Virginia Drug Discovery Rx Symposium on Academic-Industrial Partnerships in Drug Discovery

JUNE 25-26, 2018

FOUNDERS HALL
George Mason University

Virginia Drug Discovery Consortium

virginia bio
Dear Symposium Participants:

On behalf of the Organizing Committee, it is my great pleasure to welcome you to Arlington and to “VirginiaDrugDiscoveryRx: A Symposium on Academic-Industrial Partnerships in Drug Discovery” This Symposium is designed to promote collaborations between academic and industrial drug discovery scientists, and includes keynote lectures from leading researchers, panel discussions, and poster presentations by scientists from around and beyond the Commonwealth.

As already stated, one of the major purposes of this Symposium is to provide networking opportunities that could foster new inter-university and public-private collaborative projects in drug-discovery. The NIH Roadmap for Research states “The scale and complexity of today’s ... research problems increasingly demand that scientists move beyond the confines of their own discipline and explore new organizational models for team science.......”, and this Symposium has the goal of furthering such collaborations, especially when it comes to the drug discovery, development, and delivery. The organizers hope that everyone will take advantage of the poster sessions and social times to meet new colleagues and to explore new collaborations.

This Symposium represents the third collaborative program of the Virginia Drug Discovery Consortium. This Consortium has the aim of fostering collaborative drug discovery research in all disease areas between Virginia’s universities and the pharmaceutical and biotech industries, and it plans to sponsor regular Symposia on different aspects of drug discovery, with the next one tentatively scheduled for Spring 2019. A short questionnaire is included in your registration materials, and I hope that you will take the time to complete this on Tuesday to guide the organizers in planning future Symposia.

The organizers wish to thank all the sponsoring institutions (INOVA Schar Cancer Institute, Johnson and Johnson Innovations, Prince William County Economic Development Board, Biotage, Advion, AMRI, Hamilton Company, Collaborative Drug Discovery, Sciex, Key Organics, UVA Licensing and Ventures Group, MilliporeSigma and KeViRx Company) for their support, which allowed for the moderate cost of the Symposium. Full details of these sponsors are included in the following pages.

The organizers hope that you enjoy both the scientific program and the collaborative opportunities of the VirginiaDrugDiscoveryRx Symposium, and we look forward to seeing many of you at the next Symposium.

Sincerely yours

David G. I. Kingston
Symposium Chair
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Umesh Desai (Virginia Commonwealth University)
Jeffrey Gallagher (Virginia Bio)
David G. I. Kingston (Virginia Tech)
John S. Lazo (University of Virginia)
Elizabeth Sharlow (University of Virginia)
Karen Iannaccone (administrative support, Virginia Tech)
Virginia Drug Discovery Rx:
A Symposium on Academic-Industrial Partnerships in Drug Discovery
June 25-26, 2018
George Mason University Founders Hall

Day 1. Chairs: David Kingston, Paul Carlier (Virginia Tech)

10:00 am  Registration opens

1:00 pm  Symposium Opens: Welcome from David Kingston (Virginia Tech) and Ali Andalibi (George Mason University)

1:05 pm  Keynote 1: Michael Weingarten (NIH, Head of NCI Development Center)
“NCI’s multi-faceted Support for Early Stage Biotechnology Innovation”

1:45 pm  Keynote Q & A

1:50 pm  Invited Lecture 1: Umesh Desai (Virginia Commonwealth University)
“A Synthetic, Highly Potent Allosteric Inhibitor of Human Factor Xla for Prothrombotic Disorders”

2:10 pm  Invited Lecture Q & A

2:15 pm  Panel Discussion 1: What are the optimal academic-pharma partnerships for drug discovery?
Robbie Barbero (Ceres Nanosciences)
Carleen M. Bowers (UVA Licensing & Ventures)
Bruce Littlefield (Eisai)
Ronald Newbold (Otsuka US)
Eric Paradise (Medimmune)
Kevin Passarello (Buchanan, Ingersoll & Rooney)
John S. Lazo (University of Virginia, Moderator)

3:15 pm  Coffee break/Poster Session  (Posters remain throughout meeting)

4:15 pm  Keynote 2: Jeff Gallagher (Virginia Bio)
“An overview of biotech/pharma businesses in VA”
4:45 pm  **Invited Lecture 2**: Elizabeth Sharlow (KeViRx and University of Virginia): 
“Targeting an undrugged phosphatase with JMS-053”

5:05 pm  Invited Lecture Q & A

5:10 pm  **Panel Discussion 2**: How to get your drug into clinical trials.

Peter Lipsky (AMPEL BioSolutions LLC)
Paul Waymack (Kitov Pharmaceutical)
Travis Wilson (Gurnet Point Capital)
Robert J. Meyer (Greenleaf Health Inc., Moderator)

5:55 pm  **End of Session 1**

6:00 pm  **Evening Poster Session Reception**

7:00 pm  **Dinner** – after-dinner talk by Bruce Littlefield:

“**Justify**-ing a perfect (drug development) trifecta”

**Day 2. Chairs:** Elizabeth Sharlow (University of Virginia), Ali Andalibi (George Mason University)

8:00 am  **Keynote 3**: Dan Paone (GlaxoSmithKline)
“Characteristics of successful academic-pharma partnerships”

8:30 am  Keynote Q & A

8:45 am  **Panel Discussion 3**: Entrepreneurship.

Robert Gourdie (Virginia Tech Carilion Research Institute)
Andy Krouse (Cavion)
Lance Liotta (George Mason University)
Ali Andalibi (George Mason University, Moderator)

9:35 am  **Invited Lecture 3**: Webster Santos (Virginia Tech)
“Controlling sphingosine-1-phosphate levels as a therapeutic strategy”

9:55 am  Invited Lecture Q & A
10:00 am  **Coffee break/Poster Session**

10:45 am  **Invited Lecture 4**: Barney Bishop (George Mason University)  
“Novel Antimicrobial Peptides from Extreme Species”

11:05 am  Invited Lecture Q & A

11:10 am  **Panel Discussion 4**: New Technologies for Drug Discovery:

  Josep Bassaganya-Riera (Landos Biopharma): Computational Modeling of Drug Responses

  Amrie Grammer (AMPEL BioSolutions LLC)—Bioinformatics to search for repurposed Drug Candidates

  Steve Hoang (Hemoshear Therapeutics): Novel human tissue models

  Robert Newman (ATCC)— Recent Advances in the Development of In Vitro Models

  Michael Wood (Circuit Therapeutics): Circuit busting – optogenetics, behavior & transcriptomics

  Kathlynn Brown (SRI, Moderator)

12:25 pm  Lunch

1:30 pm  Symposium ends
Virginia Drug Discovery Consortium
Executive Committee Members

Ali Andalibi, Ph.D
Associate Dean for Research, College of Science, George Mason University

Milton Brown, M.D., Ph.D.
Director, INOVA Center for Drug Discovery and Development

Paul R. Carlier, Ph.D.
Professor, Chemistry, Virginia Tech
Drug Design for depression, Alzheimer’s Disease, Malaria

Umesh Desai, Ph.D.
Professor, Institute for Structural Biology, Drug Discovery & Development, Virginia Commonwealth University

Nick Farrell, Ph.D.
Professor of Chemistry, VCU
Platinum, anticancer drugs, zinc Fingers, metalogycomics

Richard Glennon, Ph.D.
Professor, VCU
Medicinal chemistry and behavioral pharmacology of neuropsychiatric agents

B. Frank Gupton, Ph.D.
Chair and Professor, Department of Chemical and Life Science Engineering, VCU

David G. I. Kingston, Ph.D., FRIC
University Distinguished Professor, Chemistry Virginia Tech, Nanoparticle Drug Delivery, Natural Products as anticancer and Antimalarial agents

John Lazo, Ph.D.
Harrison Distinguished Professor of Pharmacology and Chemistry, Associate Director for Basic Science at the UVA Cancer Center, Pharmacology

Elizabeth Sharlow, Ph.D.
Associate Professor of Research, Dept. of Pharmacology; Co-Director, Fiske Drug Discovery Laboratory, UVA
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PANEL 1 DISCUSSION:

WHAT ARE THE OPTIMAL ACADEMIC-PHARMA PARTNERSHIPS FOR DRUG DISCOVERY?

Panelists:

Robbie Barbero - Ceres Nanosciences

As Chief Business Officer at Ceres Nanosciences, Robbie works with the CEO and the rest of the team to drive business growth by supporting key product development programs and identifying new technology commercialization and industry partnership opportunities.

Robbie has over 15 years of experience operating across a range of responsibilities in the biotechnology sector, including in public policy, product development, manufacturing, and customer-facing roles. Prior to joining Ceres, Robbie was the Assistant Director of Biological Innovation in the White House Office of Science and Technology Policy where he spent more than four years developing and implementing policy on global and national life science issues. Robbie has extensive experience building and maintaining strategic partnerships with leading foundations, universities, private research institutes, non-profit organizations, federal agencies, and companies across a variety of scientific and technical topics.

Robbie received his Ph.D. in biological engineering from MIT, where he was a member of Professor Angela Belcher's Biomolecular Materials Group. Robbie received various awards at MIT, including being named an MIT Presidential Fellow and a Siebel Scholar. Before graduate school, Robbie spent five years working for three biotechnology startups -- GlycoFi (acquired by Merck), Quantum Dot Corporation (acquired by Invitrogen), and Nanostream. Robbie also holds A.B. and B.E. degrees in engineering sciences from Dartmouth College.

Carleen M Bowers – UVA Licensing & Ventures

Carleen joined the University of Virginia’s Seed Fund in 2018 as a Venture Associate, and is responsible for identifying and evaluating early stage venture investment opportunities. Although the Seed Fund invests across a range of technologies emerging from the University, Carleen’s due diligence has focused largely in the Life Sciences sector. She also works to support the growth of the Fund’s five portfolio companies. Before joining the Seed Fund, Carleen was a Principal Scientist for a university start-up that focused on the development of advanced materials and devices, where she led R&D programs in the design of novel polymer and nanocomposite materials. She completed a postdoctoral fellowship under the direction of Professor George M. Whitesides at Harvard University, where she investigated the thermodynamics of protein-ligand binding and mechanisms of charge transport across bio-organic films. Carleen earned her doctoral degree in physical chemistry from Duke University (with Professor Eric J. Toone), where she developed unconventional nanofabrication methods to pattern organic and biological molecules on surfaces at the nanoscale. She also investigated the thermodynamic parameters of molecular recognition between proteins and their ligands using single molecule force microscopy. She also holds a B.S. in chemistry from the University of Virginia.

Bruce Littlefield – Eisai

Dr. Littlefield holds the dual positions of Distinguished Scientist and Head, Translational Medicine in the Global Oncology group at Eisai, a global pharmaceutical company headquartered in Tokyo. A biochemist by training, Dr. Littlefield first joined Eisai in 1990 and since that time has overseen numerous natural product-based oncology drug discovery programs. One such program, initiated at Eisai by Dr. Littlefield in 1992 together with Professor Yoshito Kishi of Harvard, was based on the marine sponge natural product halichondrin B. This program led to the discovery and development of eribulin (Halaven®), currently approved in over 60 countries worldwide for treatment of certain patients with advanced breast cancer and liposarcoma. Dr. Littlefield has published widely in the cancer research and drug development areas, holds numerous drug-related patents, and is a frequent lecturer at universities, medical centers and scientific
conferences in the US and abroad. In addition to working at Eisai, Dr. Littlefield has held faculty positions at both Yale and Harvard Medical Schools, most recently in 2009-2011, when he temporarily moved to Harvard to become Scientific Director of their entrepreneurial natural products-based drug discovery program, before returning to Eisai in his current capacity in 2011.

**Ronald Newbold – Otsuka US**

Ron Newbold is Senior Vice President and Head of US Business Development for Otsuka America Pharmaceuticals, where his responsibilities are to identify novel new therapeutic programs in Otsuka’s core areas of Neuroscience, Oncology and Renal diseases. Ron joined Otsuka in November 2017 with 24 years of Business Development and Alliance Management experience leading business teams in negotiating over $1.5 billion in announced pharma / biotech deals.

After receiving his PhD from the University of Rochester and a postdoctoral fellowship at Harvard University, he joined Merck where he was ultimately responsible for Strategic Research Initiatives within External Scientific Affairs. Following 14 years with Merck, Ron led BD for three US-based biotech companies (Sentigen Biosciences, Celldex Therapeutics, and Auspex Pharmaceuticals) prior to joining Pfizer as Vice President of their Global Scouting Group. He started and led the Pfizer Seed Fund and over the past 4 years was Board Observer to Ab Initio, Aquinnah, Circle Pharmaceuticals, Lumena (acquired by Shire), Molecular Stethoscopes, Neoantigenics, Storm Therapeutics, and a Scientific Advisory Board member to NeoMED. He remains on the Board of the Licensing and Venture Group at the University of Virginia, where he is Vice Chairman.

**Eric Paradise – Medimmune**

Eric Paradise is the Head of Strategy for the Immuno-Oncology (IO) Franchise at AstraZeneca, a global biopharmaceutical company. In this role, Eric helps define the future direction of the late-stage IO development portfolio and leads cross-functional teams to deliver on strategic initiatives.

Previously, Eric headed the business development activities for the Respiratory, Inflammation, and Autoimmune therapeutic areas at MedImmune (the biologics R&D arm of AstraZeneca) as a Senior Director in Partnering & Strategy. He led a team to identify and execute partnerships in these therapeutic areas. He joined MedImmune in 2010 as a member of the Corporate Strategy team.

Prior to MedImmune, Eric worked at The Boston Consulting Group where he consulted with Fortune 100 companies and led teams across a variety of industry sectors. Eric graduated from North Carolina State University earning Bachelor degrees in chemical engineering and biochemistry. His doctorate work in chemical engineering at the University of California at Berkeley focused on synthetic biology and included a publication in *Nature*.

**Kevin Passarello – Buchanan, Ingersoll & Rooney**

Kevin Passarello is a Shareholder at Buchanan Ingersoll & Rooney in Washington. His practice focuses on emerging technology companies.

After practicing law since 1983, Kevin co-founded a software company in 1999 backed by Microsoft and Sequoia Capital that sold in 2005, a $60 million buyout fund in 2006, and a mobile hardware company that sold to L Catterton in 2011. In 2014, Kevin co-founded and still serves as CEO of AMP3D Inc.—which applies predictive analysis to continuous monitoring and other health-care data to enable proactive care for potentially catastrophic conditions and events. In 2015, Kevin became the Innovation Fellow at the Biocomplexity Institute of Virginia Tech, and returned to legal practice.

Kevin contributes to international forums on entrepreneurship. At Virginia Tech, he is a director of Virginia Tech Intellectual Properties and the President’s National Capital Region advisory board. He is an
entrepreneur-in-residence at the University of Virginia. Kevin has served on boards of various non-profits, commercial enterprises and emerging companies, and chaired the Academic Affairs Committee at St. Vincent College.

Kevin graduated from Georgetown University Law Center in 1986, and as valedictorian from St. Vincent College in 1983, where he majored in Philosophy. He and his wife live near Charlottesville.

