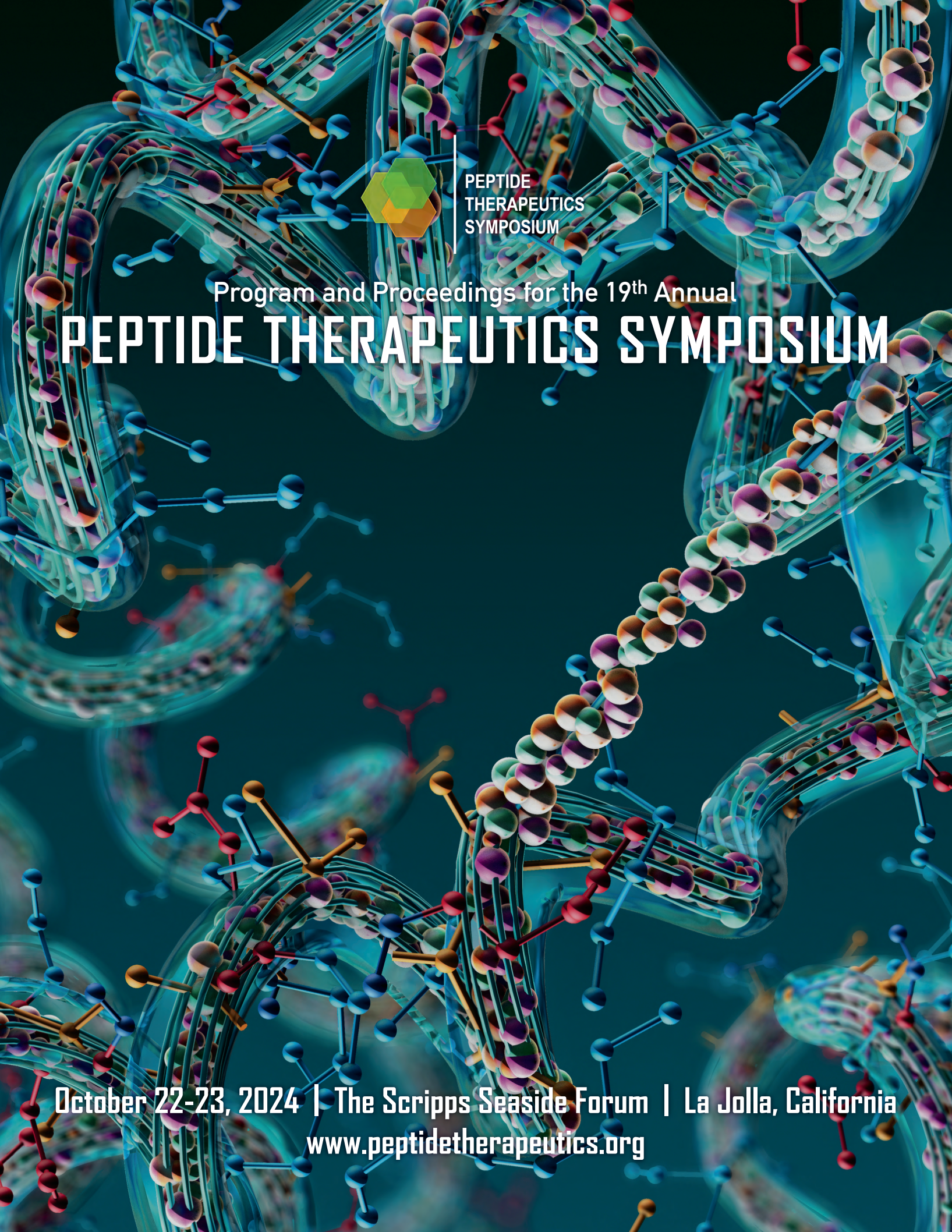

Program and Proceedings for the 19th Annual

PEPTIDE THERAPEUTICS SYMPOSIUM

October 22-23, 2024 | The Scripps Seaside Forum | La Jolla, California

www.peptidetherapeutics.org

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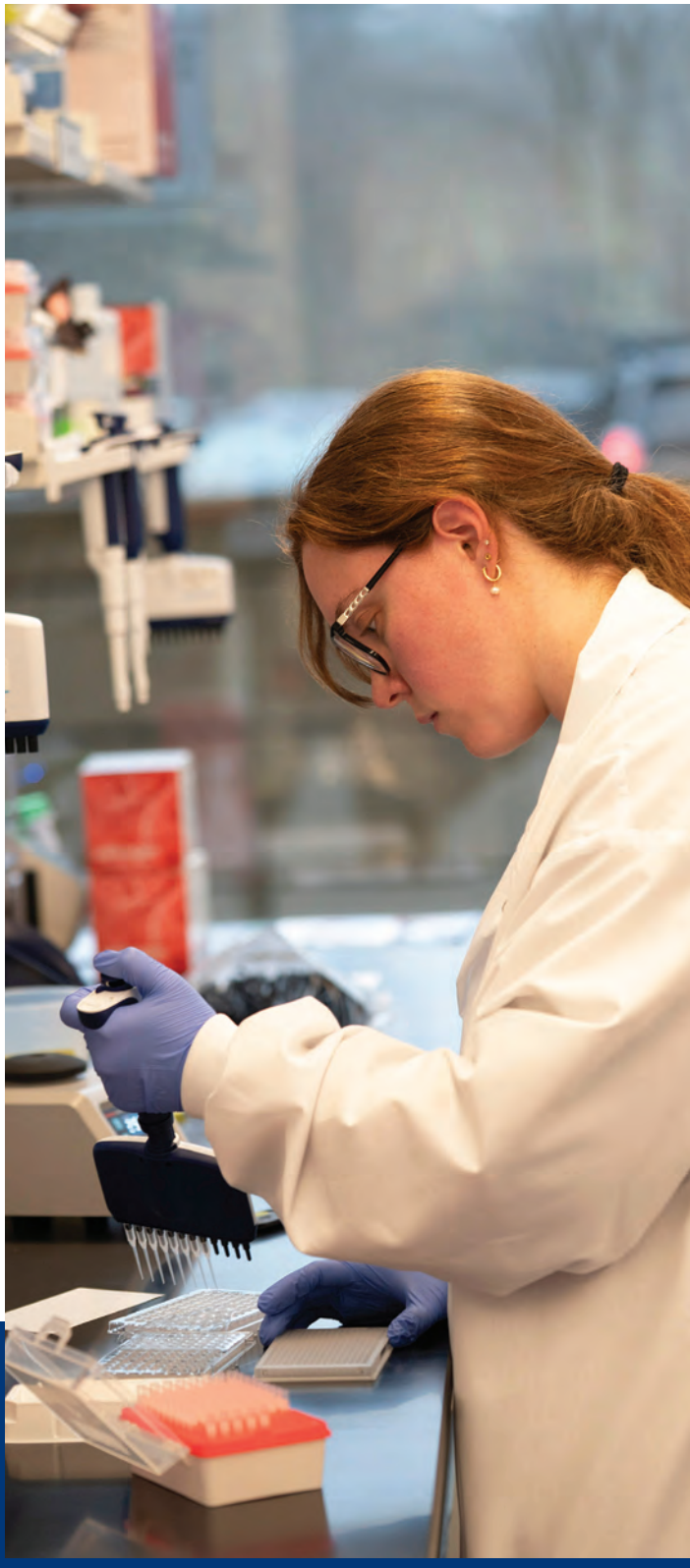

