Program and Proceedings
15th Annual Peptide Therapeutics Symposium

October 22 – 23, 2020
Held Virtually

www.peptidetherapeutics.org

15th Annual Peptide Therapeutics Symposium

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Symposium Sponsors

15th Annual Peptide Therapeutics Symposium

Dear Colleagues,

We welcome you all to our first virtual presentation of the 15th Annual Peptide Therapeutics Symposium. These unprecedented times required us to creatively adapt to the circumstances and we are excited that the live, virtual symposium has enabled our colleagues from around the globe to participate. While the program has departed from the format of prior years, we have continued our strong tradition of showcasing cutting-edge science.

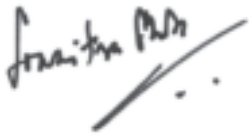
This year's 15th Annual Peptide Therapeutics Symposium will take place over two days and has been scheduled to align with the time zones of the speakers and poster presenters. The program opens with lectures by Dr. Kathryn Whitehead and Dr. Gregory Verdine, and includes Plenary lectures from Dr. Sarah Robertson and Dr. Glenn King. The Friday sessions feature talks by experts on molecular recognition, drug delivery, and novel avenues for drug and vaccine development.

We have worked hard with our colleagues at IU Conferences and the Salk Institute to take advantage of online opportunities for discussion and networking. The live streamed event will provide you with opportunities to ask questions and to have meaningful dialog with fellow attendees, poster presenters, and speakers from around the globe. There will be break out rooms for interaction with poster presenters on Thursday morning and Friday afternoon. In addition, the taped presentations will be available for viewing for 30 days following the close of the meeting. A chat board will enable you to post questions for the speakers should they not have time to answer them during the Q&A session.

Thank you for joining us, we are grateful for your participation in the symposium. Your attendance as always is key to making this annual scientific event successful.

Sincerely,

Phil Dawson
Chairman of the Board
Peptide Therapeutics Foundation



Soumitra Ghosh
President
Peptide Therapeutics Foundation

Sponsors, Peptide Therapeutics Foundation

Astra Zeneca
Ferring Research Institute Inc.
Novo Nordisk
The PolyPeptide Group
Zealand Pharma

15th Annual Peptide Therapeutics Symposium

AstraZeneca

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three therapy areas – Oncology, Cardiovascular, Renal & Metabolism and Respiratory. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. AstraZeneca has three global R&D centers, in Gaithersburg, MD, South San Francisco, CA and Cambridge' UK. For more information, please visit www.astrazeneca.com.

Ferring Research Institute, Inc.

Headquartered in San Diego, California, Ferring Research Institute, Inc., (FRI) is a critical component of Ferring Pharmaceutical's global therapeutics research and discovery engine. Established in 1996, FRI is located in the heart of the Southern California biopharmaceutical community. The center has attracted a diverse group of highly skilled professionals representing over twenty four countries of origin. FRI is focused on the following key therapeutic areas: reproductive medicine & women's health, urology and gastroenterology/hepatology. Our state-of-the art facility includes peptide and protein drug design, chemistry, pharmacology, biology, and preclinical ADME capabilities. Historically FRI has focused on the discovery of amino acid-based therapeutics utilizing the body's signaling hormones. Today FRI is committed to building a portfolio of novel, innovative therapeutics using a wide array of modalities in order to address areas of high unmet medical need in our core therapeutic areas. Driving value through personalized medicine.

Ferring Pharmaceuticals is a research-driven, specialty biopharmaceutical group committed to helping people around the world build families and live better lives. Headquartered in Saint-Prex, Switzerland, Ferring is a leader in reproductive medicine and women's health, and in specialty areas within gastroenterology/hepatology and urology. As part of its commitment to developing innovative products to treat diseases with high unmet medical need, Ferring invests heavily in its research infrastructure both in terms of people and technology. Ferring has been developing treatments for mothers and babies for over 50 years and has a portfolio covering treatments from conception to birth. Founded in 1950, privately-owned Ferring now employs approximately 6,500 people worldwide, has its own operating subsidiaries in nearly 60 countries and markets its products in 110 countries.

Novo Nordisk

Novo Nordisk is a global healthcare company with more than 90 years of innovation and leadership in diabetes care. This heritage has given us experience and capabilities that also enable us to help people defeat obesity, haemophilia, growth disorders and other serious chronic diseases. Headquartered in Denmark, Novo Nordisk employs approximately 41,700 people in 77 countries and markets its products in more than 165 countries. Novo Nordisk's B shares are listed on Nasdaq Copenhagen (Novo-B). Its ADRs are listed on the New York Stock Exchange (NVO). For more information, visit novonordisk.com.

The PolyPeptide Group

The PolyPeptide Group is a privately-held group of manufacturing sites which focus on proprietary and generic GMP-grade peptides for the pharmaceutical and biotechnological market. With more than 60 years of experience, the Group is committed to the highest quality of peptide manufacturing for commercial peptide drug substances, GMP peptides in clinical trials, or small-scale non-GMP custom syntheses.

The PolyPeptide Group has grown by selective acquisition of existing expertise, culminating in its position today as a leader in peptide manufacturing. The Group has manufacturing facilities in Sweden (Malmo), France (Strasbourg), India (Ambernath) and two sites in the USA (San Diego CA & Torrance CA). As a multinational company with about 520 employees worldwide, its diversity brings breadth and depth of knowledge and experience to the Group.

The Group's long-established core strength in GMP manufacturing and broad range of services supports peptide & peptide-like projects, including conjugation to non-peptide moieties, from the bench through to commercialization. With continually increasing capacity for GMP manufacturing, the PolyPeptide Group is stronger and better equipped to serve the needs of its customers at all stages of pharmaceutical peptide development. With its multinational organization, strict focus on peptides and solid financial base, the Group offers an almost unique security of supply to its customers.

15th Annual Peptide Therapeutics Symposium

Zealand Pharma

Zealand Pharma A/S (NASDAQ OMX Copenhagen: ZEAL) ("Zealand") is a biotechnology company specialized in the discovery, design and development of peptide-based therapeutics. The company has a portfolio of medicines and product candidates under license collaborations with Sanofi and Boehringer Ingelheim and a proprietary pipeline of product candidates, which primarily target specialty diseases with significant unmet needs.

Zealand is the inventor of lixisenatide, a once-daily prandial GLP-1 analog for the treatment of type 2 diabetes, which is licensed to Sanofi and marketed globally outside the U.S. as Lyxumia® and in the U.S. as Adlyxin®. Sanofi has also developed iGlarLixi, a fixed-ratio combination of lixisenatide and Lantus® (insulin glargine) marketed in U.S. as Soliqua® and Europe as Suliqua®.

Zealand's proprietary pipeline includes; glepaglutide*, a GLP-2 analog for the treatment of short bowel syndrome which will initiate Phase III studies in 1H18; dasiglucagon*, a glucagon analog in Phase III as a single-dose rescue therapy for severe hypoglycemia and in Phase II as a multiple-dose component in a dual-hormone artificial pancreas system; and other earlier stage clinical and preclinical peptide therapeutics. The company has approximately 130 employees and is based in Copenhagen, Denmark.

*Glepaglutide and dasiglucagon are proposed International Nonproprietary Names (pINNs)

Peptide Therapeutics Foundation

Peptide Therapeutics Foundation is a not-for-profit 501C (3), established in 2008 to promote research and development of peptide therapeutics. The Foundation is currently supported by five corporate sponsors; AstraZeneca, Ferring Research Institute, Inc., Novo Nordisk, The PolyPeptide Group, and Zealand Pharma.

The Foundation sponsors an annual meeting, Peptide Therapeutics Symposium, which brings together world leaders from academia, the biopharmaceutical industry, CMOs, CROs, and investors interested in all aspects of peptide R&D, including drug discovery, safety and toxicology, clinical development, manufacturing, pharmaceutical development, formulation, drug delivery and regulatory affairs.

Notes

15th Annual Peptide Therapeutics Symposium

Thursday, October 22, 2020

8:00 a.m. – 8:15 a.m.

Opening Remarks
Phil Dawson, Ph.D.
Chairman of the Board, Peptide Therapeutics Foundation
Professor of Chemistry, Scripps Research
Dean of the Skaggs Graduate School of Chemical and Biological Sciences

8:15 a.m. – 9:45 a.m.

Session I
Moderator:
Robert Hagopian
Director, Peptide Therapeutics Foundation
Director Business Development, PolyPeptide Group

8:15 a.m. – 8:45 a.m.

From Farm to Pharmacy: A Strawberry-Derived Solution to Oral Protein Delivery
Kathryn Whitehead, Ph.D.
Associate Professor, Carnegie Mellon University

8:45 a.m. – 9:15 a.m.

Building Novel Immune Cell Agonist Anti-Cancer Agents out of *Bicycle* Parts
Kevin McDonnell, Ph.D.
Vice President, Chemistry US, Bicycle Therapeutics

9:15 a.m. – 9:45 a.m.

Toward Universal Druggability
Greg Verdine, Ph.D.
Erving Professor of Chemistry, Harvard University and Harvard Medical School
President and Chief Executive Officer, Fog Pharmaceuticals and LifeMine Therapeutics

9:45 a.m. – 10:30 a.m.

Break

10:30 a.m. – 12:50 p.m.

Poster Break Out Sessions

10:30 a.m. – 10:50 a.m.

The U24 Protein of HHV-6A Induces the Expression of Alzheimer's Disease Risk Factors of Microglial Cells
Giovanna Schiuma
University of Ferrara, Department of Chemical and Pharmaceutical Chemistry, Italy

10:50 a.m. – 11:10 a.m.

Targeting SARS-CoV-2 Spike 1 Protein to Control Natural Killer Cells Activation via HLA-E/NKG2A Pathway
Sabrina Rizzo
University of Ferrara, Department of Chemical and Pharmaceutical Sciences, Italy

11:10 a.m. – 11:30 a.m.

Reengineering the Antimicrobial Peptide from the Scorpion Venom of *Opisthacanthus Madagascariensis* into Highly Active Peptides with Low Toxicity
Cyntia Silva Oliveira
Universidade Federal de São Paulo, Brazil

11:30 a.m. – 11:50 a.m.

Do Peptide Drugs Interact with Bile Salts in the Gastrointestinal Environment?
Tahnee Dening
Department of Pharmaceutical Chemistry, University of Kansas

11:50 a.m. – 12:10 p.m.

Anionic Nanoparticles Enable Oral Peptide Delivery by Enhancing Intestinal Permeability
Nicholas Lamson
Department of Chemical Engineering, Carnegie Mellon University

12:10 p.m. – 12:30 p.m.

Viral Insulin/IGF-1 like Peptides have Unique White Adipose Tissue Specific Characteristics in Mice
Martina Chrudinova
Biology Department, Boston College

15th Annual Peptide Therapeutics Symposium

12:30 p.m. – 12:50 p.m.	**Development of Pharmacoproteomics Assays for Dissecting the Molecular and Cellular Pathways Regulated by Anticoagulant Peptides in Platelets and Dendritic Cells** Cristina Clement *Radiation Oncology Department, Weill Cornell Medicine*
12:50 p.m. – 1:30 p.m.	**Lunch Break**
1:30 p.m. – 3:00 p.m.	**Session II** **Moderator:** David Parkes, Ph.D. *Chief Scientific Officer, Abvance Therapeutics, Inc.*
1:30 p.m. – 2:00 p.m.	**Adrenomedullin Functions at the Maternal-Fetal Interface** Kathleen Caron, Ph.D. *Professor & Chair, Department of Cell Biology and Physiology* *University of North Carolina at Chapel Hill*
2:00 p.m. – 2:30 p.m.	**Empowering Peptide Science through Easy 18F-Labeling for PET Imaging and New Stapling Methods Inspired by Natural Product Toxins** David M. Perrin, Ph.D. *Professor, Chemistry Department, University of British Columbia*
2:30 p.m. – 3:00 p.m.	**A Peptide Engineering Platform for PEG-FA Stapled Long-Acting Peptide Hormones** Weijun Shen, Ph.D. *Director, Metabolic Disease, Calibr at Scripps Research*
3:00 p.m. – 3:30 p.m.	**Break**
3:30 p.m. – 5:00 p.m.	**Plenary Lectures** **Moderator:** Adam Mezo, Ph.D. *Director, Peptide Therapeutics Foundation* *Sr. Director, Discovery Chemistry, Ferring Research Institute*
3:30 p.m. – 4:15 p.m.	**Novel Therapeutics for Inflammatory Disorders of Pregnancy – Opportunities and Challenges** Sarah Robertson, Ph.D., FAA, FAHMS *Professor and Director, Robinson Research Institute* *The University of Adelaide*
4:15 p.m. – 5:00 p.m.	**Deadly Cures: A Spider-Venom Peptide for Treating Ischemic Injuries of the Heart and Brain** Glenn King, Ph.D. *Institute for Molecular Bioscience, The University of Queensland*

15th Annual Peptide Therapeutics Symposium

Friday, October 23, 2020

8:00 a.m. – 8:15 a.m.	**Welcoming Remarks** Soumitra Ghosh, Ph.D. *Director and President, Peptide Therapeutics Foundation* *President, Doon Associates LLC*
8:15 a.m. – 9:45 a.m.	**Session III** **Moderator:** Richard DiMarchi, Ph.D. *Chairman Emeritus, Peptide Therapeutics Foundation* *Distinguished Professor of Chemistry, Gill Chair in Biomolecular Sciences, Department of Chemistry, Indiana University*
8:15 a.m. – 8:45 a.m.	**Peptides for Molecular Recognition and Brain Delivery** Ernest Giralt, Ph.D. *Professor, Institute for Research in Biomedicine (IRB Barcelona)*
8:45 a.m. – 9:15 a.m.	**Novel Pairings in the Human Peptide-Receptor Signaling System** David Gloriam, Ph.D. *Professor, University of Copenhagen*
9:15 a.m. – 9:45 a.m.	**Chimeric Macrocyclic Peptide Antibiotics Against WHO Priority 1 Gram-Negative Bacteria Targeting both Lipopolysaccharide and BamA** Daniel Obrecht, Ph.D. *CSO, Polyphor Ltd*
9:45 a.m. – 10:30 a.m.	**Break**
10:30 a.m. – 12:00 p.m.	**Plenary Lectures** **Moderator:** Jordi Alsina, Ph.D. *Research Fellow, Peptide Lead Optimization* *Biotechnology Discovery Research, Eli Lilly and Company*
10:30 a.m. – 11:15 a.m.	**Cyclic Cell-Penetrating Peptides: Mechanism of Action and Applications** Dehua Pei, Ph.D. *Kimberly Professor of Chemistry and Biochemistry, The Ohio State University*
11:15 a.m. – 12:00 p.m.	**GI Device Development in a Few Movements** Giovanni Traverso, MB, BChir, Ph.D. *Assistant Professor, Department of Mechanical Engineering, Massachusetts Institute of Technology, Assistant Professor of Medicine (part-time), Division of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School*
12:00 p.m. – 1:00 p.m.	**Lunch Break**
1:00 p.m. – 2:30 p.m.	**Session IV** **Moderator:** Michael Dunn, Ph.D. *Sr. Director Scientific Information & Intelligence, Ferring Research Institute*
1:00 p.m. – 1:30 p.m.	**GEN-009: A Neoantigen Vaccine Based on Autologous Peptide Immune Responses** **GEN-011: Transforming T Cell Therapy for Solid Tumors** Daniel B. DeOliveira, Ph.D., PMP *Senior Director; Peptide Dev., Tech. Ops. & Mfg., Genocea Biosciences Inc.*
1:30 p.m. – 2:00 p.m.	**Vasopressin: Old Dog. New Tricks**. Michael J. Brownstein M.D., Ph.D. *Senior Vice President, Drug Development, Azevan Pharmaceuticals*