John S. Lazo – University of Virginia, Moderator

John S. Lazo graduated from Johns Hopkins University and received his PhD in Pharmacology from the University of Michigan. He was a postdoctoral fellow and faculty member at Yale until his appointment as Allegheny Foundation Professor and Chairman of Pharmacology at University of Pittsburgh, a position he held for 17 years before becoming the first Director of their Drug Discovery Institute. In 2011 he became the Harrison Distinguished Teaching Professor and Associate Dean for Basic Research at the University of Virginia. Currently, he is the Associate Director for Basic Research for the Cancer Center. His primarily research focus is on the mechanism of action of novel drugs and on the fundamental biological role of protein tyrosine phosphatases. He has published more than 360 scientific articles and holds ten US issued patents. He is an elected Fellow of the American Association for the Advancement of Science. He has been on the Board of Directors for the American Association for Cancer Research, President for the American Society for Pharmacology and Experimental Therapeutics, and member of the Board of the Carnegie Museum of Natural History. He has mentored 15 PhD students and 31 postdoctoral fellows. He co-founded several early stage biopharmaceutical companies.
PANEL 2 DISCUSSION:
HOW TO GET YOUR DRUG INTO CLINICAL TRIALS
Panelists:

**Peter Lipsky – AMPEL BioSolutions LLC**

Peter is a Rheumatologist and Immunologist who immerses himself in basic and clinical research. He received his medical degree from the New York University School of Medicine, completed residency training at the Strong Memorial Hospital in Rochester, New York and his post-doctoral fellowship in NIAID at the NIH. After going to UT Southwestern Medical Center at Dallas, Peter rapidly advanced to become a professor of Internal Medicine and Microbiology as well as the Director of the Harold C Simmons Arthritis Research Center, Co-Director of the Immunology Graduate Program, and Director of the Rheumatic Disease Division of the Department of Internal Medicine. He entered the new millennium as the Director of the Intramural Research Program & the Autoimmunity Branch of NIAMS at the NIH. Peter is the co-founder of AMPEL BioSolutions LLC and directs its clinical operations. He is involved in the Lupus Clinical Investigator Network (LuCIN™) of the LRxL-STAT™ Lupus Drug Repositioning Initiative. Peter has edited several journals including the Journal of Immunology, Nature Reviews Rheumatology and Arthritis Research & Therapy. Peter’s accolades include the Carol Nachman Prize, the American College of Rheumatology Distinguished Investigator Award and the Arthritis Foundation’s prestigious Lee Howley prize.

**Paul Waymack – Kitov Pharmaceutical**

Chairman of the Board of Directors and Chief Medical Officer, Kitov Pharma. Dr. Waymack received his Bachelor of Sciences degree from Virginia Tech, his Doctor of Medicine degree from the Medical College of Virginia, and his Doctor of Sciences degree from the University of Cincinnati. After completing a surgery residency and transplantation fellowship at the University of Cincinnati, Dr. Waymack spent 10 years in academia as the chief of surgical studies at the U.S. Army's Institute for Surgical Research and as an associate professor of surgery at the University of Texas Medical Branch, during which time he published over 100 scientific papers. He next worked as a medical reviewer at the U.S. Food and Drug Administration. More recently Dr. Waymack has served since 2013 as the chairman of the board of directors and chief medical officer at Kitov Pharma, a publicly traded U.S./Israeli corporation that is developing oncology and analgesic drugs. In addition to Kitov Pharmaceuticals, Dr. Waymack serves on the boards of a number of other biotech corporations and universities.

**Travis Wilson – Gurnet Point Capital**

Travis Wilson is an investment partner at Gurnet Point Capital, a Boston-based $2 billion healthcare and life sciences fund focused on growth equity and venture opportunities worldwide. Previously, he was the President and CEO of Stealth BioTherapeutics, a late-stage clinical biotechnology company developing therapies to treat mitochondrial dysfunction in common and rare diseases. Travis has extensive experience in leading biotechnology companies and venture investing, heading transactions from seed-investments to commercial assets. For more than a decade, he was a member of the investment team at Morningside Ventures, an international firm dedicated to life science and technology startups. With Morningside, he worked on multiple financings, including several public and private biotechnology companies such as Chimerix (NASDAQ: CMRX), Genocea (NASDAQ: GNCA), BioVex (acquired by Amgen), Aduro (NASDAQ: ADRO) and Argos (NASDAQ: ARG5). Travis also served as a director and board member for nonclinical and clinical stage companies, providing operational and management support to a portfolio of companies developing technologies across a broad spectrum of therapeutic focus, including orphan diseases, cardio-renal disorders, oncology, cell-therapy and ophthalmology. He has lectured extensively on life science investing and management, and is a long-time supporter of patient-advocacy groups including the United
Mitochondrial Disease Foundation and National Organization for Rare Disorders. Travis holds a law degree and a chemical engineering degree, both from the University of Wisconsin.

**Robert J. Meyer – Greenleaf Health Inc., Moderator**

Dr. Robert Meyer is a Principal of the Drug and Biological Products team at Greenleaf Health, a boutique regulatory consulting company in Georgetown he joined in 2018. He was previously the Director of the Virginia Center for Translational and Regulatory Sciences (VCTRS) at the University of Virginia (UVA) School of Medicine and continues at UVA as an Associate Professor of Public Health Sciences. Before joining UVA in 2013, Dr. Meyer headed worldwide regulatory and pharmacovigilance activities at Merck Research Laboratories (MRL) across the entire portfolio. He was also a member of MRL’s Early Stage and Late Stage Development Review and Safety Review Committee. Prior to Merck, Dr. Meyer was at the U.S. Food and Drug Administration (FDA) from 1994-2007, including five years (2002-2007) as the Director of the Office of Drug Evaluation II within the Center for Drug Evaluation and Research (CDER). He is currently a Medical Science Trustee for the United States Pharmacopeia Board and is on the Board of Directors of two biotechnology companies (Cardiome Pharma and Chimerix). He received his medical degree from the University of Connecticut, where he also did residency and chief residency. Dr. Meyer completed his pulmonary and critical care training at the University of Vermont.
PANEL 3 DISCUSSION:

ENTREPRENEURSHIP

Panelists:

Robert Gourdie – Virginia Tech Carilion Research Institute

Rob Gourdie PhD is the Director of the Center for Heart and Regenerative Medicine (CHARM) at the Virginia Tech Carilion Research Institute and Professor in the Department of Biomedical Engineering and Mechanics at Virginia Tech. Together with its five team leaders, CHARM numbers around 25 post-docs, graduate students and staff. Gourdie is co-founder of FirstString Research Inc - a clinical-stage biotech company, now in Phase III clinical trials on its lead drug, which was developed in Gourdie’s lab. In 2016, he spun out a new biotech company from his VTCRI lab, Acomhal, which is undertaking preclinical development of a novel drug that targets cancer stem cells. Gourdie has been continuously funded by the NIH since 1997, including as Program Director of a program project grant. He has authored 150+ peer-reviewed publications (H index= 50) on heart development and function, wound healing and cancer. He holds more than a dozen issued patents, with another 50 patent applications pending. His research is on the connexins - proteins key to intercellular communication. His work includes basic mechanisms of cardiac bio-electricity, and translational research on drugs targeting connexin function in heart disease, wound healing and oncology. Gourdie received his PhD (1990) from the University of Canterbury (New Zealand), and did post-doc training at University College London (United Kingdom), as a British Heart Foundation Fellow. Prior to joining Virginia Tech, Gourdie was Professor at the Medical University of South Carolina in Charleston, SC (USA) from 1995 to 2012.

Andy Krouse – Cavion

Mr. Krouse has over a decade of biotech leadership experience as founder of Tau Therapeutics LLC, Xdynia LLC and Cavion. He has been recognized for his leadership in the industry as a CIT GAP 50 Entrepreneur in the Commonwealth of Virginia and as Chairman of the Board of the Virginia Biotechnology Association. Prior to joining the pharmaceutical industry, he worked in senior university leadership including as Vice President of the University of Virginia Darden School Foundation. He also previously served as an analyst at Goldman Sachs, NYC. In addition to his roles at Cavion, he serves on the boards of the Institute for Advanced Studies in Culture and the St. Anselm Institute for Catholic Thought, organizations promoting the intellectual community at the University of Virginia. He is a frequent speaker and published author with three patents in the T-type calcium channel space. Mr. Krouse is a cum laude finance graduate of the University of Maryland Business School. He received his MALS from Georgetown University and completed The Executive Program at the Darden Graduate School of Business Administration at the University of Virginia.

Lance Liotta – George Mason University

Dr. Lance Liotta is a Board Certified Anatomic Pathologist and has served as Co-Director and Co-Founder of the Center for Applied Proteomics and Molecular Medicine (CAPMM) at George Mason University since 2005. Prior to this appointment, Dr. Liotta served as Chief of the Laboratory of Pathology, NCI, Deputy Director of NIH, Co-Director of the NCI/FDA Clinical Proteomics Program, and Director of the Anatomic Pathology Residency Program. Dr. Liotta has invented and patented transformative technologies in the fields of diagnostics, cancer molecular therapeutics, microdissection (Laser Capture Microdissection), and proteomics (Reverse Phase Protein Microarrays, Biomarker Harvesting Nanoparticles, preservation chemistries for molecular analysis, and “protein painting” for drug target mapping) that have been used to make broad discoveries in cancer biology, and diagnostics, and therapeutics. His team at CAPMM studies the proteomics of human tissue, cultured cells, and body fluids, using this set of novel technologies. This research has directly resulted in ongoing clinical research trials applying the technology to the discovery of markers for early stage disease, individualized therapy for metastatic cancer, and adjuvant therapy of premalignant breast cancer. He is a founder of TheraNostics Health and Ceres Nanosciences. Dr. Liotta
has more than 100 issued or allowed patents and 700 publications. He is an ISI highly cited investigator and the recipient of numerous awards for biomedical research including the 2015 Outstanding Virginia Faculty Award (SCHEV), the Flemming Award for Cancer Research, the Warner-Lambert Parke Davis Award, and the Surgeon General’s Medallion.

Ali Andalibi – George Mason University, Moderator

Dr. Andalibi is the Associate Dean for Research in the College of Science at George Mason University. Prior to joining GMU, Dr. Andalibi held the position of Associate Vice President for Research at the University of Connecticut and Stony Brook University and served as the Vice President of Research and Chief Scientific Officer at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center.

Dr. Andalibi received his PhD from the Department of Microbiology and Molecular Genetics at UCLA and later joined the faculty in the Department of Medicine in UCLA. Subsequently, he was involved in several early stage biotechnology companies. He then joined the House Ear Institute (HEI) as the Director of New Technology and Project Development and held a joint appointment in the Department of Otolaryngology at the University of Southern California, School of Medicine. Dr. Andalibi then served as a Program Director in the National Science Foundation’s Division of Industrial Innovation and Partnerships, where he oversaw the NSF’s medical biotechnology SBIR/STTR grant portfolio and subsequently moved to the National Cancer Institute, where he served as the head of the Therapeutics and Diagnostics Section in the NCI’s SBIR Development Center.
Panel 4 Discussion:

New Technologies for Drug Discovery

Panelists:

Josep Bassaganya-Riera – Landos Biopharma: Computational Modeling of Drug Responses

Josep Bassaganya-Riera has published over 150 peer-reviewed publications in peer-reviewed journals, holds 15 patents, has founded 3 award-winning Companies (Landos Biopharma, BioTherapeutics and Pervida), raising over $65 million in non-dilutive and equity financing rounds, and was recently named 2017 Innovator of the Year by the Roanoke-Blacksburg Technology Council. He is a captain of industry, innovator, serial entrepreneur, and thought leader in biotech. Dr. Bassaganya-Riera and his companies have been active members of a statewide group that supports the planning behind the Governor’s 2015 Virginia Bioscience Initiative and the BioHealth Capital Region. Dr. Bassaganya-Riera is also a prominent member of the Blacksburg community and was a featured presenter at the Governor’s Forum on Bio and Big Data in Northern Virginia. He co-founded and leads the Nutritional Immunology and Molecular Medicine Laboratory at the Biocomplexity Institute of Virginia Tech that receives funding from the National Institutes of Health and the Defense Threat Reduction Agency. He applies advanced informatics and computational modeling to accelerate the development of innovative technologies into medicines that are safer and more effective. Dr. Bassaganya-Riera has >20 years of R&D, business development and fundraising experience in leading biotech companies with innovative, large-scale translational programs in autoimmune and infectious diseases.

Amrie Grammer – AMPel BioSolutions LLC: Bioinformatics to Search for Repurposed Drug Candidates

Amrie Grammer Co-Founder and COO/CSO, AMPel BioSolutions in Charlottesville, VA. She is a Translational Immunologist specializing in bioinformatics and human autoimmune diseases with degrees in Chemistry, Pharmacology and Immunology. Before moving to Charlottesville in 2013, she headed up the B Cell Biology Group in the Autoimmunity Branch of NIAMS at the NIH. As Chief Scientific Officer of AMPel, Amrie directs an R&D program focused on making Precision Medicine an everyday reality for patients suffering from autoimmune disease. Specifically, AMPel utilizes bioinformatics and machine learning to identify abnormal targets and pathways in Lupus. Drugs and biologics specific for these targets/pathways are ranked using AMPel’s drug repositioning scoring system, CoLT™, and high priority therapeutics such as Ustekinumab are tested in small, proof-of-concept Phase IIb trials at over 50 sites in the US and Canada. A positive clinical trial of Ustekinumab in Lupus was announced by last fall by Janssen. Amrie has received numerous awards during her career, including the NIH Director’s Award, “For outstanding research on signaling mechanisms induced by TNF-receptor family members expressed by B cells”. She serves as the BOD Alumni Chair for the professional Chemistry Fraternity, ACS. In December 2016, Amrie was elected to the BOD of VA Bio.

Steve Hoang – Hemoshear Therapeutics: Novel Human Tissue Models

Steve Hoang, PhD is the Head of Computational Biology at HemoShear Therapeutics. He completed his undergraduate and graduate studies at the University of Virginia, where he studied computational biology and functional genomics. His early research focused on uncovering the relationship between histone modifications and transcriptomic regulation. In general, his work has centered on using data from high-throughput experiments to build predictive models of biological systems. In the last 5 years at HemoShear Therapeutics, he has developed methods that merge state-of-the-art computational systems biology techniques with state-of-the-art human tissue models to identify potential drug targets for rare inborn errors of metabolism and non-alcoholic steatohepatitis. Relatedly, his current research also includes the molecular basis of disease progression in fatty liver disease, and general methods for understanding the genotype-phenotype relationship in metabolic disorders.
**Robert Newman – ATTC: Recent Advances in the Development of In Vitro Models**

Dr. Newman is Senior Director for ATCC Cell Systems (ACS), which is ATCC’s cell biology research and development business. ACS is creating advanced in vitro models to support basic research and translational research for drug development, toxicology testing, diagnostics, and bioproduction. Dr. Newman’s cross-functional responsibilities include driving innovation, product development, strategy development, program management, technology transfer, and financial planning. His teams develop in vitro products in the areas of cancer research, neurobiology, immunology, and regenerative medicine. Prior to joining ATCC, Dr. Newman led an advanced bioprocessing media development team at BD Biosciences that was developing GMP-grade formulations for biologic, vaccine, and cell therapy drug manufacturing. Before BD, he held roles of increasing responsibility in product development, toxicology program management, and business development at Osiris Therapeutics. He authored the ICH-compliant non-clinical safety module to support the world’s first approved stem cell drug, a mesenchymal stem cell therapy used to treat acute graft-vs-host disease in children, which is a potentially fatal complication of bone marrow transplantation. Dr. Newman earned his bachelor’s degree in molecular biology from Colgate University, his PhD in biochemistry and molecular biology from Georgetown University and completed a post-doctoral fellowship in cancer research at Georgetown University.