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19th Annual Peptide Therapeutics Symposium

October 22-23, 2024
The Scripps Seaside Forum
8610 Kennel Way, La Jolla, CA 92037

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2024 TRAVEL GRANT AWARDEES

Krishnakoli Adhikary, College of Staten Island, CUNY
Juliet Melnik, Philadelphia College of Osteopathic Medicine
Zachary St. John, Purdue University

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19th Annual Peptide Therapeutics Symposium

Dear Colleagues,

The Peptide Therapeutics Foundation, its sponsors and the Symposium sponsors welcome you to the 19th Annual Peptide Therapeutics Symposium. We continue to support a hybrid format to engage our colleagues from around the world. Our goal is to present new advances and discoveries in the field of peptide-related research and development and this year's symposium represents another cutting-edge, thought-provoking program designed to stimulate questions and conversations.

The symposium opens on Tuesday morning with two plenary lectures. Thomas Kruse, from Novo Nordisk will discuss the development of the GLP-1 receptor/amylin receptor co-agonist amycretin. Maurizio Pellecchia from UC Riverside will then present his work on histidine covalent stapled alpha-helical peptides. The next session will feature state-of-the-art talks from Henrik Fischer Munch, Yingli Ma, and Paul Titchenell regarding the preclinical development of an amylin agonist, small molecule peptide mimetics for oral delivery, and the biology of an activin type II receptor inhibitor.

After lunch we will continue with two lectures on the uses of machine learning for peptide drug discovery from Koliber Biosciences and Tufts University, followed by a discussion of an oral peptide delivery device by Biora Therapeutics. The final session of the day will include presentations from Steven Horton, Peter Caravan, and Albert Bowers; covering radionucleotide pharmaceuticals, use of peptides in imaging and discovery of cyclic peptide inhibitors. We encourage you to join us for the afternoon poster presentations and the Opening Reception that will immediately follow.

The program continues on Wednesday morning with Plenary Lectures from Nancy Thornberry and Thomas Gardella, highlighting the biology of the gut brain axis and its role in secretion of gut hormones, and the latest research regarding the role of parathyroid hormone in bone biology. The last lectures for the day from will be presented by Sung Han and Christine Esau; they will speak about CGRP biology and RNA therapeutics. We are excited to finish the day with a panel discussion with four venture capital investors; Sarah Benson-Konforty from 1010 VC, Mira Chaurushiya from Westlake Village Partners, Antoine Henninot, Curie.Bio, and Sally Wang from Viva BioInnovator.

The taped presentations will be available online for viewing for 60 days following the close of the meeting. As in previous years the program, the venue, and social time have been designed to support networking with colleagues. We are delighted to host this meeting and look forward to meeting each of you.

Sincerely,

Phil Dawson
Chairman of the Board
Peptide Therapeutics Foundation

Adam Mezo
President
Peptide Therapeutics Foundation

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Neurocrine Biosciences is a leading neuroscience-focused, biopharmaceutical company with a simple purpose: to relieve suffering for people with great needs, but few options. We are dedicated to discovering and developing life-changing treatments for patients with under-addressed neurological, neuroendocrine and neuropsychiatric disorders. The company's diverse portfolio includes FDA-approved treatments for tardive dyskinesia, chorea associated with Huntington's disease, endometriosis* and uterine fibroids*, as well as a robust pipeline including multiple compounds in mid- to late-phase clinical development across our core therapeutic areas. For three decades, we have applied our unique insight into neuroscience and the interconnections between brain and body systems to treat complex conditions. We relentlessly pursue medicines to ease the burden of debilitating diseases and disorders, because you deserve brave science. For more information, visit neurocrine.com, and follow the company on LinkedIn, X (formerly Twitter) and Facebook. (*in collaboration with AbbVie)

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PolyPeptide is a publicly listed organization, traded on the Swiss stock exchange, which focuses on manufacturing proprietary and generic GMP-grade peptides and oligonucleotides for the pharmaceutical and biotechnological market. With more than 60 years of experience, PolyPeptide is committed to the highest quality of manufacturing for commercial peptide drug substances, GMP peptides in clinical trials, or small-scale pre-clinical custom syntheses.

As an organization, PolyPeptide has grown by selective acquisition of existing expertise, culminating in its position today as a leader in peptide manufacturing. With three manufacturing facilities in Europe, two facilities in the US , and one in Asia, PolyPeptide is a multinational company with about 1200 employees worldwide with a diversity which brings breadth and depth of knowledge, as well as unique experience to the organization.

PolyPeptide's long-established core strength is in GMP manufacturing, and a broad range of services which supports peptide & peptide-like projects, including conjugation to non-peptide moieties, from bench scale through to commercialization. With continually increasing capacity for GMP manufacturing, PolyPeptide is uniquely placed to serve the needs of its customers at all stages of pharmaceutical peptide development with a proven track record in security of supply to its clients.

PLATINUM SPONSOR

Zealand Pharma

Zealand Pharma A/S (NASDAQ Copenhagen: ZEAL) ("Zealand") is a biotechnology company focused on the discovery, design and development of innovative peptide-based therapeutics. Since 1998, Zealand Pharma has been engineering peptide analogs to enhance biological activity, extend duration of action, and increase stability with the aim of providing innovative and better treatments for a broad range of diseases.

This deep understanding of peptide chemistry, formulation know-how, and intellectual property rights has led to more than 10 drug candidates invented by Zealand having advanced into clinical development, of which two have reached the market. Zealand's current pipeline of internal product candidates focuses on four therapeutic areas: obesity, rare diseases, chronic inflammation, and type 1 diabetes.

Zealand Pharma is based in Copenhagen, Denmark with more than 300 employees located in Denmark and the United States. For further information about the company's business and activities, please visit www.zealandpharma.com or follow us on LinkedIn at www.linkedin.com/company/zealand-pharma

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Bachem is a leading, innovation-driven company specializing in the development and manufacture of peptides and oligonucleotides.

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Bachem operates internationally with headquarters in Switzerland and locations in Europe, the US and Asia. The company is listed on the SIX Swiss Exchange. For further information, see www.bachem.com.

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For 25 years, Sai Life Sciences has been a trusted partner in bringing new medicines to life, fast. As a global Contract Research, Development & Manufacturing Organization (CRO-CDMO), Sai Life Sciences works with innovator biotech and pharma companies to accelerate the discovery, development and commercialization of complex small molecules. With 3000 employees across facilities in India, UK and USA, Sai supports innovators through journey from concept to commercialisation, including exploratory biology, creative chemistry, DMPK, toxicology, developability & formulations, early phase development, process & analytical development, scale-up, tech transfer, clinical supplies and cGMP manufacturing. Taking a nimble and creative approach, Sai delivers high-quality, cost-effective solutions to accelerate the time to market.