15th Annual Peptide Therapeutics Symposium

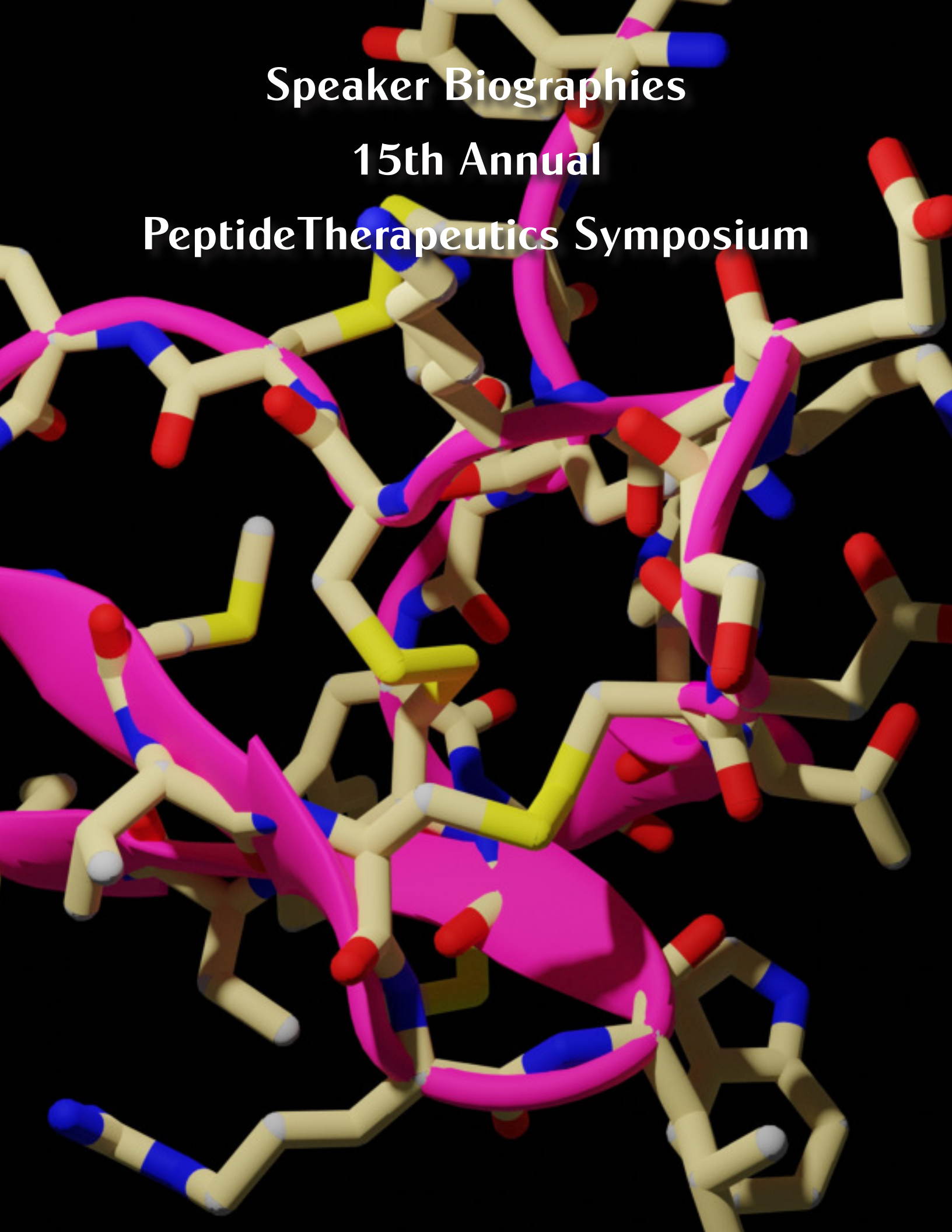
2:00 p.m. – 2:30 p.m.	**Dual Myristic Acid (Myr) and Trans Activator of Transcription (Tat) Conjugated Peptides: A Potential Platform Technology for Intracellular Cargo Delivery** Lindon H. Young, Ph.D. *Professor of Pharmacology, Philadelphia College of Osteopathic Medicine* *Founder & Chief Science Officer, Young Therapeutics* Kerry-Anne A. Perkins D.O *Obstetrician & Gynecologist, Virtua Memorial Hospital*
2:30 p.m. – 2:45 p.m.	**Closing Remarks** Adrienne Day, Ph.D. *Director and Treasurer, Peptide Therapeutics Foundation* *Founder and Principal, Blue Gum Advisors*
2:45 p.m. – 5:05 p.m.	**Poster Break Out Sessions**
2:45 p.m. – 3:05 p.m.	**Protein Kinase C-Epsilon Inhibitor Conjugated with Myristic Acid and Trans-Activator of Transcription Elicits Superior Cargo Delivery and Cardioprotective Effects in Rat Myocardial Ischemia-Reperfusion Injury** Tameka Dean *Philadelphia College of Osteopathic Medicine*
3:05 p.m. – 3:25 p.m.	**Protein Kinase C Beta II Peptide Inhibitor Conjugated to a Novel Myristic Acid-Trans- Activator – Tandem Rapidly Attenuates Superoxide Release in Isolated Rat Polymorphonuclear Leukocytes through Superior Intracellular Delivery of Cargo** Sunit Singh *Department of Biomedical Sciences, Philadelphia College of Osteopathic Medicine*
3:25 p.m. – 3:45 p.m.	**Overcoming the Blood-Brain-Barrier by a Linear 7-Mer Peptide, IF7, with Binding Specificity to Annexin A1 in Brain Tumors** Michiko Fukuda *Cancer Center, Sanford-Burnham-Prebys Medical Discovery Institute*
3:45 p.m. – 4:05 p.m.	**Amphiphilic Cell-Penetrating Peptides Containing Natural and Unnatural Amino Acids as Drug Delivery Tools and Antimicrobial Agents** David Salehi *Center for Targeted Drug Delivery, Department of Biomedical and Pharmaceutical Sciences, Chapman University School of Pharmacy*
4:05 p.m. – 4:25 p.m.	**Design and Evaluation of Cyclic and Linear Amphiphilic Peptides Against Multidrug-Resistant Bacterial Pathogens** Keykavous Parang *Center for Targeted Drug Delivery, Department of Biomedical and Pharmaceutical Sciences, Chapman University School of Pharmacy*
4:25 p.m. – 4:45 p.m.	**Characterisation of a Lunasin-Derived Anti-Inflammatory Peptide** Reynold Philip *Centre for Molecular Therapeutics, Australian Institute of Tropical Health and Medicine, James Cook University, Cairns, QLD Australia*
4:45 p.m. – 5:05 p.m.	**Potent Anticolorectal Cancer Activity of Analog Peptides Derived from Parasporin-2Aa1** Jenniffer Cruz *Universidad de Santander, Bucaramanga, Colombia*

Notes

Speaker Biographies

15th Annual

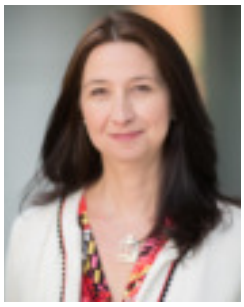
PeptideTherapeutics Symposium



15th Annual Peptide Therapeutics Symposium

Michael J. Brownstein M.D., Ph.D. | Senior Vice President, Drug Development, Azevan Pharmaceuticals
Vasopressin: Old Dog. New Tricks.

Michael Brownstein earned his bachelor's degree from Columbia University and completed his graduate training at the University of Chicago, where he earned an M.D. and Ph.D. in pharmacology. He received his clinical training at the Boston Children's Hospital and then moved to the National Institutes of Health to work with Julius Axelrod, recipient of a Nobel Prize in 1970 for his studies in the field of neuropharmacology. Dr. Brownstein remained at NIH after completing his fellowship, where he served as Chief of the Laboratory of Genetics of the National Institute of Mental Health and the National Human Genome Research Institute. For two years, he was the Scientific Director of the NIMH Intramural Research Program. While at the NIMH/NHGRI, he directed the Brain Molecular Anatomy Project. Simultaneously, he contributed to the Mammalian Gene Collection, a trans-Institutional effort to clone and sequence cDNAs corresponding to all human, mouse, and rat transcripts. Subsequently he directed the functional genomics program at the J. Craig Venter Institute in Rockville, MD for three years. He has worked in the fields of neurobiology, neuroendocrinology, biochemical pharmacology, genetics, and genomics; has published more than 300 papers in peer reviewed journals; has served on major editorial boards and continues to serve on a number of scientific advisory boards. Dr. Brownstein also co-founded several successful bio-pharmaceutical companies.



Kathleen Caron, Ph.D. | Professor & Chair, Department of Cell Biology and Physiology, University of North Carolina at Chapel Hill
Adrenomedullin Functions at the Maternal-Fetal Interface

Kathleen M. Caron, Ph.D. is a Professor and Chair in the Department of Cell Biology & Physiology in the School of Medicine at the University of North Carolina at Chapel Hill — one of the nation's largest, interdisciplinary physiology departments, consistently ranked in the Top 10 in NIH funding. Prior to her role as Department Chair, Dr. Caron served as Assistant Dean for Research in the School of Medicine. Dr. Caron graduated from Emory University with a BS in Biology and a BA in Philosophy. For her graduate work, she trained with Dr. Keith L. Parker in the Department of Cell Biology at Duke University where she elucidated the role of steroidogenesis in regulating sexual determination and adrenal and gonadal development using genetic mouse models. To gain more experience in gene targeting approaches, Dr. Caron pursued her postdoctoral training in the laboratory of Nobel Laureate Dr. Oliver Smithies at UNC-CH, where she was the first to discover the essential role of adrenomedullin peptide for embryonic survival. Her laboratory currently uses sophisticated gene targeting approaches to model human disease in mice. With a special emphasis on vascular biology, the Caron laboratory has gained valuable insights into the genetic basis and pathophysiology of lymphatic vascular disease, preeclampsia and sex-dependent cardiovascular disease. Dr. Caron has received numerous awards including a Burroughs Wellcome Fund Career Award in the Biomedical Sciences, an Established Investigator Award and an Innovator Award from the American Heart Association, a Jefferson Pilot Award in Biomedical Sciences and a UNC-CH Mentoring Award. She currently serves as Associate Editor for ACS-Pharmacology and Translational Science and holds multiple scientific advisory roles in academia, industry and the National Institutes of Health. Dr. Caron is an accomplished teacher and mentor, having served as an advisor to over 50 graduate, post-graduate and clinical trainees. She is highly regarded for her impassioned drive for excellence and approach to individualized mentoring and career advising, as recognized by her participation in numerous symposia and articles related to professional development.

Phil Dawson, Ph.D. | Chairman of the Board, Peptide Therapeutics Foundation; Professor of Chemistry, Scripps Research; Dean of the Skaggs Graduate School of Chemistry and Biological Sciences
Opening Remarks

Phil Dawson is a Professor in the Department of Chemistry, Scripps Research in La Jolla, CA and Dean of the Skaggs Graduate School of Chemical and Biological Sciences. He received an A.B. (1992) in Chemistry from Washington University, and Ph.D. (1996) from Scripps Research under the guidance of Steve Kent. After pursuing postdoctoral work at Caltech, he returned to Scripps as an Assistant Professor. He has served as President of the American Peptide Society, the Board of Directors for FASEB and co-chaired the 22nd American Peptide Symposium and the 2016 GRC. He has published over 180 papers, and has been honored with an Alfred P. Sloan Foundation fellowship, the Vincent du Vigneaud Award, the Max Bergmann Kreis Gold Medal, the Zervas Award and the RSC MedImmune Protein and Peptide Science Award and the Akabori Memorial Award. Professor Dawson is a pioneer of chemoselective ligation methods for macromolecule synthesis and modification and has applied these tools broadly to better understand biological systems.

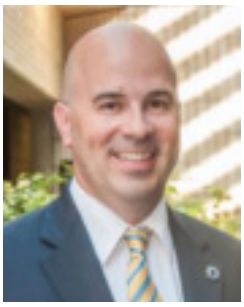
Adrienne Day, Ph.D. | Director and Treasurer, Peptide Therapeutics Foundation; Founder and Principal, Blue Gum Advisors
Closing Remarks

Dr. Day is a seasoned business development professional with more than 30 years of experience in the biotechnology and biopharmaceutical industries. She has hands-on operational and executive management experience in the non-profit, for-profit and startup environments.

Most recently she was Senior Director of Business Development for Ferring Pharmaceuticals. Prior to that Dr. Day ran a successful consulting practice. She has previously served as Vice President of Business Development at what is now the Sanford Burnham Prebys Medical Discovery Institute, Vice President of Business Development Conforma Therapeutics, Senior Director of Business Development at Molecumetics Ltd., Associate Director of Corporate Development at Ligand Pharmaceuticals. She was Ligand Pharmaceuticals' first Project Manager, and began her biotechnology career at Invitrogen Corporation where she held various positions.

Dr. Day received her B.Sc., B.Sc. Honors, and Ph.D. degrees in Biochemistry from the University of Adelaide, Australia. She completed her postdoctoral training at the University of Southern California and the La Jolla Cancer Research Center.