**Michael Wood – Circuit Therapeutics: Circuit Busting – Optogenetics, Behavior & Transcriptomics**

Michael received a B.S. in Environmental Health from Oakland University and a PhD in Pharmacology & Toxicology from Duke University. He held postdoctoral positions at Harvard Medical School (DE Clapham, MD, PhD) and Eli Lilly & Co. (CC Felder, PhD) before beginning a pharmaceutical career focused on treating CNS disorders at Astrazeneca in 1999. He moved through various positions (line manager, strategy leader, search and evaluation expert) and exited AZ in 2016. He spent a year consulting as the principal of Neupharma LLC before joining an exciting biotech company, Circuit Therapeutics, as SVP of Drug Discovery and Strategic Partnerships in October 2017. Michael has published 25 peer-reviewed papers, a book, and a patent. He is now the Program Chair for the American Society of Pharmacology and Experimental Therapeutics (ASPET) and recently co-organized two colloquium (2016 & 2017) on academic drug discovery as collaborations between ASPET and the Academic Drug Discovery Consortium (ADDC).

**Kathlynn Brown – SRI, Moderator**

Kathlynn Brown is the Director of Macromolecular Science and Cancer Biology at SRI International. Dr. Brown obtained her PhD in organic chemistry at the University of Texas at Austin during which time she received fellowships from the Mahler Memorial Foundation and the Organic Division of the American Chemical Society. She continued her training at the University of California at San Francisco, where she was a Damon Runyon Walter Winchell Postdoctoral Fellow. She began her independent career at the University of Texas Southwestern Medical Center, and after 16 years, moved to SRI International to expand her translational research. She has utilized her multidisciplinary expertise in organic chemistry, peptide chemistry, biochemistry, and molecular biology to address challenges in biomedical research. Her research team is currently focusing on the development of tumor-targeted agents for cancer diagnosis and therapy.
THE NCI SBIR/STTR PROGRAM

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The SBIR & STTR Programs are one of the largest sources of early stage technology financing in the United States. SBIR & STTR are government set-aside programs for domestic small businesses to engage in research and development that has the potential for commercialization and public benefit. The NCI SBIR Development Center administers the SBIR and STTR programs at the NCI. SBIR and STTR programs are divided into three phases – phase I (feasibility and proof of concept); phase II (research/research and development) and phase III (commercialization). In addition, the NCI SBIR Program has created the Phase II Bridge Award for previously funded NIH SBIR Phase II awardees to continue the next stage of research and development for projects in the areas of cancer therapeutics, imaging technologies, interventional devices, diagnostics and prognostics, technologies for cancer prevention and control, supportive care, and survivorship, and tools and model systems for cancer research. The objective of the Phase II Bridge Award is to help address the funding gap a company may encounter between the end of the Phase II award and the commercialization stage. For any single year of the project period, budgets up to $2 million total costs may be requested. However, the combined budget requested for the entire project period must not exceed $4 million total costs. To incentivize partnerships between awardees and third-party investors and/or strategic partners, competitive preference, and funding priority will be given to applicants that demonstrate the ability to secure substantial independent third-party investor funds (i.e., third-party funds that equal or exceed the requested NCI funds). This funding opportunity is open to current and recently expired NIH SBIR Phase II projects.

The NCI SBIR program also offers the Innovation Corps (I-Corps) program. The I-Corps at NIH program, launched in 2014, was developed in close collaboration with the National Science Foundation (NSF) as a unique educational opportunity that teaches researchers and technologists how to apply the scientific method to the entrepreneurship process. In this 8-week entrepreneurial immersion program, participants gather information by conducting ≥100 interviews with potential customers, partners, and other stakeholders. Through these interviews, participants learn how to build a scalable business model, evaluate the value of their intellectual property, and assess the prospective impact of the technology being developed under the NIH-funded Phase I SBIR/STTR award. The goal of the I-Corps at NIH program is to accelerate the translation of biomedical research to the marketplace by providing training to SBIR and STTR grantees in the areas of innovation and entrepreneurship.

The NCI SBIR Development Center is interested in connecting SBIR- and STTR-funded companies with potential investors and strategic partners to continue the research and commercialization efforts initially funded by NCI. To help facilitate the connection, NCI SBIR have come up with different strategies to provide companies with a platform to present their technologies to interested third party investors. NCI SBIR has conducted NCI-specific investor forums from 2009 to 2014 and since 2015, has been organizing Investor Initiatives to connect companies with targeted investors and strategic partners on a regular basis throughout the year. The NCI SBIR Investor Initiatives program provides selected SBIR companies with resources to present at national/international showcases where they can explore partnering opportunities. Participation in the investor initiatives is determined on a competitive basis, using an annual application process. Based on external reviewer feedback of submitted applications, selected companies will receive NCI support to present at one industry hosted investor showcase.
The NCI SBIR Development Center also offers a two-day commercialization workshop for current NCI SBIR/STTR awardees. The workshop provides awardees an opportunity to learn how to utilize federal and local resources in order to advance commercialization. The workshop brings together representatives from federal agencies including the FDA, CMS, and BARDA, as well as experts from local and private organizations to share their expertise with attending companies. Attendees will also have a chance to engage in one-on-one meetings with their respective NCI Program Directors, as well as with speakers at the event.

The NCI SBIR Peer Learning and Networking (PLAN) Webinar Series provide a forum for SBIR- and STTR-funded companies to hear best practices of their peer awardees and to network with other companies. The goal of PLAN webinar series is to help SBIR-funded companies learn from peers and facilitate collaboration amongst awarded companies. Each featured company will share expertise on each webinar topic and also discuss particular technology areas in which they hope to collaborate with other companies.

Biography
Michael Weingarten is the Director for the Small Business Innovation Research (SBIR) Development Center at the National Cancer Institute in Bethesda, MD. In this role, Mr. Weingarten leads a team of nine Program Directors who manage all aspects of the NCI SBIR & STTR Programs including a portfolio of $158M in grants and contracts annually. The SBIR & STTR programs are NCI's engine of innovation for developing and commercializing novel technologies and products to prevent, diagnose, and treat cancer. Mr. Weingarten has implemented a set of key initiatives for optimizing the performance of the NCI SBIR Program at the NIH. These include the establishment of a new model at the NCI for managing the program - the SBIR Development Center. Under Mr. Weingarten's leadership, the NCI SBIR Development Center has launched a range of new initiatives to facilitate the success of small businesses developing cancer-related technologies. Recent initiatives include the launch of the NIH I-CorpsTM pilot program in which teams of budding entrepreneurs engage in a hypothesis-driven approach to validate their proposed business models by conducting over 100 interviews with potential customers. Companies adjust their strategies based on direct customer feedback and analyze the information they collect to determine if there is a product-market fit. Other NCI SBIR initiatives introduced under Mr. Weingarten's leadership include the NCI SBIR Investor Forums, the NCI SBIR Phase II Bridge Award, and the workshop titled Federal Resources to Accelerate Commercialization (FRAC). Thus far, NCI SBIR has held three investor forums that in total have facilitated the closing of investment deals with NCI-funded SBIR companies valued at over $300M. The NCI SBIR Phase II Bridge Award, which was launched in 2009, incentivizes partnerships between NIH's SBIR Phase II awardees and third-party investors and/or strategic partners to help small businesses bridge the funding gap between the end of their SBIR Phase II awards and the next round of financing needed to advance a promising cancer therapy or imaging technology.
AN OVERVIEW OF BIOTECH/PHARMA BUSINESSES IN VA

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The talk will identify the research institutions, private companies, non-profits and health care systems involved in the research and development of new pharmaceuticals, and highlight notable efforts. Attention will be paid to: biological and clinical foci of interest, expertise and specialization; developers and users of the tools and methods to assist, enhance and accelerate drug discovery in this era of science and technology convergence; and, the community of skills and capabilities necessary to support and enable this complex, lengthy and collective endeavor of discovery. Also considered will be opportunities and risks looking ahead, noting the role of resources in the “near abroad” (Maryland, DC and North Carolina) that, it will be suggested, are strategic resources to Virginians engaged in this important work.

Biography
Jeffrey M. Gallagher, CEO of Virginia Bio, is responsible for leading the premier statewide trade group that promotes the considerable scientific and economic impact of the life sciences industry in the Commonwealth of Virginia. Prior to taking on the leadership of Virginia Bio in May 2012, Jeff was a co-founder and served as VP & General Counsel for Lyotropic Therapeutics. This small specialty pharma company used its proprietary formulation technology to create new drug products based on both NCIs and already approved API for license, further development and commercialization by mid and large pharma. Previously he practiced corporate law in Richmond, focusing on new technology company formation, international business and intellectual property transactions. He was a co-founder and longtime Chairman of the Richmond based nonprofit World Pediatric Project. He holds an A.B. in Government from Harvard, a J.D. from the University of Wisconsin Law School, and an LL.M in Public International Law from the University of Virginia School of Law. He resides with his family in the Ginter Park area of Richmond, VA.
CHARACTERISTICS OF SUCCESSFUL ACADEMIC-PHARMA PARTNERSHIPS

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GSK’s Discovery Partnerships with Academia (DPAc) is a unique approach to early drug discovery that is designed to provide industrial drug discovery resources and expertise to academic researchers. The concept is simple but powerful: bring together the insight and creativity of the academic world with the drug discovery expertise of GSK to establish truly integrated partnerships to translate innovative research into clinical benefit for patients. Under these collaborations, primary investigators co-lead a unified team with a DPAc scientist, jointly sharing and publishing data and collectively working towards a medicine. Using this model as a backdrop, shared learnings and experiences will be discussed, including specific examples of partnerships and what constitutes ‘success’ from both parties.

Biography
Dan received his B.S. in Chemistry at the University of Delaware where he performed undergraduate research for Professor Cynthia McClure. He then attended the University of Pennsylvania to pursue graduate studies while working in the laboratories of Professor Amos B. Smith, III towards the total synthesis of (-)-cylindrocyclophanol A. After receiving his Ph.D., Dan accepted a post-doctoral position with Professor Larry Overman at the University of California, Irvine where he completed total syntheses of polypyrroloindoline alkaloids including (-)-chimonanthine and ditryptophenaline. He began his medicinal chemistry career at Merck (West Point) in 2001 where he contributed significantly to the design of multiple preclinical candidates, including telcagepan, a CGRP receptor antagonist for acute migraine which advanced through Phase III clinical trials. In 2014, Dan joined GlaxoSmithKline as a member of the Discovery Partnerships with Academia team. In his current role, he coordinates the medicinal chemistry efforts of multiple small molecule drug discovery programs, leading large chemistry matrix teams and serving on project joint steering committees while working collaboratively with scientists at academic institutions. Additionally, he is responsible for guiding the externalization of chemistry, DMPK, and biology operations for the broader DPAc group with the accompanying logistics/operations and financial responsibilities, and is highly involved in identifying and evaluating potential projects at research institutions.
A SYNTHETIC, HIGHLY POTENT ALLOSTERIC INHIBITOR OF FACTOR Xla FOR PROTHROMBOTIC DISORDERS

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Institute for Structural Biology, Drug Discovery and Development, Virginia Commonwealth University, Richmond, VA 23219  
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Factor XI or Xla (FXI(a)) is being actively pursued to develop safer antithrombotics. Recent work with antisense oligonucleotides, aptamers, and small molecule active site inhibitors suggest major potential in realizing clinically relevant candidates. Our long standing hypothesis has been that allosterism, originating from heparin-binding site(s) present on coagulation enzymes, is a promising approach to novel antithrombotics. We present SCI (see structure), a fully synthetic and homogeneous agent as an allosteric inhibitor of FXIa that exhibits major promise (IC50 = 280 nM; Selectivity >100-fold). SCI preferentially binds to the anion-binding site of FXIa to conformationally alter its active site. Its FXIa inhibition is rapidly reversed by protamine, the antidote used in heparin therapy. SCI preferentially prolongs human plasma clotting initiated with recalcification rather than thromboplastin. Rat tail bleeding and maximum-dose-tolerated studies indicated that SCI exhibits no major bleeding or toxicity concerns. FeCl3-induced arterial and thromboplastin-induced venous thrombosis model studies in the rat indicated that 0.25 mg/animal SCI reduces thrombus formation almost equal to enoxaparin at 2.5 mg/animal. Overall, SCI is the first-in-class, novel allosteric inhibitor of FXIa that induces potent anticoagulation in vivo. Clinical viability of SCI is likely to be in the areas of acute or surgical needs, where rapidity of both induction of anticoagulation and its reversal is critical.

Biography  
Umesh Desai is a professor of medicinal chemistry at VCU School of Pharmacy. His lab is involved in designing glycosaminoglycan (GAG) and non-saccharide glycosaminoglycan mimetics (NSGMs) for therapeutic use. He directs an extramurally funded laboratory of about 10 to 12 researchers working on targeted projects related to thrombosis, cancer, emphysema/COPD and viral infection. He also serves as the Director of Institute for Structural Biology, Drug Discovery and Development (ISB3D), which has a mission of translating fundamental science discoveries/designs into therapies and/or therapeutics. He also serves as the program director (PD) of a NIH-funded Program of Excellence in Glycosciences (PEG) project (2011–2018), which is a joint effort by 7 Universities and 1 Center (Virginia Commonwealth, Utah, Texas, Pittsburgh, Vanderbilt, Maryland, & Harvard) to address and resolve current issues of thrombosis. The anti-thrombotic agents being presented in this talk were developed as a part of this program project.
TARGETING AN UNDRUGGED PHOSPHATASE WITH JMS-053

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Overexpression of the PTP4A3 protein tyrosine phosphatase is common in many human cancers and is often associated with poor patient prognosis and survival. Since PTP4A3 appears to regulate several key malignant processes, such as invasion, migration, and angiogenesis, this phosphatase may play a pivotal regulatory role in cancer and endothelial signaling pathways. While phosphatases, in general, are attractive therapeutic targets, they remain largely “undrugged” and, therefore, not as well studied as kinases. We identified a potent and selective PTP4A family inhibitor, JMS-053, that pharmacologically phenocopies PTP4A3 genetic knockdown. JMS-053 treatment impaired colony formation, spheroid formation, migration, and adherence versus inactive control compound treated cells (i.e., JMS-038). Reduction in cancer cell viability and colony formation by JMS-053 occurred in both mouse and human cancer cell lines and required PTP4A3 expression. JMS-053 blocked growth factor-induced RhoA activation in cancer model systems confirming that RhoA signaling cascades are regulated by the PTP4A phosphatases and providing a potential pharmacodynamic endpoint. Importantly, JMS-053 displayed anticancer activity in a murine xenograft model of drug resistant human ovarian cancer. Thus, these data demonstrate that PTP4A phosphatases can be pharmacologically targeted in cancer cells.