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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.

19th Annual Peptide Therapeutics Symposium

October 22-23, 2024
The Scripps Seaside Forum
8610 Kennel Way, La Jolla, CA 92037

Tuesday, October 22, 2024

8:00 a.m. - 4:00 p.m.	**Registration Check-In** The Scripps Seaside Forum Lobby
8:00 a.m. – 8:30 a.m.	**Breakfast & Poster Viewing** The Scripps Seaside Forum Lobby
8:30 a.m. – 5:00 p.m.	**19th Annual Peptide Therapeutics Symposium** Samuel H. Scripps Auditorium
8:30 a.m. – 8:35 a.m.	**Opening Remarks** Adam Mezo, Ph.D. *President, Peptide Therapeutics Foundation* *Vice President, Research, Peptide Chemistry* *Neurocrine Biosciences, Inc.*
8:35 a.m. – 10:05 a.m.	**Plenary Lectures** Moderator: Nick Cox, Ph.D. *Director, Peptide Therapeutics Foundation* *Senior Director, Chemical Biology, Novo Nordisk*
8:35 a.m. – 9:20 a.m	**Discovery of Amycretin: A GLP-1/amylin Co-agonist for Oral Administration** Thomas Kruse, Ph.D. *Senior Principal Scientist, Novo Nordisk, Denmark*
9:20 a.m. – 10:05 a.m.	**NMR- and Structure-based Design of Novel Reversible and Covalent Therapeutic Peptides** Maurizio Pellecchia, Ph.D. *Professor of Biomedical Sciences, School of Medicine, University of California Riverside*
10:05 a.m. – 10:35 a.m.	**Beverage Break & Poster Viewing** The Scripps Seaside Forum Lobby
10:35 a.m. – 12:05 p.m.	**Session I** Moderator: David Parkes, Ph.D. *President, DGP Scientific, Inc.*

Tuesday, October 22, 2024 (Continued)

10:35 a.m. – 11:05 a.m.

The Discovery of Petrelintide, a Potent, Stable, Long-acting Human Amylin Analog
Henrik Fischer Munch, Ph.D.
Principal Scientist, Department of Medicinal Chemistry, Zealand Pharma, Copenhagen

11:05 a.m. - 11:35 a.m.

Developing Small Molecule Agonists of GLP-1R and other Peptide-Binding GPCRs
Yingli Ma, Ph.D.
Chief Technology Officer, Structure Therapeutics

11:35 a.m. – 12:05 p.m.

Preserving Skeletal Muscle Mass and Enhancing Fat Loss by Targeting Activin Type II Receptors in Obesity
Paul M. Titchenell, Ph.D.
Associate Professor of Physiology, Perelman School of Medicine at the University of Pennsylvania

12:05 p.m. – 1:30 p.m.

Lunch & Poster Viewing
The Scripps Seaside Forum Lawn

1:30 p.m. – 3:00 p.m.

Session II
Moderator: Ron He, Ph.D.
Senior Principal Scientist, Neurocrine Biosciences, Inc.

1:30 p.m. – 2:00 p.m.

Advancing Peptide Optimization: Machine Learning-Driven Predictions for Potency, Stability, and Permeability
Ewa Lis, Ph.D.
Founder and CEO, Koliber Biosciences Inc.

2:00 p.m. – 2:30 p.m.

Structure Prediction of Cyclic Peptides Via Molecular Dynamics and Machine Learning
Yu-Shan Lin, Ph.D.
Professor, Tufts University

2:30 p.m. – 3:00 p.m.

Empowering Peptide Self-Administration with Needle Free Smart Capsules
Sharat Singh, Ph.D.
Head of Research, Biora Therapeutics

3:00 p.m. – 3:30 p.m.

Beverage Break & Poster Viewing
The Scripps Seaside Forum Lobby

3:30 p.m. – 5:00 p.m.

Session III
Moderator: Bryan Fuchs, Ph.D.
Head, Ferring Ventures San Diego

19th Annual Peptide Therapeutics Symposium

Tuesday, October 22, 2024 (Continued)

3:30 p.m. - 4:00 p.m.

Development of Radiopharmaceutical Therapy Agents for Treatment of GPC3-Expressing Tumors
Steven Horton, Ph.D.
Oncology Scientist, RayzeBio

4:00 p.m. - 4:30 p.m.

Development and Application of ^{68}Ga-CBP8, a Type-I Collagen Targeted Peptide-based Positron Emission Tomography Probe
Peter Caravan, Ph.D.
Professor of Radiology, Harvard Medical School
Co-Director of the Institute for Innovation in Imaging, Massachusetts General Hospital

4:30 p.m. - 5:00 p.m.

Building on Natural Product Motifs for Cyclic Peptide Inhibitor Discovery
Albert Bowers, Ph.D.
UNC Eshelman School of Pharmacy

5:00 p.m. - 6:30 p.m.

Opening Reception
The Scripps Seaside Forum Lawn

Wednesday, October 23, 2024

8:00 a.m. - 10:00 a.m.

Registration Check-In
The Scripps Seaside Forum Lobby

8:00 a.m. - 8:30 a.m.

Breakfast & Poster Viewing
The Scripps Seaside Forum Lobby

8:30 a.m. - 12:45 p.m.

19th Annual Peptide Therapeutics Symposium
Samuel H. Scripps Auditorium

8:30 a.m. - 8:45 a.m.

Welcoming Remarks
Nick Cox, Ph.D.
Director, Peptide Therapeutics Foundation
Senior Director, Chemical Biology, Novo Nordisk

8:45 a.m. - 10:15 a.m.

Plenary Lectures
Moderator: Soumitra Ghosh, Ph.D.
President, Doon Associates LLC

8:45 a.m. - 9:30 a.m.

Identification of Hormonal and Neural Circuits Involved in Gut-Brain Signaling
Nancy A. Thornberry
Founding CEO, Kallyope

19th Annual Peptide Therapeutics Symposium

Wednesday, October 23, 2024 (Continued)

9:30 a.m. - 10:15 a.m.

Parathyroid Hormone Peptide Development for Diseases of Bone and Calcium Metabolism
Thomas J Gardella, Ph.D.
Associate Professor in Medicine, Massachusetts General Hospital and Harvard Medical School

10:15 a.m. - 10:45 a.m.

Beverage Break & Poster Viewing
The Scripps Seaside Forum Lobby

10:45 a.m. - 11:45 a.m.

Session IV
Moderator: Antoine Henninot
Senior Director, Drug Discovery, Curie.Bio

10:45 a.m. - 11:15 a.m.

Revealing the Role of Neuropeptides in Neural Circuit Function and Behavior
Sung Han, Ph.D.
Associate Professor, Salk Institute for Biological Studies

11:15 a.m. - 11:45 a.m.