15th Annual Peptide Therapeutics Symposium



Daniel B. DeOliveira, Ph.D., PMP | Senior Director; Peptide Dev., Tech. Ops. & Mfg., Genocea Biosciences Inc.
GEN-009: A Neoantigen Vaccine Based on Autologous Peptide Immune Responses
GEN-011: Transforming T Cell Therapy for Solid Tumors

Dr. Daniel B. DeOliveira has 20 plus years of contributing to drug discovery and pharmaceutical science primarily in the area of peptides and peptidomimetics. He has led drug discovery efforts focusing on rare diseases, oncology and nuclear medicine. He received his Ph.D. in Medicinal Chemistry from Boston University, under the leadership of Prof. Richard Laursen. He went on to do his initial immunology studies, at MIT, designing tight binding MHC antigens that could function as synthetic T-cell antigens. After several years at MIT, Dr. DeOliveira took a position in the private sector at Dyax Corp. where he established and managed a peptide research group to meet the needs of peptide-based projects at Dyax Corp, a company focused on rare hereditary diseases. Dr. DeOliveira's research while at Dyax contributed to the eventual FDA approval of Kalbitor (Ecallantide, DX-88) a treatment for hereditary angioedema. Following Dyax, he took an opportunity at Ipsen Bioscience with a focus on peptides as therapeutic drugs for rare diseases. While at Ipsen, he worked on several peptide-related projects including a Ghrelin agonist (Relamorelin™, BIM-28131) and a MC4R agonist (Setmelanotide™, BIM-22943) both currently in Phase-3 clinical studies. He also led a nuclear medicine program aimed at targeting Neuroendocrine Tumors, where he developed a successful, novel approach to solve the kidney rate limiting effects of Peptide Radio-Theranostics (PRRT) and successfully designed a peptide / small molecule combo to target Neuroendocrine tumors via a non-SSTR mechanism. He is currently Director of Peptide Development, Pharmaceutical Sciences & Manufacturing at Genocea Biosciences, again working on T-cell immunity, aiming to successfully develop peptide based neoantigen cancer vaccines for Genocea's GEN-009 program (currently in clinical trials) as well as for GEN-011, an adoptive T-Cell therapy program.

Ernest Giralt, Ph.D. | Professor, Institute for Research in Biomedicine (IRB Barcelona)
Peptides for Molecular Recognition and Brain Delivery

Prof. Dr. Ernest Giralt is a Group Leader at the Institute for Research in Biomedicine (IRB Barcelona) where is also the Head of the Chemistry & Structural Biology Node. He is also a professor at the University of Barcelona.

Prof. Dr. Giralt is an internationally renowned scientist in the field of peptide synthesis, medicinal chemistry, structure determination, and NMR (Nuclear Magnetic Resonance). Besides, he is an expert on the design of therapeutic ligands for interaction with protein surfaces. He has received several awards, among others the Dimitrios Theodoropoulos Award (2010) and the Josef Rudinger Memorial Lecture Award (2014), both from the European Peptide Society; the Novartis Chemistry Lectureship Award (2011) and the Max Bergmann Medal (2014).

His major interests lie in the study of complex molecular recognition processes, with emphasis on the design of specific ligands for interaction with protein surfaces, related to possible therapeutic uses. This includes studies concerning new drug delivery systems for the treatment of central nervous system pathologies.

David Gloriam, Ph.D. | Professor, University of Copenhagen
Novel Pairings in the Human Peptide-Receptor Signaling System

David Gloriam is a Professor in Computational Receptor Biology at the Department of Drug Design and Pharmacology, University of Copenhagen. His research is devoted to structure, function and drug/ligand discovery for G protein-coupled receptors. His group runs the database, GPCRdb.org serving over 4,000 researchers every month, and combines computational drug design, data science and structural biology. In recent years Prof. Gloriam has published on online resources for structure determination (Munk et al. Nat Methods 2019), structure models and ligands (e.g. Pándy-Szekeres et al. Nucl Acids Research 2018), pharmacogenomics (Hauser et al. *Cell* 2018), GPCR drugs (Hauser et al. *Nat Rev Drug Discov* 2017) and G protein selectivity (Flock et al. *Nature* 2017).

David Gloriam got his Ph.D. from Uppsala University, Sweden in 2006. The thesis involved the bioinformatics identification of 24 novel human G protein-coupled receptors and the overall repertoires in dog, mouse, rat and chicken. He then moved on to UK for two postdocs at EMBL-European Bioinformatics Institute and GlaxoSmithKline.

In 2008, he joined the University of Copenhagen and in 2011 he setup his own group. In 2013, his group build the best structure model of the 5-HT_{1B} receptor (and 3rd place for ligand complex) in the global GPCR Dock competition. In 2014-5, he received ERC Starting Grant and Lundbeck Foundation Fellowship to study the least characterised 'orphan' receptors. Last year, he published discovery of proposed physiological ligands for five such orphan receptors in *Cell*.

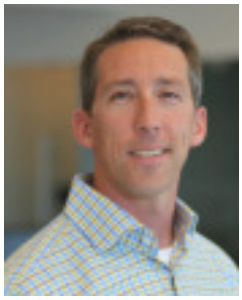
Soumitra Ghosh, Ph.D. | Director and President, Peptide Therapeutics Foundation; President, Doon Associates LLC
Welcoming Remarks

Soumitra Ghosh is a biopharmaceutical industry consultant and entrepreneur with extensive experience in drug development, technology licensing and in formulating and implementing R&D strategy. He is a co-founder of Avexegen Therapeutics, Abvance Therapeutics and Aquros Bio, start-ups focused on GI indications, diabetes and urological disorders, respectively. His experience includes R&D leadership positions at Amylin Pharmaceuticals and MitoKor, where he led research programs for the development of small molecule, peptide and protein-based drug candidates for the treatment of metabolic diseases and CNS disorders. Multiple drug candidates were advanced to the clinic during his tenure, or were partnered with companies for clinical development. He has been a recipient of several SBIR and California state grants for his work in the industry. He received his MS and Ph.D. degrees in Chemistry from the Indian Institute of Technology and the University of Chicago, and conducted his post-doctoral work at the Rockefeller University in New York.

15th Annual Peptide Therapeutics Symposium

Glenn King, Ph.D. | Institute for Molecular Bioscience, The University of Queensland, Australia
Deadly Cures: A Spider-Venom Peptide for Treating Ischemic Injuries of the Heart and Brain

Glenn did his Ph.D. at the University of Sydney before postdoctoral studies at the University of Oxford. After academic stints at the University of Sydney and the University of Connecticut Health Center, he joined the Institute for Molecular Bioscience at The University of Queensland in 2007. Glenn is a pioneer in the field of venoms-based peptide drug discovery, in particular the development of drugs and environmentally-friendly insecticides derived from spider venoms. His early work on venoms lead to him to found an agricultural biotechnology company (Vestaron Corporation, Kalamazoo, USA) that is developing bee-safe, eco-friendly peptidic bioinsecticides. Glenn's current research is focused on the development of peptide drugs to treat chronic pain, epilepsy, cardiac ischemia, and stroke. His laboratory at the University of Queensland maintains the largest collection of venoms in the world, comprising more than 700 venoms from ants, assassin bugs, caterpillars, centipedes, cone snails, scorpions, spiders, and wasps. Glenn has published 3 books, 19 book chapters, and more than 265 peer-reviewed articles in international scientific journals. Glenn was previously President of the Australian Society for Biophysics and Chair of the Australian & New Zealand Society for Magnetic Resonance. He has served on the editorial board of numerous journals, and is currently Editor-in-Chief of the journals Toxicon and Toxicon:X.

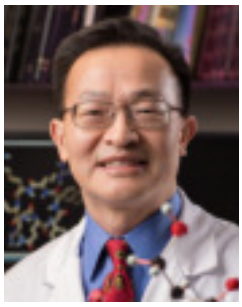


Kevin McDonnell, Ph.D. | Vice President, Chemistry, Bicycle Therapeutics
Building Novel Immune Cell Agonist Anti-Cancer Agents out of Bicycle Parts

Dr. Kevin McDonnell obtained his Ph.D. with Prof. Barbara Imperiali at MIT. He began his career working on FcRn targeted peptides and Fc fusion protein therapeutics at Syntonix Pharmaceuticals and Biogen. He then headed up the discovery chemistry efforts at BIND Therapeutics and focused on the development of small molecule, peptide and protein-conjugated polymeric nanoparticles for targeted delivery of anti-cancer agents. As Vice President of Chemistry for Bicycle Therapeutics, Dr. McDonnell is responsible for advancing bicyclic peptide therapeutics in the oncology discovery programs, with a focus on immuno-oncology.

Daniel Obrecht, Ph.D. | CSO, Polyphor Ltd
Chimeric Macrocyclic Peptide Antibiotics Against WHO Priority 1 Gram-Negative Bacteria Targeting both Lipopolysaccharide and BamA

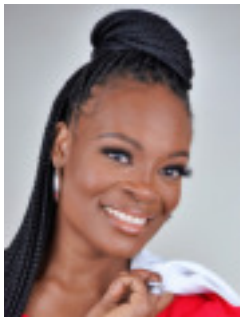
After a Ph.D. in organic chemistry obtained from the University of Zurich (1983), D. Obrecht spent two years of postdoctoral studies working in Prof. R. E. Ireland's group at the California Institute of Technology on the total synthesis of avermectin. He then joined the Central Research Laboratories of F. Hoffmann-La Roche in Basle (1985), where he worked on several drug discovery projects. In 1989 he started a project with the aim to find small molecule peptidomimetics of exposed protein epitopes. In 1993 he was awarded Roche Lecturer, and in 1994 he headed the combinatorial chemistry project at Roche Basle. End of 1996 he co-founded Polyphor with his brother Dr. Jean-Pierre Obrecht. The main expertises of D. Obrecht are synthetic organic chemistry with particular emphasis on macrocycles, medicinal chemistry and drug discovery. He is currently CSO at Polyphor and author and co-author of 70 publications and >40 patents, including key patents on the Protein Epitope Mimetics (PEM) Technology and products, such as POL6014, POL7080, and POL6326.



Dehua Pei, Ph.D. | Kimberly Professor of Chemistry and Biochemistry, The Ohio State University

Cyclic Cell-Penetrating Peptides: Mechanism of Action and Applications

Dehua Pei is the Charles H. Kimberly Professor of Chemistry and Biochemistry at The Ohio State University. He received his Ph.D. degree in organic chemistry from University of California, Berkeley and was a Damon Runyon-Winchell Walter Cancer Fund postdoctoral fellow at Harvard Medical School, before joining Ohio State in 1995. His research group discovered cyclic cell-penetrating peptides (CPPs), a unique class of cell-penetrating molecules that effectively deliver a wide variety of drug modalities into the cytosol of mammalian cells, and elucidated their mechanism of action. His team also developed the methodology for chemical synthesis and screening of peptide-encoded macrocycle libraries to discover ligands against protein targets. His group is currently applying these technologies to develop intracellular biologics for the treatment of previously intractable diseases, such as rare genetic diseases and those caused by aberrant intracellular protein-protein interactions. He is a co-Founder and Chief Scientific Advisor of Entrada Therapeutics.



Kerry-Anne A. Perkins D.O | Obstetrician & Gynecologist, Virtua Memorial Hospital

Dual Myristic Acid (Myr) and Trans Activator of Transcription (Tat) Conjugated Peptides: A Potential Platform Technology for Intracellular Cargo Delivery

Dr. Kerry-Anne A. Perkins received her B.S. degree in Kinesiology, Exercise and Sports Science from Temple University in 2007. She received her first Master's degree in Biomedical Sciences from the Philadelphia College of Osteopathic Medicine (PCOM) in 2009. Thereafter, Dr. Perkins began her medical degree also at PCOM as a dual-degree student and received her Executive Master's degree in Healthcare Business Administration from St. Joseph's University in 2012 and her D.O. degree in 2014. She began her career as an obstetrician and gynecologist (OBGYN) in 2015 trained at St. John's Episcopal Hospital in Queens, New York and now works in private practice in New Jersey. Dr. Perkins is also a captain in the United States ARMY reserves.

Dr. Perkins worked in Dr. Lindon Young's laboratory from 2007 to 2015 in which she worked on mechanisms related to endothelial nitric oxide synthase uncoupling in myocardial ischemia/reperfusion (I/R) injury. This study led to pioneering other research expanding our understanding of reactive oxygen species (ROS)-mediated I/R injury in various organ models that include real time measurement of ROS release *in vivo*.

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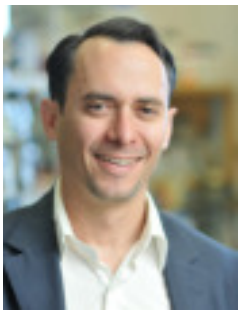


David M. Perrin, Ph.D. | Professor, Chemistry Department, University of British Columbia

Empowering Peptide Science through Easy 18F-Labeling for PET Imaging and New Stapling Methods Inspired by Natural Product Toxins

David M. Perrin obtained his Ph.D. at UCLA with David Sigman where he worked on nucleic acid bioconjugates of phenanthroline copper that would target oxidative DNA scission. He then completed independent postdoctoral work with Professor Claude Helene in Paris where he discovered the first RNaseA-mimicking DNAzyme. In 2000, he accepted a position at the University of British Columbia in the Chemistry Department and now holds the rank of full professor. Professor Perrin has amalgamated synthetic organic chemistry, molecular biology, physical organic chemistry and radiochemistry to address long-standing challenges in molecular recognition, catalysis, and synthetic/radiosynthetic methods in the development of precision therapeutics, a theme that now unites his work. Professor Perrin sought a broadly empowering methodology for one-step ^{18}F-radiolabeling based on novel applications of boron-based chemistries, which in turn provided for a long-sought method for late-stage ^{18}F-labeling of peptides. With publications on numerous PET imaged peptides, including an ocrtreotate-BF3 that is now advancing to a first-in-man application, Professor Perrin is now applying this method for dual-mode fluorescent-PET tracers for use in fluorescent guided surgery. Recently he has reported the first total synthesis of amanitin, a deadly toxin of considerable commercial interest for use in antibody drug conjugates. This work, featured in C&E News as one of 8 notable "molecules of 2018" has involved creating new synthetic methods for indole oxidation and led to the first total synthesis of alpha-amanitin, a classic toxic natural product along with easily-conjugated derivatives of the toxin. His extensive publication record in high-profile peer-reviewed journals along with several granted patents, Perrin provides a unique chemical approach for addressing difficult problems at the chemical-biology interface to provide new compositions of matter that are transforming applications in diagnosis and therapy.

