, the PPI between the voltage-gated Na^+ (Na_v) channel isoform 1.6 and its auxiliary protein fibroblast growth factor 14 (FGF14) represents a promising surface to target to ameliorate the perturbed neuronal activity underlying neuropsychiatric disorders.

Methods: The split-luciferase complementation assay (LCA); surface plasmon resonance (SPR); patch-clamp electrophysiology; *in vivo* single-unit electrophysiological recordings; reward cue task.

Results: To develop probes targeting the FGF14:Na_v1.6 PPI interface, we screened ~45,000 small molecules against the complex using the LCA. This screening, in tandem with a Lipinski's analysis, potency studies, and selectivity studies identified 4 non-toxic compounds with favorable drug-like properties that had potent and selective effects on the FGF14:Na_v1.6 complex. SPR analyses revealed that the 4 compounds had binding to FGF14 or Na_v1.6. Then, a combination of patch-clamp electrophysiology and molecular docking was used, which revealed that the 4 ligands had conserved effects on Na_v1.6 channel inactivation, effects on MSN firing, and predicted interactions with residues at the FGF14:Na_v1.6 PPI interface with established roles in regulating Na_v1.6 channel inactivation. On account of its superior potency, 1028 was selected as a representative ligand from this class for mechanism of action studies. Consistent with our molecular docking studies and models of Na_v channel inactivation, 1028 was shown to bind to FGF14, modulate FGF14:Na_v1.6 complex assembly, and manipulate Na_v1.6 channel inactivation through a mechanism dependent upon an intact interaction between $FGF14^{R117}$ and the $Na_v1.6^{D1846:R1866}$ salt bridge. *Ex vivo*, 1028 was shown to potentiate MSN firing through a mechanism dependent upon FGF14. Based upon its *in vitro* and *ex vivo* performance, coupled with its determined blood-brain barrier permeability, 1028 was selected for *in vivo* studies. Consistent with our *ex vivo* studies, 1028 was shown to potentiate firing rates of accumbal neurons *in vivo*. At the behavioral level, these electrophysiological changes were found to correlate with sustaining motivation in satiated states.

Conclusions: We show that small molecule modulation of the FGF14:Na_v1.6 complex increases Na_v channel availability through manipulating the interaction between $FGF14^{R117}$ and $Na_v1.6^{D1846:R1866}$, which increases MSN firing and leads to maintenance of motivation in satiated states. Furthermore, our studies demonstrate that PPIs represent tractable targets for the development of an entirely new class of neuropsychopharmaoclogical agents.

Acknowledgements: NIH Grant R01MH095995 (FL), R01MH12435101 (FL), NIH Grant 1R01MH111107 (FL, JZ), John Sealy Memorial Endowment Funds (FL), R01 DA038446 (JZ), P30 DA028821 (JZ), CPRIT RP150578 (CS), and HAMBP training grant no. T32GM008280 (NMD).

Poster 10

Identifying Phenotypes Associated with Coupling the Epithelial-to-Mesenchymal Transition and Metabolic Reprogramming

Galbraith M[1], Jia D[2], Levine H[3], Onuchic J[1]

1. Center for Theoretical Biological Physics, Rice University, Houston, TX USA
2. National Cancer Institute, National Institutes of Health, Bethesda, MD USA
3. Center for Theoretical Biological Physics, Northeastern University, Boston, MA USA

Corresponding author: Madeline Galbraith, Center for Theoretical Biological Physics, Rice University, 6566 Main Street, Houston, TX, E-mail: mlg19@rice.edu

Background The leading cause of cancer-related deaths is metastasis accounting for about 90% of deaths. There are many regulatory networks involved in metastasis and tumor proliferation, including the epithelial-to-mesenchymal transition (EMT) and metabolic reprogramming. During EMT cells increase their capacity for migration, invasiveness, and resistance to apoptosis. A hybrid EMT state allowing for the collective migration of tumor cells during metastasis was hypothesized and verified. Another hallmark of cancer, metabolic reprogramming is also important to metastasis, giving cancer cells the ability to survive in a multitude of environments. Typically, in normoxic conditions cells utilized oxidative phosphorylation (OXPHOS) and under anaerobic conditions use glycolysis. However, cancer cells often prefer glycolysis even in the presence of oxygen, referred to as the Warburg effect. Metabolic reprogramming of the glucose metabolic pathway can lead to mixed metabolic phenotypes in which cells use both OXPHOS and Warburg metabolic phenotypes. Both the hybrid EMT and mixed metabolic states are correlated with high metastatic potential and poor prognosis, and recently, the connection between EMT and metabolic reprogramming has been shown.

Hypothesis/Goals We propose the hybrid EMT and mixed metabolic phenotypes are coupled. Additionally, by identifying the mechanism leading to this hybrid phenotype associated with aggressive metastatic potential, we can identify therapeutic targets that disrupt both EMT and metabolic reprogramming.

Methods We model the core regulatory networks of EMT and metabolic reprogramming using coupled rate equations that include production, degradation, transcriptional regulation, micro-RNA regulation, and competition. The crosstalks between these core networks are included.

Results In modeling the network, we found that only a subset of the crosstalks is necessary to drive EMT and metabolic reprogramming. The key regulators of the coupled EMT and metabolic networks include reactive oxygen species (ROS), Hif-1, and the micro-RNAs mir34 and mir200. Additionally, we were able to identify regions of the crosstalk parameter space in which only the coupled hybrid EMT and metabolic phenotype existed. Further, if the hybrid states were initially inaccessible, the same set of regulators could drive the system to fully hybrid EMT and mixed metabolic phenotype. We also noticed external signals may be important in the mutual driving of EMT and metabolic reprogramming.

Conclusion These results confirm EMT and metabolic reprogramming are strongly coupled and mutually drive the system towards a highly aggressive cancer phenotype with poor prognosis. Additionally, we suggest incorporating other pathways that may have competing effects. Lastly, we propose a potential feedback loop between the key regulators that could be targeted to disrupt both networks which may have therapeutic advantages compared to disrupting only one of the networks.

Acknowledgements This work was supported by the National Science Foundation GRFP no. 1842494 and PHY 1522550.

Poster 11

Targeting PKMYT1 Member of the Wee Kinase Family in Cancer Treatment

Ghoteimi R[1], Deng L[1], Monroy EY[1], Qi X[1], Chen A[2], Foulds CE[2], Ellis MJ[2], Wang J[1]
1. Department of Pharmacology and Chemical Biology, Baylor College of Medicine
2. Department of Lester and Sue Smith Breast Center, Baylor College of Medicine

Corresponding author: Wang Jin, Pharmacology and Chemical Biology, Baylor College of Medicine, 1 Baylor Plaza, Houston, Texas, wangj@bcm.edu

Background:

PKMYT1 is a member of the Wee kinase family and is involved in the cell cycle regulation at the G2/M transition. It plays a pivotal role in the inhibitory phosphorylation of cyclin-dependent kinase (CDK1) leading to the separation of the complex CDK1-cyclin B and their subsequent deactivation. As a result, the cell cycle is blocked until DNA damage is repaired. Interestingly, in more than 50% of cancer cases, the p53 pathway is compromised and the G1 checkpoint defective. As a consequence, cancer cells rely on the G2 checkpoint more than normal cells to repair damaged DNA. Moreover, PKMYT1 is overexpressed in several solid tumors including hepatocellular carcinoma, colon cancer, glioblastoma, non-small-cell lung, neuroblastoma, and gastric cancer.

Hypothesis/Goals:

Given the important position of PKMYT1 in the cancer cell cycle, a strategy for cancer treatment is to target this kinase to induce G2 checkpoint abrogation, mitotic catastrophe, and subsequent cell death. Therefore, the project aims to design, synthesize and study selective PKMYT1 inhibitors.

Methods:

This multidisciplinary project involves the use of virtual screening, chemical synthesis as well as biological evaluation of the potential inhibitors.

Results:

We have identified 11 hits as selective PKMYT1 inhibitors and determined the key interactions within its active sites. This initial study provided the bases for further chemical modification and a library of compounds has been synthesized to complete our Structure-Activity Relationship (SAR) study. To evaluate their activity toward PKMYT1, we are developing a cell-based NanoBRET assay.

Conclusion:

Overall, the understudied PKMYT1 plays an essential role in the cell cycle and more for cancer cells. For these reasons, developing selective PKMYT1 inhibitors is a promising approach to target cancer cells over normal cells.

Acknowledgments: This project is supported in part by a Cancer Therapeutics Training Program fellowship (CPRIT Grant No. RP210043 to R.G.), NCI SPORE (P50-CA186784 to M.J.E.) SPORE Developmental Research Project to J.W.

Poster 12

An Ongoing Study Of DND1 Function In Somatic Cancers

Godavarthi JD, Williams A, Zhang Y*
Dept. of Pharmaceutical Sciences, Texas Southern University, Houston, TX.

*Corresponding author: Yun Zhang, Dept. of Pharmaceutical Sciences, Texas Southern University 3100 Cleburne Street, Houston, Texas, yun.zhang@tsu.edu.

Background:
Dead-End (DND1) is an RNA-binding protein involved in translational regulation by interacting with mRNA. Defects in *DND1* gene causes germ cell tumours and sterility in rodents. Our previous *in-silico* analysis of *DND1* showed that it is altered in many human cancers and in some cases with worse survival. *DND1* either positively or conversely co-expressed with many genes in a variety of cancers. The Ingenuity Pathway Analysis (IPA) of these co-expressed genes identified many canonical signalling pathways in each cancer type, whose activation or deactivation are significantly associated with DND1 expression. Importantly, some cancers exhibit strikingly similar profiles of DND1-correlated signalling pathway activation or suppression. Our data suggest that the biological role of DND1 is cell-type specific and that DND1 may play opposing role by exerting anti-proliferative effects in some cancer cells while being pro-proliferative in others.

Hypothesis/Goals:
We hypothesize that DND1 largely exhibits tumour suppressive function in somatic cancers. In this study, our goal is to experimentally verify the effects of DND1 on identified signalling pathways.

Methods:
For our study, we cloned FLAG-tagged-DND1 ORF into a pLVX-TetOne-Puro vector. The modified vector was then subjected to sequencing to verify the gene insertion and replicated using Lenti-X packaging single shots (VSV-G) in HEK293T. The lentivirus produced will be used to establish a stable cell line that overexpress DND1 upon induction. The stable cell lines will further be used to examine the cellular features and the signalling pathways, at both RNA and protein levels, upon DND1 overexpression using RT-qPCR, Western Blot assay and/or RNA sequencing.

Results:
The cloned gene was successfully transfected with a titre value of $3.6x10^6$ – $3.6x10^7$ IFUs/ml. Using this, a stable cell line will be established which can inducibly overexpress DND1. We expect that upon DND1 overexpression, these cells will exhibit change of cellular features and at least some of the signalling pathways suggested by our *in-silico* study will be affected.

Conclusions:
Our results would help us understand the role of DND1 in cancers. The inducible cell lines generated might be an essential tool to study the functional role of DND1.