RNAi Delivery to the Central Nervous System
Christine Esau, Ph.D.
Vice President, Arrowhead Pharmaceuticals

11:45 a.m. - 12:30 p.m.

Investor Panel
Moderator: Rumit Maini
Senior Director, Peptide Discovery, Eli Lilly

Sarah Benson-Konforty, MD
General Partner at 1010VC, Board Member at AAIH and Pepticom

Mira Chaurushiya, Ph.D.
Senior Director, Drug Discovery, Curie.Bio

Antoine Henninot
Senior Director, Drug Discovery, Curie.Bio

Sally Wang Liang, JD MPH
Partner, Highlight Capital

12:30 p.m. - 12:45 p.m.

Closing Remarks
Phil Dawson, Ph.D.
Chairman of the Board, Peptide Therapeutics Foundation
Professor of Chemistry, Scripps Research

12:45 p.m. - 1:45 p.m.

Networking Lunch
The Scripps Seaside Forum Lawn

Notes

SPEAKER BIOGRAPHIES

19th Annual
Peptide Therapeutics Symposium

Sarah Benson-Konforty, MD
General Partner at 1010VC
Board Member at AAIH and Pepticom
Investor Panel

Sarah Benson-Konforty, MD, is a serial entrepreneur and Medical Doctor turned investor based in Palo Alto, CA (Silicon Valley). Sarah founded her first software company at the age of 18. With over 15 years of cross-industry experience, she is a globally recognized transformational leader.

Sarah is the Founder and General Partner at 1010VC, an early-stage bioconvergence fund investing in exceptional founders to advance cures and unlock the potential of multidisciplinary research and tech bio to advance healthcare and medicine.

She serves on the Board of Directors of The Alliance for Artificial Intelligence in Healthcare (AAIH), a global nonprofit organization dedicated to the responsible and ethical adoption of AI/ML in healthcare and life sciences across Big Pharma, academic institutions, and industry startups. Sarah has published white papers on AI ethics, policy, and regulation, and created a new category called "VC Activism," which encourages VCs to engage in AI regulation and policy work. Additionally, she is on the advisory board of Pepticom, an early-stage drug discovery company that has developed cutting-edge AI/ML technology for the de novo design and discovery of peptide therapeutics (peptidomimetics), where she provides hands-on guidance with business development, strategy, and fundraising. Sarah is also a board member of Public Invention, a nonprofit organization focused on humanitarian invention, including the development of open-source medical devices.

Previously, Sarah was the Managing Director US at BIE, a family office with over $2B in assets under management. She earned her MD from TSMU and studied entrepreneurship and innovation at Wharton.

Albert A. Bowers, Ph.D.
Professor and Vice-Chair
Division of Chemical Biology and Medicinal Chemistry,
UNC Chapel Hill
Building on Natural Product Motifs for Cyclic Peptide Inhibitor Discovery

Born and raised in Trenton, NJ, Dr. Bowers obtained his BA from the University of Chicago and went on to complete his Ph.D. in organic chemistry in 2007, at the University of Illinois at Chicago, under the guidance of Prof. David Crich. He was an NIH postdoctoral fellow in the labs of Professor Robert M. Williams at Colorado State University and Professor Christopher T. Walsh at Harvard Medical School, where he studied the chemistry and biosynthesis of peptide-based natural products. In 2012, he joined the faculty at the University of North Carolina at Chapel Hill in 2012. He is jointly appointed in the School of Pharmacy and Department of Chemistry. The labs research focuses on biochemical and biosynthetic methods for the discovery of new peptide therapeutics, including mRNA display and macrocycles. For this work, Dr. Bowers has won a number of awards including the Beckman Young Investigator Award and Young Investigator Award of the Boulder Peptide Society.

Peter Caravan, Ph.D.
Professor of Radiology, Harvard Medical School
Co-Director of the Institute for Innovation in Imaging, Massachusetts General Hospital
Development and Applications of ^{68}Ga-CBP8, a Type-I Collagen Targeted Peptide-based Positron Emission Tomography Probe

Peter Caravan is the Co-Director of the Institute for Innovation in Imaging (i3) at Massachusetts General Hospital and Professor of Radiology at Harvard Medical School. He leads a multidisciplinary and translational molecular imaging lab focused on the invention of novel molecular probes and their broad applications in cardiovascular, pulmonary, renal, and hepatic diseases as well as in cancers. His research spans novel chemistry technologies to advanced MRI, PET imaging, and novel therapeutics in animal models through to applications in patient populations. Dr. Caravan received his BSc(Hons) from Acadia University followed by a PhD in Inorganic Chemistry from the University of British Columbia. Following a NSERC post-doctoral fellowship at the Université de Lausanne, he worked in industry developing targeted MRI probes. He joined the faculty of Harvard Medical School in 2007 and has been a continuously funded NIH researcher ever since. Dr. Caravan has published over 200 peer-reviewed articles and is a named inventor on over 25 issued patents. He has brought five novel PET and MRI probes that he co-invented to first-in-human studies and has co-founded two companies to commercialize his inventions.

Mira Chaurushiya, Ph.D.
Senior Partner, Westlake Village BioPartners
Investor Panel

Dr. Mira Chaurushiya is a Managing Director at Westlake Village BioPartners. As a biologist who worked in industry research before entering the venture capital industry, she has a long and successful track record in both biological sciences and life-sciences investing.

Dr. Chaurushiya is a fellow of the Society of Kauffman Fellows. After a postdoctoral fellowship in physiological chemistry at Genentech, she joined 5AM Ventures as an associate and took on positions of increasing responsibility, culminating as a partner. During her tenure at 5AM Ventures, she invested in and served as director or observer on the boards of multiple organizations, including Precision Nanosystems (acquired by Danaher), Ideaya Biosciences (IDYA), Enliven Therapeutics, Escient Pharmaceuticals, Magnetic Insight, Novome Biotechnologies, Purigen Biosystems, NodThera and TMRW.

Dr. Chaurushiya received her Ph.D. in biological sciences from the University of California, San Diego in conjunction with the Salk Institute for Biological Studies, where she was awarded the Martin Kamen Thesis Prize in Biochemistry. She received her bachelor's degree in biology from Carleton College. She serves on the board of Biotech Connection Bay Area, a non-profit that focuses on career development for academic scientists.

Nick Cox, Ph.D.
Director, Peptide Therapeutics Foundation; Senior Director of Chemical Biology, Novo Nordisk
Welcoming Remarks

Dr. Cox is the Senior Director of Chemical Biology at Novo Nordisk's R&D hub in the greater Boston area, where his team drives peptide, protein, and other therapeutic discovery efforts targeting chronic conditions including obesity, diabetes, cardiovascular disease, and rare blood and endocrine disorders. Prior to joining Novo Nordisk, he completed his training as a Postdoctoral Scholar in Stanford's ChEM-H institute (2014-2016) under the mentorship of Prof. Chaitan Khosla and Dr. Mark Smith, serving as chemistry lead on numerous projects in early-stage drug discovery. Dr. Cox received his Ph.D. in Chemistry from the University of Washington (2013) in the laboratory of Prof. Gojko Lalic, where he studied organic methodology and transition metal catalysis.