Sarah Robertson, Ph.D., FAA, FAHMS | Professor and Director, Robinson Research Institute, The University of Adelaide

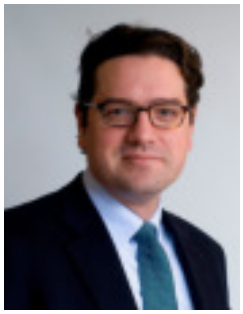
Novel Therapeutics for Inflammatory Disorders of Pregnancy – Opportunities and Challenges

Sarah Robertson Ph.D. is Professor of Reproductive Immunology and Director of the Robinson Research Institute, at the University of Adelaide. Her research focus is the immune response to conception and pregnancy, and consequences for reproductive success and offspring health. Defining fundamental biological pathways and developing novel interventions targeting immune pathways to tackle infertility and gestational disorders, is the goal of her work. She is funded by the National Health and Medical Research Council of Australia, The Australian Research Council and works with industry partners including Ferring Pharmaceuticals, Guerbet P/L and Origio A/S. She has over 200 peer-reviewed scientific journal papers and reviews and has graduated more than 30 Ph.D. students. She is an elected Fellow of *The Australian Academy of Science*, the *Australian Academy for Health and Medical Sciences*, and *Fellow of the Society for Reproductive Biology*. She serves on several Editorial Boards including *Immunology and Cell Biology*, *Endocrinology* and the *Journal of Clinical Investigation*.

Weijun Shen, Ph.D. | Director, Metabolic Disease, Calibr At Scripps Research
A Peptide Engineering Platform for PEG-FA Stapled Long-Acting Peptide Hormones

Weijun is Director of Metabolic Disease at Calibr, the drug discovery arm of the Scripps Research Institute since 2019. Previously, Weijun has been a Principal Investigator of California Institute for Biomedical Research (Calibr) from its inception in 2012. Weijun has more than 10 years of drug discovery experience in large pharma and institute settings, including small molecules, peptide therapeutics and antibody engineering for novel therapeutics for metabolic and cardiovascular diseases, autoimmune diseases and cancer. Prior to joining Calibr at 2012, he was a Research Investigator I and II, and project team leader for regenerative medicine for type 1 diabetes (T1D) at Novartis/GNF. He previously worked as a Postdoctoral Fellow in chemical biology at the Scripps Research Institute under the supervision of Prof. Peter G. Schultz from 2007-2009. Weijun received his Ph.D. degree in Bio-organic Chemistry from University of Nebraska (Lincoln, NE) and his MS degree in Condensed Matter Physics from Chinese Academy of Sciences. In his scientific career so far, Weijun has over 40 scientific publications in peer-reviewed journals and 20 patent applications, with multiple preclinical candidates going into IND enabling and clinical studies in the next 1-3 years.

In addition, Weijun also serves as the Industrial Advisory Board Member for the Department of Chemistry, University of Nebraska and is a member of the American Peptide Society and American Diabetes Association. Weijun also serves as Vice President, Board of Directors, and Chair of the Pacific Alliance Committee of Sino-American Biotechnology & Pharmaceutical Professional Association (SABPA) and Vice President for US Zhejiang General Chamber of Commerce San Diego Chapter.



Giovanni Traverso, MB, BChir, Ph.D. | Assistant Professor, Department of Mechanical Engineering, Massachusetts Institute of Technology, Assistant Professor of Medicine (part-time), Division of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School
GI Device Development in a Few Movements

Dr. Traverso is an Assistant Professor in the Department of Mechanical Engineering at the Massachusetts Institute of Technology and in the Division of Gastroenterology, Brigham and Women's Hospital (BWH), Harvard Medical School. Dr. Traverso grew up in Peru, Canada and the United Kingdom. He received his BA from Trinity College, University of Cambridge, UK, and his Ph.D. from the lab of Prof. Bert Vogelstein at Johns Hopkins University. He subsequently completed medical school at the University of Cambridge, internal medicine residency at the Brigham and Women's Hospital and his gastroenterology fellowship training at Massachusetts General Hospital, both at Harvard Medical School. Dr. Traverso's previous work focused on the development of novel molecular tests for the early detection of colon cancer. For his post-doctoral research, he transitioned to the fields of chemical and biomedical engineering in the laboratory of Professor Robert Langer at the Massachusetts Institute of Technology (MIT) where he developed a series of novel technologies for drug delivery as well as physiological sensing via the gastrointestinal tract.

Dr. Traverso's work has been published in the *New England Journal of Medicine*, *The Lancet*, the *Journal of the American Medical Association*, *Nature*, *Science*, *Nature Biotechnology*, *Nature Materials*, *Nature Communications*, *Science Translational Medicine and Cancer Research*. He has been the recipient of the Grand Prize of the Collegiate Inventors Competition, a Research Fellowship from Trinity College, and was named one of the most promising innovators under 35 by the MIT Tech Review's TR 35.

His current research program is focused on developing the next generation of drug delivery systems to enable efficient delivery of therapeutics through the gastrointestinal tract as well developing novel ingestible electronic devices for sensing a broad array of physiologic and pathophysiologic parameters. Additionally, Dr. Traverso continues his efforts towards the development of novel diagnostic tests that enable the early detection of cancer.

15th Annual Peptide Therapeutics Symposium

Greg Verdine, Ph.D. | Erving Professor of Chemistry, Harvard University and Harvard Medical School; President and Chief Executive Officer, Fog Pharmaceuticals and LifeMine Therapeutics

Toward Universal Druggability

Gregory Verdine is an award-winning university educator, pioneering scientist and innovator, life science entrepreneur, venture capitalist and successful biotech company-builder. Verdine is an originator of STEMgenesis, a new model for fostering community economic and intellectual growth through the convergence of philanthropy, workforce development, and institution creation. In a distinguished academic career spanning three decades at Harvard University and Harvard Medical School, Verdine reinvented the teaching of organic chemistry to focus intensively on its fundamental connectivity to biology, and he founded two fields of science that meld basic research and new medicines discovery: chemical biology, the pursuit of chemistry in the service of uncovering the mysteries of biology; and new modalities, the discovery and development of novel structural classes of therapeutics.

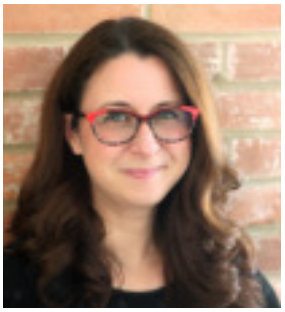
In his academic research, Verdine made fundamental discoveries into how living organisms manage their genomes, tagging them for cell-type specification, and conducing search-and-destroy operations for cancer-causing abnormalities. He invented a powerful new class of therapeutics termed stapled peptides, which enable intervention into diseases previously considered "undruggable." Hundreds of laboratories worldwide now conduct basic and translational research on stapled peptides, and an optimized stapled peptide pioneered at Harvard is currently in Phase II clinical development for the treatment of blood-borne cancers.

Verdine has been among the most active and successful entrepreneurs translating academic research into new medicines. As an academic founder at Harvard and a Venture Partner at several prominent life science investment firms, he is responsible for the creation of ten biotechnology companies, including Enanta Pharmaceuticals, Gloucester Pharmaceuticals (acquired by Celgene) and WaVe Life Sciences. These companies have succeeded in gaining FDA approval for three breakthrough medicines and have multiple additional candidates in development. He moved beyond company ideation and creation into company-building and management at WaVe Life Sciences, Warp Drive Bio, and currently FOG Pharmaceuticals and LifeMine Therapeutics.

Verdine's concept of STEMgenesis took form with his founding and inaugural Presidency of the non-profit Gloucester Marine Genomics Institute and Gloucester Biotechnology Academy, which together aim to promote the creation of a vibrant life science industry on Cape Ann Massachusetts through coordinated establishment of a world-class ocean-based genomics research entity and an educational institution that trains high school graduates for rewarding careers in biotechnology.

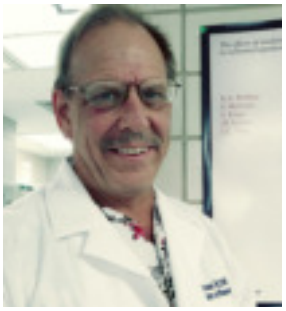
Verdine's contributions to science and society have been recognized by numerous honors and awards, including his being named a Fellow of the Royal Society of Chemistry, and a Fellow of the American Association for the Advancement of Science. He is the recipient of a Presidential Investigator Award, the Nobel Laureate Signature Award, and the Award for Excellence in Chemistry in Cancer Research.

Verdine received a B.S. and Ph.D. in chemistry from St. Joseph's University and Columbia University, respectively, and he is the recipient of honorary degrees from Harvard University and Clarkson University.



Kathryn Whitehead, Ph.D. | Associate Professor, Carnegie Mellon University
From Farm to Pharmacy: A Strawberry-Derived Solution to Oral Protein Delivery

Kathryn A. Whitehead is an Associate Professor and Dean's Career Fellow in the Departments of Chemical Engineering and Biomedical Engineering (courtesy) at Carnegie Mellon University. Her lab develops RNA and protein drug delivery systems and has a long-term goal of predicting the behavior of delivery materials in humans. She received an H.B.Ch.E Degree with Distinction from the University of Delaware (2002) and a Ph.D. in chemical engineering from the University of California, Santa Barbara (2007) before serving as an NIH Ruth L. Kirschstein Postdoctoral Fellow at the Massachusetts Institute of Technology (2008 – 2012). Prof. Whitehead is the recipient of numerous awards, including the NIH Director's New Innovator Award, the DARPA Young Faculty Award, the DARPA Director's Fellowship, the ASEE Curtis W. McGraw Research Award, and the Kun Li Award for Excellence in Education. Prof. Whitehead was named as a Pioneer on the MIT Technology Review's Innovators Under 35 list in 2014 as well as one of the Brilliant Ten by Popular Science in 2015. Her publications have been cited over 6,000 times, and several of her patents have been licensed and sublicensed for reagent and therapeutic use.



Lindon H. Young, Ph.D. | Professor of Pharmacology, Philadelphia College of Osteopathic Medicine; Founder & Chief Science Officer,Young Therapeutics
Dual Myristic Acid (Myr) and Trans Activator of Transcription (Tat) Conjugated Peptides: A Potential Platform Technology for Intracellular Cargo Delivery

Lindon Young received his B.A. degree in Biology from Immaculata University in 1986 (with honors). He received his Ph.D. in Pharmacology from the Philadelphia College of Pharmacy & Science (now known as University of the Sciences) in 1997. Thereafter, Dr. Young began his post-doctoral career conducting myocardial research in Dr. Margaret Weis's laboratory from 1997 to 1999 at the University of the Sciences. In 1999, he received a training grant from the NHLBI of NIH and studied the biochemical mechanisms related to *myocardial ischemia-reperfusion (I/R) injury* in Dr. Allan Lefer's laboratory until 2001.

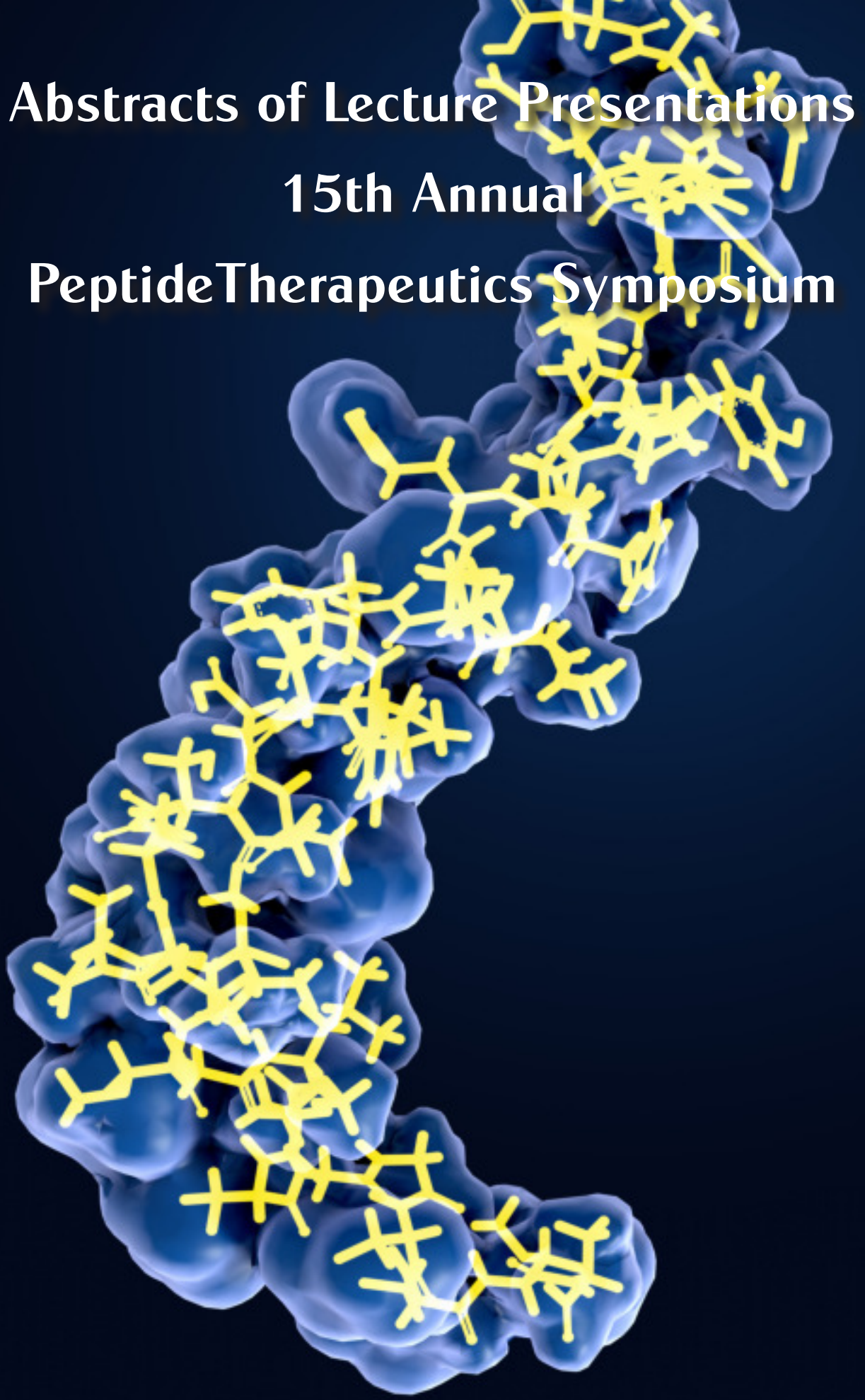
In 2002, He was hired by the Philadelphia College of Osteopathic Medicine (PCOM) as an Assistant Professor and he continued to pursue his research related to upstream regulation of reactive oxygen species (ROS) induced myocardial I/R injury using myristic acid (Myr) conjugated peptides that regulate selective protein kinase C (PKC) isoform function to mitigate I/R injury. Dr. Young received NIH grants from the NHLBI from 2004 to 2011 and PA Dept. of Health Grant from 2011 to 2015 and founded Young Therapeutics (YT), a PCOM life sciences start-up company in 2015. During this time, Dr. Young has mentored many PCOM graduate and medical school students to help his laboratory conduct I/R related studies.