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

Poster 1

Kinase Regulation of Voltage-gated Na+ Channels Cell Surface Expression

Goode NA, Arman P, Laezza F

Department of Pharmacology & Toxicology, University of Texas Medical Branch

Corresponding Author: Dr. Fernanda Laezza, Department of Pharmacology & Toxicology, University of Texas Medical Branch, 301 University Blvd. Galveston, TX, E-mail: felaezza@utmb.edu

Background: Voltage-gated sodium (Nav) channels are responsible for the initiation and propagation of action potentials in excitable systems such as neurons. In response to changes in membrane potential, Nav channels undergo conformational changes that lead to shifts between resting, activated, and inactivated states. Phosphorylation plays an essential role in regulating Nav channels and excitability. Yet, a surprisingly limited number of kinases have been identified as regulators of Nav channels. In previous studies we showed that glycogen synthase kinase 3 (GSK3), a critical kinase found associated with numerous brain disorders, directly phosphorylates Nav1.2 and Nav1.6 channels producing opposite effects on Na+ current amplitudes. However, whether these changes are associated with corresponding changes in channel cell surface expression is not known. Understanding how regulation of GSK3 confers changes in Nav channel cellular trafficking and neural activity has important implications for unraveling the complex signaling cascades that fine-tune neuronal excitability.

Hypothesis/Goals: The goal of this study was to determine the effect of kinase inhibitors within the GSK3 pathway on surface expression of Nav1.6 and Nav1.2 channels. We hypothesize that increased activity of GSK3 by Akt-mediated disinhibition would alter the surface expression of Nav1.6 and Nav1.2 channels.

Methods: Cell surface biotinylation and Western blotting.

Results: Using cell surface biotinylation, we treated HEK-293 cells stably expressing Nav1.6 or Nav1.2 with either the Akt inhibitor, triciribine, or vehicle, labeled the cells with biotin and performed pulldown of the labeled fraction with neutravidin. Treatment with triciribine led to a statistically significant increase in the surface expression of Nav1.6 and a decrease in surface expression of Nav1.2, indicating that the Akt/GSK3 pathway exerts an isoform-specific regulation of Nav channel trafficking to the cell surface.

Conclusion: These findings provide evidence for a signaling mechanism by which the Akt/GSK3 pathway modulates Nav channel cell surface expression that might be critical for regulating neuronal activity in several brain disorders associated with dysfunction of Nav channels.

Acknowledgements: We acknowledge our funding sources as follows: NIH Grant R01MH12435101 (FL), R01ES031823 (FL); U18DA052504 (FL).

Optimization of PLGA Nanoparticles of AC1LPSGZ using Central Composite Design (CCD) and In Vitro Characterization

Gupta R[1], Sarkar M[1], Chen Y[1], Xie H[1]*
1. Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Texas Southern University,3100 Cleburne Street, Houston, Texas 77004, USA.
*Corresponding author Email: huan.xie@tsu.edu

Background

Design of experiment (DOE) is a systematic and efficient approach to study the effect of multiple input variables (factors) on key output variables (responses). In this work we demonstrate the capability of central composite design (CCD), a robust and high-resolution response surface design for nanoparticles (NPs) optimization using Design Expert® software (version 13). Two factors, drug amount in organic phase (mg) and aqueous phase volume (ml) were varied over five different levels and corresponding responses for entrapment efficiency (EE), size, drug load and zeta potential were measured. Both factors, the drug amount, the aqueous phase volume, and their interaction significantly influence the EE, size, and drug load.

Methods

Nanoprecipitation method was used to prepare Poly(lactide-co-glycolide) (PLGA-50:50) NPs of chemotherapeutic agent AC1LPSZG. Briefly, 60 mg PLGA and 5mg AC1LPSZG were dissolved in 2mL acetone and added dropwise into aqueous phase containing 3% Poloxamer P188 under magnetic stirring (0.3 ml/min, 30°C, 750 rpm) using syringe pump (New Era Pump Systems, Inc.). Organic solvent was removed on hot plate stirrers (VWR, Troemner LLC) at 60°C, 400 rpm for 3hours. NPs were washed three times with water at 14000 rpm, 4°C for 45 min using Eppendorf centrifuge (5417R) and lyophilized (SP Scientific BenchTop Pro) using 10% sucrose as lyoprotectant. In vitro drug release was determined in phosphate buffer pH 6.8 with 2% CTAB (cetrimonium bromide) employing USP-4 apparatus (SOTAX®) incorporated with Float-A-Lyzer dialysis cells at 300 kDa molecular weight cut–off (MWCO).

Results

Experimental data were fitted into different model equations of increasing polynomial complexity. ANOVA results show two-factor interaction (2FI) is significant model for EE, size, and drug load ($p<0.05$). Mean model is sufficient to describe zeta potential data. Lack of fit is insignificant for all selected models. Predicted R^2 for EE 0.9622 is in reasonable agreement with adjusted R^2 of 0.9471. Diagnostic normal plot, perturbation plots, interaction plots and 3D-surface plot confirm model robustness. EE and size both increased with the increase of aqueous phase volume and decrease of drug amount. Drug load increased with increase of both factors. Predicted optimum response (with goal set to maximize EE) was checked experimentally. Batch prepared with 5 mg drug and 4 mL aqueous phase volume has EE of 45.1% (predicted 47.6%), size of 124.7 nm (predicted 133.5 nm), drug load of 2.56% (predicted 2.27%) and zeta potential of – 14.8 mV (predicted – 17.2 mV) at desirability of 0.961 and coefficient of variance well within 15%. Optimized batch showed 31 % drug release in 72 hrs.

Conclusion

CCD efficiently identified the interaction of factors and their indirect impact on NP characteristics prepared via nanoprecipitation. We conclude that similar designs can help to understand and optimize innovative manufacturing processes, needed for the quality by design (QbD) preparation of nano-formulations.

Acknowledgements

Cancer Prevention & Research Institute of Texas Core Facilities Support Awards (RP180748) and NIH's Research Centers in Minority Institutes Program (RCMI, U54MD007605).

Conflict of Interest-Authors declare no conflicts of interest.

Poster 14

Probing the FGF:Na_v Channel Protein:Protein Interface with Short Peptidomimetics

Haghighijoo Z, Arman P, Chen H, Zhou J, Laezza F

Department of Pharmacology & Toxicology, University of Texas Medical Branch

Corresponding Author: Dr. Fernanda Laezza, Department of Pharmacology & Toxicology, University of Texas Medical Branch, 301 University Blvd. Galveston, TX, E-mail: felaezza@utmb.edu

Background:
The structure-function (SF) properties of voltage-gated Na^+ (Na_v) channels have been subjected to intense studies due to the high therapeutic potential of these channels for a wide range of pathologies including neurological and neuropsychiatric disorders. *In vivo*, Na_v channels are composed of a pore forming α-subunit in addition to auxiliary β-subunits. Among the nine pore-forming α-subunit isoforms ($Na_v1.1$–$Na_v1.9$), $Na_v1.2$ and $Na_v1.6$ are of particular importance due to their preferential distribution and relative expression in the central nervous system (CNS) with connections to epilepsy, schizophrenia, and bipolar disorder (BD). Despite the tremendous progress in the past decades towards understanding the mechanisms regulating the fundamental properties governing channel voltage sensitivity, pore opening, activation, and inactivation, there are still many properties of these channels that are not yet known. Furthermore, because of limited structural information and high homology among Na_v channels subtypes, therapeutic compounds that selectively target individual isoforms remain a major challenge.

The protein:protein interaction (PPI) interface between the Nav channel C-terminal tail domains (CTD) and the intracellular fibroblast growth factors (iFGFs; FGF11-14) is considerable divergent and rich in druggable pockets providing an opportunity for in-silico drug design. To that end, we have identified a novel class of FGF14 peptidomimetics that can selectively modulate FGF14:$Na_v1.6$ complex assembly and produce functional effects on Na+ currents and neuronal excitability.

Hypothesis/Goals: The goals of this study were to build $Na_v1.2$ and $Na_v1.6$ homology models and investigate the interaction sites of an FGF14-derived peptidomimetic against these two channel isoforms for future drug discovery and lead optimization studies.

Methods: Computational drug design approaches such as homology modeling, molecular docking, and binding studies were used. In addition, we complemented these methods with automated-planar whole-cell patch clamp electrophysiology.

Results: We built homology models for the $Na_v1.2$ and $Na_v1.6$ channel based on available crystal structures and evaluated docking of the peptidomimetic ZL1077 to these models through different software. These studies revealed that ZL0177 binds strongly to residues Glu 1884 in Na_v 1.2 and Met 1869 in $Na_v1.6$ via H bonds. Additionally, hydrophobic and π- π interactions of ZL1077 with Lys1891 ($Na_v1.2$), Arg 1891 ($Na_v1.6$), as well as Tyr 1883 and Thr 1887 which are both conserved between the two isoforms were identified.

Conclusions: Our findings provide evidence for structural divergence among various Nav channel isoforms using peptide-derived probes.

Acknowledgements: We acknowledge our funding sources as follows: NIH R01MH12435101 (FL), U18DA052504 (FL); Technology Commercialization Program (FL).

Poster 15

The Discovery of IACS-9779 and IACS-70465 as Potent Inhibitors Targeting Indoleamine 2,3-Dioxygenase 1 (IDO1) Apoenzyme

Hamilton MH[*1], Mseeh F[1], McAfoos TJ[1], Leonard PG[1], Reyna NJ[1], Harris AL[2], Xu A[1], Han M[1], Soth MJ[1], Czako B[1], Theroff JP[1], Mandal PK[1], Burke JP[1], Virgin-Downey B[1], Petrocchi A[1], Pfaffinger D[1], Rogers NE[1], Parker CA[1], Yu SS[1], Jiang Y[1], Krapp S[3], Lammen A[3], Trevit G[4], Tremblay MR[5], Mikule K[5], Wilcoxen K[5], Cross JB[1], Jones P[1], Marszalek JR[2], and Lewis RT[1].

1. Institute for Applied Cancer Science, UT, MD Anderson Cancer Center
2. Translational Research to Advance Therapeutics and Innovation in Oncology, UT, MD Anderson Cancer Center
3. Proteros Biostructures GmbH
4. XenoGesis Ltd
5. Tesaro Inc.

Corresponding Author: Matthew M. Hamilton, IACS (**I**nstitute for **A**pplied **C**ancer **S**cience), University of Texas, MD Anderson Cancer Center, 1881 East Road, Houston, TX, 77054 USA, E-mail: mmhamilton@mdanderson.org

Background: Indoleamine 2,3-dioxygenase 1 (IDO1) is a heme-containing enzyme that mediates the rate-limiting step in the metabolism of L-tryptophan (Trp) to kynurenine (KYN). IDO1-mediated Trp catabolism and KYN accumulation in the tumor microenvironment exert a profound inhibitory effect on T cells, leading to an immunosuppressive response and tumor immune evasion. Increased levels of IDO1 expression in tumors correlate with a lower presence of tumor infiltrating lymphocytes (TILs), a higher percentage of Treg cells, and a worse disease outcome.

Hypothesis: Inhibition of IDO1 has the potential to maintain an active immune response in the tumor microenvironment and it is expected to be an effective strategy for disease mitigation.

Methods: A review of the literature of known IDO1 inhibitors and crystallography were used as starting points for the design of novel series of inhibitors. IDO1 cellular activity, physical properties, and standard *in vitro* metabolic and safety assays were used to select compounds for further evaluation *in vivo*. Pharmacokinetics, target engagement in a SKOV3 mouse tumor model, and a human whole blood assay were used to select molecules for advancement.

Results: We developed a class of inhibitors with a conformationally constrained bicyclo[3.1.0]hexane core. These potently inhibited IDO1 in a cellular context by binding to the apoenzyme, as elucidated by biochemical characterization and X-ray crystallography. IACS-9779 (62) and IACS-70465 (71) displayed excellent potency, pharmacokinetics, and tumor target engagement.