Phil Dawson, Ph.D.
Chairman of the Board, Peptide Therapeutics Foundation; Professor of Chemistry, Scripps Research
Closing Remarks

Phil Dawson is a Professor in the Department of Chemistry, Scripps Research in La Jolla, CA and former Dean of the Skaggs Graduate School of Chemical and Biological Sciences (2017-2024). 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 cochaired the 22nd American Peptide Symposium and the GRC on Biology and Chemistry of Peptides. He has published over 200 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, the RSC MedImmune Protein and Peptide Science Award, the Akabori Memorial Award from the Japanese Peptide Society, the Cathay Award from the Chinese Peptide Society, the ACS Cope Scholar Award and will receive the Bruce Merrifield Award in 2025.

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.

Christine Esau, Ph.D.
Vice President, Arrowhead Pharmaceuticals
RNAi Delivery to the Central Nervous System

Christine Esau is Vice President of Biology at Arrowhead Pharmaceuticals, which develops RNAi medicines. Dr. Esau has more than twenty years experience in the discovery and development of RNA-based therapeutics. Previously she oversaw a portfolio of siRNA and mRNA therapeutic programs at Genevant Sciences and Arcturus Therapeutics. She also performed pioneering work in microRNA targeting and biology at Ionis Pharmaceuticals and Regulus Therapeutics. Dr. Esau earned a B.S. degree in biology from Caltech and a Ph.D. from MIT.

Thomas J. Gardella, Ph.D.
Associate Professor in Medicine, Massachusetts General Hospital and Harvard Medical School
Parathyroid Hormone Peptide Development for Diseases of Bone and Calcium Metabolism

Dr. Gardella studies the basic biology of the parathyroid hormone receptor and its modulation by peptide ligands. After earning his PhD from the University of Massachusetts Medical School for his thesis work in phage genetics in 1988, Dr. Gardella moved to the Endocrine Unit of the Massachusetts General Hospital in Boston MA, USA, where he began his research on PTH peptides and the PTH1R. His studies spanning more than three decades have helped elucidate how one receptor can bind two distinct endogenous peptide ligands, PTH and PTH-related protein, to thereby control two distinct biological processes, i.e, the maintenance of calcium homeostasis via PTH and the control of skeletal development via PTHrP. His work also helped establish the so-called two-site model of ligand-binding for the PTH1R, now known to apply to each of the 15 related class B GPCRs, including the receptors for glucagon, GLP-1 and CRF. His work also led to the development of minimized N-terminal fragment PTH peptides, such as the modified "M"-PTH(1-14) and (1-11) peptides that act as potent agonists on the PTH1R in vitro and bind only to the receptor's transmembrane helical bundle domain (TMD) region, rather than to both the TMD and to the receptor's N-terminal extracellular domain, as used by non-modified PTH(1-34) and PTHrP(1-36) peptides. His work on PTH1R conformations led to the finding that the PTH1R can mediate distinct modes of ligand-induced signaling-- i.e. prolonged signaling from endosomes via a ligand like PTH that can bind with high affinity to the G protein-uncoupled conformation, R0, versus transient signaling from the cell surface via a ligand like PTHrP that binds selectively to the G protein-coupled conformation, RG. This work led to the development of a novel R0-selective PTH/PTHrP hybrid peptide that induces sustained calcemic responses and is now in phase-3 trials as a candidate therapy, named eneboparatide, for the treatment of hypoparathyroidism. Dr. Gardella collaborates widely, and his research extends also to the development of peptides that function as inverse agonists on constitutively active PTH1R mutants that cause Jansens skeletal chondrodysplasia and could potentially be used to treat this ultra-rare disease as he is now pursuing with collaborators at the National Institute of Health.

Sung Han, Ph.D.
Associate Professor at the Salk Institute for Biological Studies
Revealing the Role of Neuropeptides in Neural Circuit Function and Behavior

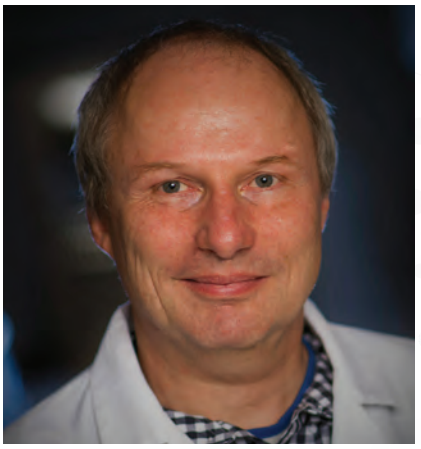
Sung Han is an associate professor of the Peptide Biology Laboratory at Salk. With more than seven years at Salk, his research focuses on understanding the roles of neuropeptides and their receptors in the brain's neural circuits. His work explores how these elements influence physiological and emotional processes including pain, fear, anxiety, panic, and reward, and their impact on abnormal brain functions.

Antoine Henninot, Ph.D.
Senior Director and Drug Maker in Residence, Curie.Bio
Investor Panel

Antoine Henninot is a Senior Director and Drug Maker in Residence at Curie Bio. In this role, he supports portfolio companies by designing and executing strategic drug discovery plans, as well as participating in due diligence to evaluate new ideas. Antoine trained as a pharmacist at the University of Lille in France, where he also completed his Ph.D. in medicinal chemistry and chemical biology under the supervision of Prof. Benoit Deprez, in collaboration with LFB Biotechnologie, focusing on the identification of modulators of antibody post-translational modifications.

He began his industrial career at the Ferring Research Institute in San Diego, initially as a postdoctoral researcher, before transitioning to a Scientist position. Subsequently, at Takeda in San Diego, he established and led the peptide and bioconjugation team, overseeing multiple projects in peptide drug discovery and siRNA delivery.

Thomas Kruse, Ph.D.
Senior Principal Scientist, Novo Nordisk, Denmark
Discovery of Amycretin: A GLP-1/amylin Co-agonist for Oral Administration



TK studied medicine, biology and chemistry at Odense University 1982-93 and obtained his PhD in organic chemistry about organic superconducters in 1991 under supervision of Professor Jan Becher. He did postdoctoral work in Bangor, Wales (professor Alan Underhill), Durham, UK with Professor Martin Bryce and Tuscaloosa, Alabama with Professor Michael Cava. In 1993 TK was employed at Novo Nordisk in Copenhagen as small molecule medicinal chemist. In 2001 TK changed focus from small molecules to peptides and led the chemistry effort that resulted in semaglutide in 2004. TK has since been continuously engaged in applications of fatty acid acylation technology within metabolically active peptides for diabetes, obesity and CVD indications including cagrilintide and amycretin. TK is also involved in Novo Nordisk' efforts within glucose sensitive insulins.