Acknowledgement
We thank Alex Cheung, Sophie Lewandowski, Jennifer Ahn and Paula Pekic for their technical assistance. This research was supported by grants from the National Institute of Health [Grants R21CA191944, F31CA196062 and S10OD021723], the Fiske Drug Discovery Fund, the Owens Foundation, the Ivy Foundation, and by discretionary funding from Boehringer-Ingelheim Pharmaceuticals, Ridgefield, CT, USA.

Biography
Dr. Sharlow is an Associate Professor of Research in the Department of Pharmacology at the University where she is also Co-Director of the Fiske Drug Discovery Laboratory. Dr. Elizabeth Sharlow has >20 years of drug discovery experience obtained in academia and industry with a focus on assay development, high throughput screening, lead discovery and preclinical development. While at Johnson & Johnson she was part of the research team whose work led to the Active Naturals Aveeno product line. Dr. Sharlow then led the scientific component of a Phase I clinical trial while at ProX Pharmaceuticals (now part of Seattle Genetics), a NCI SBIR funded company. She joined the University of Pittsburgh Drug Discovery Institute (UPDDI) and was part of the Pittsburgh Molecular Libraries Screening Center (part of the NIH’s Molecular Libraries Screening Center Network pilot phase) where she worked with investigators nationwide to implement high throughput screening assays. At the University of Virginia she is continuing her drug discovery efforts in the areas of cancer (i.e., ovarian, breast and colorectal cancer) and neurodegeneration. Dr. Sharlow is also Chief Executive Officer of KeViRx, Inc. a company spin out from the University of Virginia.
CONTROLLING SPHINGOSINE-1-PHOSPHATE LEVELS AS A THERAPEUTIC STRATEGY

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Sphingosine 1-phosphate is a pleiotropic lipid that is chemotactic when acting extracellularly via five G protein coupled receptors (S1P1-5) but also may act intracellularly at less well-defined targets. The role of S1P in lymphocyte trafficking is firmly established; indeed, an S1P1 receptor agonist is an FDA approved immunosuppressive therapy for multiple sclerosis. The S1P blood (high):tissue (low) gradient functions to maintain endothelial barrier function. The sole biosynthetic route to S1P is phosphorylation of sphingosine catalyzed by sphingosine kinases (SphK1,2). We have discovered and characterized best-in-class SphK1 and SphK2 inhibitors for use as chemical probes of S1P biology. As expected, application of either SphK1 or SphK2 inhibitors lowers S1P levels in cultured cells. In vivo, administration of SphK1 inhibitor lowers bloodstream S1P, but SphK2 inhibitors drive an increase blood S1P levels. These responses recapitulate the observations made with SphK1 and SphK2 null mice. While the mechanism of SphK1 inhibitor's lowering S1P blood levels is obvious, the mechanism underlying the rise in blood S1P in response to SphK2 inhibition is unclear at present. Our SphK inhibitors provide the opportunity to discover whether inhibiting these enzymes, with concomitant rapid excursions in blood S1P levels, is efficacious in disease models.

Biography

Webster Santos is the Cliff and Agnes Lilly Fellow of Drug Discovery and Professor of Chemistry at Virginia Tech. He received his B.S. and Ph.D. at the University of Virginia, which was followed by an NIH postdoctoral fellowship in the department of chemistry and chemical biology at Harvard University. His research efforts include designing inhibitors of RNA involved in HIV-1, sphingosine kinase inhibitors, mitochondrial uncouplers, and developing synthetic chemistry methods involving boron and silicon. He is the recipient of numerous awards including Innovators Award and an endowed Blackwood Faculty Fellowship at Virginia Tech. He is a co-founder of Continuum Biosciences Inc. and SphynKx Therapeutics and an inventor on over 13 patents. He serves on the editorial boards of Medicinal Research Reviews and Current Topics in Medicinal Chemistry.
NOVEL ANTIMICROBIAL PEPTIDES FROM EXTREME SPECIES

Barney Bishop, Monique van Hoek

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The emergence of multidrug and extensively drug-resistant bacteria threaten the utility of available antibiotics and has the potential to impact almost all aspects of modern medicine. Hence, there is an urgent need for new antimicrobial therapeutics and treatment strategies. We are analyzing host-defense peptides found in the plasma from reptiles, including the American alligator and Komodo dragon, in order to identify novel cationic antimicrobial peptides (CAMPs), which may provide new templates and models for the development of new generations of antimicrobial therapeutics to address this challenge. CAMPs are fundamental elements of innate immunity in higher organisms, frequently serving in multiple capacities in defending the host from infection. These peptides exhibit very high degrees of sequence and structural diversity. In order to more effectively analyze the host-defense peptidome and identify low abundance peptides, we have developed a novel bioprospecting-inspired approach to CAMP discovery. Our process utilizes custom functionalized hydrogel particles to preferentially enrich peptides with CAMP-like properties from plasma and other complex biofluids for subsequent analysis via tandem mass spectrometry, from which we can determine the sequences of the intact native peptides. We have successfully employed this process to identify novel natural CAMPs from the American alligator and Komodo dragon. Moreover, these studies have yielded peptides that exhibit broad-spectrum antimicrobial effectiveness, including against multidrug resistant strains.

References

Acknowledgement
This work was supported in part by the Defense Threat Reduction Agency (DTRA), HDTRA1-12-C-0039. It was also supported in part by the College of Science at George Mason University. Neither DTRA nor GMU were involved in study design, data collection and analysis, or preparation of the presentation. We are very grateful to Dr. Kent Vliet of the University of Florida and the St. Augustine Alligator Farm Zoological Park and its staff for their support and for providing the blood samples used in these studies.
Biography
Barney Bishop, PhD is an associate professor in the Department of Chemistry and Biochemistry at George Mason University. He received a PhD in chemistry from the University of North Carolina at Chapel Hill in 1997, where his graduate research focused on peptide chemistry. Dr. Bishop then joined the laboratory of Dr. Lynne Regan at Yale University as a postdoctoral associate where his research focused on protein engineering and biophysical characterization. From spring of 2001 until the fall of 2003, Dr. Bishop was a Senior Research Scientist at New River Pharmaceuticals, a specialty pharmaceutical company focused on the development of novel pro-drug and drug delivery technologies. New River Pharmaceuticals was acquired by Shire Pharmaceuticals in 2007.

Dr. Bishop joined the Department of Chemistry and Biochemistry at George Mason University in the fall of 2003. His current research interests include antimicrobial peptides, the design of novel therapeutic agents for combating infection, and development of new technologies and strategies for the discovery and identification of antimicrobials from biological and environmental samples.
POSTER ABSTRACTS

Poster Categories

P01– P06: Drug Discovery Projects Seeking Research Partners or Collaborators

P07– P13: Novel Drug Discovery Technologies or Platforms

P14– P34: General Drug Discovery

P35– P38: Institutional Resources/Facilities within Virginia to Support Drug Discovery
RY-1002: A SPECIFIC AND POTENT LIGAND AT SIGMA RECEPTORS

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Sigma 1 (σ₁) and sigma 2 (σ₂) receptors were cloned in 1996 and 2017, respectively, and have been implicated in a variety of medical conditions: amyotrophic lateral sclerosis (ALS), anxiety, attention/learning/memory dysfunctions (Alzheimer’s disease, ADHD), cancer, depression, HIV, pain, Parkinson’s disease, schizophrenia, stroke and ischemia, traumatic brain injury (TBI) and substance use disorder (SUD). Although a number of drugs have been promoted as “specific” sigma receptor ligands (for either σ₁ and/or σ₂), their greatest drawback is the lack of specific affinity for just sigma receptors. Most often, these drugs (a) also interact (potently) with serotonin (5-HT), dopamine (D), norepinephrine (NE) and/or other neurotransmitter receptor sites or (b) have been tested only at sigma sites.

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<th>RY-1002</th>
<th>Rimcazole</th>
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RY-1002 is a prototype drug that was evaluated in 44 receptor binding assays, which indicated specific and potent affinities at σ₁ and σ₂ receptors (σ₁ (Kᵢ = 12 nM) and σ₂ (Kᵢ = 28 nM)). RY-1002 displayed no appreciable affinity at α-adrenergic, β-adrenergic, benzodiazepine, peripheral, dopamine D₁, D₂, D₃, D₄, GABA<sub>₁</sub>, histamine H₁, H₂, H₃, muscarinic M₁, M₂, M₃, M₄, opioid μ, δ, κ, DOR, MOR, serotonin 5-HT₁A, 1B, 1D, 1E, 2A, 2B, 2C, 3, 5A, 7, receptors or transporters DAT, NET, SERT. In comparison and contrast, the reference drugs rimcazole and (+)-3-PPP [(+)-3-(3-hydroxyphenyl)-N-(1-propyl) piperidine)] were not as specific or as potent at sigma receptors.

Structurally, RY-1002 is distinct from previously reported sigma (or marketed neuropsychiatric) drugs. RY-1002 could represent “first-of-its-kind” pharmacotherapy that relies solely on sigma receptor interactions to treat medical conditions. However, it will need further research to evaluate its potential efficacy in sigma-related therapeutic-like indications.

References

Acknowledgement
Patent pending: U.S. and foreign rights available. This technology is available for licensing to industry for further development and commercialization. Ki data were generously provided by the National Institute of Mental Health/Psychoactive Drug Screening Program (NIMH/PDSP). Inquiries are welcome for chemical and/or pharmacological collaborations.
RY-1004 AS POTENTIAL CHEMOTHERAPY FOR CANCER

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Sigma receptors are classified into two subtypes: sigma-1 (σ₁) and sigma-2 (σ₂). Sigma-2 receptors have been implicated in central nervous system (CNS) disorders, cancer and may exert a role in the regulation of cell survival, morphology and differentiation. Recently, the molecular identity of this receptor was linked to the protein coding gene TMEM97 (Transmembrane Protein 97), a protein for which gene and protein sequence are available. TMEM97 is known to be involved in the regulation of cellular cholesterol homeostasis; although cholesterol is normally linked with cardiovascular diseases, it also may exert an important role in the onset and progression of Alzheimer’s disease.

Sigma-2 receptors are highly expressed in proliferating malignant cancer cells, and they are currently under investigation as target for anticancer therapeutics or adjuvant anticancer treatment agents. RY-1004 was synthesized as a prototype σ₂ receptor drug that may produce therapeutic effects for cancer.

The National Institute of Mental Health/Psychoactive Drug Screening Program (NIMH/PDSP) evaluated RY-1004 in 45 receptor binding assays and results indicated very selective and potent affinities at σ₁ (Kᵢ = 12 nM) and σ₂ (Kᵢ = 6 nM) receptors.

The National Cancer Institute’s Development Therapeutics Program (NCI/DTP) agreed to evaluate RY-1004 (screen concentration = 1.00E-5 Molar) in the NCI-60 cancer cell screen test; cell lines are derived from 9 different cancer panels (leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate and breast). RY-1004 inhibited cancer cell growth in all 60 cell lines by at least 25% and demonstrated greater than 50% inhibition in cancer growth in 43 of 60 cell lines (i.e. 72% of cell lines) from the 9 cancer panels; lethality to cancer cells (4% to 57%) was reported in 7 of 60 cell lines.

RY-1004 also was evaluated in initial side-effect-like tests as measured by motor activity tests in mice and rats. Results indicated that it did not significantly alter dependent activity measures (i.e. movement time or distance) over a 300-fold range of doses (0.1 mg/kg to 30 mg/kg; IP) and over a 100-fold range of doses (0.1 mg/kg to 10 mg/kg; IP) in mice and rats, respectively.

RY-1004 is structurally distinct from previously reported sigma (σ or σ₂) receptor or cancer chemotherapy drugs. Initial results demonstrate this prototype drug as potential chemotherapy across a broad range of human cancers.

References

Acknowledgement
Patent pending: U.S. and foreign rights available. This technology is available for licensing to industry for further development and commercialization. Receptor binding and cancer cell screening data were generously provided by NIMH/PDSP and NCI respectively. Inquiries are welcome for chemical and/or pharmacological collaborations.
SENSITIZATION OF BREAST CANCER TO CHEMOTHERAPIES BY TARGETING THE EPigenetic REGULATOR NURF.

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Gene expression is abnormally regulated in cancer cells to promote several hallmarks of cancer (1). The dysregulation of epigenetic regulatory mechanisms plays a prominent role in promoting abnormal gene expression in cancer cells (2). Epigenetic regulators, including a variety of histone modifying enzymes and chromatin associated proteins, have been targeted therapeutically to treat a number of different cancers, usually in combination with established therapies (3). Our previous studies identified an epigenetic regulator, the Nucleosome Remodeling Factor (NURF) (4), as a critical regulator of cancer cell gene expression that suppress tumor cell immunogenicity (5,6). Using the 4T1 breast tumor model, we determined if the antitumor effects of NURF inhibition could be further improved when combined with standard of care therapies for breast cancer. We observed that NURF inhibition selectively enhances the anticancer effects of the DNA damaging agent, doxorubicin, and the microtubule poison, paclitaxel in terms of growth inhibition, DNA damage and ER stress in vitro. Doxorubicin, but not paclitaxel, treatment of NURF inhibited cells results in increased autophagy. These studies were recapitulated using a novel bromodomain inhibitor which specifically targets NURF, demonstrating that NURF can be targeted pharmacologically (Figure 1)(7). Sensitization to doxorubicin and paclitaxel also occurs in 4T1 tumor bearing immune competent mice. In studies with doxorubicin, these same effects were not observed in immune compromised NSG mice, suggesting that sensitization also occurs to the antitumor effects of immune cells. Furthermore, in vitro, NURF inhibited cells were more sensitive to doxorubicin enhanced NK cell killing, supporting the immune cell component to enhanced tumor growth control in vivo. Future experiments will determine if sensitization of NURF inhibited cells to doxorubicin and paclitaxel occur through a common mechanism (e.g. Topoisomerase II inhibition), define the importance of autophagy for sensitization, and if sensitization occurs commonly in breast cancer cell lines. These studies indicate that inhibiting NURF is a novel means to sensitize cancer cells to both the cell autonomous and non-cell autonomous effects of chemotherapies, which occur in addition to enhancements in tumor immunogenicity resulting from NURF inhibition (5,6). Most importantly, these studies demonstrate that the novel NURF inhibitor has potent anti-cancer effects which could readily be optimized and transitioned into the clinic.

References

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CARDIOVASCULAR HYPOXIA AND EXPERIMENTAL THERAPEUTICS

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More than twenty years have passed since the discovery that cyclooxygenase-2 and other targets of pharmaceutical interest are transcriptionally regulated by hypoxia in human vascular endothelium. This understanding has not yet led to the approval of a new drug for the treatment of cardiovascular diseases. The cell biology of hypoxia and the major pharmaceutical industry initiatives that have followed are reviewed in this presentation, along with alternatives that are being developed at Coeurative, Inc.