Notes

Abstracts of Lecture Presentations

15th Annual

PeptideTherapeutics Symposium



Vasopressin: Old Dog. New Tricks.

Michael J. Brownstein M.D., Ph.D. | Senior Vice President, Drug Development
Azevan Pharmaceuticals
Bethlehem, PA

Arginine vasopressin (AVP) regulates water homeostasis by activating V2 receptors in the kidney. Its effects on blood pressure and ACTH secretion are mediated by V1A and V1B receptors, respectively. In the last decade the peptide's behavioral effects have received attention as well. Azevan has developed first-in-class, orally available, CNS-active V1A receptor antagonists. In animal models, these compounds inhibit anxiety, aggressive behavior, and conditioned fear responses. In humans, they appear to affect vasopressin-sensitive circuits that are activated by angry faces[1]. On the strength of these studies, we have advanced one of our compounds, SRX246, into Phase 2 clinical trials in patients with Intermittent Explosive Disorder, PTSD, and Huntington's disease[2-4]. All of the subjects who enrolled in these studies suffered from irritability, anger, and aggressive behavior. I will outline our findings in my talk.

1 Lee, RJ et al. A novel V1a receptor antagonist blocks vasopressin-induced changes in the CNS response to emotional stimuli: an fMRI study. *Front Syst Neurosci.* **2013**:7:100.
2 https://www.clinicaltrials.gov/ct2/show/NCT02055638?term=SRX246&rank=3
3 https://www.clinicaltrials.gov/ct2/show/NCT02733614?term=SRX246&rank=2
4 https://www.clinicaltrials.gov/ct2/show/NCT02507284?term=SRX246&rank=4

Adrenomedullin Functions at the Maternal-Fetal Interface

Kathleen Caron, Ph.D. | Professor & Chair
Department of Cell Biology and Physiology
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599

Adrenomedullin and its receptors are highly expressed in female reproductive tissues and are required for the normal development of the cardiovascular system, including the heart, lymphatic vessels and placenta, which we have shown by gene targeted animal models. For example, female mice with a modest 50% reduction in adrenomedullin gene expression suffer from subfertility due to abnormal uterine receptivity, implantation and placentation. Moreover, loss of adrenomedullin from fetal tissues leads to pathological features of preeclampsia in the placenta. Therefore, the precise genetic dosage of adrenomedullin, both from the mother and the fetus, is crucial for establishing and maintaining a normal pregnancy and modulating the innate immune response at the maternal-fetal interface. Administration of adrenomedullin peptide to the mouse uterus prior to implantation improves embryo implantation and spacing, highlighting the potential therapeutic benefits of this peptide in normal and assisted reproductive cycles. Through our extensive and productive collaborations with clinician scientists, we have translated our discoveries to humans by showing that polymorphisms in the genes encoding adrenomedullin signaling are associated with poor pregnancy outcomes and that adrenomedullin peptide can serve as a highly predictive plasma biomarker for severe preeclampsia.

GEN-009: A Neoantigen Vaccine Based on Autologous Peptide Immune Responses
GEN-011: Transforming T Cell Therapy for Solid Tumors

Daniel B. DeOliveira, Ph.D., PMP | Senior Director
Peptide Dev., Tech. Ops. & Mfg.
Genocea Biosciences Inc.

GEN-009

BACKGROUND: Neoantigens have emerged as tumor specific targets, yet the accurate identification of those neoantigens to which patients can generate functional T cell responses has been a major barrier to the development of successful vaccines and immunotherapies. Genocea's ATLAS™ platform identifies neoantigens for vaccine inclusion via comprehensive ex vivo screening of patient-specific mutations to identify pre-existing $CD4^+$ or $CD8^+$ T cell responses and excludes inhibitory peptides (Inhibigens™) that may suppress immunity and accelerate tumor progression. GEN-009-101 is an ongoing phase 1/2a study testing the safety, immunogenicity, and clinical activity of a personalized neoantigen cancer vaccine in combination with CPI +/- chemotherapy.

METHODS: For each patient, next-generation sequencing (NGS) of their primary tumor is followed by screening via ATLAS to identify the neoantigens for vaccine inclusion. Up to 20 stimulatory peptides are manufactured using a conventional yet fast and efficient cGMP process to render GEN-009 drug substance. The drug substance is formulated and filled to render the GEN-009 vaccine drug product. Following release, the GEN-009 vaccine is adjuvanted at the clinic with poly-ICLC to comprise each personalized vaccine.

RESULTS: The GEN-009 vaccine was successfully manufactured for all patients with adequate numbers of stimulatory peptides in both Part-A and thus far in Part-B of the trial. In Part-A of the GEN-009-101 study, eight patients were vaccinated with GEN-009 vaccine. The vaccine is given in 5 doses over 6 months. The manufacturing process and immunogenicity results will be presented.

GEN-011

'Adoptive T cell therapy" involves the isolation and expansion of tumor- or neoantigen-specific T cells to create therapeutics targeting patients' cancers. There are currently a variety of methods being used to develop ACTs, most of which involve genetic engineering of a patient's T cells and delivering them back to the patient.

In our GEN-011 program, we are using ATLAS to identify patient-specific neoantigens that stimulate that patient's immune system and exclude Inhibigens™, and then isolating the T cells that are activated by those neoantigens. We can then expand these autologous (the patient's own) T cells to create a therapeutic.

We believe that our first-in-class GEN-011 approach could provide several advantages over existing methodologies such as TIL (tumor infiltrating lymphocyte) therapy or TCR (T cell receptor) therapy, including:

- Greater potential immunogenicity and efficacy by:
  - Including both CD4+ (helper) and CD8+ (killer) T cells identified through ATLAS
  - Excluding Inhibigens™ (inhibitory peptides)
  - Including multiple antigen-specific T cells to broaden the anti-tumor effect and mitigate risk of tumor escape
- Using a patient's own non-engineered T cells could improve on safety and the speed and cost of manufacturing

We are currently conducting preclinical studies of GEN-011 and have filed an IND with the FDA.

Peptides for Molecular Recognition and Brain Delivery

Ernest Giralt, Ph.D. | Professor
Institute for Research in Biomedicine (IRB Barcelona)

The breakthrough concept that proteins function as a contact network rather than as independent individuals is not only one of the most important advances in our comprehension of living systems, but also translates to a new era in drug discovery. The few reported examples of diseases caused by "impolite" protein social behavior certainly represent only the tip of the iceberg. Therapeutic intervention through molecules designed to selectively modulate the strength and specificity of protein-protein interactions (PPIs) is becoming a reality. In this context, peptides are destined to play a major role as therapeutic agents. My laboratory is contributing to speeding up this process. On the one hand, we devote efforts to studying the molecular details and dynamics of the events that occur during molecular recognition at protein surfaces. We succeeded to design and synthesize peptides able to modulate these recognition events either permanently or in response to light.[1] On the other hand, we are discovering and designing peptides able to cross biological barriers. Our aim is to use these peptides as shuttles for targeting therapeutic agents to organs, tissues, or cells, with a special emphasis on drug delivery to the brain. The treatment of CNS disorders is severely hampered by the presence of the blood-brain barrier (BBB). Several peptides have emerged as 'privileged' structures with the capacity to cross the BBB efficiently and thus as potential BBB-shuttles for drug delivery into the brain.[2] Degradation by proteases is, however, an important limitation of this approach. In recent years, we have focused on the use of non-proteinogenic amino acids, including D-amino acids, for the design of BBB-shuttles that are resistant to degradation by proteases.[3,4]

Given their capacity to reach the CNS without causing inflammation, venoms are a potentially rich source of novel BBB-shuttles. We have recently explored the use of venom-derived cyclic peptides as protease-resistant BBB-shuttles. Apamin is an 18-mer peptide from bee venom that accumulates in significant amounts in the brain and spinal cord. Starting from apamin, we have designed a series of simplified peptides stabilized via cyclization either via a disulfide bridge or through lactamization (see figure). Among these molecules, MiniAp-4 has proved to be the most permeable candidate and, accordingly to preliminary studies, it is able to promote the translocation of proteins and nanoparticles both in a human-cell-based assay and in vivo brain.[5,6]

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Novel Pairings in the Human Peptide-Receptor Signaling System

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GPCRs are involved in nearly all physiological processes and mediate the effect of ~34% of drugs[1]. The pairing of understudied, 'orphan' receptors with physiological ligands (a.k.a. deorphanization) can uncover physiological signaling systems and targets for future therapeutic interventions. However, the recent progress in deorphanization of the remaining orphan receptors has slowed dramatically, despite a sustained research effort directed towards delineating orphan GPCR biology[2]. There are many contributing factors to this trend, as there are challenges at every stage of the process: i) natural ligands are often unstable or not adequately represented in the commercially available compound libraries, ii) most remaining orphan receptors lack homology with liganded GPCRs, and iii) many pharmacological assays cannot be validated and optimized due to the lack of a reference ligand or knowledge of the signaling pathway.

This talk will describe an alternative route to deorphanization of peptide-activated receptors. This method exploits the facts that peptide ligands can be identified from the human genome, as were most orphan receptors. As both possess unique characteristics of the peptidergic signaling system, we were able to recognize new candidate peptides and their receptors using machine learning. We employed a multifaceted primary screening platform based on dynamic mass redistribution, receptor internalization and arrestin recruitment assays. This led to the validated pairing of five orphan receptors to proposed physiological ligands, as well as identification of intriguing secondary targets and ligands for several of the known receptor families.[3]

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Deadly Cures: A Spider-Venom Peptide for Treating Ischemic Injuries of the Heart and Brain

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Myocardial sensitivity to ischemia-reperfusion injury (IRI) remains a primary point of vulnerability underlying cardiovascular disease, which is the leading cause of morbidity and mortality worldwide. Despite decades of preclinical therapeutic development, there are currently no drugs that block the acute injury response to cardiac ischemia. During cardiac ischemia, the build-up of acidic metabolites results in decreased intracellular and extracellular pH that can reach as low as 6.0–6.5. Severe acidosis exacerbates the ischemic injury and significantly impacts cardiac function. The proton-gated acid-sensing ion channel 1a (ASIC1a) is known to mediate injury responses during cerebral ischemia, but little is known about its role during cardiac IRI. We show that genetic ablation of ASIC1a leads to improved functional recovery following global myocardial IRI in ex vivo mouse hearts, and that this effect can be recapitulated by therapeutic blockade of ASIC1a using Hi1a, a potent and specific peptidic inhibitor of Hi1a derived from venom of the Australian funnel-web spider. Hi1a yields improved post-IRI cardiac viability and function in an *ex vivo* rodent model of myocardial infarction and rodent models of donor heart procurement for heart transplantation. Consistent with a key role for ASIC1a in human cardiac ischemia, we used GWAS data to show that polymorphisms in the ASIC1 genetic locus are strongly associated with myocardial infarction. Collectively, our data provide compelling evidence that ASIC1a is a key target for cardioprotective drugs to reduce the burden of disease associated with myocardial ischemia, and that the disulfide-rich Hi1a peptide is an exciting lead compound for treatment of cardiac IRI. I will present variants of the Hi1a peptide that may be more suitable for certain clinical applications.

Building Novel Immune Cell Agonist Anti-Cancer Agents out of *Bicycle* Parts

Kevin McDonnell, Ph.D.
Vice President, Chemistry
Bicycle Therapeutics

Bicycles® are bicyclic peptides constrained via a chemical scaffold, which confers structural stability leading to high affinity and selectivity. Bicycles have been used in a modular fashion to generate tumor targeted immune cell agonists (TICAs™), which simultaneously bind to overexpressed cell-surface targets on tumor cells (e.g. EphA2 or Nectin-4) and costimulatory receptors on immune cells (e.g. CD137). This interaction leads to highly precise activation of immune cells in the tumor microenvironment, resulting in anti-cancer immunity. TICAs represent a new generation of fully synthetic peptide-based immune modulatory anti-cancer agents.

Chimeric Macrocyclic Peptide Antibiotics Against WHO Priority 1 Gram-Negative Bacteria Targeting both Lipopolysaccharide and BamA

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WHO priority 1 Gram-negative bacteria constitute a significant threat in the fight against antimicrobial resistance (AMR). Unfortunatly, the pipeline of urgently needed novel classes of antibiotics with novel targets and/or modes of mechanisms of action is scarse.

By linking two macrocyclic pharmacophores against two essential bacterial targets, lipopolysaccharide (LPS) and BamA, located in proximity at the outer-membrane of Gram-negative bacteria, a novel class of antibiotics with potent activity against carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* and carbapenem and 3rd generation cephalosporin-resistant Enterobacteriacea (WHO priority-1 pathogens) was discovered. First hits with good activity against MDR-XDR strains were discovered by phenotypic screening of a library constituted of 14-amino acid macrocyclic β-hairpin mimetics[1] derived from active peptide sequences of antimicrobial peptides, such as protegrin-1[2]. By linking a 7-amino acid macrocycle derived from colistin, known to have affinity towards the lipid A part of LPS, we anticipated synergistic binding of such a chimeric antibiotic to LPS and essential β-barrel outer-membrane proteins such as LptD and/or BamA. After a significant library synthesis effort optimizing the β-hairpin and linker sequences as well as finding the optimal positioning of the linkage to the 7-amino acid macrocycle derived from colistin, chimeric antibiotics with potent in vitro antimicrobial activity against all priority-1 Gram-negative bacteria were discovered. The compounds were selective against Gram-negative bacteria with no residual activity against Gram-positive bacteria nor fungi. In a substantial medicinal chemistry effort initial hits were then optimized to obtain molecules with potent in vivo activity in various murine infection models with appropriate ADME properties. The chimeric antibiotics are bactericidal, non hemolytic and show a very low propensity to generate resistance. By combining biochemical, biophysical, structure biological, and genetic experiments the mechanism of action could be identified and confirmed our initial hypothesis[3]. Optimized lead compounds are currently in preclinical evaluation. This presentation will focus on the discovery, *in vitro* and *in vivo* antimicrobial profiling, resistance and MoA studies of the novel chimeric antibiotics.