Yu-Shan Lin, Ph.D.
Professor, Tufts University
Structure Prediction of Cyclic Peptides Via Molecular Dynamics and Machine Learning

Yu-Shan Lin obtained her Ph.D. in Chemistry from University of Wisconsin, Madison, in 2009, and she was a postdoctoral fellow at Stanford from 2009 to 2012. In 2012, Yu-Shan established her research group at Tufts University, where she received tenure in 2018. Yu-Shan's current research endeavors focus on using molecular dynamics simulation and machine learning to understand and design structures and properties of peptides, in particular cyclic and other restrained peptides. Yu-Shan recently received the Machine Learning in the Chemical Sciences & Engineering Award from the Camille and Henry Dreyfus Foundation (2020), the Rising Innovator Award from Tufts University (2023), and the Annual Women Leadership Award from the Rotary Club of Cambridge Massachusetts (2023).

Ewa Lis, Ph.D.
Founder and CEO, Koliber Biosciences Inc.
Advancing Peptide Optimization: Machine Learning-Driven Predictions for Potency, Stability, and Permeability

Dr. Ewa Lis is the Founder and CEO of Koliber Biosciences, a pioneering computational biology company that leverages an advanced AI platform for the discovery and optimization of peptides. With a rich background in both computer science and biological sciences, Dr. Lis's expertise encompasses deep learning, data augmentation, graph networks, and various domains of biology and chemistry. Before establishing Koliber Biosciences in 2014, she held key positions at Life Technologies, Genomatica, and Reveal Biosciences, where she contributed to the development of diverse technologies ranging from algorithms for pathology tissue classification to tools for genome engineering research and sustainable microbial chemicals. Dr. Lis earned her BA in Chemistry from Cornell University and her Ph.D. in Biological Sciences from The Scripps Research Institute.

Yingli Ma, Ph.D.
Chief Technology Officer, Structure Therapeutics
Developing Small Molecule Agonists of GLP-1R and other Peptide-Binding GPCRs

Dr. Ma has more than 15 years of technology and drug discovery experience in pharmaceutical and biotech settings and currently Chief Technology Officer of Structure Therapeutics. Prior to this role, Dr. Ma was General Manager of Amgen Biopharmaceutical R&D (Shanghai) and she led Amgen's structural biology and China research platforms, supporting all preclinical drug discovery projects including small molecules and biologics in cardiometabolic, oncology and inflammatory disease areas. Prior to Amgen, she was at GSK (Shanghai), supporting multiple preclinical drug discovery programs across a variety of target classes (kinase, PPI, channel, membrane receptor, nuclear receptor etc.) for target validation, protein characterization and structural biology studies in the fields of neuroscience, regenerative medicine and mitochondrial biology. Dr. Ma completed a postdoctoral training in Nobel laureate Dr. Gunter Blobel's lab and she obtained a Ph.D. in Biochemistry and Molecular Biophysics from the University of Pennsylvania.

Adam Mezo, Ph.D.
President, Peptide Therapeutics Foundation; Vice President, Research, Peptide Chemistry, Neurocrine Biosciences, Inc.
Opening Remarks

Dr. Adam Mezo has worked in the pharmaceutical industry for over 20 years with a focus on the discovery of novel peptide, small molecule and protein therapeutics. Dr. Adam Mezo is currently Vice President, Research, Peptide Chemistry at Neurocrine Biosciences, Inc in San Diego. In his current role at Neurocrine, he is focused on the discovery of novel peptide therapeutics for a range of unmet medical needs. Prior to this role, he led teams of chemists, biochemists and drug hunters at the Ferring Research Institute, Eli Lilly, Biogen Idec and Syntonix. He has worked in various therapeutics areas, including diabetes, hemophilia, immunology and reproductive and women's health. Although peptides are his focus, he has also led teams in other modalities including small molecules and proteins as projects and priorities dictate. Dr. Mezo has over 50 published manuscripts and conference presentations, along with over 20 issued US patents. He received his undergraduate degree in chemistry from Queen's University (Canada), PhD from the University of British Columbia in organic chemistry and performed postdoctoral work at the Massachusetts Institute of Technology in the field of bioorganic chemistry.

Henrik Fischer Munch, Ph.D.
Principal Scientist, Department of Medicinal Chemistry, Zealand Pharma, Copenhagen
The Discovery of Petrelintide, a Potent, Stable, Long-acting Human Amylin Analog

Henrik obtained his Ph.D. from the University of Copenhagen, Denmark in the group of Professor Knud J. Jensen, where he worked on controlling the self-assembly of pharmaceutically relevant peptides and proteins, such as insulin. After obtaining his Ph.D. he moved to the group of Professor Matthew B. Francis as a postdoctoral researcher for two years at U.C. Berkeley California applying modern bioconjugation reactions to develop new biomaterials.

He joined Zealand Pharma in 2014, where he contributed as lead medicinal chemist and project lead in the fields of inflammation and Metabolic Disease to several drug discovery programs spanning from hit finding to IND. He has contributed to three clinical candidates during his career at Zealand Pharma. Further, he is an author of several peer-reviewed scientific publications and patents.

Steven Horton, Ph.D.
Oncology Scientist, RayzeBio
Development of Radiopharmaceutical Therapy Agents for Treatment of GPC3-Expressing Tumors

A pre-clinical oncology biologist working at Rayzebio for 3 years, focusing on the GPC-3 program among others. Dedicated efforts towards target validation, lead optimization and drug discovery, as well as translational implications. Has worked in the oncology space for 6+ years with 10 years of research experience.

Maurizio Pellecchia, Ph.D.
Professor of Biomedical Sciences, School of Medicine, University of California Riverside
NMR- and Structure-based Design of Novel Reversible and Covalent Therpeutic Peptides

Maurizio Pellecchia is chemical biologist with a strong background in pharmaceutical chemistry, biophysics, medicinal chemistry, and translational medicine. He trained at the University of Naples (Italy) where he obtained a MS in Organic Chemistry and a Ph.D. in Pharmaceutical Sciences, at the ETH-Zurich (working with 2002 Nobel Laureate Prof. Dr. Kurt Wüthrich), and the University of Michigan as research fellow. Prior to his recruitment in 2002 at the Burnham Institute for Medical Research as Associate Professor, he spent a few years in the pharmaceutical industry. He was promoted to full Professor in June 2007 at the now Sanford-Burnham-Prebys Medical Discovery Institute where he served as the Associate Director for Translational Research for the Institute's NCI designated Cancer Center, and as an Associate Dean of Graduate Studies. Since 2015 he was recruited as Professor of Biomedical Sciences at the University of California at Riverside, School of Medicine where he also holds the Daniel Hays endowed Chair in Cancer Research. At UCR he also served as Associate Dean for Pre-Clerkship Medical Education (2022-2024), and currently serves as Director of the Pharmacology Thread, and as the founding director of the Center for Molecular and Translational Medicine (both since 2015). His research is at the forefront of academic drug discovery and chemical biology initiatives to support target identification and validation studies in oncology and neurodegenerative diseases. His studies focus primarily on the development of innovative drug discovery strategies and to apply those to develop novel pharmacological tools. Subsequently such agents form the basis for target validation studies in cellular and animal models, both internally and via collaborations, and for continued lead optimization and drug development studies in collaboration with the NIH and private biotech or pharmaceutical companies. Central to these activities is the developing and the application of novel methods and strategies to drug discovery and translational medicine, several of which will be presented during his lecture.