Conclusion: IACS-70465 was more potent than linrodostat (BMS-986205) in a human whole blood assay. IACS-9779 with a predicted human efficacious once daily dose below 1 mg/kg to sustain >90% inhibition of IDO1 displayed an acceptable safety margin in rodent toxicology and dog cardiovascular studies to support advancement into preclinical safety evaluation for human development.

Acknowledgements: University of Texas, MD Anderson Cancer Center and Tesaro Inc. for funding and supporting this work.

Poster 16

The Design and Development of GMC1 Analogues: Targeting the Regulation of FKBP52 and Hormonal Receptors in Prostate Cancer Cells

Idowu KA, Olaleye OA, Xie H
Department of Pharmaceutical Science, College of Pharmacy and Health Sciences, Texas Southern University
Corresponding author: Kehinde Idowu Ademola, Department of Pharmaceutical Science, Texas Southern University, 3100 Cleburne Street, Houston, Tx, 77004

Abstract

Background
Prostate cancer (PC) is a proliferative disorder characterized by abnormal cell growth that originates in the prostate gland. An effective way of treating PC is androgen deprivation therapy (ADT). However, at an advance stage, PC stops to respond to ADT, and this is referred to as castrate-resistant prostate cancer (CRPC). Earlier research reported GMC1 effectively inhibit androgen receptor (AR) and glucocorticoid receptor (GR) activities in a variety of PC lines. However, poor solubility of GMC1 in water and lipid has made it desirable and necessary to design and develop new pharmacophores/analogues with suitable water solubility, liquid stability, and therapeutically potent against PC.

Hypothesis/Goals
This study is aimed at designing and developing new analogues of GMC1, and this study employed both computational and *in vitro* methods to identified compounds with inhibitory potentials against CRPC related proteins and PC cells. SWISS-similarity and Zinc databases were utilized for screening of compounds to identify GMC1-structurally related compounds with better physicochemical properties.

Results
A search of the databases identified over 7000 analogues of GMC1. Out of the over 7000 GMC1 analogues, 231 were predicted to show better solubility in lipid and water than GMC1. And the results of the molecular docking analysis revealed 27 compounds exhibited higher docking scores toward the FK1 domain of FKBP52 protein compared to the reference drug, FK506 and GMC1. For the AR and GR, 35 and 40 analogues respectively exhibited higher docking scores towards their ligand binding domain (LBD) than the reference drugs and GMC1. A further molecular dynamic simulations study of the best docked compounds showed 8, 4 and 7 compounds showed better binding affinities and stable conformation at the binding sites of GR, FKBP52 and AR, respectively.

Conclusions
This study identified the lead compounds as promising inhibitors of these proteins. *In vitro* evaluation of the antiproliferation and inhibitory potentials of identified compounds against PC and its associated proteins in treating CRPC is ongoing.
Funding sources: This project is funded by Cancer Therapeutics Training Program - CTTP (CPRIT Grant RP210043).

Keywords: Prostate cancer, hormone therapy, GMC1, *In silico*, *In vitro.*

Poster 17

Screening of FGF12 Ligands for Modulation of Nav1.2 Activity

Jamison DA, Baumgartner TB, Goode N, Singh AK, Laezza F

Department of Pharmacology & Toxicology, University of Texas Medical Branch

Corresponding Author: Dr. Fernanda Laezza, Department of Pharmacology & Toxicology, University of Texas Medical Branch, 301 University Blvd. Galveston, TX, E-mail: felaezza@utmb.edu

Background: Voltage-gated sodium (Na_vs) channels play a critical role in action potential initiation and propagation. Structurally, the Na_v channel features a pore-forming α subunit, of which nine isoforms have been described ($Na_v1.1$-$Na_v1.9$), that is tightly regulated through protein:protein interactions (PPI) with auxiliary proteins. One of the alpha subunits, $Na_v1.2$, is of particular interest. $Na_v1.2$'s PPI with its auxiliary protein fibroblast growth factor 12 (FGF12), part of the intracellular fibroblast growth factor family (FGF11-14), occurs through interactions at its C-terminal domain (CTD). Specifically, FGF12 has been shown to interact with $Na_v1.2$ to increase its fast inactivation kinetics and slow its recovery from fast inactivation. Notably, co-expression of FGF12 and $Na_v1.2$ is enriched in the cerebral cortex, suggesting that FGF12:$Na_v1.2$ interaction is a potential determinant of activity in this region. Various mutations in FGF12 have been implicated in either gain-of-function (GOF) or loss-of-function (LOF) regulatory effects on $Na_v1.2$ channel activity. Compounds that can modulate the interaction of FGF12 with $Na_v1.2$ could be therapeutically valuable for autism spectrum disorder (ASD) and developmental and epileptic encephalopathy (DEE), two diseases affected by FGF12 mutations and subsequent $Na_v1.2$ channel activity alterations. This evidence suggests that pharmacologically targeting FGF12 represents a promising method of modulating $Na_v1.2$ activity for disorders such as ASD and DEE.

Hypothesis/Goals: The goals of this study are to: i. screen a library of 50 small molecules with ideal drug-like properties against the FGF12:$Na_v1.2$ complex assembly using the split-luciferase complementation assay (LCA) and electrophysiological assays; and ii. generate FGF12 short hairpin RNAs (shRNA) for knockdown in human cortical induced pluripotent stem cells (iPSCs). We hypothesize that pharmacological modulation of the FGF12:Nav1.2 complex will allow for mitigation of disease related phenotypes in FGF12 associated with DEE and ASD.

Methods: Split-luciferase complementation assay (LCA), whole-cell patch clamp electrophysiology, molecular cloning, and neuronal culturing.

Results: Sub-cloning resulted in the successful creation of FGF12 constructs for reconstituting the FGF12:Nav1.2 complex assembly and compound screening using the LCA. The 50 small molecules of interest have been successfully counter screened for cell toxicity and false positive effects on the luciferase reporter. Sequences have been obtained for rodent and human shRNA generation. The sequences will be screened for matching the necessary criteria, and subsequent hits will then be scored based on factors such as GC content and specificity. Successful creation of shRNA will be validated *in vivo* using immunohistochemistry (IHC).

Conclusions: These studies will allow for pharmacological targeting of FGF12 as a novel, promising avenue for potential neurotherapeutics against aberrant $Na_v1.2$ activity in ASD and DEE.

Acknowledgements: We acknowledge our funding sources as follows: UTMB Presidential Scholars Program (DJ); NIH Grant R01MH12435101 (FL), R01ES031823 (FL); U18DA052504 (FL); NIH Grant no. T32AG0679 (TB).

Poster 18

In Vitro Assessment of An Anti-tumor Pharmaceutical loaded Nano-carriers

Kuo C-F, Philips S
Department of Biomedical Engineering, University of Houston

Dr. Sheereen Majd, Department of Biomedical Engineering, University of Houston, 3517 Cullen Blvd, Room 2021, Houston, TX 77204-5060, smajd9@uh.edu

Background: In malignant cells, iron metabolism is re-programmed to augment the iron intake in order to fuel rapid cellular proliferation. The use of iron chelators that can deplete iron from these cells has proven to be a promising strategy in cancer treatment. Di-2-pyridylketone-4-cyclohexyl-4-methyl-3-thiosemicarbazone (DpC), a second-generation thiosemicarbazone based chelator that binds both iron and copper, has been reported as a potent anti-proliferative compound against various types of cancers both *in vitro* and *in vivo*. However, the low hydrophilicity of DpC can limit its bioavailability, potentially reducing its therapeutic effectiveness. This suggests that integrating DpC into a biocompatible carrier, such as a stealth nanoparticle (NP), for its delivery to tumors may provide a better formulation for cancer treatments.

Hypothesis/Goals: The goal of this study is to evaluate the anti-tumor efficacy of DpC-loaded NPs (DpC NPs) *in vitro*.

Methods: DpC was encapsulated inside of PLGA (poly lactic-co-glycolic acid) NPs, which incorporated a single layer of phospholipids on the NP surface, via nanoprecipitation. Characterization of the particles, such as their size, polydispersity index (PDI), and zeta potential were carried out by DLS (dynamic light scattering) and laser Doppler electrophoresis, using a Zetasizer Nano ZS (Malvern Instruments, Malvern, UK). The drug release behavior was evaluated using dialysis at 37 °C. Finally, we applied MTT assay to investigate the *in vitro* cytotoxicity of the DpC NPs on human glioblastoma cells (U87) and human breast cancer cells (MCF7).

Results: In this study, we were able to encapsulate DpC inside of the lipid-coated NPs with an encapsulation efficiency of around 60%, presumably located primarily inside of the PLGA core due to drug and polymer interaction. The DLS results revealed that the particle size, PDI, and zeta potential of the DpC NPs (~126 nm, ~0.12, and ~ -3.62 mV), are not significantly different than the NPs without DpC (~137 nm, ~0.12, and ~ -3.62 mV). This suggests that DpC encapsulation did not alter the physicochemical properties of the particles. DpC release examination indicated that after a 6-hour incubation only ~35% of the DpC released out of the NPs and dialysis membrane, compared to a ~90% release out of the dialysis membrane for the unencapsulated DpC. This percentage difference demonstrates that the PLGA polymer core plus the lipid coating on the particles can support a more sustainable release behavior of the drug. Lastly, the cytotoxicity assessment showed that DpC NPs presented an IC_{50} value of ~30.82 nM and ~17.38 nM towards U87 and MCF7 cells, respectively. This indicates the promising anti-cancer effect of DpC NPs while not triggering the drug metabolism inhibition in the body (<10 μM).

Conclusions: To this end, the encapsulation of the DpC did not influence the particle properties. The DpC NPs exhibited a slower and more sustainable release kinetic, compared to the free form DpC. In addition, DpC NPs showed a promising cytotoxicity towards human glioblastoma and human breast cancer cells. Overall, this study revealed the potential of using nano-carriers to deliver DpC for future cancer treatment.

Acknowledgements: Research supported by the National Science Foundation (DMR-1753328) and Grants to Enhance and Advance Research (GEAR) award from the University of Houston.

Poster 19

IACS-8300 - A Novel DLK Inhibitor For CIPN

Le K[1], Liu G[1], Cross J[1], Ma J[2], Goodwani S[2], Acton PJ[2], Buggia-Prevot V[2], Jamal I[3], Mahant ID[3], Liu Z[1], Mseeh F[1], Roth BL[2], Chakraborty C[2], Wu Q[1], Jiang Y[1], Kavelaars A[3], Heijnen CJ[3], Zebisch M[4], Ray WJ[2], Jones P[1], Soth MJ[1]

1. Institute for Applied Cancer Science, MD Anderson Cancer Center

2. The Neurodegeneration Consortium, MD Anderson Cancer Center

3. Laboratories of Neuroimmunology, Department of Symptom Research, MD Anderson Cancer Center

4. Evotec (UK) Ltd.

Corresponding author: Kang Le, *Institute for Applied Cancer Science*, MD Anderson Cancer Center, 1881 East Road, Houston, TX, E-mail: kle3@mdanderson.org

Background: Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a major unmet medical need in which cancer patients on chemotherapy develop pain and/or loss of sensation in their extremities. Currently there is no effective treatment for prevention or reversal of CIPN.

Hypothesis/Goals: While the exact mechanisms underlying CIPN are debated, it is thought that the active axon degeneration program, which involves activation of the dual leucine zipper kinase (DLK, or MAP3K12), is engaged following chemotherapy and contributes to CIPN.