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Cyclic Cell-Penetrating Peptides: Mechanism of Action and Applications

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Current biologic drugs work almost exclusively against extracellular targets, because they cannot cross the cell membrane. Numerous attempts are being made to deliver biologics into mammalian cells, usually by leveraging the endocytic processes. Unfortunately, most of the endocytosed materials remain entrapped inside the endosomal/lysosomal pathway and poor endosomal escape represents a key bottleneck during the development of intracellular biologics. We recently discovered small cyclic peptides as well as nonpeptidic molecules as highly active endosomal escape vehicles (EEVs), which effectively deliver all major drug modalities (e.g., small molecules, peptides, proteins, and nucleic acids) into the cytosol of mammalian cells *in vitro* and *in vivo*. These EEVs enter the cell by endocytosis followed by efficient and, in some cases, nearly quantitative release from the early endosome. We previously proposed that the EEVs exit the endosome by inducing budding and collapse of small vesicles from the endosomal membrane, based on experimental data on model membranes. We have since developed sensitive assays to directly visualize the budding and collapse events in live cells. Cytosolic delivery of peptides and proteins with the EEVs has led to several preclinical candidates for the treatment of previously intractable diseases such as acute respiratory distress syndrome (ARDS) and mitochondrial neurogastrointestinal encephalomyopathy (MNGIE).

Empowering Peptide Science through Easy 18F-Labeling for PET Imaging and New Stapling Methods Inspired by Natural Product Toxins

David M. Perrin, Ph.D. | Professor
Chemistry Department
University of British Columbia

Molecular medicine offers promise for personalized cancer treatments. New antibody-drug conjugates (ADCs) for therapy and new approaches in PET imaging for personalized diagnostics support this promise.

Key to PET imaging is the ability to work with F-18 fluoride, the only scalable PET-isotope. Yet its application has posed considerable challenges in terms of labeling peptides for clinical applications. To meet this challenge, we have developed a user-friendly one-step approach to 18F-labeling that is made possible by an organotrifluoroborate prosthetic group that is conjugated to the peptide to create a radiosynthetic precursor. We have used this approach to advance new radiotracers for unmet needs in cancer-specific imaging agents. The application of this novel method and its outcome to produce excellent preclinical PET images will be discussed.

For therapeutic applications, ADCs are seeing a renewed interest due to improved antibody chemistries and new cytotoxic payloads. Alpha-amanitin, is a well-known peptide cytotoxin that inhibits RNA polymerase II thus killing both growing and quiescent cells. Recently, antibody-amanitin antibodies were found to be effective against pancreatic cancer in mice while Herceptin-amanitin conjugates are entering clinical trials. For over 8 decades, the total synthesis of amanitin has remained an elusive challenge. This year we completed the first total synthesis of amanitin — how we accomplished this and what we learned will be discussed.

Novel Therapeutics for Inflammatory Disorders of Pregnancy - Opportunities and Challenges

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Inflammation is a central feature and is implicated as a causal factor in common and serious disorders of reproduction and pregnancy that affect around 25% of couples or individuals seeking to have children. Infertility and recurrent miscarriage are increasingly prevalent conditions associated with a growing, multi-billion dollar reproductive medicine industry. Preeclampsia and preterm birth occur in ~20 million pregnancies each year and contribute substantially to the developmental origins of metabolic, neurocognitive and autoimmune/allergy diseases in children. Events around the time of conception that promote maternal adaptation to pregnancy and induce a state of adaptive immune tolerance of paternally-inherited fetal alloantigens are central to healthy embryo implantation, development of a robust placenta, optimal fetal growth and on-time birth. Insufficient tolerance, with elevated inflammatory mediators and leukocytes, is common to each of these conditions and contributes to the underlying pathophysiological processes including hypertension and compromised placental development and function. Regulatory T (Treg) cells are central mediators of pregnancy tolerance and direct other immune cells to counteract inflammation and promote robust placentation. There is evidence Treg cell insufficiency has a causal role in many forms of infertility and the common gestational disorders. This is implied by increasing evidence that poor Treg cell parameters predate symptoms in women, and mouse studies showing sufficient numbers of functionally competent Treg cells are essential from conception, to support maternal vascular adaptation and prevent later placental inflammatory pathology. Treg cells may therefore provide a tractable target for both preventative strategies and treatment interventions in preeclampsia. Steps to boost Treg cell activity require investigation and could be incorporated into pregnancy planning and preconception care. Pharmacological interventions developed to target Treg cells in autoimmune conditions warrant consideration for evaluation, utilizing rigorous clinical trial methodology, and ensuring safety is paramount. These may also include immunobiologics that suppress inflammation and/or redirect immune effector mechanisms. Emerging cell therapy tools involving *in vitro* Treg cell generation and/or expansion may in time become relevant. The success of preventative and therapeutic approaches will depend on resolving several challenges including developing informative diagnostic tests for Treg cell activity applicable before conception or during early pregnancy, selection of relevant patient subgroups, and identification of appropriate windows of gestation for intervention.

A Peptide Engineering Platform for PEG-FA Stapled Long-Acting Peptide Hormones

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Zaid Amso, Candy Lee, Van Nguyen-Tran, Weijun Shen

As a drug class, peptides offer exquisite specificity and potency, but also present challenges associated with poor stability and short half-life, manifesting in the need for frequent injections, poor patient compliance, and overall compromised efficacy. We have developed a novel peptide engineering strategy that incorporates a serum protein binding motif onto a covalent side-chain stapling and applied to multiple peptide hormones to enhance their helicity and stability, and therefore, to enhance their in vitro potencies and in vivo half-lives and efficacies. In this presentation, I will detail the rational design of this platform technology and its application into long acting GLP1R single and dual agonist, and long acting GLP2R single agonist. Rodent and cyno PK indicate once weekly projected half-life in human. Detailed rational on target selection, peptide engineering and in vitro and in vivo efficacies in multiple disease models will be presented.

GI Device Development in a Few Movements

Giovanni Traverso, MB, BChir, Ph.D. | Assistant Professor
Department of Mechanical Engineering
Massachusetts Institute of Technology
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Harvard Medical School

Medication non-adherence (non-compliance) represents a major barrier to effective clinical care. In developed nations, only 50% of patients take their medications as prescribed, manifesting in more than $100 billion in avoidable hospitalizations every year in the United states alone and the numbers are far worse in the developing world. In his seminar, Dr. Traverso will present a series of novel technologies being developed with the goal to enhance and facilitate medication administration. Specifically, Dr. Traverso will discuss the development of new technologies for the delivery of macromolecules through the oral route.

Toward Universal Druggability

Greg Verdine, Ph.D. | Erving Professor of Chemistry; President and Chief Executive Officer
Harvard University and Harvard Medical School
Fog Pharmaceuticals and LifeMine Therapeutics

An frustratingly elusive goal of drug discovery has been to reach a state of advancement at which all protein targets are capable of being drugged, *i.e.* to achieve *universal druggability*, with biological and medical criteria being the sole determinants of which targets are prosecuted. Recent advances in the discovery of Helicon™ peptides — conformationally constrained alpha helical peptides — suggest this new modality represents a true contender toward enabling the majority of human proteins to be drugged. Progress toward the discovery of Helicon™ peptides will be presented.

From Farm to Pharmacy: A Strawberry-Derived Solution to Oral Protein Delivery

Kathryn Whitehead, Ph.D. | Associate Professor
Department of Chemical Engineering
Department of Biomedical Engineering
Carnegie Mellon University

Oral delivery is the most patient-friendly mode of drug administration. Unfortunately, it is not possible for protein and other macromolecular drugs because the gastrointestinal tract is not permeable to undigested large molecules. Although many chemical permeation enhancers have been identified that improve the intestinal absorption of biologics, they often cause cytotoxicity or damage the intestinal mucosa. To address this issue, we sought to identify a permeation enhancer derived from fruits and vegetables, hypothesizing that the compounds found in natural foods would be well-tolerated by the gastrointestinal tract. Following a screen of over 100 fruits, vegetables, herbs, and fungi, we identified strawberry as a potent enhancer of macromolecular permeability both *in vitro* and *in vivo*. Natural product chemistry techniques revealed pelargonidin, an anthocyanidin, as the active compound in strawberry. In mice, pelargonidin enabled 100% bioactivity of oral insulin relative to the current gold standard of subcutaneous injection, without causing toxicity. These results underscore the potential of naturally derived compounds in biomedical applications and demonstrate pelargonidin as an especially potent new enhancer for the oral delivery of biologics.

Dual Myristic Acid (Myr) and Trans Activator of Transcription (Tat) Conjugated Peptides: A Potential Platform Technology for Intracellular Cargo Delivery

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Philadelphia College of Osteopathic Medicine
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Kerry-Anne A. Perkins D.O | Obstetrician & Gynecologist
Virtua Memorial Hospital

Myr and Tat conjugation to peptides have been used since the early 90's to increase peptide permeability through the cell membrane to target intracellular substrates and enhance efficacy of peptide mechanisms.Myr peptide conjugation augments cell permeability via a simple diffusion mechanism, whereas Tat peptide conjugation augments via an endocytosis-type mechanism. Both types of conjugation have proven to be effective in pre-clinical studies. Tat-conjugated peptides have also been tested clinically. Described herein, is a novel approach to enhance peptide (cargo) delivery of therapeutics that employs an N-terminus Myr + Tat (YGRKKRRQRRR) + cysteine- cysteine (C-C) + cargo (peptide inhibitors of protein kinase C [PKC] epsilon [PKCε] or beta II [PKCβII]) in isolated rat hearts subjected to ischemia-reperfusion (I/R) injury. Previous studies using Myr conjugated PKCε or PKCβII peptide inhibitors have been shown to be effective at attenuating myocardial I/R injury by reducing reactive oxygen species (ROS) induced myocardial I/R injury, in part, by inhibiting I/R induced mitochondrial-derived ROS (both PKCε and PKCβII inhibitors), NADPH oxidase (NOX-2) ROS (PKCβII inhibitor) and uncoupled endothelial nitric oxide synthase (eNOS) ROS (PKCε inhibitor) when given at the beginning of reperfusion.

Abstracts of Poster Presentations

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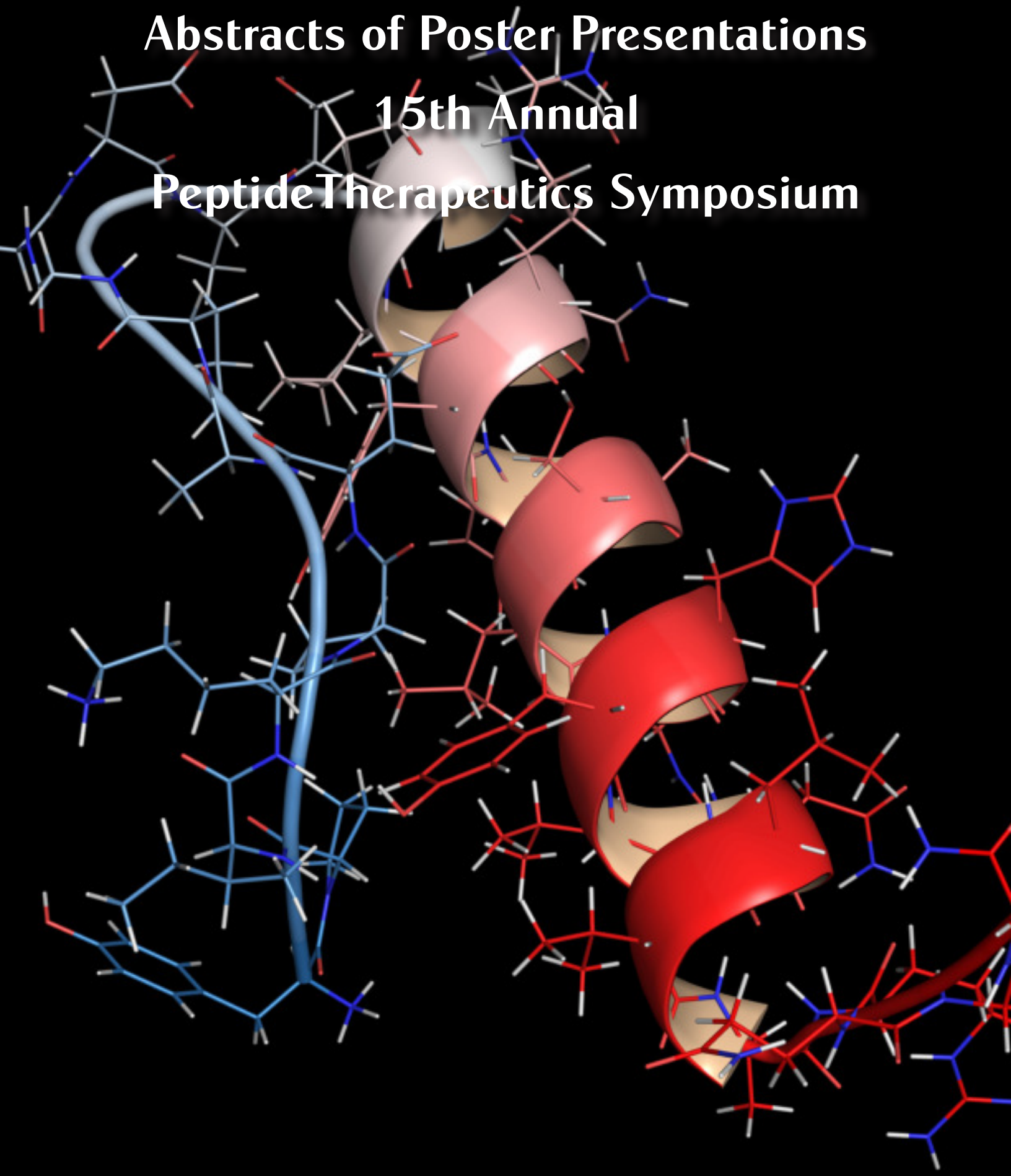

Protein Kinase C-Epsilon Inhibitor Conjugated with Myristic Acid and Trans-Activator of Transcription Elicits Superior Cargo Delivery and Cardioprotective Effects in Rat Myocardial Ischemia-Reperfusion Injury

Alison Baker, Tameka Dean, Sunit Singh, Melinda Beale, Alison Baker, Megan Michaels, James Fagan, Erika Foerst, Qian Chen, Robert Barsotti, Lindon Young
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In separate studies, myristic acid (Myr) and trans-activator of transcription (Tat) conjugated with an inhibitory peptide of PKC-epsilon (PKCε-; EAVSLKPT) have been shown to mitigate myocardial IR injury via inhibiting reactive oxygen species (ROS) and cytokine release. Myr- PKCε- was effective (20μM to 5μM) but was not effective at 1μM (McIntyre et al. 2018) and Tat-PKCε- was ineffective in clinical studies (Moodie et al. 2013) that used 0.46 mg/kg (~5μM in blood) which may be due to limited penetration. We hypothesize that dual conjugated Myr-Tat-PKCε- would improve peptide intracellular transport and significantly reduce infarct size by using concentrations less than 5μM.