Sharat Singh, Ph.D.
Head of Research, Biora Therapeutics
Empowering Peptide Self-Administration with Needle Free Smart Capsules

Sharat Singh brings over 25 years of experience as a dynamic and innovative scientific leader to his role at Biora Therapeutics, where he is focused on development of the company's ingestible drug-device combination product candidates.

Dr. Singh previously held scientific leadership roles at Aclara Biosciences, Prometheus Laboratories, and Nestle Health Sciences, where he established partnerships with leading biotech/pharmaceutical companies and conducted multiple phase I/II clinical trials in both oncology and gastrointestinal disease.

Dr. Singh is the key inventor of multiple platform technologies (CEER, ANSER, eTag, and LOCI) and has authored over 100 patents. In his academic career, Sharat conducted inter-disciplinary research as a postdoctoral fellow at Columbia University. He holds a PhD in Chemistry from IISc, Bangalore, and has authored over 100 manuscripts and presentations.

Nancy Thornberry
Founding CEO, Kallyope
Identification of Hormonal and Neural Circuits Involved in Gut-Brain Signaling

Nancy A. Thornberry has decades of experience in the pharmaceutical and biotech industries, with responsibilities spanning research and development, business development, customer engagement, and strategy. From 2015-2021 she was CEO of Kallyope, a NYC-based biotechnology company focused on the discovery and development of novel therapeutic agents targeting the gut and gut-brain axis. She remains on the Board of Directors and is Chair of R&D. Prior to joining Kallyope, she was Senior Vice President and Franchise Head, Diabetes and Endocrinology, for Merck & Co. Inc. , with responsibility for discovery and clinical research in diabetes, obesity, and Women's Health. Before becoming Franchise Head Nancy initiated and led Merck's dipeptidyl peptidase 4 (DPP-4) project, which resulted in the discovery of JANUVIA® for the treatment of Type 2 diabetes, the best-selling oral product franchise in Merck's history. She has also achieved several other notable scientific accomplishments, including the identification of the first caspase, caspase-1. For her contributions she has received numerous awards, including the Merck Presidential Fellowship, Merck Directors Award, Heroes of Chemistry Award by the American Chemical Society, and in 2011 received the Pharmaceuticals Research and Manufacturers of America (PhRMA) Discoverers Award, which honors research scientists whose work has been of special benefit to humankind.

In addition to her role at Kallyope, Nancy currently serves on the Boards of Directors of Vertex Pharmaceuticals, Adimab, Schrodinger, Denali Therapeutics, and the New York Genome Center, and is an advisor to Google Ventures.

Paul M. Titchenell, Ph.D.
Associate Professor of Physiology, Perelman School of Medicine at the University of Pennsylvania
Preserving Skeletal Muscle Mass and Enhancing Fat Loss by Targeting Activin Type II Receptors in Obesity

Paul Titchenell, Ph.D. leads an academic research group focused on how nutrients, growth factors and metabolites regulate metabolism in health and disease. Dr. Titchenell earned his B.S. in Biochemistry and Molecular Biology from Dickinson College. Following his undergraduate studies, Dr. Titchenell obtained a Ph.D. from Pennsylvania State University. During his graduate training, he investigated the signaling mechanisms responsible for diabetic vascular complications and identified and patented a series of small molecular kinase inhibitors for the treatment of retinal edema induced by pro-inflammatory and angiogenic growth factors. Following his Ph.D. studies, Dr. Titchenell trained as a NRSA-supported postdoctoral fellow with Dr. Morris Birnbaum where he developed several novel mouse models to dissect the tissue-specific actions of insulin in the control of hepatic lipid and glucose metabolism. In 2017, Dr. Titchenell joined the faculty at the Perelman School of Medicine at the University of Pennsylvania and is currently an Associate Professor (with tenure) in the Department of Physiology and Institute for Diabetes, Obesity, and Metabolism at Penn. Dr. Titchenell also serves as a Director for the Rodent Metabolic Phenotyping Core at the University of Pennsylvania. Dr. Titchenell has published over 40 refereed manuscripts in the world's leading scientific journals, including Cell, Science, Nature, and Journal of Clinical Investigation. In his own laboratory, Dr. Titchenell's research is focused on hormone and nutrient signaling in the regulation of glucose, fat and protein metabolism with a particular focus on skeletal muscle biology in health and metabolic diseases such as obesity. Throughout his career, Dr. Titchenell has been active in national and international societies including serving on the Planning Committee for American Diabetes Association Scientific Sessions. He is currently on the Editorial Board for Diabetes and is a recent recipient of the American Physiological Society's New Investigator Award for Excellence in Endocrinology and Metabolism research.

Sally Wang Liang, JD MPH
Partner, Highlight Capital
Investor Panel

Sally Wang Liang JD MPH is the US-based Investment Partner at Highlight Capital (HLC), responsible for the life sciences VC group of an internationally ranked Growth Equity and Venture Capital firm with a global footprint. She has been actively involved in the biotech startup ecosystem: as a Venture Partner at Viva Bioinnovator (VBI) and a board member/observer to eight early-stage biotechs, as a Scientific Advisory Board member, and as Expert-in-Residence at the Harvard iLab.

She comes to Highlight as a life sciences investor, business executive and a multidisciplinary IP & Regulatory lawyer with 20+ years of healthcare industry experience. Previously, she was Entrepreneur-in-Residence (Acting VP of Investments and General Counsel) at the biotech involved in in-licensing promising university technology into NewCo. She was CEO and Co-founder of an international telemedicine company, and as Chief Strategy Officer and EVP of IP and Regulatory of a leading digital therapeutics company. As a lawyer, she practiced pharmaceutical patent litigation and IP licensing at the premier intellectual property firm and clerked for a federal judge. She was also involved in healthcare policy making on the national level at the Food and Drug Administration Office of Policy and the US Senate Health Education Labor Pension Committee Health Office. She began her career as a management consultant at Clarion Healthcare (now Lumanity), advising many of the world's largest pharmaceutical companies and top biotech firms on business strategy. Sally received a A.B. in Biology from Harvard College, a J.D. from Harvard Law School, and a M.P.H from Harvard T.H. Chan School of Public Health.

ZEALAND PHARMA

Zealand Pharma A/S is a biotechnology company founded in 1998 and headquartered in Denmark. Our purpose is to make a difference for those living with unmet medical needs through the discovery, design, and development of innovative peptide-based medicines.

More than 10 drug candidates invented by Zealand have advanced into clinical development, of which two have reached the market and three candidates are in late-stage development. Today, Zealand's R&D pipeline consists of candidates designed to address a broad range of disease areas, including obesity, rare diseases, chronic inflammation, and type 1 diabetes.