Methods: Starting from a literature compound designed for a non-CIPN indication, we developed our own DLK inhibitor program. A DLK screening funnel was used to select the inhibitors with best *in vitro* potencies and *in vivo* properties. *In vivo* mouse CNS target engagement of the compounds was measured by reduction of p-c-Jun/c-Jun levels. Neuroprotective efficacy at preventing cisplatin-induced mechanical allodynia was measured with the Von Frey test.

Results: We discovered a series of novel DLK inhibitors, which contain a unique bicyclo[1.1.1]pentyl group. *In vivo* tool IACS-8300 is potent and selective, with excellent in vitro and in vivo properties across species with a predicted human half life of 12 hrs. It showed strong mouse CNS target engagement, and efficacy preventing cisplatin-induced mechanical allodynia and axonal damage *in vivo*, validating the use of DLK inhibitors for the prevention of CIPN.

Conclusions: Inhibitors of DLK protect against axonal degeneration of sensory neurons and prevent the effects of cisplatin in mouse models of CIPN. Tool compound IACS-8300 was used to demonstrate proof-of-concept efficacy in mouse models of CIPN, and served as the foundation for a lead optimization program that advanced to IND-enabling studies.

Acknowledgements: Magnolia NeuroSciences, Magnolia Tejas Corp.

Poster 20

Clinical 3-D PK/PD Correlations of Atorvastatin and Simvastatin in Obese Patients Post-Roux-en-Y Gastric Bypass Surgery

El-Zailik A[1], Liao H[1], Wu L[1], Cheung LK[2], Sherman V[3]
1. Department of Pharmacological and Pharmaceutical Sciences, University of Houston
2. Department of Pharmacy Practice and Clinical Health Sciences, Texas Southern University (Retiree)
3. Department of Surgery, Houston Methodist Hospital

Corresponding author: Diana S-L Chow, Department of Pharmacological and Pharmaceutical Sciences, University of Houston, 4849 Calhoun Rd, Houston, TX, E-mail: phar33@Central.UH.EDU

Background
Roux-en-Y Gastric Bypass (RYGB) surgery is one of the recommended treatments for patients with a body mass index (BMI) ≥ 40 or ≥ 35 with obesity-related disease. The surgery causes changes in the pharmacokinetics (PK) and pharmacodynamic (PD) of statins post-surgery.

Hypothesis/Goals
The purpose of the study is to establish a 3D PK/PD correlation for atorvastatin (ATV) and simvastatin (SMV) in obese patients post-RYGB surgery, which may offer guidance to individualize treatment regimens post-surgery, against the current practices of either entirely discontinuing or continuing with the same regimen of ATV and SMV.

Methods
The study recruited fourteen obese patients [BMI 33-50 Kg/m^2, 34-68 (mean age of 53.21± 9.27) year old, 5 males and 9 females) including five and nine patients on ATV and SMV, respectively. The blood samples were collected, and body weights, and low-density lipoprotein levels (LDL) were monitored at pre-surgery (baseline), and 3, 6 and 12 months (M) post-surgery. Validated LC-MS/MS assay with LLOQ of 0.25 ng/ml was used to quantify the concentrations of ATV and its two active metabolites, 2-hydroxy atorvastatin (2-OH-ATV) and 4-hydroxy atorvastatin (4-OH-ATV), and SMV and its active metabolite simvastatin acid (SMV-A). The 3D PK/PD correlations of % LDL change [(LDL level at post-RYGB surgery time point - baseline LDL)/ baseline LDL] *100, with weight loss outcomes, BMI, and drug exposure were analyzed by using Design Expert 9.

Results
ATV treatment group exhibited a statistically significant linear model of PK/PD correlation ($p<0.05$, % LDL change = -26.92 - 1.77*Total Molar Concentration + 0.51*BMI) that the % LDL changed was affected by both patients' total ATV (with metabolites) molar concentrations and BMI. Meanwhile, for SMV treatment group, a quadratic model (% LDL change = -2944.2 – 8.22* Total Molar Concentration + 180.6*BMI + 0.26* Total Molar Concentration*BMI – 0.01* Total Molar Concentration^2 – 2.77*BMI^2) seemed to be a better fit model. RYGB surgery in ATV receiving patients resulted in an improvement of LDL levels correlating with both higher total molar concentrations of ATV and lower BMI.

Conclusions
The clinical 3D correlations of PK/PD in obese patients post-RYGB surgery are established for both atorvastatin and simvastatin, but in different patterns. These models may provide guidance for individualized dose regimen modifications of atorvastatin and simvastatin post-RYGB surgery, pending further validation. Properly modified regimens post-surgery may offer significant benefits to patients, reducing the recurrence of hyperlipidemia and thus substantial medical costs.

Acknowledgements
Funding sources: Research Centers in Minority Institutions (RCMI), grant number 5G12MD007605-23

Poster 21

E3 Ligase Complex Structure-Based Rational Design Accelerating the Lead Optimization of PROTACs

Lin H[1], Lu D[1], Cheng R[1], Yu X[1], Jin F[1], Ding L[1], Wang J[1,*]
1. Department of Pharmacology and Chemical Biology, Baylor College of Medicine.
Corresponding author: Jin Wang, Department of Pharmacology and Chemical Biology, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX, E-mail: wangj@bcm.edu

Background: Research on proteolysis targeting chimera (PROTAC), the most well-characterized targeted protein degradation strategy hijacking E3 ligases to degrade target protein, has led to insights on its mode of action, target selectivity, PK/PD properties, and therapeutic effects. Although the design of PROTAC molecules seems to be bimodular, the linker also plays a critical role in both the PK and PD properties of PROTACs. However, due to the highly dynamic nature of the complex formed by target protein, PROTAC, E2, E3 ubiquitin ligases, and their auxiliary proteins, very limited structural biology information is available. Therefore, the current lead optimization of PROTACs still largely relies upon empirical adjustment of the linker length and trial-and-error attempts of different linker modules.
Hypothesis/Goals: Here we hypothesize that PROTACs with both enhanced potency and specificity can be designed by incorporating geometry-restricted rigid linkers between two functional modules. This may enforce the PROTAC-induced target protein-E3 ligase complex to adopt a confined conformation enhancing the ubiquitin transfer efficiency.
Methods: Combining biochemical binding and PROTAC-induced degradation assay as well as affinity purification-MS ubiquitin site scanning, we are developing a molecular modeling pipeline using molecular dynamics (MD) simulation to model the entire E3 ligase complex and E2-conjugation enzyme, in order to explain how the PROTAC potency relates to the orientation adopted by the target protein in the E3 complex to the proximity of E2 enzyme primed with ubiquitin.
Results: As a proof of concept, we first built the model of MZ1-induced BRD4(BD2)-VBC-Cullin2 E3 complex structure and performed a 40 ns all-atom MD simulation. The result shows that the N-terminal Lys349 of BRD4 (next to the Ub site Lys346) is able to move to a position in proximity of the E2~Ubiquitin active site (within 25 Å). Using RIPK1 as the model target protein, we subsequently developed a series of RIPK1 PROTACs with flexible or rigid linkers. As expected, different linker designs will lead to alternative ubiquitination patterns on RIPK1. Further modeling of flexible linker PROTAC reveals a large conformational space of PROTAC-RIPK1 loaded onto the E3 complex, within which some of these potential Ub site lysines are already in great proximity to the E2 active site. On the contrary, the rigid linker PROTAC with good potency has relatively confined conformational space and the Ub site is primed on the E2 active site for ubiquitin transfer. Surprisingly, we discovered that serine, in addition to lysine, can also function as a potential PROTAC-induced Ub site and contributing to target protein degradation.
Conclusions: This research studied how different linker designs of PROTAC would impact their degradation potencies and provided potential explanations through in-silico modeling of ubiquitin transfer.
Acknowledgments: The research was supported in part by National Institute of Health (R01-CA250503 to J.W.), Cancer Prevention and Research Institute of Texas (CPRIT RP220480), Texas Advanced Computing Center (TACC-CHE21040), and the Michael E. DeBakey, M.D., Professorship in Pharmacology (to J.W.).

Poster 7

Evaluation of Combination Therapy of Paclitaxel and Cyclopamine for the Treatment of Hepatocellular Carcinoma (HCC)

Lu. D[1], Hsiao C-H[1], Li C[2], Chow D S-L[1]

1. Department of Pharmacological and Pharmaceutical Sciences, University of Houston
2. Department of Cancer Systems Imaging, University of Texas MD Anderson Cancer Center.

Corresponding author: Diana. S.-L. Chow, Department of Pharmacological and Pharmaceutical Sciences, University of Houston, 4329 Martin Luther King Blvd, Houston, Texas, E-mail: dchow@uh.edu

Background: Hepatocellular carcinoma (HCC) is the most common form of liver cancer. However, long-term survival of HCC patients is hindered by high recurrence and drug resistance. To overcome drug resistance in HCC, two drugs instead of one can be a feasible option.

Hypothesis/Goals: A sonic hedgehog inhibitor, cyclopamine (CPA) was combined with paclitaxel (PTX), a mitosis inhibitor with antineoplastic effects. The combination of CPA and PTX may be more effective than a single agent in treating HCC. This project aims to 1) optimize combination strategy of CPA and PTX against HCC. 2) predict the potential of drug-drug interaction (DDI) of CPA and PTX *in vivo*.

Methods: *In vitro* study, HCC cells were seeded in 96 well plates. PTX (1-500 nM) and CPA (5-12.5 μM) were added in quadruplicates for 72h. CalcuSyn Biosoft software calculated combination index (CI) was to determine the effect of combination. CI < 1, CI = 1 and CI > 1 indicate synergistic, additive, and antagonistic effects, respectively. *In vivo* study, Healthy Sprague Dawley rats were intravenously injected CPA or/and PTX with the same dosage of 1 mg/kg. The PTX and CPA concentrations in samples were measured using a validated LC-MS/MS assay with LLOQ of 0.5 ng/mL in biomatrices. Phoenix WinNonlin® v8.0 was used to develop PK models and derive PK parameters.

Results: Our preliminary data of *in vitro* study suggested that CPA combination with PTX had yielded a synergistic anticancer effect in Hep3B cells compared to the mono-treatment. CIs were less than 1 when PTX/CPA ratios were less than or equal to 1/250, indicating a synergistic impact. CIs were below 1 in additional studies involving PTX concentrations ranging from 10 to 100 nM. PK studies were performed to understand the fates of CPA and PTX within body and to design future doses. PK profiles of CPA and PTX showed two-compartment PK. The PK parameters of CPA and PTX in blood and plasma samples were calculated based on two-compartment analysis. There is no significant difference on PK parameters or concentrations of CPA in the presence or absence of PTX. However, PTX combination treatment resulted in lower V_1, and CL_1, but higher C_{max} of PTX in both blood and plasma than with PTX alone treatment. According to results from the 2-compartment model, PTX combination treatment maintained over 10 nM for 22.94 hours, longer than that with PTX alone treatment group (16.55 hours) in blood.

Conclusion: The selection of optimal concentration ratio of CPA to PTX is crucial for the combination treatment. According to the data of synergistic study of the two drugs, PTX (10 nM -100 nM) combined with CPA (> 5 μM) can be used for further efficacy study. This PK study revealed, for the first time, a potential DDI happens between CPA and PTX. In addition, CPA concentrations were below therapeutic concentrations after IV injection of 1 mg/kg dose. Dose adjustment is needed for achieving the synergistic effect in future preclinical efficacy studies.