Hypoxia induces a cellular transformation that leads to phenotype shifting as a function of oxygen tension. Hypoxia is measured in time and space as well as by partial pressure of oxygen. There are rapid changes, such as ion channel modulation, and relatively lasting changes, such as HIF- and NF-κB- mediated events. The cell-specific distribution of cardiovascular hypoxia is also a key determinant of its pathophysiologic impact. Coeurative, Inc. is developing a paradigm-shifting new class of small molecule pharmaceuticals. Oximetricans have been designed to take advantage of changes in the cell membrane induced by hypoxia to mediate focused delivery of therapeutic vascular endothelial messengers resulting in vasodilatation and anti-inflammatory effects when and where relative hypoxic disease states appear.

Therapeutics focused on inhibition of prolyl hydroxylases have been developed on the assumption that HIF is a friend, but off-target effects are certain to appear. Accordingly, Coeurative, Inc. is pursuing the development of the Oximetricans and related experimental therapeutics to address the massive public health challenges that are posed by cardiovascular diseases.
NON-ANTICOAGULANT HEPARIN MIMETIC AS AN INHIBITOR OF HUMAN NEUTROPHIL ELASTASE

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Human neutrophil elastase (HNE) is a serine-protease of the chymotrypsin superfamily stored in the azurophilic granules of neutrophils and comes into play in most inflammatory responses. Several natural anti-proteases including α1-antitrypsin, secretory leukocyte protease inhibitor, and elafin inhibit HNE. Yet, hyper-expression or -release of HNE causes protease–antiprotease imbalance resulting in inflammatory lung conditions such as chronic obstructive pulmonary disease, cystic fibrosis, acute lung injury, and adult respiratory distress syndrome. Generally, the treatment for these disorders is palliative and no FDA approved agent is available to halt the progression of HNE-dependent disease. This has led to a two-fold increase in the mortality rate over the past thirty years. It is predicted that appropriate HNE inhibitors will be beneficial in such disorders. Glycosaminoglycans, such as heparin, are potent inhibitors of HNE. However, the anticoagulant potency of heparins impose a serious limitation for use in inflammatory conditions. We reasoned that Non-Saccharide Glycosaminoglycan Mimetics (NSGMs) may allosterically and selectively inhibit HNE and serve as suitable agents for the management of HNE hyperactivity, alleviating HNE-dependent inflammatory disorders.

We studied a diverse in-house library of 60 NSGMs belonging to 5 different chemical classes carrying varying levels of sulfation as inhibitors of HNE. The sulfation level varied from 1 to 12 sulfates to mimic the diversity of glycosaminoglycans. Screening this library of 60 NSGMs using a chromogenic substrate hydrolysis assay led to identification of 23 agents that displayed nanomolar to micromolar IC₅₀ values for HNE inhibition. Ten NSGMs showing high potency against HNE (IC₅₀ = 40 – 600 nM) were selected from the 23 promising NSGMs identified in initial screen. Considering that the current cystic fibrosis therapy utilizes hyper-tonic saline to relieve mucus build up in patients, we studied the dependence of HNE inhibition potential of the 10 most promising NSGMs on high salt levels (0 – 400 mM). Salt dependence studies showed that 6 of these 10 these agents retained HNE activity at NaCl levels as high as 400 mM (2.34% w/v), which enhanced their potential further. Of these, four NSGMs were chosen and studied for HNE inhibition in the presence of elastin-congo red, a macromolecular substrate. Only 2 compounds, NSGMs 32 and 60, retained their inhibitory activity for over 48 hours whereas the other 2 showed a decrease in HNE inhibition with time. We then studied the anti-coagulant potency of NSGMs 32 and 60 by measuring the concentration of these agents required to double the activated partial thromboplastin time (aPTT) and prothrombin time (PT) in human plasma. These results indicated that NSGM 32 is not an anticoagulant in human plasma. In contrast, NSGM 60 is a moderate anticoagulant. To the best of our knowledge, this is the first unique, small non-saccharide heparin mimic that has been discovered as a promising anti-HNE agent. The intellectual property of NSGM 32 is being pursued by VCU Technology Transfer and the pre-clinical potential of 32 is currently being studied in the ex-vivo and in-vivo models of inflammatory disorders.

In conclusion, our studies validate the principle that NSGMs as a class of drugs is promising in inhibiting HNE. We identified a specific, structurally unique NSGM as potent inhibitor of HNE. This molecule is relatively easy to synthesize, homogeneous, and highly stable at room temperature. Further, NSGM 32 is a not an anti-coagulant, and hence, possesses good qualities necessary in an agent for further development as a clinically relevant compound.
NON-ANTICOAGULANT GLYCOSAMINOGLYCANS AS ANTI-NEUTROPHIL ELASTASE AGENTS IN THE MANAGEMENT OF CYSTIC FIBROSIS

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Cystic fibrosis (CF) is a genetic disease that affects multiple organs of the body. The lungs are the most impacted, and CF patients experience persistent infections and progressively deteriorating lung function. Dysfunction of protease–antiprotease balance plays an important role in CF with neutrophil elastase (NE) levels shown to be markedly elevated. Current CF management employs DNase, hypertonic saline and antibiotics, however, no anti-NE agents are administered to address the protease-antiprotease balance and thus, the elevated NE levels in the lungs of CF patients.

Although unfractionated heparin is a potent NE inhibitor, its anticoagulant property limits its usefulness in CF. We hypothesized that non-anticoagulant glycosaminoglycans (GAGs) having anti-NE activity will work better in CF. We thus studied the in vitro anti-NE activity of various GAG species having different chain lengths and sulfation patterns. Our studies indicate that GAG sulfation patterns different from those required for anticoagulant property are needed for NE inhibition. Additionally, sequences longer than hexasaccharides are minimally required. Michaelis-Menten kinetics studies point to an allosteric mechanism of inhibition and salt dependence studies show that both ionic and non-ionic interactions are vital. Per computational analysis, the NE GAG binding site is an electropositive domain comprising Arg75, Arg87, Arg178 and Arg187 which is in agreement with the allosteric nature of the interaction. Screening of a virtual library of oligosaccharides, including hexasaccharides, octasaccharides and decasaccharides, against the putative GAG binding site indicates that a particular tetrasaccharide sequence may be important for GAG recognition of NE.

Further, we studied the effectiveness of selected GAG species, especially 2-O,3-O-desulfated heparin (ODSH), a non-anticoagulant heparin, alone and in combination with CF therapeutic agents, for anti-NE activity in CF sputum. The results obtained demonstrate that GAGs are only useful in the presence of DNase, with sputum disrupters such as sputolysin being ineffective. Using computational and biochemical techniques, we demonstrate that DNA, which is present in sputum, and ODSH possibly bind to a common site, thus the results observed with DNase.

Overall, these studies indicate that GAG based compounds are a promising avenue to develop clinical anti-NE agents for the management of CF and provide information on treatment options to restore protease anti-protease balance in CF.

Acknowledgement
This work was supported by grant HL107152 from the National Institutes of Health to U.R.D; and supported by CFF Research Grant VOYNOW15IO to J.A.V. We also thank the computational resource provided by National Center for Research Resources (grant S10 RR027411). We thank Dr. Stephen Marcus, Cantex Pharmaceuticals, for the gift of ODSH.
A USER-FRIENDLY MICROFLUIDIC CHIP FOR ANTI-EPILEPTOGENIC DRUG SCREENING

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New pharmacological treatments for epilepsy will be discovered through the development of new screening platforms that are rapid, reliable, and can identify novel disease-modifying therapies, or anti-epileptogenic treatments. Xona Microfluidic, LLC (“Xona”) is in a unique position to provide such screening tools and services for epilepsy research. Xona focuses on the development of microfluidic platforms for neuron cell culture and provides devices that allow compartmentalization and fluidic isolation of axons and/or dendrites, and somata. We have patented technology and have sold devices to hundreds of labs world-wide, including many pharmaceutical laboratories. Epileptogenesis induces an imbalance in inhibitory/excitatory circuits within the brain, leading to hyper-excitability and seizures. A common cause of epilepsy is brain damage due to traumatic brain injury or stroke, often involving pyramidal cells within the hippocampus. Our academic partners at UNC recently demonstrated the reliable induction of hyper-excitability in pyramidal cells using a standard neuron device (SND) configuration microfluidic chamber in response to axotomy (Nagendran et al., Nature Communications, 2017). This hyper-excitability, which involves an imbalance of excitation and inhibition, develops reliably and with a delay, at two days after axotomy. Xona has dramatically improved the manufacturability of our platform leading to fully assembled, more robust devices. Our current work focuses on developing a new platform optimized for screening anti-epileptogenic compounds using this new manufacturing approach to provide a much-needed screening service to researchers as well as current and future pharmaceutical customers.

References


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DESIGNER ANTIMICROBIALS TO TREAT DISEASES DUE TO MULTIDRUG RESISTANT PATHOGENS

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Abstract: Drug resistant bacterial pathogens have become more common especially in intensive treatment facilities like hospitals and senior care centers. This resistance is even more acute in food animal production as well as in other animals. One approach to addressing the ongoing problem of antimicrobial resistance is to explore ways to repurpose conventional antibiotics by complementing or enhancing their mechanism of action. We hypothesize that drug resistance in bacterial pathogens can be addressed by designing 10 to 12 nucleotide long synthetic oligonucleotide called a peptide nucleic acid (PNA) that is designed to \textit{complementarily} bind the DNA and mRNA coding for essential gene(s) and/or to gene(s) associated with efflux pump systems of drug resistance (1). \textbf{PNAs basically interfere with gene expression.} To enhance uptake, a small cell penetrating peptide (CPP) is attached to PNA for efficient delivery into the pathogens. Results: To test this hypothesis \textit{in vitro}, a minimum inhibitory concentration (MIC) assay was performed, in which a drug resistant bacterial pathogen was incubated with a 15 uM concentration of the anti-TetA CPP-PNA (inhibits expression of the efflux pump), combined with varying concentrations of tetracycline, ranging from 64 ug/mL down to 0.25 ug/mL. Treatment with anti-TetA CPP-PNA caused the MIC to decrease four-fold (32 ug/mL to 8 ug/mL) of \textit{Salmonella Typhimurium DT104}, and the minimum bactericidal concentration (MBC) to decrease two fold (< 64 ug/mL to 16 ug/mL) of strain DT104. We have shown that CPP-PNAs designed complementary to a drug resistance gene \textbf{enhances their susceptibility to the tetracycline}. We have tested in a similar setting other CPP-PNAs designed against essential genes and found them to be effective in killing pathogens \textit{in vitro} as well as in infected macrophages (2,3).

Our initial conclusions are that treating \textit{in vitro} with a CPP-PNA designed to suppress efflux pump expression was effective for repurposing by lowering the MIC and MBC suggesting that these molecules may be used synergistically with conventional antimicrobials. The \textit{in vivo} results treating mice infected with strain DT104 were equivocal as to the benefit of treating with CPP-PNA targeting the efflux pump. At this time, we feel this is due to difficulty in delivering such small molecules to the target efficiently. At present, we are looking for partners with funding to develop systems for the efficient delivery of CPP-PNAs to the target and develop a commercially viable system to address drug resistance.

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DEVELOPMENT OF PHOTODEGRADABLE MOF NANO-CAGES FOR CONTROLLED RELEASE OF 5-FLUOROURACIL

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The development of controlled drug delivery systems is crucial for reducing toxicity and minimizing off target drug effects for patients. A novel PEG functionalized nanoMOF containing an azobenzenedicarboxylate linker (UiO-AZB) shows great promise as a potential nanocarrier. Nanoparticles were loaded with 5-fluorouracil (5-FU), a common FDA approved therapeutic used to treat cancer patients. A maximum loading of 15 wt% 5-FU is achieved after 3 days. Upon loading, decreases in both surface area and pore volume are observed, which is indicative of successful incorporation of the drug into MOF pores. PEGNH$_2$@5-FU-UioAZB nanoparticles also exhibit successful cellular uptake and enhanced biocompatibility after encapsulation with the PEG coating. Upon irradiation with light (340 nm), the azobenzene linkers isomerize, resulting in degradation of the nano-cages and controlled drug release. Preliminary in vitro studies show that the components of the nano-cage itself do not result in cell toxicity. Current work focuses on modifying the photo-responsive linker in order to shift the absorbance of the system into the therapeutic window of 650-850 nm. These findings suggest great potential for the use of nanoMOFs as drug delivery vehicles.

References


NATIVE CELL MEMBRANE NANOPARTICLES SYSTEM

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We devised a native cell membrane nanoparticles system for high-resolution structure determination of membrane proteins using cryo-EM, which we applied in a study of the multidrug exporter AcrB. Lipid-AcrB nanoparticles were prepared directly from membranes without any use of detergents. A 3D reconstruction in C1 symmetry achieved a final density map at 3.2 Å resolution, an atomic model of quasi-C3-symmetric AcrB was fitted to this map, and the residual density revealed many ordered lipid molecules. Most remarkably, a central cavity between the three transmembrane domains contains a 24-lipid patch of well-ordered bilayer structure. In AcrB D407A, a putative proton-relay mutant, lipid bilayer buttresses protein interactions lost in crystal structures after detergent-solubilization. Our detergent-free system preserves protein-lipid interactions for visualization. This system should be broadly applicable for membrane protein structural biology and structure-based drug discovery.

References

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NEXT-GEN SEQUENCING OLIGOS (NGSO) FOR CONSISTENT AND EFFICIENT SEQUENCE ASSEMBLY

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Target identification is often the first step in any drug discovery workflow. An efficient and unbiased screen of the entire genome for specific cellular phenotypes can lead to rapid identification of potential molecular targets for therapeutic intervention. Whole-genome screening applications often require next-generation sequencing (NGS) of cell populations with the desired phenotype. Regardless of NGS platform, universal and index adapter sequences are required for the proper assembly of sample fragments. Adapters – especially index adapters since they contain the multiplex identifier (MID) or barcode – containing too high a proportion of truncated sequences (unacceptably low purity) or too high a proportion of other adapter sequences (excessive cross contamination) can lead to compromised sequence read integrity as well as excessive adapter dimerization and improper sequence assembly, respectively, during multiplexing experiments. These types of problems are undetectable until the data analysis stage, which makes them costly in terms of time and money. Therefore, the production process used for the adapter sequences is critical for a successful sequencing run. Affordable, custom Next-Gen Sequencing Oligos (NGSO) are manufactured under rigorous conditions to ensure suitable purity and low cross contamination and to meet research, commercial, and molecular diagnostic needs. Our approach eliminates failed sequencing runs that could have resulted from poor adapter quality. Customer testing has shown our NGSO to be 70% less expensive than a popular adapter kit (on a per library preparation basis) as well as capable of preparing libraries with adapter dimers and cross contamination as low as 6.28% and 0.015%, respectively. Use of NGSO will be of tremendous benefit to drug discovery workflows that require next-generation sequencing.
"NEXT GEN" OVARIAN CANCER THERAPEUTICS

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Ovarian cancer (OvCa) is the 5th leading cause of cancer deaths in US women with a approximate 45% five year survival rate. OvCa recurrence and drug resistance is common, but the current OvCa therapeutic standard of care lacks innovation and is ineffective against recurrent drug resistant OvCa. Unfortunately, kinase inhibitors and immunotherapies have been largely unsuccessful at treating OvCa. We are now developing a small molecule therapeutic that is effective against recurrent, drug resistant OvCa. JMS-053 is a potent small molecule inhibitor of PTP4A3 phosphatase, which is a known cancer causing protein. JMS-053 is a reversible, non-competitive inhibitor of PTP4A3 activity that exhibits cell-based and in vivo activity. We are currently expanding the in vitro and in vivo analysis of JMS-053 and are targeting PK/PD, formulation and process chemistry for more advanced studies. JMS-053 further supports the tractability of phosphatases as novel drug targets.