Isolated hearts from male SD rats (~300g) perfused with Krebs' buffer at 80 mmHg were subjected to I (30 min)/R (50 min). Myr-PKCε-, Tat-PKCε-, Myr-Tat-PKCε-, or Myr-Tat-PKCε-scram (10μM-100pM) were given during the first 5 min of reperfusion. Infarct size was determined by 1% triphenyltetrazolium chloride staining. Data were evaluated using ANOVA Bonferroni-Dunn analysis.

Compared to control (23±3, n=5; p<.05), the Myr-Tat PKCε- groups significantly reduced infarct size (%): 10μM (5±2, n=4), 1μM (5±2, n=5), 100nM (8±2, n=5), and 1nM (10±3, n=5), but was ineffective at 100 pM (18±1, n=5). Whereas, Myr-PKCε- and Tat-PKCε- (both 10μM) decreased infarct size to (15±4, n=5) and (18±2, n=4), respectively. Scrambled peptides were ineffective.

Results suggest that Myr-Tat-PKCε- dose dependently reduces infarct size and improves intracellular delivery of cargo. Therefore, Myr-Tat conjugation may be an effective delivery platform to optimize cargo effect.

Structural and Functional Orthology in β-Defensins Embellishing Buffalo Spermatozoa Provide Unique Clues to Male Fertility

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The β-defensins (BDs) are the innate effector molecules that perform diverse molecular functions. A mutation in the primate BD gene, DEFB-126 has been implicated in the decreased conception rates observed in various human cohorts. Its protein product has been demonstrated to assist the spermatozoa in performing several crucial functions like immune-evasion, capacitation, and zona-binding in the female reproductive tract (FRT). We have previously demonstrated that the Buffalo BD-129 (BuBD-129) shares similarities in several physio-chemical properties with the primate DEFB-126 and proposed the BuBD-129 to be the structural/functional ortholog of DEFB-126.The LC-MS/MS analysis identified several BDs including the BuBD-129 and 126 on sperm surface. The removal of these 'surface proteins' either by the elevated salt concentration or by PIPLC-treatment or blocking by antibodies resulted in a decrease in the lectin binding. The immunocytochemistry experiments revealed a differential spatial distribution of the BuBD-126 and 129 wherein the BuBD-129 adorns the entire sperm surface, a pattern similar to the primate DEFB-126. Furthermore, the western-blot using antibody against all 'surface proteins' and the subsequent MALDI-TOF analyses divulged that BDs are not antigenic when immunized in female wistar rats. Intriguingly, the addition of antibody to BuBD-129 decreased the cleavage and blastocyst formation rates in the buffalo IVF model. Overall, the data indicates that BuBD-129 is a heavily O-glycosylated molecule distributed along the periphery of buffalo spermatozoa which appears to assist the sperm in immune-evasion and fertilization. Further studies are warranted to determine the molecular reproductive functions performed by BuBD-129 in fertilization specific activities.

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Viral Insulin/IGF-1 like Peptides have Unique White Adipose Tissue Specific Characteristics in Mice

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We recently showed that four viruses in the *Iridoviridae* family possess genes that are highly similar to human insulin and IGF-1. By chemically synthesizing single chain (sc, IGF-1 like) forms of these viral insulin/IGF-1 like peptides (VILPs), we showed that sc VILPs can stimulate human receptors. However, characteristics of double chain (dc, insulin-like) VILPs remain unknown. In this study, we characterized dc forms of VILPs for Grouper iridovirus (GIV), Singapore grouper iridovirus (SGIV) and Lymphocystis disease virus-1 (LCDV-1) in vitro and in vivo. GIV and SGIV VILPs can bind to both human insulin receptor isoforms and to human IGF-1R. They stimulate receptor phosphorylation and post-receptor signaling in vitro and in vivo. Both GIV and SGIV VILPs stimulate glucose uptake in mice. In vivo infusion experiments in awake mice revealed that while insulin (2.5 mU/kg/min) and GIV VILP (125 mU/kg/min) stimulate a comparable glucose uptake in heart, skeletal muscle and brown adipose tissue, GIV VILP stimulates ~2 fold higher glucose uptake in white adipose tissue (WAT) compared to insulin. This is due to increased Akt phosphorylation and glucose transporter type 4 (GLUT4) expression compared to insulin specifically in WAT. These results show that dc GIV and SGIV VILPs are active members of the insulin superfamily with unique characteristics and evoke questions about their potential roles in human disease. Elucidating the mechanism of tissue specificity for GIV VILP will help us to better understand insulin action and design new analogues that specifically target the tissues.

Development of Pharmacoproteomics Assays for Dissecting the Molecular and Cellular Pathways Regulated by Anticoagulant Peptides in Platelets and Dendritic Cells

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Pharmacoproteomics uses advanced proteomic technologies for promoting drug discovery and development by highlighting protein expression profiles of diverse cellular and molecular pathways in response to different drug treatment. The research presented herein highlights two major achievements of such pharmacoproteomics approaches, including 1) the discovery of novel anticoagulant tetrapeptides and anti-thrombin direct inhibitors (DTI) enabled by the analysis of their effects upon the global protein expression profiles in human platelets, and 2) mapping the pro-coagulative and pro-inflammatory cellular pathways activated in the dendritic cells (DC) treated with bradykinin (BK) peptide RPPGFSPFR. Label free quantification (LFQ) analysis of proteomics data generated by nanoLC-MS/MS on a Q-Exactive/Orbitrap mass spectrometer was coupled with Ingenuity Pathways Analysis (IPA) bioinformatics analysis and facilitated the discovery of the downregulation of actin, integrin and RhoA signaling pathways in human platelets treated with DTI. This in turn supported the discovery of new DTIs which act as potent inhibitors of thrombin-activated platelets aggregation, i.e., peptides with drug-like properties that can be used in the treatment of acute coronary diseases (ACD). Using a similar pharmacoproteomic platform we observed that mouse DCs stimulated with the BK peptide (RPPGFSPFR) became active in the production of molecules involved in migration/chemotaxis, MHC-I, and MHC-II expression, antigen presentation, inflammation, and cytokines secretion, further mediating the production of coagulation factors V and VIII. In short, this research highlights the advantages of employing pharmacoproteomic technologies as a reliable analytical platform that help to the discovery and development of peptide-drugs with anti-coagulant activities.

Potent Anticolorectal Cancer Activity of Analog Peptides Derived from Parasporin-2Aa1

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Parasporin-2Aa1 (PS2Aa1) is a toxic protein (30 KDa, toxic fragment) that was shown to be cytotoxic against specific human cancer cells, although its mechanism of action has not been elucidated yet. We investigated the cytotoxic effect of analog peptides from domain-1 of PS2Aa1. Through a rational design, the conserved regions were identified, and changes were made in some positions to increase charge and hydrophobicity. Peptides were synthesized using the Fmoc solid-phase synthesis and characterized by mass spectrometry (MS). Circular dichroism revealed an α-helix structure for the analog peptides (P264-V268K, P264-V268W, and P264-V268H) and for the peptide derived from PS2Aa1 (P264-G274). The latter was taken as the native sequence. Peptides showed a hemolysis percentage of less than 20% at 100 µM concentration compared with the positive control TritonX-100 (TX-100). Besides, peptide P264-V268K exhibited stronger anticancer activity against the SW480 and SW620 cell lines, after exposure for 48 h, with an EC50 value of 14.3±0.9 and 6.3±0.5 µM, respectively. P264-G274, P264-V268W, and P264-V268W showed an EC_{50} value from 11.28±0.52 to 111.6 ± 0.8 µM. Annexin V-CY3 staining analysis showed that peptide P264-V268K was positive for both annexin V-Cy3 and 6-CFDA, which is indicative of the early stage of apoptosis. Likewise, these compounds showed significantly lower toxicity against normal cells CHO-K1. 5-Fluorouracil (5-FU) was taken as positive control in all experiments. Results obtained in this study are promising, because of the potent anti-colorectal cancer activity of peptide P264-V268K. Further in-depth evaluations are required to develop this new therapeutic strategy against colorectal cancer and obtain more scientific input in the mode of action of PS2Aa1.

Do Peptide Drugs Interact with Bile Salts in the Gastrointestinal Environment?

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Unfavorable properties of peptide drugs such as their susceptibility to enzymatic degradation and low membrane permeability necessitate that these difficult-to-deliver molecules be administered via injection, which is undesirable from a patient perspective. There is major interest in developing peptide drugs for oral administration, however, the impact of the aqueous gastrointestinal environment on peptide drug behavior in solution and oral absorption (beyond enzymatic degradation) has been largely neglected. An improved understanding of peptide drug-bile salt interactions in solution is essential, especially given large inter- and intra-individual variability in bile salt concentrations *in vivo* which may contribute to low and variable oral peptide bioavailability (typically <0.1%).

The aim of this study was to investigate the interaction of the model peptide drug, octreotide, with biologically relevant bile salts in solution. *In vitro* flux studies using a side-by-side diffusion cell and cellulose dialysis membrane revealed octreotide to interact with seven bile salts in solution at both monomeric and micellar concentrations (Figure 1). Dihydroxy bile salts had a greater effect on octreotide flux than did trihydroxy bile salts. Proton nuclear magnetic resonance (^{1}H NMR) spectroscopy was utilized to characterize peptide-bile salt interactions in solution. Octreotide and Ala-mutated analogs were investigated via titrations and chemical shift analysis, Diffusion Ordered Spectroscopy (DOSY), and high resolution 2D ^{1}H-^{1}H Nuclear Overhauser Effect Spectroscopy (NOESY). Association of octreotide with bile salt micelles was confirmed, and NOESY spectra suggested that the interface between aromatic protons of the peptide and hydrophobic moieties of bile salts drives the association in solution.

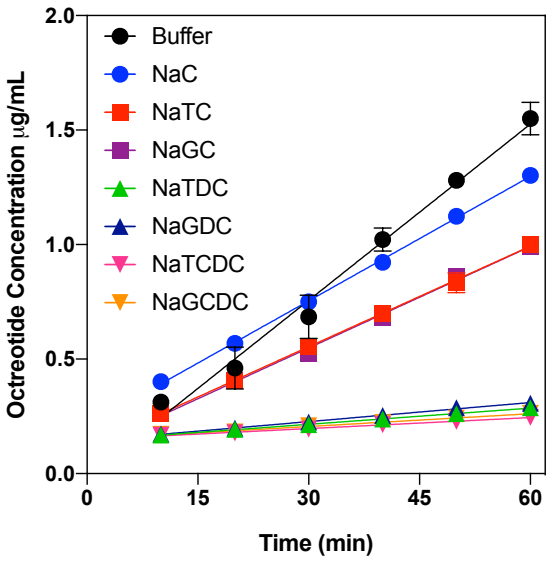

Figure 1. Concentration versus time profiles for octreotide in the receiver compartment during in vitro flux studies with micellar solutions of seven different bile salts.

Overcoming the Blood-Brain-Barrier by a Linear 7-Mer Peptide, IF7, with Binding Specificity to Annexin A1 in Brain Tumors

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Brain malignancies are difficult to eradicate, as chemotherapeutics injected intravenously cannot reach cancer cells in stroma due to the blood-brain-barrier (BBB). Previously we identified a linear 7-mer peptide that we designate IF7 binds to the N-terminal domain of annexin A1 (Anxa1)[1]. Although Anxa1 is normally expressed intracellularly in numerous cell types, Anxa1 is found on the endothelial cell surface in malignant tumors[2]. When fluorescently labeled IF7 was injected intravenously into brain tumor model mice, IF7 reached tumor vasculature and targeted tumor cells in stroma, overcoming the BBB[3]. In a dual tumor mouse model harboring subcutaneous and brain tumors, IF7-conjugated to the anti-cancer drug SN-38 suppressed growth of both tumors. In a brain metastatic model of syngeneic melanoma, tumors continued shrinking after IF7-SN38 administration. When melanoma cells were injected subcutaneously into recovered mice, CD8+ cytotoxic T cells infiltrated the injection site, suggesting a heightened immune response against tumor cells[3]. These results suggest that IF7-SN38 can overcome BBB and efficiently suppress growth of malignant brain tumors, and also suggest that high efficacy of IF7-SN38 therapy may lead an immunotherapeutic response by the host. IF7Cure Inc. is preparing for the first-in-human clinical trial of IF7-SN38 on glioblastoma patients.

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2. Oh et. al., *Nature*, 429: 629-35, **2004**.
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Anionic Nanoparticles Enable Oral Peptide Delivery by Enhancing Intestinal Permeability

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Oral delivery of bioactive peptides and proteins is one of the greatest unmet needs in modern medicine. Widespread oral peptide delivery has not been possible because the epithelial transport barrier, formed by intercellular tight junction complexes, blocks the intestinal absorption of macromolecules. Here, we demonstrate that anionic nanoparticles induce tight junction relaxation, increasing intestinal permeability and enabling the oral delivery of peptides without chemical modification, conjugation, or loading. This permeation-enhancing effect was a function of nanoparticle size and charge, with smaller (≤ 200 nm) and more negative particles (i.e. silica) improving efficacy *in vitro*, while a nanoparticle size greater than 20 nm was required for *in vivo* efficacy. Silica nanoparticles co-delivered with therapeutic peptides enabled the oral delivery of insulin and exenatide in mice. A 10 unit/kg insulin dose induced hypoglycemia extending more than 10 hours with 35% bioactivity compared to subcutaneously injected insulin, and was effective in both healthy and type 1 diabetic mice. The permeation-enhancing effect of silica nanoparticles was reversible, non-toxic, and attributable to an integrin-binding mechanism on the epithelial cell surface. Together, these data reveal a previously unappreciated property of silica nanoparticles and demonstrate their potential as an inexpensive, safe, and versatile approach to oral peptide delivery.