Acknowledgements: Funding source: Gillson Longenbaugh Foundation

Poster 22

Discovery of Balanced and Novel G Protein Biased Agonists for the Orphan Receptor GPR52

Murphy RE[1,2], Felsing DE[1,2], Wang P[2], Chen H[2], Zhou J[2], Allen JA[1,2]

1. Center for Addiction Research, University of Texas Medical Branch, Galveston, TX
2. Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX

Corresponding author: John A. Allen, Ph.D., Department of Pharmacology and Toxicology, 301 University Blvd., University of Texas Medical Branch, Galveston, TX, Email: joaallen@utmb.edu

Background: GPR52 is a class A orphan G protein-coupled receptor that activates the G_s/cAMP signaling pathway and is primarily co-expressed in the human striatum with the dopamine D2 receptor. The unique expression profile of GPR52 has distinguished this orphan receptor as a promising drug target for psychiatric disorders including schizophrenia, motor dyskinesias, and substance use disorders. We recently synthesized and pharmacologically evaluated a series of novel indoline-carboxamide based GPR52 agonists in which the lead compound shows antipsychotic-like activity to inhibit amphetamine-induced hyperlocomotion in mice (Wang, Felsing et al *J. Med. Chem.* 2020 Nov 25;63(22):13951-13972). **Goal:** Here, we describe the evaluation of a new series of novel aniline-carboxamide GPR52 agonists with G protein-biased activity relative to the parent indoline-carboxamide compound. **Results:** In a HEK293 cell-based cAMP assay, we observed substantial increases in efficacy (>200%) over the parent compound with the opening of the indoline ring. Substitutions around the aniline and lower aromatic moieties are amenable to medicinal chemistry and modulate both potency and efficacy. We then tested a selection of the most potent compounds (EC50: ~30-200 nM) in a cell-based β-arrestin TANGO recruitment assay. The opening of the indoline ring in the parent compound yields over 20-fold decrease in potency for β-arrestin activation, with further modulation of potency resulting from modifications to the aniline and lower aromatic moieties. These G protein-biased agonists induce less GPR52 desensitization for cAMP signaling when compared to the parent compound and balanced agonists. To identify variations in binding modes that might confer bias for G protein signaling, we docked both the parent compound and a highly G protein-biased compound into the recently discovered GPR52 crystal structure. The compounds display a conserved position within the binding pocket with no obvious alterations to the protein-ligand interactions to explain any differences in functional selectivity. GPR52 has been suggested to be self-activating through its extracellular loop 2 domain (ECL2). The binding mode of our agonists supports an allosteric mode of action, potentiating the activity induced by ECL2 interactions with the typical class-A GPCR orthosteric pocket. To assess the necessity of the ECL2 interaction for agonist activity, we generated a mutated GPR52 in which the agonist-like motif of the ECL2 was replaced with an equivalent span of alanine residues. In our cell-based cAMP assay, this mutant GPR52 greatly reduces constitutive signaling of the receptor and eliminates agonist response entirely. **Conclusions:** Together, our studies have resulted in novel GPR52 agonists with optimized potency and efficacy, demonstrated potential for optimization of functional selectivity for G protein signaling, and supplied evidence of GPR52 self-activation and an allosteric mechanism of action for these novel GPR52 agonists. These novel ligands also provide important tools to further evaluate the efficacy of GPR52 activation in both health and disease.

Acknowledgements: The UTMB Center for Addiction Research and NIDA 1U18DA052543-01 (JAA).

Poster 23

Design and Synthesis of Novel Menin PROTACs for Pediatric Leukemia

Nieves-Merced K[1], Jiang D[2], Hart MJ[2], McHardy SF[1]

1. Center for Innovative Drug Discovery, Medicinal Chemistry Core Facility, Department of Chemistry, University of Texas at San Antonio
2. Center for Innovative Drug Discovery, High-throughput Screening Core Facility, Department of Chemistry, University of Texas at San Antonio

Corresponding author: Stanton F. McHardy, Department of Chemistry, University of Texas San Antonio, 1 UTSA Circle, San Antonio, Texas, E-mail: stanton.mchardy@utsa.edu

Background
Mixed lineage leukemia is a very aggressive blood cancer that predominantly occurs in pediatric patients and is characterized by the presence of MLL fusion proteins that are the result of chromosomal translocations affecting the *MLL* gene at 11q23. A critical component of MLL-fusion protein complex is a protein called Menin. Numerous studies have demonstrated a critical role of Menin as an oncogenic cofactor in leukemic transformations mediated by MLL fusion proteins. MI-503 is a small molecule inhibitor that binds to Menin and inhibits its interaction with MLL-fusion proteins. MI-503 has been shown to be effective in mouse models of MLL leukemias. PROTACs or proteolysis targeting chimeras are compounds that target proteins for degradation by hijacking the activity of E3 ubiquitin ligases to promote degradation. PROTACs are particularly effective in cancers of the circulatory system and have the advantage over traditional therapeutics in that permanent occupancy of the targeted protein is not necessary as the PROTAC uses the *in vivo* degradation machinery to catalytically degrade proteins of interest.

Hypothesis/goals
Our hypothesis is that the development of PROTACs targeting fusion proteins produced as a result of chromosomal rearrangements in pediatric tissues or their interacting proteins will provide compounds that can directly address the critical mutated proteins that drive the etiology of certain pediatric cancers and thus provide novel therapeutics for the treatment of pediatric cancers. Our goal is to identify linkers and E3 recruiting elements and develop medicinal chemistry approaches to develop PROTACS using the MI-503 small molecule.

Methods
We will build a library of small molecules that bind E3-ligases known to work in the PROTAC paradigm. In addition, we will acquire linkers of varying chemical properties, length and flexibility. Medicinal chemistry approaches for generating linker-E3 binding small molecules will be defined and pursued. Our first candidate “war head” for developing a functional PROTAC will be MI-503.

Results
We have successfully synthesized two novel PROTACs, CIDD-0160855 and CIDD-0160908, through a 25-26 steps synthesis. Both PROTACs were reacted under “Click” chemistry conditions with an azide that possess glycol linkers to the E3 ligands and tested for Menin binding.

Conclusions
Binding of our novel PROTACs to the target Menin was confirmed and a protein degradation assay is ongoing.

Acknowledgements
Funding: NIH Grant 5UL1TR002645-04

Poster 24

Therapeutic Implications of Riluzole in Patients with Spinal Cord Injury

Nguyen A[1], Park J[1], Wu L[1], Toups E[2], Harrop J[3], Smith K[4], Guest J[5], Fehling M[6], Grossman RG[2], Chow DS-L[1]

1. Department of Pharmacological and Pharmaceutical Sciences, University of Houston
2. Department of Neurosurgery, Houston Methodist Neurological Institute, Houston, TX
3. Department of Neurosurgery, Thomas Jefferson University, Philadelphia, PA
4. Department of Neurosurgery, Health Science Center, University of Texas, Houston, TX
5. Department of Neurological Surgery, Miller School of Medicine, University of Miami, Miami, FL; Division of Neurosurgery and Spine Program, Toronto Western Hospital, University of, Toronto, Ontario, Canada.

Junghwa Park, Department of Pharmacological and Pharmaceutical Sciences, University of Houston, 4349 Martin Luther King Boulevard, Houston, TX 77204, E-mail: jpark35@central.uh.edu

Background: Spinal Cord Injury (SCI) is a devastating acute neurodegenerative condition. Pharmacological treatments so far offer minimal improvements in neurological and functional outcomes. Riluzole is indicated for the treatment of Amyotrophic Lateral Sclerosis (ALS), a progressive neurodegenerative disease, with extended survival time of 60 to 90 days, due to its neuroprotective activity.

Hypothesis/Goals: In this study, we evaluated the potential neural benefit of riluzole in patients with SCI by assessing the temporal improvements in motor outcomes.

Methods: Patient data were collected from the Riluzole in Acute Spinal Cord Injury Study (RISCIS), a multi-center, randomized, placebo controlled, double-blinded, phase 2/3 clinical trial. Patients in the treatment group received a 100 mg of riluzole twice on day 1 as a loading dose, then 50 mg of riluzole twice daily for the rest of 13 days as a maintenance dose. Their plasma samples were drawn at 3 hours post dose and before the next dose, on days 3, 7, 10 and 14. Plasma samples were quantified using, validated LC-MS/MS assay with LLOQ of 800 ng/ml. PK analysis was performed using, Phoenix NLME version 8.2. To examine therapeutic outcomes of riluzole, changes in Total Motor Score (TMS) were measured by International Standards for Neurological Classification of Spinal Cord Injury Examination (ISNCSCI) between baseline, 3 months and 6 months. Then, the different changes in TMS were evaluated. Correlations between 6 month TMS vs $AUC_{D0\text{-}D14}$ and baseline TMS were also evaluated by 3 dimensional surface response methodology using Design Expert, version 9. Between-group differences in TMS were analyzed by unpaired t-test.

Results: Twenty-nine SCI patients were enrolled (N=18 in placebo and N=11 in treatment groups), mean changes in TMS within 6 months was 35.63 with riluzole treatment and 20.80 with placebo. Most patients in both groups exhibited increases of TMS, characterized by natural recovery after spinal cord injury. However, it is noteworthy that 5 out of 8 subjects (62.5%) in the treatment group showed increases of more than 30 points of TMS while only 2 out of 10 subjects (20%) in the placebo group within 6-month period. Although our p-values were not desirable due to small sample size and two outliers in the placebo group, it is remarkable that the TMS increase in the treatment group display clinically significant improvements over the 6- month period. 3-dimensional response surface was derived to correlate the temporal recovery of motor functions and riluzole exposure. TMS at 6 months were significantly correlated with the baseline TMS and $AUC_{D0\text{-}D14}$ of riluzole, with P-value of 0.03.

Conclusions: Our study shows that riluzole may exert therapeutic effects on motor functions in SCI patients. TMS improvements were apparently greater with riluzole compared to placebo. This longitudinal neurological recovery was significantly correlated with the exposure to riluzole for 14-day treatment.

Acknowledgements: US ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY, Contract No. W81XWH-16-C-0031

Poster 25

The Effect of Gastric Acid Secretion Blockade on the Oral Bioavailability of OJT007

Rincon Nigro ME, Ma J, Kaur M, Xie H, Olaleye OA, Liang D
Department of Pharmaceutical Science, Texas Southern University

Background. OJT007, a methionine aminopeptidase 1 (MetAP1) inhibitor, is a novel class of drug with potent antiproliferative effects against *Leishmania Major*. Previous studies from our group, have determined that OJT007 has a low oral bioavailability due to presystemic metabolism. Moreover, orally administered drugs encounter through the gastrointestinal (GI) tract a varied pH environment. For drugs with pH dependent stability, the varied pH conditions through the gastrointestinal tract may reduce oral bioavailability.

Hypothesis/Goals. We hypothesize that drug degradation under acidic conditions may contribute towards OJT007 low oral bioavailability. Thus, the purpose of this study was to determine the effect of acid stability on the oral bioavailability of OJT007 both *in vitro* and *in vivo*.

Methods We evaluated *in vitro* the stability of OJT007 in various buffers (pH 1.2-10). The buffers were spiked with OJT007 (10 ug/mL) and incubated at 37ºC for 24 hours. Aliquots were taken at predetermined time points up to 24 hours. The collected samples were analyzed by UPLC. We further validated the in vitro findings by evaluating the effect of controlled gastric conditions in rats. The proton pump inhibitor rabeprazole (Rbz) was used to increase gastric pH in the stomach. Crossover study design was used. OJT007 (25 mg/Kg) was administered orally, and blood samples were collected from rats via jugular vein before administration of OJT007 and at predetermine time points. Following a week washout period, rbz (10 mg/Kg) was administered intravenously 30 minutes before oral administration of OJT007 (25 mg/Kg) and blood samples were collected at predetermined time points.