Acknowledgement

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A POTENT AND SELECTIVE ALLOSTERIC PTP4A3 PHOSPHATASE INHIBITOR ENHANCES MICROVASCULAR BARRIER FUNCTION AND INHIBITS HUMAN TUMOR CELL GROWTH

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The metastasis-associated protein tyrosine phosphatase PTP4A3 is highly expressed in both tumor and endothelial cells. Deletion of the Ptp4a3 gene results in tumors with a decreased vascularity. PTP4A phosphatases appear to regulate several key malignant processes, such as invasion, migration, and angiogenesis, suggesting a pivotal regulatory role in cancer and endothelial signaling pathways. We have identified a potent, selective, reversible, and noncompetitive PTP4A3 inhibitor, JMS-053, which markedly enhanced microvascular barrier function after exposure of endothelial cells to vascular endothelial growth factor or lipopolysaccharide. JMS-053 also blocked the concomitant increase in RhoA activation and loss of Rac1. In human cancer cells, JMS-053 impeded migration, disrupted spheroid growth, and decreased RhoA activity. These data demonstrate that PTP4A3 phosphatase can be targeted in both endothelial and ovarian cancer cells, and further confirm that RhoA signaling cascades are regulated by the PTP4A3.

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The work was supported by grants from the National Institutes of Health (R21 CA191944, R01 CA207288, S10 OD021723, and F31 CA196062), the Fiske Drug Discovery Fund, 4-VA Collaborative Research Grant, and the Ivy Foundation.
COORDINATED CHEMICAL-GENETICS APPROACH IDENTIFIES PTP4A3-MEDIATED REGULATION OF COLON CANCER CELL MIGRATION AND EXTRACELLULAR MATRIX INTERACTIONS

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Aberrant regulation of protein phosphorylation is an exceedingly common driver of human cancers. It is notable that we understand much less about the role of protein tyrosine phosphatases in human malignancies compared to tyrosine kinases. The membrane-associated, intracellular, protein tyrosine PTP4A3 is highly overexpressed in multiple tumor types including colorectal cancer and has been associated with tumor metastases. We have, therefore, investigated the role of PTP4A3 in colon cancer migration and invasion. The \textit{Ptp4a3} gene was expunged from colon tumor cells derived from \textit{Ptp4a3} \textit{floxflox} mice and the resulting cells exhibited impaired migration, invasion and colony formation compared to the wildtype isogenic cells. We characterized a new potent, selective, noncompetitive small molecule inhibitor of PTP4A3, JMS-631-053, which also disrupted colon cancer cell migration, invasion, and colony formation. PTP4A3 deletion increased the expression of extracellular matrix (ECM) and adhesion genes, including the tumor suppressor Emilin 1. Expression of these extracellular matrix genes are mutually exclusive with PTP4A3 expression in tumors derived from patients with colorectal cancer. These chemical and biological reagents reveal a previously unknown communication between the intracellular PTP4A3 phosphatase and the ECM and support continued efforts to pharmacologically target PTP4A3 for cancer therapy.

Acknowledgement
The work was supported by grants from the National Institutes of Health (R21 CA191944, R01 CA207288, S10 OD021723, and F31 CA196062), the Fiske Drug Discovery Fund, 4-VA Collaborative Research Grant, and the Ivy Foundation.
SELECTIVELY TARGETING PIK3CB/P110B TO TREAT Glioblastoma

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Abstract
Glioblastoma multiforme (GBM) is lethal even after surgical removal of the tumor, radiation, and chemotherapies. Residual tumor cells form an intractable tumor in nearly all patients within two years (1). Recurrent GBM is incurable due to resistance to current therapies. Targeting PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase) signaling—a signaling pathway that causally contributes to tumor formation/recurrence—to treat original and recurrent glioblastoma has been extensively explored, but with limited success (2), possibly because non-selective inhibition of PI3K isoforms, yields intolerable toxicity. Class IA PI3K isoforms include three catalytic subunits (PIK3CA, B, or D that encodes p110α, β, or δ) and three regulatory subunits (PIK3R1-3 that encodes p85 isoforms). Based on our recent work, PI3K catalytic isoforms display distinct correlations with GBM recurrence. We find that only PIK3CB levels positively correlate with the chances/risk of GBM recurrence, while being inversely associated with patient prognosis (3). To further our understanding of PI3K isoforms in GBM and test the hypothesis that selectively targeting PI3K isoforms will yield a better response with low toxicity to normal brain, we carried out the following comprehensive studies. First, we measured the expression of PI3K isoforms in a panel of 9 GBM cell lines, 8 primary GBM cell lines, and 6 glioma stem cell (GSC) lines. GBM cell lines expressing higher levels of p110β, coincided with increased levels of phosphorylated AKT. Next, we knocked down PIK3CA, B, and D in human U87MG cells and found that only depletion of PIK3CB/p110β resulted in an inactivation of AKT and GSK3β. Moreover, knockdown of PIK3CB/p110β, but not other isoforms, induced substantial growth inhibition of U87MG, SF295 and U251 cells. This is congruent with the result that inhibition of PIK3CB/p110β activated apoptosis in U87MG cells. Finally, we determined the efficacy of isoform specific inhibitors of PI3K catalytic isoforms. Selective inhibitors of p110β, but not other PI3K isoforms, remarkably suppressed the viability and growth of GBM cell lines, primary cells, and xenograft tumors in mice, with minimal cytotoxic effects on astrocytes. Collectively, our results demonstrate that PIK3CB/p110β is an important selective survival factor for GBM, underscoring the divergent roles of PI3K isoforms in GBM disease progression/recurrence and the importance of selectively targeting PIK3CB/p110β as an effective therapy for GBM.

References
DIFFERENTIAL CHEMOTHERAPY RESPONSE IN MODELS OF TRIPLE NEGATIVE BREAST CANCER BASED ON GLYCOSAMINOGLYCAN STATUS

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We report enhanced in vivo activity for a series of polynuclear platinum compounds (PPCs) in models of triple negative breast cancer (TNBC) compared to the clinical compounds, cisplatin and carboplatin. We hypothesize that the efficacy of positively charged PPCs over clinical compounds in certain models may be due to their high affinity for binding sulfated glycosaminoglycans (GAGs). GAGs are highly negatively-charged carbohydrates attached to cell membrane proteins, known collectively as proteoglycans. GAGs mediate interactions with angiogenic factors and their respective cell surface receptors. The extent of sulfation, length, and number of glycosaminoglycan attachment sites on the proteoglycans are all factors that contribute to the angiogenic and metastatic signaling events associated with cancer progression. The upregulation of sGAGs in TNBC occurs through mechanisms that include an increase in expression of proteoglycans (eg., syndecans), enzymes involved in sGAG synthesis (eg., xylosyltransferases) or modulation of the sulfotransferase/sulfatase balance. Recently, we discovered that sGAGs mediate the cellular accumulation and cytotoxicity of PPCs, block heparanase and fibroblast growth factor (FGF-2) binding to sGAGs and inhibit downstream metastatic signaling pathways [1-3]. Here, we show that PPCs specifically target tumors with higher GAGs in vivo, and that the cellular accumulation of PPCs is dependent upon the extent of sulfation of GAGs. Furthermore, we show that PPCs are more effective than carboplatin in the WHIM2 PDX model showing high levels of the syndecans-1 (Sdc1), but equal to, or less effective than carboplatin in WHIM30 and PT52 PDX models showing lower levels of Sdc1. We plan to further evaluate the relative levels of sulfated GAGs in each of these PDX models using GAG-specific staining reagents (1,9 Dimethyl-Methylene Blue and RuRed) and antibodies that detect the total levels of heparan sulfate proteoglycans (3G10), N-sulfated heparan sulfate (10E4), and sulfated chondroitin sulfate type A/C (CS-56). We will continue to correlate the activity of PPCs and clinical agents in additional PDX models profiled for relative levels of sulfated GAGs. This effort will generate valuable preclinical data on sulfated GAGs as a viable target in TNBC and help to establish a rational approach for stratification of TNBC patients that could benefit the most from treatment with PPCs.

References


Acknowledgement

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CHEMORESISTANCE OF CANCER CELLS GROWING UNDER ANCHORAGE-INDEPENDENT CONDITIONS IS INDEPENDENT OF THEIR ABILITY TO FORM 3D STRUCTURES: IMPLICATIONS FOR ANTICANCER DRUG SCREENING.

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Three dimensional (3D) cultures systems such as floating spheroids (FSs) and floating tumourspheres (FTs) are widely used by academics and industry researchers as tumors models of chemoresistance. Both systems form complex 3D structures creating cellular heterogeneity, pH and metabolic gradients as well as physical barriers that limit drug penetration. FTs are also considered to be enriched in cancer stem-like cells (CS-LCs) that are inherent chemoresistant [1, 2]. All these factors have been associated with chemoresistance of 3D systems. In this study we compared the chemoresistance of cancer cells lines able to form FSs under anchorage–independent conditions (lung H460, prostate LnCAP and breast MCF-7) to cell lines that do not form FSs under similar conditions (prostate PC3 and breast MDA-MB-231). We found that all cell lines growing under anchorage-independent conditions become highly resistant to Obatoclax, Colchicine and Hydroxyurea compared to cells growing under anchorage-dependent conditions. LnCAP cells grown in the presence or absence of anti E-cadherin antibody (that blocked the formation of FSs) showed similar chemoresistance. Our results demonstrate that development of chemoresistance is not due to the formation of complex 3D structure and/or enrichment of CS-LCs but is it likely the result of cell detachment per se and their ability to survive under anchorage-independent conditions. We propose that FSs and FTs could be useful models to study chemoresistance of cancer cells associated with cell detachment (e.g. circulating tumor cells) but they may not be representative of other types of chemoresistance that arise in vivo in attached cells.

References

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DESIGN, DEVELOPMENT AND TESTING OF NOVEL FATTY ACID SYNTHASE INHIBITORS

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Fatty acid synthase (FASN) is an enzyme which catalyzes de novo synthesis of palmitate from acetyl-CoA and malonyl-CoA. FASN is over expressed in cancer cells to meet their higher lipid and energy requirement to sustain high proliferation rate. This makes FASN a potential therapeutic target for cancer treatment. There are several natural and synthetic FASN inhibitors such as cerulenin, C75, orlistat, triclosan, EGCG etc. However, they either lack stability, solubility or has undesired side effects which render them unfit to be used as anticancer drugs1. We have designed and developed a series of novel palmitate based FASN inhibitors. These inhibitors have shown potent anticancer activity in lung, breast and prostate cancer cells with IC50 in low µM range. Western blot analysis showed that these inhibitors increased the phosphorylation of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) which are associated with decreased Malonyl CoA synthesis and reduced synthesis of palmitate. This finding was further supported by mass spectrometric quantification of 13C labeled palmitate which demonstrated about 80-90% reduction in the production of labeled palmitate upon treatment with these inhibitors. We are currently developing second generation of palmitate based FASN inhibitors and exploring targeted delivery of these inhibitors by employing nanoparticles and nanospheres as potential carriers.

References

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RATIONALLY DESIGNED SHORT ANTIMICROBIAL PEPTIDE VARIANT DERIVED FROM SNAKE VENOM-ASSOCIATED CATHELICIDIN DEMONSTRATES ANTI-INFECTIVE AND ANTI-CANCER THERAPEUTIC POTENTIAL

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The rampant spread of antimicrobial resistance and emergence of multidrug and extensively drug resistance strains of bacterial pathogens all over the world threaten the effectiveness of existing antibiotics. Each year in USA, infections caused by antibiotic-resistant bacteria result in over 2 million illnesses and about 23000 deaths [1]. Cationic antimicrobial peptides (CAMPs) are important components of innate immunity in animals and plants and are being explored as potential leads for the development of new therapeutics against drug resistant pathogens. Cathelicidins are a class of CAMPs found in vertebrates. Cathelicidins, that are often over 30 amino acid residues in length, often adopt secondary structures containing both helical and extended segments [2]. Truncated synthetic helical peptides derived from the sequences of cathelicidins frequently retain varied degrees of antimicrobial effectiveness, with many new designed variants exhibiting improved potencies relative to the peptides upon which they were based. However, very few studies have focused on the functional importance of the C-terminal extended segments, which are often present in predominantly helical cathelicidins [2]. The 34-residue cathelicidin, NA-CATH, identified from Chinese cobra cDNA library, contains an N-terminal helix followed by a predominantly hydrophobic random coil segment [3]. A short 11-residue synthetic peptide (ATRA1) with a sequence based on the N-terminal segment of NA-CATH was identified by Bishop lab to possess antimicrobial properties [4], but only in low ionic strength media conditions. We have introduced a peptide segment, hydrophobic tail, with a sequence based on the C-terminal 8-residue segment of NA-CATH, at the C-terminus of ATRA1 and the peptide variant ATRA1-R3W2, affording the 21-residue chimeric peptides, ATRA1-HYD and ATRA1-R3W2-HYD respectively. These peptides demonstrated improved bacterial membrane disruptive and antimicrobial activities. ATRA1-R3W2-HYD demonstrated selective toxicity against cancerous lung epithelial cells. The activities exhibited by ATRA1-R3W2-HYD against both susceptible and antibiotic-resistant pathogenic strains under near physiological conditions, such as serum, and potent selectivity against cancer cells suggest that it may provide a promising lead for further developments for anti-infective and anti-tumor therapeutic purposes.

References

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TARGETING GLUTAMATE METABOLISM FOR THE TREATMENT OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS

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Despite combined antiretroviral therapy (cART) effectively inhibiting HIV viral replication and extending life, about 50% of all HIV+ individuals develop HIV-Associated Neurocognitive Disorders (HAND). HIV infection of perivascular macrophages, microglia, and astrocytes in the brain occurs early in disease, and has been linked to persistent neuroinflammation and cognitive impairment even when peripheral viral loads are suppressed. HAND symptoms have also been linked to upregulated expression of the primary glutamate-synthesizing enzyme, glutaminase, which may contribute to observed excess glutamate production in the brain leading to aberrant excitatory neurotransmission, excitotoxicity, and impaired cognitive function. Glutaminase inhibition may thus represent a novel drug target to confirm treatment of HAND. We recently developed JHU083, an orally available, brain penetrant prodrug of the glutaminase inhibitor 6-diazo-5-oxo-1-norleucine (DON). Here, we show that JHU083 reduces excess glutamate levels in the central nervous system, normalizes microglia glutaminase activity and restores cognitive function in HIV-infected mouse models. Therefore, glutaminase inhibition can reduce toxic glutamate levels and may serve as a novel target for HAND treatment.