Reengineering the Antimicrobial Peptide from the Scorpion Venom of *Opisthacanthus Madagascariensis* into Highly Active Peptides with Low Toxicity

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The poisons have several bioactive molecules and are therefore considered a potential source of new drugs. In this work, we reprogrammed the cationic amphipathic antimicrobial peptide (AMP) IsCT1, derived from the scorpion venom *Opisthacanthus madagascariensis*, seeking to reduce the toxicity to human cells and enhance its intrinsic antimicrobial properties. In this attempt, synthetic variants with a net charge ranging from +2 to +6 were generated through the simultaneous replacement of 1 to 4 amino acid residues in the original sequence positions, resulting in 7 scorpion-derived antimicrobial peptide IsCT1. The resulting synthetic peptides showed increased antimicrobial activity against Gram-positive bacteria (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and Gram-negative bacteria (*Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca* and *Pseudomonas aeruginosa*) and provoked a decreasing in the hemolytic activity compared to the native molecule. Glutamic acid (position 7) was shown to be important in the interaction with the erythrocyte membrane, with a reduction in hemolysis when replaced by another amino acid residue. It was also observed that several peptides have anti-cancer activity due to their ability to target the human breast cancer cell line MCF-7. In general, we show a mutation-based approach to manipulate the peptide structure influencing its biological function, enabling new therapeutic properties.

Design and Evaluation of Cyclic and Linear Amphiphilic Peptides Against Multidrug-Resistant Bacterial Pathogens

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[1]Center for Targeted Drug Delivery, Department of Biomedical and Pharmaceutical Sciences, Chapman University School of Pharmacy, Irvine, CA, USA; [2]Chemistry Department, Faculty of Science, Menoufia University, Shebin El-Koam 51132, Egypt; [3]School of Biotechnology, KIIT Deemed to be University, Bhubaneswar 751024, India

We have designed and synthesized a series of small amphiphilic peptides by incorporating various non-genetically coded hydrophobic amino acids, followed by positively-charges amino acids on the opposite side. To identify the optimum balance of positive charges and hydrophobicity, the number and position of both positively-charged and hydrophobic residues were modified. Antibacterial screening results revealed the broad-spectrum activity of lead peptides with predominant activity against most of the Gram-positive bacteria, including the drug-resistant strains like methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) with MIC values in the range of 1.5-3.1 μg/mL. Moderate activity was observed against Gram-negative bacteria with MIC values of 12.5 to 50 μg/mL. Negligible changes in MICs of lead peptides was observed against *S. aureus* and *E. coli* in the presence of serum and other physiologically relevant cationic salts (NaCl, KCl, NH_4Cl, $MgCl_2$, or $CaCl_2$), reflecting their therapeutic compatibility in the intended biological environment. We evaluated the toxicity of the compounds on human red blood cells (hRBCs), and the lead peptides were found to be significantly less hemolytic (HC_{50}>200 μM) when compared with other known antibacterial peptides. In addition, lead peptides showed no significant toxicity against liver cells (Hepa RG) and minimal toxicity against myocardium cells at the highest tested concentrations (100 μM). Moreover, plasma stability study results revealed the low susceptibility of designed peptides against peptidases. These results highlight the therapeutic potential of newly designed amphiphilic peptides as the next generation of peptide-based antibiotics.

Acknowledgment: This research was sponsored by AJK Biopharmaceutical LLC.

Characterisation of a Lunasin-Derived Anti-Inflammatory Peptide

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Lunasin is a bioactive soy peptide with potential in the treatment of cancer and obesity related diseases. Although the peptide is only 43 residues in length, it contains three regions with different proposed activities/functions and appears to have oral bioavailability, albeit in the presence of other proteins. The full-length peptide has an effect on inflammatory cytokines and extensive studies have shown that lunasin is involved with the acetylation-deacetylation process that leads to cell apoptosis of various cancer cells. Here we have analysed truncated forms of lunasin and their effects on inflammatory cytokine suppression with the aim of developing novel anti-inflammatory drugs.

Targeting SARS-CoV-2 Spike 1 Protein to Control Natural Killer Cells Activation via HLA-E/NKG2A Pathway

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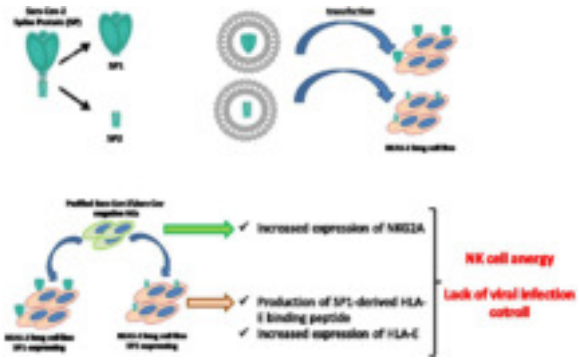
Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV–2) outbreak in December 2019, several studies investigated the response of the immune system during the SARS-CoV–2 infection. Natural killer (NK) cells are the first line of defense towards viral infection and their activation depends on inhibitory/regulatory receptors whose expression could be modulated by viral products. Among NK receptors, NKG2A inhibitory receptor binds the non-classical HLA (Human leukocyte antigen) class-I molecule-E (HLA-E) (PMID:9103421), inducing NK anergy. The SARS-CoV-2 spike proteins (SP) has been deeply studied because of its crucial role during viral infection and spread. Despite the interest in studying SP function, to date its involvement in NK cells regulation has not yet been explored.

We evaluated the possible effect of SARS-CoV-2 SP1 and SP2 in controlling NK cell activation via HLA- E/NKG2A pathway, testing peripheral blood NK cells from SARS-CoV and SARS-CoV-2 naïve subjects for activation, degranulation and interferon-gamma expression in the presence of SARS-CoV and SARS-CoV-2 SP expressed by transfected Baes-2 lung cells, by flow cytometry and immune-fluorescence.

The results showed that SP1 intracellular expression increased the expression of HLA-E on target cells due to the production of a SP1-derived HLA-E binding peptide and, simultaneously, SP1 up-modulated the inhibitory receptor NKG2A/CD94 on NK cells, inducing NK cells exhaustion.

In conclusion, we report for the first time that SP1 affects NK cells activation via HLA-E/NKG2A interaction, suggesting its role in immunopathogenesis during SARS-CoV-2 infection. These data suggest a possible use of SP targeting as a therapeutic approach in SARS-CoV-2 infection control.



Amphiphilic Cell-Penetrating Peptides Containing Natural and Unnatural Amino Acids as Drug Delivery Tools and Antimicrobial Agents

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We have previously shown that cyclic peptide [WR]5 containing alternative tryptophan (W) and arginine (R) residues improved the cellular uptake of cell-impermeable compounds across the phospholipid bilayer. Herein, we investigated peptides containing alternate arginine and unnatural hydrophobic residues as a molecular transporter of cell-impermeable compounds. A series of cyclic and linear peptides containing alternate arginine and unnatural 3,3-diphenyl-L- alanine (Dip) were synthesized based on [WR]5 scaffold using Fmoc solid-phase synthesis. The cyclic and linear peptides, $[(DipR)_4(WR)]$, $[(DipR)_3(WR)_2]$, $[(DipR)^2(WR)^3]$, $[(DipR)(WR)_4]$, and $[DipR]_5$, showed no significant cytotoxicity in human leukemia cell line (CCR-CEM) at concentrations of less than 10 µM after 24 and 72 h incubation. Cyclic peptide $[DipR]_5$ improved the cellular uptake of a fluorescence-labeled phosphopeptide (F´-GpYEEI), stavudine (F´-d4T), lamivudine (F´-3TC), emtricitabine (F´-FTC), and siRNA (F´-siRNA) in CCRF-CEM and human ovarian cancer (SK-OV-3) cells. For example, $[DipR]_5$ (10 µM) was able to improve the cellular uptake of F'-FTC (2 µM) by 98-fold after 3 h incubation in CCRF-CRM cells when compared with F'-FTC alone. These data indicate that cyclic peptides containing arginine and Dip can act as molecular transporter of negatively-charged compounds (phosphopeptide and siRNA) and small molecule anti-HIV compounds. Furthermore, $[DipR]_5$ showed MIC values of 0.74-11.9 µg/mL against Gram-positive bacteria strains: *Methicillin-Resistant Staphylococcus aureus*, *Staphylococcus aureus*, *Enterococcus faecium*, *Enterococcus faecalis*, *Streptococcus pneumoniae,* and *Bacillus subtilis* bacteria. On the other hand, $[DipR]_5$ showed moderate antibacterial activity against Gram-negative strains *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli* with MIC values of 23.8-47.5 µg/mL.

The U24 Protein of HHV-6A Induces the Expression of Alzheimer's Disease Risk Factors of Microglial Cells

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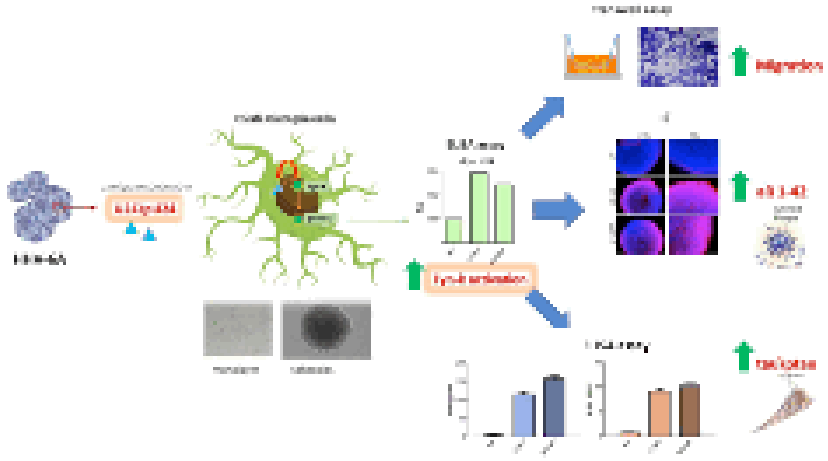
Alzheimer's Disease (AD) is characterized by peculiar pathological features, including extracellular plaques formed by amyloid-β (Aβ) peptide and intraneuronal neurofibrillary tangles (NFT) formed by tau protein. Recent findings suggest a possible implication of Human Herpesvirus-6A (HHV- 6A) in AD (PMID:29937276), and we showed the ability of HHV-6A to induce the expression Aβ and tau expression (PMID:31831060).

In particular, HHV-6A U24 protein appears to be involved in the neurogenerative processes (PMID:25225878) due to its high homology with MBP protein. Furthermore, U24 activates Fyn- kinase, a kinase involved in tau phosphorylation and Aβ induction (PMID:23175838), suggesting its role also in AD pathogenesis.

We evaluated the effect of U24 HHV-6A protein on microglial cells, that represents the main sentinels for brain viral infections, analyzing Aβ and tau\ptau expression and its involvement in Fyn-kinase activation and microglia migration. HMC3 microglial cells monolayers and spheroids were infected with HHV-6A for 1, 3, 7 and 14 days or treated with U24 protein alone. We analyzed viral DNA and RNA to prove cells permissivity to HHV-6A infection by Real-Time and we evaluate apoE, Aβ (1-40, 1-42), tau and phospho-tau (Threonine 181) expression, Fyn- kinase activation and cell migration, immunofluorescence, ELISA and transwell migration assay.

Interestingly, the treatment with U24 gave results comparable to HHV-6A infection, showing increased Aβ 1-42 expression, Fyn-kinase activation, tau\ptau percentage and microglia migration. These data report the key role of HHV-6A U24 protein in inducing AD risk factors, suggesting its targeting as a promising therapeutic strategy to counteract AD development in presence of HHV-6A infection.



Protein Kinase C Beta II Peptide Inhibitor Conjugated to a Novel Myristic Acid-Trans- Activator – Tandem Rapidly Attenuates Superoxide Release in Isolated Rat Polymorphonuclear Leukocytes through Superior Intracellular Delivery of Cargos

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Phorbol 12-myristate 13-acetate (PMA) activation of polymorphonuclear (PMN) superoxide (SO) release is mediated, in part, by protein kinase C beta II (PKCβII) phosphorylation of NADPH oxidase (NOX-2). Previously, trans-activator of transcription (Tat) conjugated NOX-2 peptide inhibitor (100μM, Nox2ds-tat) and myristic acid (myr) NOX-2 peptide inhibitor (10μM, myr-Nox2ds) resulted in ~35% and ~70% inhibition of PMA-induced SO release, respectively (1,2). By combining anchoring (myr) and endocytic (Tat) mechanisms, we hypothesized that dual myr-Tat conjugated PKCβII peptide inhibitor (myr-Tat-PKCβII-; N-myr-Tat-CC- SLNPEWNET) would significantly inhibit PMN SO compared to myr-PKCβII inhibitor (myr- PKCβII-; N-myr-SLNPEWNET), scrambled myr-PKCβII- (myr-PKCβII-scram), and PMA control. Rat PMNs were incubated for 15 min at 37oC with SO dismutase (SOD;10μg/ml), unconjugated PKCβII-, myr-PKCβII-, myr-Tat-PKCβII-, or myr-PKCβII-scram (all 20μM). SO release was measured by the change in absorbance at 550 nm over 390 sec via ferricytochrome c reduction after PMA stimulation (100nM). Data were analyzed by ANOVA using Bonferroni- Dunn analysis. Myr-Tat-PKCβII- significantly attenuated SO release compared to all study groups ($p<0.05$) (0.121 ± 0.02, n = 5), myr-PKCβII- (0.303 ± 0.02, n = 27), unconjugated PKCβII- (0.433 ± 0.02, n = 22), and PMA control (0.463 ± 0.01, n = 73), and was similar to SOD (0.044 ± 0.01, n = 8). Unexpectedly, myr-PKCβII-scram (0.645 ± 0.04, n = 22) augmented SO release compared to all groups ($p<0.05$). Results suggest myr-Tat conjugation is superior to myr alone, potentially through improved intracellular delivery. Future immunolabeling studies will determine the myr-Tat delivery mechanism.

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