Results The *in vitro* degradation was rapid at pH 1.2-3, and by 0.5 hours 50% or less remained of the drug. There is a clear relation between pH and drug stability: the lower the pH, the higher the degradation. These results suggest that OJT007 is likely to be unstable on stomach pH and special formulation considerations must be accounted. Thirty minutes after Rbz administration, stomach pH increased to 6.5. Table 1 summarizes the PK parameters obtained from the crossover study.

Table 1. PK Parameters for OJT007 With and Without Rabeprazole (Mean ± SD)

PK Parameter	OJT007	OJT007+Rab
$T_{1/2}$ (hr)	2.06±0.27	2.34±0.55
C_{max} (ng/mL)	461±144	208±75.3
T_{max}(hr)	3.5±1.91	2.13±0.63
Vz/F(L/Kg)	12.5±3.89	31.1±19.1
Cl/F (L/hr/Kg)	4.17±0.92	8.61±3.58
AUC $_{0-\infty}$ (hr*ng/ml)	2255±578	936±354
MRT(hr)	4.9±0.85	4.30±0.45

Contrary to our hypothesis, following pretreatment with rabeprazole, statistically significant reductions in C_{max} ($P = 0.022$) and $AUC_{0-\infty}$ ($P = 0.011$) of approximately 40% were observed compared to OJT007 alone. High gastric pH has been shown to significantly decrease the absorption of basic drugs which have low solubility at high pH.

Conclusion OJT007 exhibited poor stability at acidic pH. We hypothesize that this is caused due to OJT007 being a Schiff base. OJT007 contains an imine functional group that could be prone to acid-catalyzed hydrolysis. Nonetheless, increasing gastric pH did not increase exposure possibly due to low solubility of OJT007 at high gastric pH. Further studies are required to elucidate what mechanism drives the decreased exposure. In summary, low oral bioavailability for OJT007 is not significantly due to acid degradation but due to low solubility. (Supported in part by CPRIT fund RP180748 and NIH fund U54MD007605)

Poster 26

Novel Adult Brain Processing Method Reveals Age-, Sex-, and Species-dependent Effects of Pharmaceutical Compounds on Neuron Survival and Neuritogenesis

Sefiani A[1], Geoffroy CG[1]*
1. Department of Neuroscience and Experimental Therapeutics, College of Medicine, Texas A&M University, Bryan, TX 77807, USA

*Corresponding author: Cédric G. Geoffroy
Department of Neuroscience and Experimental Therapeutics, College of Medicine, Texas A&M University, Bryan, TX 77807
E-mail: geoffroy@tamu.edu

Background: Neurodegenerative diseases and neurotraumatic injuries are typically age-associated disorders that can reduce neuron survival, axon and neurite outgrowth, and synaptic plasticity leading to loss of cognitive capacity, executive function, and motor control. In pursuit of reducing the loss of said neurological functions, novel compounds must be identified that augment neuron survival, axon regeneration/neuritogenesis, and synaptic plasticity. However effective high-throughput *in-vitro* screenings are at finding compounds, most screens use iPSC derived, embryonic, or post-natal neurons. This is a major issue as they are likely to have different characteristics than the targeted neurons in clinical settings. Indeed, the majority of the patients suffering from neurodegenerative diseases and neurotrauma are of middle-age and older. This dichotomy in age between the neurons used in drug screens and patients certainly impedes chances of translational success. It has been historically challenging to culture adult neurons let alone conduct screenings; therefore, age-appropriate drug screenings have previously not been plausible.

Hypothesis/Goals: We aim to discover novel pharmaceutical agents that can treat neurodegenerative diseases and neurotrauma.

Methods: We have developed a novel adult neuron processing method and created the first high content morphology-based screening system using age-appropriate adult cortical neurons. This novel method allows for rapid and economical mass processing of large mammalian brains to maximize neuron survival for increased screening capacity.

Results: After conducting targeted screens utilizing cortical neurons from 2-3-year-old sheep (equating to humans in their 20s), and mice of all ages, we have discovered age-, sex-, and species-dependent effects of compounds on neuritogenesis and neuron survival.

Conclusions: Our discovery pipeline is expected to 1) prevent the premature dismissal of compounds with no effect in iPSC/embryonic screens yet which would be advantageous to adults, 2) reduce the false positivity rate by efficiency vetting compounds with no benefit to adults neurons, and 3) provide quick multi-species validation to better predict success in clinical settings. Therefore, utilizing age-, sex-, and species-appropriate *in-vitro* models to find novel compounds increasing neuron survival and neurite outgrowth, made possible by our novel neuron processing method, will greatly increase the probability of translational success.

Acknowledgements: Texas A&M Start-up fund used for all experiments and development.

Poster 27

Impact of Host Physiological and Pathological Conditions on the Activity of Gut Microbial Beta-glucuronidases Towards Hydrolysis of Baicalin

Siddiqui NS, Ting DU, Xie HU, Liang DO, Gao SO*

Department of Pharmaceutical Science, College of Pharmacy and Health Sciences, Texas Southern University, 3100 Cleburne Street, Houston TX 77004.

*Corresponding author Dr. Song Gao [Tel: +713-313-7526; Fax: +713-313-1091. E-mail: song.gao@tsu.edu]

Purpose: The purpose of this paper is to determine the impact of host physiological and pathological conditions on the activity of gut microbial beta-glucuronidases towards hydrolysis of flavonoid-glucuronides.

Methods: Fecal S9 fractions were prepared using feces collected from different types of rats at different ages with different genders. Baicalin, wogonoside, and luteolin-glucuronide were used as the substrates. A waters acquity performance liquid chromatography (UPLC) system was used to quantify the metabolite baicalein to analyze the rate of the reaction of the enzymes. The rates were compared by obtaining enzymes through S9 fractions to confirm microbiota ability to hydrolyze the glucuronide and release of the parent compound, baicalein. Fecal S9 prepared from The Fischer 344 (F344) rats at three different ages (i.e., 5, 9, and 16 weeks) and different inflammatory conditions treated with Docusate Sodium (DSS) or anti-inflammatory agent herbal mixture Xiao-Chai-Hu Tang (XCHT). Additionally, fecal S9 from genetically modified pirc rats, which spontaneously have inflammation in the colon, was also tested.

Results: The results depicted that age had an impact on hydrolysis of the compound baicalin into its parent compound and this method was best suited to determine the rate of hydrolysis. The $p<0.05$ making the results statistically significant. The wild type enzymes had a clear increase in Km and Vmax. While PRIC enzymes and enzymes treated with DSS and XCHT had a clear difference in rates, but the Km and Vmax did not increase significantly.

Conclusion: The data shows that microbial GUS activity was higher at elder age. Fecal S9 from Pirc rats has lower activity and anti-inflammatory agent XCHT can increase microbial GUS activity.

Acknowledgements: Dr. Gao, Dr.Ting and Imoh

Funding Source: NIH grant funding for a Center for Biomedical and Minority Health Research

Poster 28

FGF13 Ligand Prevents Mechanical Hypersensitivity and Nociceptive Behavior by Selectively Blocking Hyperactive Nav1.7 Channels

Singh AK[1], Dvorak NM[1], Di Re J[1], Bernabucci M[1], Folorunso O[1], Tapia CM[1], Wang P[1], Chen H[1], Hankerd K[2], Wang J[2], Kadakia F[3], Wadsworth PA[1], Grace PM[4], Davidson S[3], Rajarathnam K[5], Zhou J[1], La J[2], Chung J[2], Green D[2], Yuan S[2], Laezza F[1,2,5*]

1. Department of Pharmacology and Toxicology
2. Department of Neuroscience and Cell Biology, The University of Texas Medical Branch, Galveston, Texas, USA
3. Department of Anesthesiology, University of Cincinnati, College of medicine, Cincinnati, OH, USA
4. Department of Symptom Research, University of Texas MD Anderson Cancer Center, Houston Texas, USA
5. Department of Biochemistry and Molecular Biology, The University of Texas Medical Branch, Galveston, Texas, USA

Corresponding Author: Dr. Fernanda Laezza, Department of Pharmacology & Toxicology, University of Texas Medical Branch, 301 University Blvd. Galveston, TX, E-mail: felaezza@utmb.edu

Background: The voltage-gated Na^+ (Nav) channel Nav1.7 is a molecular determinant of action potential firing of dorsal root ganglia (DRG) sensory neurons. Despite the canonical role of the pore-forming α subunit in conferring this function, protein:protein interactions (PPI) between the α subunit and its auxiliary proteins are necessary for the full physiological function of the Nav1.7 channel. Among such auxiliary proteins, fibroblast growth factor 13 (FGF13) is of particular prominence, and its PPI with the C-terminal domain of the Nav1.7 channel regulates conversion of noxious stimuli into persistent DRG firing and consequently pain sensation. Crucially, in response to painful stimuli, there is an increase in FGF13 expression and a corresponding increase in transient Na^+ current (I_{Na}) and excitability of DRG neurons, which collectively contribute to inflammatory pain. As these electrophysiological and behavioral responses are attenuated by genetic deletion of FGF13 and resultant reductions in FGF13:Na_v1.7 complex assembly, targeting the PPI could represent a novel therapeutic strategy for pain management.

Hypothesis/Goals: We hypothesize that pharmacological inhibition of FGF13:Na_v1.7 complex assembly will reverse the potentiated activity of DRG sensory neurons induced by noxious stimuli and mitigate inflammatory pain.

Results: Firstly, we employ a peptidomimetic derived from the PLEV motif of the β12 sheet of FGF13 (PW164) and show that the ligand inhibits FGF13:Nav1.7 complex assembly. Functionally, PW164 prevents FGF13-mediated potentiation of Nav1.7 currents, reduces channel availability in heterologous cells and human DRG neurons, and suppresses firing in donor-derived DRG neurons. In preclinical pain models associated with hyperactivity of Nav1.7 channels, intradermal injection of PW164 prevents capsaicin-induced mechanical hypersensitivity at the level of single afferent fibers and nociceptive behavior without affecting normal mechanosensitivity and, furthermore, reduces postoperative mechanical hypersensitivity. Secondly, we employ a peptidomimetic derived from FLPK motif of the β12 sheet of FGF13 (ZL192). Whereas PW164 reverses the potentiated Nav1.7-mediated I_{Na} induced by noxious stimuli, ZL192 augments Na_v1.7-mediated I_{Na}, suggesting that FGF13 is able to bidirectionally control electrophysiological responses to painful stimuli.

Conclusions: These studies demonstrate that pharmacological manipulation of the FGF13:Nav1.7 complex confers selective anti-hyperalgesic effects by acting exclusively on hyperactive Nav1.7 channels associated with nociception without compromising normal sensory function. In addition to providing novel probes to guide drug discovery efforts for pain management, these studies demonstrate that PPI interfaces between Nav channels and their auxiliary proteins represent druggable surfaces that could be pharmacologically targeted for a broad range of clinical indications.

Acknowledgments: We acknowledge our funding sources as follows: NIH Grant R01MH095995 (FL), R01MH12435101 (FL) NIH Grant R01MH111107 (FL, JZ), John Sealy Memorial Endowment Funds (FL), R01

DA038446 (JZ), P30 DA028821 (JZ), CPRIT RP150578 (CS), PhRMA Foundation (PAW), and HAMBP training grant no. T32GM008280 (NMD).