References

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DEVELOPMENT OF (R)-PROLINOL BASED DERIVATIVES TARGETING SPHINGOSINE KINASE-1

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Abstract
Sphingosine kinase 1 (SphK1) is the key enzyme catalyzing the formation of sphingosine-1-phosphate (S1P), which is an important signaling molecule regulates multiple biological process including inflammatory responses. Elevated SphK1 activity as well as upregulated S1P level is linked to various diseases, such as cancer, fibrosis and sickle cell disease. Therefore, there is a growing interest in studying on SphK1 as a potential target for aforementioned diseases. Through high throughput screening, various SphK1 inhibitors have been discovered, among which PF543 is the most potent inhibitor reported to date (K_i = 3.6 nM). Previous research indicated that SphK1 inhibitor PF543 are effective in reducing S1P levels and slowing down the development of sickle cell disease in vivo. However, the lack of in vivo stability of PF543 still makes it necessary to develop inhibitors with improved pharmacokinetic profile. In this study, PF543 was employed as the lead compound, and the influence of different tails groups upon binding affinity and in vivo stability were investigated. In brief, (R)-prolinol based derivatives with various tail groups including alkyl, alkoxy and biphenyl groups were synthesized. Their inhibition potency was tested by broken-cell assay, and hit compounds were further evaluated on yeast cell assay for EC50 values. U937 cell line was utilized for hit compounds to quantify S1P reduction in vitro. Our preliminary results indicated compounds SLL051666 and SLL05637 were best 2 hits discovered so far, with the SphK1 inhibition of 71% and 88%, respectively at 1 µM. In addition, SLL05166, with K_i of 0.68 µM and EC50 of 0.15 µM, reduced S1P level of U937 cells by 90% at 1 µM. Future study will focus on head group modification to improve in vivo stability.

References

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BIOENERGETICS @ VIRGINIA TECH:
INNOVATIVE AND COMPREHENSIVE SCREENING FOR MITOCHONDRIAL EFFICACY/TOXICITY

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Mitochondrial dysfunction has been implicated in a host of disease states, and mitochondria are being recognized as a burgeoning target for therapeutic development. We provide innovative and comprehensive approaches for assessing the impact of novel therapeutic interventions on mitochondrial function. Using a comprehensive, vertically integrated approach, we are able to assess bioenergetic function in whole organs and tissues, isolated muscle fibers, cultured and isolated cells, and isolated mitochondria. This is accomplished through the use of cutting edge, custom-designed high resolution respirometry, fluorometric detection assays, high content imaging, novel approaches for assessing mitochondrial toxicity and high throughput extracellular flux analyses. Utilizing these tools, we are able to evaluate the functional state of mitochondria in both health and disease and can better decipher the effects of therapeutic interventions. In addition to these canonical bioenergetic assays we have developed novel imaging techniques to visualize mitochondria. Employing these techniques in intact beating hearts and isolated cardiomyocytes facilitates a completely new approach to understanding the role of therapeutic treatments in mitochondria. Furthermore, we are able to measure the impact of bioenergetic changes in cultured cells on precisely-aligned nanofibers by capturing force production, rates of migration and cell protrusion formation. When taken together this cache of customizable assays affords us a unique capacity to better understand what mitochondrial dysfunction looks like and the best techniques with which to intervene.

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ANTIMICROBIAL PEPTIDES WITH ACTIVITY IN A MURINE PNEUMONIC TULAREMIA MODEL

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Using our Bioprospector process with custom-made hydrogel particles, our group identified a C-terminal fragment of apolipoprotein C-1 from Alligator mississippiensis blood with broad-spectrum activity against a range of bacteria, including drug-resistant strains. In this work, we tested this peptide fragment (Apo6) and synthetic derivatives (GATR-1 to -7) against strains of Francisella tularensis to determine activity in vitro and in vivo and to examine mechanism of action. The synthetic derivatives were produced by altering amino acids in the peptide to increase hydrophobicity, positive charge, and hydrophobic moment. The antimicrobial activity of the peptides was found to increase as they increased in hydrophobicity and charge, but only to a certain point. We examined mechanism of action using DiSC3(5) and ethidium bromide for membrane disruption and using dimethylmethylene blue for LPS binding. It was found that all of the peptides disrupted the bacterial membrane of Francisella and bound this bacteria's atypical LPS. Altered peptide sequences increased activity of both mechanisms to a certain point. The highest performing peptides were tested in a murine pneumonic tularemia model using F. tularensis subspecies holarctica Live Vaccine Strain. All of the tested peptides rescued at least some of the mice. However, GATR-3, a moderately derived peptide, was found to have the most effective activity in vivo. GATR-3 rescued 60% of mice and decreased severity of symptoms over the course of infection.

References
TARGETING Dxr/IspC TO DEVELOP DRUGS AGAINST MALARIA AND TUBERCULOSIS


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The methylerythritol phosphate pathway (the MEP pathway) of isoprenoid biosynthesis is essential for the survival of many pathogenic organisms, including Plasmodium falciparum and Mycobacterium tuberculosis, causative agents of malaria and tuberculosis, respectively. The MEP pathway is absent in humans, making it an important drug target. There are seven enzymes in this pathway. 1-Deoxy-D-xylose 5-phosphate reductoisomerase (Dxr/IspC) catalyzes the first committed step in the pathway. It converts the substrate 1-Deoxy-D-xylose 5-phosphate (DXP) into 2-C-methyl-D-erythritol 4-phosphate (MEP), which in turn is the substrate for the downstream enzymatic steps. We have expressed and purified IspC of Plasmodium falciparum (PfIspC) and Mycobacterium tuberculosis (MtIspC) using E. coli as an expression system. Finally, we carried out enzyme inhibition assays using rationally designed IspC inhibitors, showing IC₅₀ results ranging from 0.17–2.8 µM.

References

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TARGETING THE ESKAPE PATHOGENS: KINETIC CHARACTERIZATION AND INHIBITION OF ACINETOBACTER BAUMANNII AND KLEBSIELLA PNEUMONIAE 1-DEOXY-D-XYLULOSE 5-PHOSPHATE REDUCTOISOMERASE

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Acinetobacter baumannii and Klebsiella pneumoniae are gram-negative pathogens frequently encountered in the health and military sectors. They comprise two of the ESKAPE pathogens, a group of multidrug resistant pathogens that are the leading cause of nosocomial infections worldwide. The rapid increase of multidrug-resistant (MDR) gram-negative pathogens, has led to increased use of the “last-resort drug” colistin. With the elevated usage of colistin, the emergence of colistin-resistant pathogens poses a dire health threat. In September 2016, a patient died in Reno, Nevada due to K. pneumoniae induced sepsis. The specific strain of K. pneumoniae isolated from the infection was found to be resistant to all 26 antibiotics available in the United States, including colistin. The methylerythritol phosphate (MEP) pathway is an attractive target for the development of new antimicrobial drugs. The MEP pathway governs the synthesis of isoprenoids, which are key lipid precursors for vital cell components such ubiquinone and bacteriohopanoids. Additionally, the MEP pathway is entirely distinct from the corresponding mammalian pathway, the mevalonic acid (MVA) pathway. Therefore, the first committed enzyme of the MEP pathway, 1-Deoxy-D-Xylulose 5-Phosphate Reductoisomerase (IspC), is an attractive target for antibiotic development. To facilitate drug development against two of the ESKAPE pathogens, Acinetobacter baumannii and Klebsiella pneumoniae, we cloned, expressed, purified, and characterized IspC from A. baumannii and K. pneumoniae. We have determined the apparent kinetic constants for A. baumannii and K. pneumoniae IspC, as well as the IC50 values for two natural IspC inhibitors, fosmidomycin and FR900098. Fosmidomycin and FR900098 were potent inhibitors of A. baumannii and K. pneumoniae IspC. Finally, we crystallized and determined the molecular structure of A. baumannii IspC to facilitate future drug design.

References
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SYNTHESIS OF α,β-UNSATURATED PHOSPHONATE ESTERS AS DXR INHIBITORS

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Plasmodium falciparum (Pf) and Mycobacterium tuberculosis (Mtb) are infectious microorganisms of particular interest, as these organisms infect millions worldwide. Unfortunately, both Pf and Mtb continually develop resistance to current drug therapies. Thus, resistance presents an imperative need to develop next-generation drugs to combat these infectious agents. One such approach is by inhibition of the non-mevalonate pathway (NMP), a pathway not found in humans. The NMP is responsible for the biosynthesis of five-carbon building blocks, called isoprenes. By inhibiting the NMP, isoprene biosynthesis in microorganisms is halted, and the growth and spread of the infectious agents are impeded. We aim to disrupt the NMP through inhibition of the enzyme 1-deoxy-D-xylulose-5-phosphate reductoisomerase (Dxr), which is the first committed step of the pathway. In our prior work, an α,β-unsaturated lipophilic phosphonate prodrug, RCB-185, was shown to have potent activity against Pf. New analogs of RCB-185 are being synthesized in effort to understand the relationships between structure and in vitro/in vivo activities.

References

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SYNTHESIS OF PAN-CMP MIMICS TO INHIBIT COABC

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The increase in multidrug-resistant pathogens due to the overuse of antibiotics, as well as the lack of development of novel therapeutics, has presented an urgent need for the discovery of next-generation antibacterial agents. The enzyme cofactor CoA plays an essential role in the biosynthesis of fatty acids and the generation of energy. The significant differences between microbial and mammalian CoA biosynthesis pathways make it an attractive target for drug development. In *Mycobacterium tuberculosis* (Mtb), CoA precursor pantothenate (Pan) is synthesized by PanB, PanC, PanD, and PanE. In the second stage of biosynthesis, Pan is converted to CoA in five steps that are catalyzed by PanK, CoaBC, CoaD, and CoaE enzymes. It was recently shown that, of all the enzymes in the pathway, depletion of only CoaBC resulted in bactericidal activity, while the depletion of other enzymes was only bacteriostatic. The importance of CoaBC in prokaryotic metabolism leads to the hypothesis that inhibitors of CoaBC will disrupt CoA synthesis and kill bacterial cells. Bacterial CoaBC is bifunctional and contains both phosphopantothenoylcysteine synthetase (PPCS) and phosphopantothenoyl-cysteine decarboxylase (PPCDC) activities. Together, these activities catalyze the transformation of 4'-phosphopantothenic acid (P-Pan) into 4'-phosphopantetheine (P-PantSH). This reaction proceeds through formation of the reactive 4'-phosphopantothenoyl-CMP (Pan-CMP) intermediate. Mimics of Pan-CMP have been synthesized as inhibitors of CoaBC. This family of compounds has the potential to chemically validate CoaBC as a new antibacterial drug target and serve as leads towards novel inhibitors.

Figure 1. Generalized Pan-CMP inhibitor.

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PERFECTING AN OLD BULLET: REDESIGNING FOSMIDOMYCIN ANALOGS AS NOVEL ANTIMICROBIALS

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Antibiotic resistance, improper drug administration, co-infection with multiple organisms, and other factors ensure our continued vulnerability to several pathogens and necessitate the discovery and development of new drugs. Molecules with new mechanisms of action are especially needed to stem the tide of infectious diseases. 1-Deoxy-D-xylulose 5-phosphate reducto-isomerase (Dxr) catalyzes the first committed step in the methylerythritol phosphate (MEP) pathway of isoprenoid biosynthesis and is essential in most pathogens. Dxr is not found in humans and, thus, represents a promising opportunity for drug discovery. We have identified new inhibitors based on the structure of natural products fosmidomycin and FR900098. Termed MEPicides, these compounds specifically target Dxr. We determine the MEPicide SAR against several Dxr homologs and in a variety of whole cell assays. Our most active compounds display nM activity against \textit{P. falciparum} parasites and \textit{in vivo} efficacy against \textit{P. berghei}-treated mice. MEPicides are on-target as MEPicide-treated \textit{P. falciparum} is rescued by the addition of IPP (the product of the MEP pathway), and metabolite analysis shows a substantial reduction in MEP metabolites downstream of Dxr following MEPicide treatment. Toxicity profiles are favorable, and our current synthetic work aims at improving key PK parameters. Collectively, our data demonstrate that these MEPicides potently and selectively inhibit Dxr of the MEP pathway in \textit{P. falciparum} (and other organisms) support further exploration of MEPicides as promising leads in the search for new antimicrobials.

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Isopentenyl pyrophosphate (IPP) biosynthesis is an attractive target for antimalarial drug discovery. Not only is IPP essential for parasite development, but malaria parasites synthesize it via the MEP pathway, which is absent in humans. A phenotypic screen of the 400 compounds of the “Malaria Box” against Plasmodium falciparum-infected red blood cells identified MMV008138 (1a) as an inhibitor of IPP biosynthesis. Subsequent exploration of numerous analogs determined that i) antimalarial potency requires at least one halogen substituent at 2′- or 4′- of the D-ring, and ii) that inhibition of P. falciparum growth was well-correlated to inhibition of the MEP pathway enzyme PfispD.

Current lead optimization work involves improving blood exposure of 1a and its analogs. To block potential oxidative metabolism of the C1-H bond, analogs 2a-d featuring C1-Me substitution, and spiro-analogs 3b and 3d appeared attractive. These compounds were prepared by Pictet-Spengler reaction of Trp-Oi-Pr with substituted acetophenones and indanones, followed by hydrolysis. Interestingly, in the course of preparing 2a and 2c, C-ring-expanded analogs 4a and 4c were isolated. The structures of 4a,c were determined by 1D and 2D NMR techniques, and confirmed by X-ray crystallography of the methyl amide derivative of 4a. To the best of our knowledge such compounds have never before been characterized. The antimalarial activities of these and other compounds will be disclosed.

References

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A NEW METHOD FOR STEREOCHEMICAL ASSIGNMENT OF 1,3-DISUBSTITUTED TETRAHYDRO-β-CARBOLINES

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1,3-Disubstituted tetrahydro-β-carbolines are prominent in medicinal chemistry. Representative examples include the erectile dysfunction drug tadalafil (1), the anticancer candidate AZD9496 (2, currently in Phase I trials), and preclinical antimalarial agents 3 and 4a.

The tetrahydro-β-carboline scaffold is conveniently prepared via Pictet-Spengler reaction of tryptophan esters and aldehydes, which typically gives a mixture of cis- and trans-isomers (e.g. 6a, 7a). Historically, the assignment of cis- and trans- relative stereochemistry has relied upon the empirical rule of Cook and co-workers, which is based on 13C NMR chemical shifts. In this poster we present a stereochemical assignment method that relies on 1H NMR coupling constants, which we believe has a more secure theoretical foundation than the aforementioned 13C NMR method. The conformational preferences of 6a and 7a (and their unsubstituted phenyl analogs 6b, 7b) predicted by 1H NMR coupling constants and NOE measurements are confirmed by density functional theory (DFT) calculations. In turn we show that the 1H NMR coupling constant-based stereochemical assignment of 26 analogs of tetrahydro-β-carboline methyl ester 6a matches those made by the 13C NMR empirical rule. Finally, we used DFT to calculate 13C NMR chemical shifts for 6a/7a and 6b/7b. We find that DFT accurately reproduces the upfield shift of C1 and C3 in trans-configured 6a/6b relative to cis-configured 7a/7b, which the 13C NMR empirical rule predicts. However, our examination of the calculated 13C NMR chemical shifts for individual conformers of 6a/6b demonstrates that the observed upfield shifts are not the simple consequence of steric crowding, contrary to the proposed “gamma-gauche effect” basis of the 13C NMR empirical rule.