Poster 29

The GCC CPRIT Center for Advanced Microscopy and Image Informatics

Singh PK[1], Bolt MJ[1], Stossi F[2], Davies PJ[1], Mancini MA[1, 2]
1. Texas A&M Health Science Center, Institute of Biosciences and Technology, Houston, TX
2. Baylor College of Medicine, Houston, TX

Corresponding author: Michael A. Mancini[1, 2] ; Email : mancini@bcm.edu

The Center for Advanced Microscopy and Image Informatics (CAMII) is a multi-institutional, multi-disciplinary core facility designed to meet the need of GCC investigators for access to customized, project-driven, quantitative imaging-based solutions that can be applied to important questions in both basic and translational cancer research. In partnership with the GCC drug discovery CFSA (core facility) programs, CAMII serves as a component in a drug discovery pipeline that supports the movement of promising lead drugs and antibodies from *in vitro* testing to *in vivo* validation and pre-clinical development.

The Center has assembled a multi-disciplinary team of experts in imaging and image informatics to operate an imaging core facility equipped with specialized imaging technologies and the expertise in light, super-resolution, live cell microscopy, and quantitative and multi-dimensional image informatics and biostatistics. The center has expertise in 3D image analysis, single cell analytics, live cell tracking, spatial organization of TME (tumor micro-environment), and other image-based analysis using traditional algorithms and machine/deep learning techniques.

CAMII is committed to having a transformative impact on cancer research in Texas. By promoting highly collaborative and productive partnerships between experts in advanced imaging research and investigators pursuing critical questions in cancer research, CAMII will continue to contribute to CPRIT's goal of supporting innovation in cancer research and promoting breakthroughs in the search for prevention of and cures for cancer. Projects that have been approved following the CAMII project review process receives a highly subsidized rate.

Funding Agency: CPRIT (RP170719)

Development of a Novel Combination Therapy Targeting MET and LGR5 to Overcome Resistance in Colorectal Cancer

Subramanian S, Posey T, Jacob J, Carmon KS

1. Center for Translational Cancer Research, Brown Foundation Institute of Molecular Medicine, University of Texas Health Science Center, Houston, TX, USA
2. University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, Houston, TX, USA

Corresponding author: Shraddha Subramanian, Center for Translational Cancer Research, Brown Foundation Institute of Molecular Medicine, University of Texas Health Science Center, 1825 Pressler Street, Houston, TX, Email: Shraddha.Subramanian@uth.tmc.edu

Background

The chief culprits behind colorectal tumor relapse are cancer stem cells (CSCs). CSCs promote tumor progression and clonal heterogeneity owing to their self-renewability, plasticity, and differentiation capacity. Upon therapy termination, CSCs can exit dormancy and circulate to secondary sites where they spawn metastases leading to disease-induced mortality. The mystifying properties of CSCs makes them a promising therapeutic target. Leucine rich repeat-containing G protein-coupled receptor 5 (LGR5) is highly expressed in CRC and is bona fide marker of functional CSCs. $LGR5^+$ CSCs are often responsible for tumor initiation and metastatic outgrowth, however their conversion into a chemo-resistant $LGR5^-$ state is vital for metastatic dissemination. Our group and others showed LGR5-targeted therapy resulted in tumor regression, yet $LGR5^-$ tumors eventually relapsed due to plasticity. Therefore, to successfully eliminate CRC tumors it is important to identify molecular mechanisms that are upregulated with loss of LGR5. We demonstrated that both shRNA-mediated knockdown and CRISPR-induced knockout of LGR5 enhanced chemoresistance in multiple CRC cell lines. Follow-up studies suggest that $LGR5^-$ CRC cells, at least in part, rely on the MET/STAT3 pathway to evade therapy. MET is a well-characterized oncogene upregulated and associated with poor prognosis in may solid tumor types, including CRC.

Hypothesis

For this project, we are generating MET-targeted antibody-drug conjugates (ADCs), which will act as guided missiles to deliver cytotoxic agents to CRC cells expressing high levels of MET, including therapy-resistant $LGR5^-$ CRC cells.

Methods

We have cloned and are producing MET monoclonal antibodies (mAbs) for characterization of binding and internalization in vitro. Secondary ADCs will be used in a cell-based cytotoxic assay to pre-screen the efficacy of MET mAbs against a panel of CRC cell lines to identify an optimal payload for ADC development.

Conclusions

Our ultimate goal is to determine if MET- and LGR5-targeted ADCs in combination are more effective than an ADC monotherapy for destroying both $LGR5^+$ CSCs and $LGR5^-$ CRC cells. This proposed dual-targeting therapeutic strategy has the potential to overcome resistance due to plasticity and improve treatment efficacy and survival.

Acknowledgements

This work is supported by funding from the National Institutes of Health (NCI R01 CA226894) to Carmon KS and a fellowship of the Gulf Coast Consortia, on the Training Interdisciplinary Pharmacology Scientists program (T32 GM139801) to Jacob J.

Poster 31

Design, Synthesis and Structure-Activity Relationship of CNS Penetrant Small Molecule ER-Beta Agonists for Glioblastoma (GBM) Therapies

Tidwell MW[1], McHardy SF[1], Wang L[1], Nieves-Merced K[1], Brenner A[2], Vadlamudi R[2], Pratap U[2], Viswanadhapalli S[2]

1. Center for Innovative Drug Discovery, University of Texas at San Antonio
2. Mays Cancer Center, UT Health San Antonio

Corresponding author: McHardy SF, Center for Innovative Drug Discovery, University of Texas at San Antonio, One UTSA Circle, San Antonio, Texas, Stanton.McHardy@utsa.edu

Although the incidence of glioblastoma (GBM) in the United States is only 4.7 per 100,000, the devastating nature of this disease cannot be overstated with 5-year prognosis approaching 5%. There are no agents with proven survival benefit in the recurrent setting with anti-angiogenic or further alkylating therapy often chosen in the absence of better drugs. At issue remains the selective permeability of the blood brain barrier (BBB) to pharmaceutical intervention, the heterogeneous and immunosuppressive nature of the glioma microenvironment, and the associated morbidity of tumors with central nervous system (CNS) involvement. Our team's preliminary studies suggested that GBM selectively express estrogen receptor beta (ER-β) and demonstrated that ERβ agonists exert tumor suppressive functions in GBM. Our results also demonstrated that ERβ knockout increases GBM GSC representation whereas overexpression results in loss of GSCs. Thus, the goal of this highly collaborative and multi-disciplinary program is to develop novel, potent, and CNS penetrant ER-β agonist with therapeutic potential and thus create a new paradigm of using ER-β specific agonist as novel therapy for curbing GBM progression. This poster will focus on the development of structurally-novel ER-β specific agonists to support translational studies and advance the program toward a viable clinical candidate. The seminar will focus on the design, synthesis and iterative structure-activity relationship (SAR) studies to improve the ER-β potency and physicochemical properties of lead compounds. In vivo efficacy in GBM models and pharmacokinetic profiles of two lead compounds, CIDD-0149897 and CIDD-0150184, will also be presented.

Acknowledgements

Support from CPRIT Grant RP160844 is gratefully acknowledged.

Poster 32

Novel Mitochondria-Targeting Compounds Selectively Kill Human Leukemia Cells

Panina SB*[1], Pei J*[1], Baran N*[2], Tjahjono E[1], Patel S[2], Alatrash G[3], Konoplev SN[4], Stolbov LA[5], Poroikov VV[5], Konopleva M[2], Kirienko NV[1]

1. Department of BioSciences, Rice University
2. Department of Leukemia, The University of Texas MD Anderson Cancer Center
3. Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center
4. Department of Hematopathology, The University of Texas MD Anderson Cancer Center
5. Institute of Biomedical Chemistry, Moscow, Russia

Corresponding author: Natalia V. Kirienko, Department of BioSciences, Rice University, 6100 Main Street, Houston, TX, E-mail: kirienko@rice.edu

Background
Acute myeloid leukemia (AML) is a heterogeneous group of aggressive hematological malignancies commonly associated with treatment resistance, high risk of relapse, and mitochondrial dysregulation. We previously identified eight mitochondria-affecting compounds (PS compounds) that triggered events associated with mitophagy in *Caenorhabditis elegans*.

Hypothesis/Goals
We hypothesized that treatment of leukemia cells with these PS compounds would lead to similar outcomes for their mitochondria, triggering selective cell death in AML cells due to their sensitivity to mitochondrial damage.

Methods
We performed cytotoxicity assays, mitochondrial physiology assessment, viability and apoptosis evaluation in primary AML and healthy bone marrow patient samples, and cytotoxicity study *in vivo* (MOLM14/GFP/LUC cell xenograft model in NSG mice).

Results
We identified six compounds (and six analogs) that exhibit selective cytotoxicity against AML cells *in vitro*. Mechanistically, all hit compounds reduced ATP and selectively impaired both basal and ATP-linked oxygen consumption in leukemic cells. Compounds derived from PS127 significantly upregulated production of reactive oxygen species (ROS) in AML cells and triggered ferroptotic, necroptotic, and/or apoptotic cell death in AML cell lines and refractory/relapsed AML primary samples. These compounds exhibited synergy with several anti-leukemia agents in AML, acute lymphoblastic leukemia (ALL), or chronic myelogenous leukemia (CML). Pilot *in vivo* efficacy studies indicate anti-leukemic efficacy in a MOLM14/GFP/LUC xenograft model that extended survival in mice injected with leukemic cells pre-treated with PS127B or PS127E and mice treated with PS127E at a dose of 5 mg/kg.

Conclusions
These compounds are promising leads for development of future combinatorial therapeutic approaches for mitochondria-driven hematologic malignancies such as AML, ALL, and CML.

Acknowledgements
The work is funded by the CPRIT grant RR150044 and NIH NIGMS grant R35GM129294 to NVK; R01CA231364 P50 CA100632 to MK. Computer-aided estimation of which regions of the chemical scaffold are relevant for cytotoxicity (L.A.S. and V.V.P.) was performed in the framework of the Russian Federation Fundamental Research Program for the long-term period for 2021-2030.

Poster 33

Targeting Intracellular Oncogene Cyclin E (CCNE) With Peptide-HLA-Specific CAR-T Cells

Yan J[1], Yang GJ[1], You JP[1], Chen M[1], Shi S[1], Tian Z[1], Molldrem JJ[1,2], Heffernan TP[1,3]

1. ORBIT Platform, Division of Therapeutics Discovery
2. Department of Stem Cell Transplantation and Cellular Therapy
3. TRACTION Platform, Division of Therapeutics Discovery, The University of Texas MD Anderson Cancer Center, Houston, Texas

Corresponding Author: Jeffrey J. Molldrem, Department of Stem Cell Transplantation and Cellular Therapy, Email: jmolldre@mdanderson.org; Timothy P. Heffernan, Division of Therapeutics Discovery, Email: TPHeffernan@mdanderson.org, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA

Hypothesis/Goals: Cyclin E is highly expressed in multiple malignancies, and two nonameric HLA-A2 restricted peptides from CCNE1 or CCNE2 found significantly elevated in AML patients. The goal was to develop CAR-T targeting the HLA-A2/CCNE peptide complex as a potential therapeutic.