References
ISOLATION AND STRUCTURE ELUCIDATION OF ANTIPLASMODIAL SESQUITERPENOID LACTONES FROM TRICHOPIRA VERTICILLATA

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A dichloromethane extract of Trichospira verticillata from the Natural Products Discovery Institute was discovered to have good antiplasmodial activity (IC₅₀ ~ 5 μg/mL). After purification by liquid-liquid partition and C₁₈ reverse phase HPLC, four new germacranolide-type sesquiterpene lactones named trichospirolides A-D (1-4) were isolated. The structures of the new compounds were elucidated by analysis of their 1D and 2D NMR spectra and mass spectrometric data, and the relative configurations were assigned based on NOESY experiments. The absolute configurations were assigned based on comparison of calculated and experimental internuclear distances and ECD spectra. Among these four compounds, the conjugated dienone 1 displayed the most potent antiplasmodial activity, with an IC₅₀ value of 1.5 μM.

References

Acknowledgement
This project was supported by the National Center for Complementary and Integrative Health under award 1 R01 AT008088, and this support is gratefully acknowledged. This work was also supported by the National Science Foundation under Grant No. CHE-0619382 for purchase of the Bruker Avance 500 NMR spectrometer and Grant No. CHE-0722638 for the purchase of the Agilent 6220 mass spectrometer. We thank Mr. B. Bebout for obtaining the mass spectra, Dr. N. Shanaiah for assistance with the NMR spectra, and Dr. T. Grove for the use of the JASCO J-815 spectrometer. We gratefully acknowledge A. Rodriguez of INBIO for the collection of plant material. T.D.C. was supported by the National Science Foundation under grant CHE-1465149 and K.C.P. by a graduate fellowship from the Virginia Tech Institute for Critical Technology and Applied Science. The authors acknowledge Advanced Research Computing at Virginia Tech for providing computational resources and technical support that have contributed to the results reported within this paper.
THE RESEARCH OF KS0 AND USE IT FOR FUTURE DRUG DISCOVERY VIA COMBINATORIAL BIOSYNTHESIS

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Protein-protein engineering is a powerful tool for PKS module manipulation for the purpose of generating new novel natural products. Type I trans-AT Polyketide synthases (PKSs) are a primary source of naturally occurring small molecules that are used for different medicinal aspects. The type I trans-AT modular PKSs have a non-canonical modular architecture, like the presence of a non-elongation module which are found in several locations of trans-acyltransferase polyketide synthases (trans-AT PKS). The non-elongation modules all contain a condensation-incompetent ketosynthase (KS0), where both KS0 function and interactions with other surrounding domains are still unknown. Module five of Difficidin biosynthase is a split/non-elongation module, consisting of C-terminus KS0 (DfnKS05), N-terminus dehydratase (DfnDH5), and an acyl carrier protein (DfnACP5). We intent to create a method that allows for the easy engineering of the type I trans-AT PKSs to lead the production of some novel polyketide products that are not produced by any natural systems to the best of our knowledge. Our method will provide and easy and convent way for engineering of PKSs system to help with the discovery of new novel drug or improve the existing drug(s) via combinatorial biosynthesis. Our results show that the KS50 domain can act as mediator between two cognate ACPs and non-cognate ACPs. The results from this study will allow us to generate a method for engineering trans-AT PKSs using the KS0-ACP translocation function as the backbone for engineering novel compounds using combinatorial biosynthesis.
SELF-ASSEMBLED DIPEPTIDE HYDROGELS FOR SIGNALING GAS DELIVERY

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Signaling gases are small gas molecules such as NO, CO, and H2S, which produced exogenously or endogenously in mammalian. They play important roles in many biological functions and regulation physiological functions. H2S, as one of the gasotransmitters, has shown its therapeutic applications in treating cardiovascular diseases, diabetes, wound, and even cancer. However, the delivery of H2S is the bottleneck to utilize the H2S as a therapeutic factor.

To solve the issue, in this study, self-assembled dipeptide Phe-Glu (FE) and Try-Glu (YE) were used to form hydrogels and provided localized delivery of H2S. S-Aroylthiohydroxylamine (SATO) was chosen to conjugated to peptide as the H2S donor, because it specially responses thiol triggers to release H2S. The resulted SATO-FE and SATO-YE dipeptides self-assembled into nanoribbons with lengths in μm and widths about 20 nm. β-sheet was found in the self-assembled structure, as well as aromatic stacking interaction.

H2S was released instantaneously from SATO-FE and SATO-YE when cysteine was added. For 0.1 mM SATO-FE and SATO-YE solutions with 10 eqv. of cysteine, H2S release half-lives were 24 and 22 min. Hydrogels were formed when pH around 6.5, and providing a longer release of H2S. The storage modulus of SATO-FE and SATO-YE gels were around 300-500 Pa, making them useful hydrogels for bioengineering applications.

References
DEVELOPMENT OF H₂S RELEASING PEPTIDE HYDROGELS FOR LOCALIZED H₂S DELIVERY

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H₂S-releasing donors, with sustained H₂S release, are often employed to study its role in regulating various physiological processes. Thiooximes are cysteine triggered H₂S-releasing donors with structure dependent H₂S release but lack water solubility and localized delivery.¹ The localized H₂S delivery is required to maintain high local H₂S concentrations for better understanding in the therapeutic models like wound healing and SMC proliferation. As a result, the thiooximes were appended onto an aromatic peptide amphiphile, which formed hydrogels with Ca²⁺.²

Herein, we show how structural modification of the peptide components can affect its hydrolytic stability and self-assembly. We changed the linker segment (one of the four components of APAs) to include electron withdrawing groups, electron donating groups and groups with extended conjugation. Hydrolysis of the peptides was followed using UV-Vis spectroscopy at a range of different pH values and exhibited pseudo first-order kinetics. Changing the linker also affected the self-assembling properties of the peptides and the robustness of the hydrogel which was studied using rheology and optical imaging.

References

Acknowledgement
We thank the NIH (AI128362 (PRC), AI082581 (PRC), and AI108819 (MBC)), Fralin Life Science Institute and the Virginia Tech Center for Drug Discovery for funding.
The ISB\textsuperscript{3}D X-ray Crystallography Facility is a Virginia Commonwealth University-supported resource that is directed by Martin K Safo, PhD (msafo@vcu.edu) and managed by Faik N Musayev, PhD (fmoussae@vcu.edu). The facility provides investigators equipment and resources for crystallographic analysis of macromolecules and/or small molecules. It offers and operates as a full service core by performing crystallization, X-ray diffraction data collection, processing, phasing, crystallographic refinement, model building, and visualization. The structural data obtained by the core provides scientists with a wealth of information, including but not limited to 3D-structures, biological functions, structure-based drug design, ligand or DNA binding to protein, mutational effect of target macromolecules, or absolute stereochemistry of chiral compounds. Available equipments include a state-of-the-art X-ray diffraction system, consisting of MicroMax-007HF generator, VariMax-HF Arc Optics, Hybrid Photon Counter, Eiger R 4M Detector, AFC11 Goniometer and Oxford Cobra Cryo-system. Other supporting resources are Gryphon Crystallization Robot, Minstrel DT UV/CrystalMation –Gallery DT, CrystalTrack, XTAL 750, Alchemist Liquid Handling System, Incubators, CrysCam Digital, Olympus SZ51 and Nikon SMZ-2T Microscopes. Available services include:

- **Protein and Small Molecule Crystallization**
  - Robotic nanoliter-scale screening of macromolecules
  - Monitoring crystal growth with Minstrel DT UV/Gallery imaging system
  - Optimization of conditions from crystal growth
  - Screening with known ligands
  - Co-crystallization or soaking of protein with ligands
  - Screening of protein-protein and protein-DNA/RNA complexes
  - Crystallization of small molecules (organic/or metallo-organic compounds)

- **X-ray Diffraction Data Collection and Structure Determination of small and macromolecules**
  - Data collection, reduction, phasing, model building and structure refinement
  - Structure interpretation
  - Ligand binding analysis
  - Advice on medicinal chemistry

The facility is complemented by a variety of training mechanisms and services to enhance access and user capability. In addition to providing service to the VCU community, we also offer crystallography services to outside organizations, including academia, pharmaceutical and biotech companies, and private individuals. Please contact us for your crystallographic and other structural biology service needs/or potential collaborations. Webpage:

https://isb3d.pharmacy.vcu.edu
https://isb3d.pharmacy.vcu.edu/media/structural-biology/resources/FacilityDescription.pdf

**Acknowledgement**

NIH Shared Instrumentation Grant S10-OD021756 (MKS) and Virginia General Assembly Higher Education Equipment Trust Fund (HEETF) provided structural Biology Resources to Virginia Commonwealth University.
BIOPHYSICAL ANALYSIS & HIGH THROUGHPUT SCREENING FACILITIES AT VCU

Facility Directors: Drs. Umesh Desai (urdesai@vcu.edu) & Aaron May (aemay@vcu.edu)

Facility Manager: Dr. Srinivas Sistla (ssistla@vcu.edu)

The Institute for Structural Biology, Drug Discovery, and Development (ISB3D) has developed a Biophysical Analysis and high throughput screening (HTS) facility that is now open to researchers from within and outside VCU. Instrumentation that is currently available include BMG Labtech Clariostar microplate reader; BioTek MultiFlo FX bulk liquid dispenser; BioTek Cytation 5 imager; and Labcyte Echo 550 acoustic liquid handler. The ISB3D hosts several libraries of chemical compounds with diverse structures including FDA approved molecules (ApexBio; 1300 compounds). These chemical compounds are available for HTS and biophysical analysis. No biomacromolecular study is complete without biophysical study of biomacromolecules – ligand interaction. The biophysical facility at the ISB3D consists of multiple instruments that support fundamental and applied research on mechanism of action, structure – activity relationships, and drug discovery and development. These instruments include PTI spectrofluorometer, NanoTemper Microscale Thermophoresis, Reichert Surface Plasmon Resonance, Waters UPLC coupled to TQD-ESI-MS, Beckman Ultracentrifuge, Olis Circular Dichroism with stopped flow assembly, and Malvern dynamic light scattering.
MOLECULAR MODELING FACILITY @ VCU INSTITUTE FOR STRUCTURAL BIOLOGY, DRUG DISCOVERY AND DEVELOPMENT (ISB3D)

Philip D. Mosier, Glen E. Kellogg, Umesh R. Desai

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pdmosier@vcu.edu

The VCU Institute for Structural Biology, Drug Discovery and Development (ISB3D) Molecular Modeling Facility is a VCU-supported resource located in the Virginia Biotechnology Research Park I building (aka Biotech I) and is directed by Drs. Glen E. Kellogg and Philip D. Mosier. This facility provides access to a comprehensive suite of computational resources in support of structural biology and drug discovery, including the powerful suite of HINT tools developed by Drs. Donald Abraham and Glen Kellogg at VCU. The molecular modeling facility is supported by graphics workstations and a GPU cluster, supplemented with a Linux cluster back-end with over 5,000 cores provided by the VCU Center for High Performance Computing (CHiPC), as well as a wide selection of powerful software packages. The facility is complemented by a variety of training mechanisms and services, both through formal classes and one-on-one sessions to enhance user access and capability.

Services

- Hardware and software access
- Training/Consulting

Equipment and Resources

- **Hardware**
  - Multi-core Linux and MacPro graphics workstations
  - Silicon Mechanics GPU cluster
  - ~5000-core Linux cluster (provided by VCU CHiPC)

- **Software**
  - General Model Building and Refinement: SYBYL-X, MODELLER
  - Automated Docking: CCDC GOLD, AutoDock
  - Quantum Mechanics: Gaussian, GAMESS, ORCA, NWChem
  - Molecular Dynamics: NAMD, Amber, GROMACS
  - Structure-Based Drug Design: HINT (Hydrophobic INTeractions)
  - Ligand-Based Drug Design: Cambridge Structural Database System (CSDS) 2018 Enterprise
  - Structural Biology: PHENIX, ccp4
  - Visualization: VMD, Chimera, PyMOL
  - and many more (just ask!)

References


<table>
<thead>
<tr>
<th>Author</th>
<th>Presentation Number</th>
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<td>Afosah</td>
<td>Daniel K.</td>
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<td>Wipf</td>
<td>Peter</td>
</tr>
</tbody>
</table>
Wonilowicz  Laura G.  P21
Wood     Michael         Panel 4
Xu       Guoyan          P10
Yakisich  Juan S.        P17, P18
Yao      Zhong-Ke       P30
You      Young-OK        P32
Young    Richard         P01, P02
Zainab   Mosufa          P25
Zhang    Yan             P10
Zhang    Zhong-Yin       P13
Zheng    Shuo            P06
Zubi     Mohammad A.     P16
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KeViRx is an early stage drug discovery company whose mission is to advance new anticancer therapeutics to clinical testing. We focus on novel molecular targets for cancer. Our goal is to discover safer and more effective drugs that enable people to live longer and to live well. KeViRx was founded in 2016 by Drs. John S. Lazo and Elizabeth R. Sharlow from the University of Virginia and Dr. Peter Wipf from the University of Pittsburgh. At KeViRx, we are thinking BIG with small molecules.
Network Contacts
Conference Notes
This Symposium is designed to promote collaborations between academic and industrial drug discovery scientists, and includes keynote lectures from leading researchers, panel discussions, and poster presentations by scientists from around and beyond the Commonwealth.

The NIH Roadmap for Research states “The scale and complexity of today’s … research problems increasingly demand that scientists move beyond the confines of their own discipline and explore new organizational models for team science……”, and this Symposium has the goal of furthering such collaborations, especially when it comes to the drug discovery, development, and delivery.
GLYCERALDEHYDE TOLERANCE AND GELATIN NANO PARTICLE STABILIZATION FOR PEPTIDE ENCAPSULATION TO TREAT TRAUMATIC BRAIN INJURY

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Abstract

The use of nanoparticles (NPs) to protect and ultimately release therapeutic molecules to treat disease has become an important concept in drug delivery. Biocompatible polymers such as gelatin, are appealing materials for use as nanoparticles to deliver potentially therapeutic molecules to treat traumatic brain injury. While researchers have utilized gelatin NPs to treat brain injuries in murine models, their typical sizes are above 200 nm using complicated emulsion techniques and the use of toxic crosslinkers for particle stability decrease their translational ability. Here, the use of glyceraldehyde as a non-toxic crosslinker is revealed by measuring the viabilities of numerous brain cell types. All cells were able to tolerate higher concentrations of glyceraldehyde compared to glutaraldehyde. Gelatin NPs were formed using desolvation and crosslinked with glyceraldehyde to be less than 200 nm in average diameter monodispersed and negatively charged. Furthermore, incorporation of a short peptide capable of inhibiting the EphA4 receptor within the NPs afforded slower cumulative release profiles compared to the plain peptide control. In all, applying concise experimental methods and adequately characterizing new NP formulations is expected to facilitate nanoscale property reproducibility and enable greater translation of drug delivery devices to industry use.