Methods: A highly specific antibody targeting the complex has been developed and then converted to CAR format. CCNE CAR-T cells were generated through lentiviral transduction of healthy donor T cells. CAR-T cells were characterized *in vitro* for their expansion, exhaustions, memory phenotypes, and cytotoxicity, and their *in vivo* efficacy and safety were also evaluated with several CDX and PDX models.

Results: CCNE CAR-T demonstrated highly specific and dramatic responses to the target complex and lysed the target cells efficiently *in vitro*. The built-in suicide switch led to quick removal of CAR-T cells with cetuximab treatment. Efficacy studies showed the best tumor control for CCNE CAR-T with bbz format. Tox studies demonstrated a satisfying safety profile. CCNE CAR-T generated out of HLA-A2+ donors exhibited a certain degree of fratricide. The issue could be resolved either through knocking out *HLA-A2* or switching to HLA-A2- donor T cells.

Conclusions: The study provided evidence that targets of CAR-T cell therapy can be expanded to intracellular proteins, and this TCR-like CAR-T format could engage and lyse the target cells with low peptide complex abundance. Our results suggest CCNE CAR-T can be an efficient therapeutic for AMLs and triple negative breast cancer, which at this point are difficult to treat.

Acknowledgements: The work was supported by MDA Internal Funding.

Poster 34

Drug Repurposing and Development for Main Protease of SARS-CoV-2

Yang KA, Vatansever EC, Ma XR, Ma Y, Alugubelli YR
Texas A&M Drug Discovery Laboratory, Department of Chemistry, TAMU

Corresponding author: Shiqing Xu (shiqing.xu@tamu.edu) and Wenshe R. Liu (wsliu2007@tamu.edu), Texas A&M Drug Discovery Laboratory, Department of Chemistry, TAMU, College Station, TX, 77843.

The COVID-19 pathogen, SARS-CoV-2, requires its main protease (Mpro) to digest two of its translated long polypeptides to form several mature proteins that are essential for viral replication and pathogenesis. Inhibition of this vital proteolytic process is effective in preventing the virus from replicating in infected cells and therefore provides a potential COVID-19 treatment option.

Guided by a computational docking analysis, about 30 Food and Drug Administration/European Medicines Agency (FDA/EMA)-approved small-molecule medicines were characterized on their inhibition of the Mpro. Of these small molecules tested, six displayed a concentration that inhibits response by 50%IC50) value below 100 μM in inhibiting Mpro, and, importantly, three, that is, pimozide, ebastine, and bepridil, are basic molecules that potentiate dual functions by both raising endosomal pH to interfere with SARS-CoV-2 entry into the human cell host and inhibiting Mpro in infected cells. A live virus-based modified microneutralization assay revealed that bepridil possesses significant anti−SARS-CoV-2 activity in both Vero E6 and A459/ACE2 cells in a dose-dependent manner with low micromolar effective concentration, 50% (EC50) values. This study urges serious considerations of using bepridil in COVID-19 clinical tests.

Guided by previous medicinal chemistry studies about SARS-CoV-1 Mpro, we have designed and synthesized a series of Mpro inhibitors that contain β-(S-2-oxopyrrolidin-3-yl)-alaninal (Opal) for the formation of a reversible covalent bond with the Mpro active-site cysteine C145. All inhibitors display high potency with Ki values at or below 100 nM. The most potent compound, MPI3, has as a Ki value of 8.3 nM. Crystallographic analyses of Mpro bound to seven inhibitors indicated both formation of a covalent bond with C145 and structural rearrangement from the apoenzyme to accommodate the inhibitors. Virus inhibition assays revealed that several inhibitors have high potency in inhibiting the SARS-CoV-2-induced cytopathogenic effect in both Vero E6 and A549/ACE2 cells. Two inhibitors, MPI5 and MPI8, completely prevented the SARS-CoV-2-induced cytopathogenic effect in Vero E6 cells at 2.5–5 μM and A549/ACE2 cells at 0.16–0.31 μM. Their virus inhibition potency is much higher than that of some existing molecules that are under preclinical and clinical investigations for the treatment of COVID-19. Our study indicates that MPI8 is a Mpro inhibitor with ultrahigh antiviral potency.

Poster 35

Modulating the Sigma2 Receptor (TMEM97) is an Effective Strategy for Treating Neuropathic Pain

Yousuf MS[1,3], Sahn JJ[2,3], David E[1], Zhang J[1], Mancilla MM[1], He L[1], Truong V[4], Walsh P[4], Liebl DJ[5], Martin SF[2,3], Price TJ[1,3]

1. Center for Advanced Pain Studies and Department of Neuroscience, School of Behavioral and Brain Sciences, University of Texas at Dallas, Richardson, TX 75080
2. Department of Chemistry, University of Texas at Austin, Austin, TX 78712
3. NuvoNeuro, Austin, TX 78712
4. Anatomic Incorporated, Minneapolis, MN
5. University of Miami School of Medicine, Miami, FL

Corresponding author: Theodore J. Price, Center for Advanced Pain Studies and Department of Neuroscience, School of Behavioral and Brain Sciences, University of Texas at Dallas, 800 W Campbell Rd, Richardson, TX 75080

Background: Neuropathic pain is a major medical problem that is poorly treated with existing therapeutics. The Sigma 2 receptor was described pharmacologically more than 3 decades ago but its genetic identity was only recently identified as *TMEM97*. We and others have shown that TMEM97-binding compounds produce analgesia in mouse neuropathic pain models particularly spare nerve injury (SNI).

Hypothesis/Goals: We aim to understand the unique anti-neuropathic pain effect of TMEM97-modulating compounds in the SNI model of neuropathic pain. We address the molecular specificity, potency, and efficacy of the TMEM97 compounds, UKH-1114 and FEM-1689, as well as speculate on the downstream mechanisms underlying reduced pain hypersensitivity.

Methods: We generated global TMEM97-knockout (KO) mice and subjected them to spared nerve injury (SNI) in order to assess their susceptibility to developing neuropathic pain. We further treated both TMEM97KO and wild-type (WT) littermates with novel TMEM97 modulators, UKH-114 and FEM-1689, to ascertain the specificity of each compound. We also treated cultured sensory neurons from WT and KO mice as well as human organ donors with TMEM97-binding compounds to investigate the underlying mechanism.

Results: Global TMEM97-KO demonstrated no aberrant phenotype and were otherwise comparable to wild-type (WT) littermates. Following SNI, male and female TMEM97KO and WT mice developed robust mechanical pain hypersensitivity. TMEM97KO animals presented with more pronounced pain responses than WT mice in the SNI model supporting the conclusion that positive modulators of TMEM97 would be desired as analgesics. As such, treating TMEM97KO and WT mice following SNI with UKH-1114, and a novel TMEM97-binding compound, FEM-1689, reversed mechanical hypersensitivity in WT mice for at least 72 hours but had no effect in TMEM97KO littermates. This suggests that these compounds require the presence of *Tmem97* to produce analgesia in neuropathic pain models. We also demonstrate that TMEM97 is expressed widely in human and mouse sensory neurons and treatment with FEM-1689 promotes AMPK signaling *in vitro*.

Conclusions: Our results show that novel small-molecule modulators of Sigma2 receptor/TMEM97 relieve neuropathic pain suggesting that TMEM97 is a viable target for further development for the treatment of neuropathic pain.

Acknowledgements: We would like to thank donors, their families, and the Southwest Transplant Alliance for their generosity.

Poster 36

Pharmacologic Degradation of RIPK1 Enhances Anti-Cancer Immunity

Yu X, Lu D, Qi X, Lin H, Wang J*
Department of Pharmacology and Chemistry Biology, Baylor College of Medicine

Corresponding author: Jin Wang, Department of Pharmacology and Chemistry Biology, Baylor College of Medicine, One Baylor Plaza, Houston, TX, E-mail: wangj@bcm.edu

Background: Cancer immunotherapies, such as immune checkpoint blockades (ICBs), chimeric antigen receptor (CAR) T cells, and recently developed CAR natural killer (NK) cells, have achieved unprecedented clinical responses and are revolutionizing cancer treatments. Unfortunately, despite of the tremendous success of cancer immunotherapies, it remains unclear why only a subset of individuals responds to treatment and how to turn non-responders to become responsive. One common feature for ICB activated cytotoxic T cells, CAR-T and CAR NK cells is that they all kill cancer cells through granule exocytosis and death ligands to activate programmed cell death. However, cancer cells that are insensitive to these programed death mechanisms will evade killing mediated by the antitumor immunity.

Hypothesis: Receptor-interacting protein kinase 1 (RIPK1) is a master regulator of cell fate and controls proinflammatory signaling downstream of multiple innate immune pathways, including those initiated by tumor necrosis factor-α (TNF-α), toll-like receptor (TLR) ligands, and interferons (IFNs). In TNF-α signaling, the kinase activity of RIPK1 is required for inducing apoptosis and necroptosis. RIPK1 also serves as a kinase-independent scaffolding protein to recruit the NF-κB activation complex, leading to activation of the NF-κB pathway and cell survival. Interestingly, mice with a kinase-dead *Ripk1* mutation (mimicking inhibitors) and with *Ripk1* knockout (mimicking degraders) showed completely different phenotypes. Recently, our own work, along with three other independent studies, showed that knockout of RIPK1 in cancer cells significantly sensitizes tumors to anti-PD1, leading to favorable changes in the tumor microenvironment. Therefore, we hypothesize that developing RIPK1 degraders can phenocopy the genetic studies and synergize with ICBs to promote antitumor immunity.

Methods and Results: Leveraging the Proteolysis targeting chimera (PROTAC) technology, we developed a first-in-class RIPK1 degrader LD4172. In our preliminary study, we showed that LD4172 potently degrades RIPK1 protein in a panel of human cancer cell lines with DC_{50} in the range of 5-40 nM and inhibits NF-κB activities. The degradation specificity of LD4172 was confirmed with proteomics profiling. LD4172 has a reasonable plasma half-life of 3.4 h in mice. In a B16F10 mouse melanoma immunocompetent model, LD4172 significantly synergized with anti-PD1. Combination of LD4172 and anti-PD1 mAb achieved 77% tumor growth inhibition, while LD4172 or anti-PD1 alone showed little inhibition on tumor growth compared with the vehicle control treatment.

Conclusions: Immune profiling of tumors showed that LD4172 treatment led to recruitments of a higher percentage of CD4+ T cells, antigen-presenting cells, such as macrophages and conventional dendritic cells, and B cells to the tumor microenvironment (TME), which works in concert with Anti-PD1 to activate the functional cytotoxic T cells and trigger anti-tumor immune responses. Additionally, significantly increased IL2 and IFN-γ in plasma were observed only in the LD4172 + Anti-PD1 combo group, suggesting a positive feedback loop of activated T cells in TME. The mouse plasma cytokine array showed that the immunogenic cell death (ICD) marker HMGB1 increased by >100 folds after treating mice with LD4172, while no appreciable difference was observed for IL18 among different treatment groups, suggesting that LD4172 triggered inflammasome-independent necroptosis mediated ICD in tumors.

Acknowledgments: The research was supported in part by National Institute of Health (R01- CA250503 to J.W.), and Cancer Prevention and Research Institute of Texas (CPRIT RP220480 to J.W.), and the Michael E. DeBakey, M.D., Professorship in Pharmacology (to J.W.). Additionally, we thank Baylor College of Medicine Cytometry and Cell Sorting Core and Drs. Douglas Green, Lisa Bouchier-Hayes, Weiyi Peng, Xi Chen, Shawn Zhang and Jeff Rosen for their advice and support.