For more information, visit www.zealandpharma.com.

BACHEM

Bachem is a leading, innovation-driven company specializing in the **development and manufacture** of **peptides** and **oligonucleotides**.

With **50 years of experience** and expertise Bachem provides products for research, clinical devpment and commercial application to pharmaceutical and biotechnology companies **worldwide** and offers a comprehensive range of services.

Bachem operates internationally with headquarters in Switzerland and locations in Europe, the US and Asia.

www.bachem.com

Notes

ABSTRACTS OF SPEAKER PRESENTATIONS

19th Annual
Peptide Therapeutics Symposium

Building on Natural Product Motifs for Cyclic Peptide Inhibitor Discovery

Albert A. Bowers, Ph.D.
Professor and Vice-Chair
Division of Chemical Biology and Medicinal Chemistry, UNC Chapel Hill

Peptide macrocycles are increasingly being exploited to attack some of the most challenge therapeutic targets. Many natural products exploit cyclization to augment peptide affinity by helping pre-adopt a lower energy binding conformation and to makes the resultant compounds more resistant to proteolysis and more cell permeable. Our lab uses mRNA display for the discovery of new peptide macrocycles. mRNA display is particularly powerful, because it tightly integrates rapid synthesis and testing of some of the largest libraries (up to 10 13 molecules) of peptide-based macrocycles, in high fidelity, and with relatively minimal effort. Biosynthesis is the key to this power. In contrast to DNA-encoded libraries (DELs) and other small molecule libraries, mRNA display libraries are synthesized directly from their genetic barcodes, allowing for multiple, iterative rounds of screening to be easily performed for the enrichment of high affinity ligands. We are working to expand the diversity of mRNA display macrocycles to access new target space through the incorporation of new motifs and biotechnology derived from natural product biosynthesis. This approach, based on a combination of enzymes and biocompatible chemistry will open the door to natural product chemical space, decrease the time and investment required to access these chemical libraries, and speed the development of new macrocycle therapeutics.

Development and Applications of ^{68}Ga-CBP8, a Type-1 Collagen Targeted Peptide-based Positron Emission Tomography Probe

Peter Caravan, Ph.D.
Professor of Radiology, Harvard Medical School
Co-Director of the Institute for Innovation in Imaging, Massachusetts General Hospital

Fibrosis, or scarring of tissue, is a hallmark of many chronic diseases. It is estimated that over half of the mortality in the US arises from diseases with a fibroproliferative component. Despite the importance of fibrosis, current noninvasive techniques are only sensitive to the detection of advanced disease, underscoring a need for more sensitive and quantitative methods. Fibrosis is characterized by the replacement of functional tissue by excess extracellular matrix proteins, chiefly type I collagen. We developed a type I collagen specific positron emission tomography (PET) probe, ^{68}Ga-CBP8, to noninvasively detect and stage organ fibrosis. In this presentation I will describe the identification and preclinical development of this molecule. I will report on clinical trials deploying ^{68}Ga-CBP8 in diseases of the lung, the heart, pancreatic cancer, and Crohn's disease which highlight its potential in disease detection, in predicting disease progression, and in reporting on therapeutic response.

RNAi Delivery to the Central Nervous System

Christine Esau, Ph.D.
Vice President, Arrowhead Pharmaceuticals

The Arrowhead TRiM™ platform utilizes ligand-mediated delivery of RNAi and is a robust and versatile drug discovery and development platform. Delivery of RNAi to the central nervous system (CNS) has potential to treat a broad range of neurological disorders. We have developed an optimized intrathecal TRiM™ platform which shows effective and long-lasting target inhibition throughout the CNS and in multiple cell types in preclinical species. Using SOD1 targeting for SOD1-ALS as an example, we show that treatment with ARO-SOD1 in rodent models of SOD1-ALS delayed disease progression, preserved motor function, and prolonged survival. Intrathecal delivery of ARO-SOD1 to NHP effected deep knockdown of SOD1 mRNA and protein with effective silencing up to six months after a single administration. These results highlight the potential for Arrowhead's CNS-targeting TRiM™ platform to be broadly applied to treat neurological diseases.

Parathyroid Hormone Peptide Development for Diseases of Bone and Calcium Metabolism

Thomas J. Gardella, Ph.D.
Associate Professor in Medicine
Massachusetts General Hospital and Harvard Medical School

The parathyroid hormone receptor type 1, or PTH1R, is a key drug discovery target for osteoporosis, hypoparathyroidism and potentially other diseases of bone and mineral metabolism. Osteoporosis affects millions of people, particularly postmenopausal women, and brings significant medical and economic burden due to debilitating and painful bone fractures. Hypoparathyroidism impacts ~ 80,000 people in the U.S, and patients suffer from chronic hypocalcemia, seizures, muscle pain and low quality of life due to a lack natural PTH. Current treatments for these diseases are limited by factors such as efficacy, side effects and compliance. The PTH1R binds two endogenous peptide ligands and thus controls two critical and distinct biological processes--PTH to maintain calcium homeostasis and PTH-related protein to regulate bone development. The PTH1R is a class B GPCR and thus shares homology with the receptors for glucagon, GLP-1, CRF, and several other peptide hormone receptors. As for each of these GPCRs, the PTH1R binds its cognate peptide ligand, such as PTH(1-34), via a two-site mechanism that involves "docking" interactions between the C-terminal portion of the ligand and the receptor's N-terminal extracellular domain, and "signaling" interactions between the N-terminal portion of the ligand and the receptor's transmembrane helical domain (TMD). Minimized N-terminal PTH fragment peptides, such as Modified "M"-PTH(1-14) and M-PTH(1-11) bind only to the receptor's TMD and act as potent PTH1R agonists in vitro. Structurally distinct PTH and PTHrP peptides can bind selectively to distinct PTH1R conformations and thereby induce markedly different modes of signaling. Thus, peptides that can bind with high to the G protein-uncoupled conformation (R0) mediate sustained cAMP signaling responses, likely from internalized endosomes, whereas peptides that bind selectively to the G protein-coupled conformation (RG) mediate transient cAMP responses, likely from the cell surface. This temporal and spatial bias in signaling may underlie the distinct biological effects mediated by the PTH1R in response to endogenous PTH versus PTHrP. It may also provide a strategy for developing new PTH1R-directed therapeutics. Thus, for osteoporosis where the goal is to stimulate new bone formation, an RG-selective ligand would be sought, as bone formation seems to be promoted by pulsatile or transient PTH1R activation. For hypoparathyroidism where the goal is to achieve sustained normalization of blood calcium, an R0-selective ligand that mediates prolonged signaling would be sought. The advance of one such long-acting, R0-selective PTH/PTHrP hybrid peptide called Eneboparatide into a phase 3 trial for hypoparathyroidism provides support for this approach. These concepts and approaches will be highlighted in the presentation.

Revealing the Role of Neuropeptides in Neural Circuit Function and Behavior

Sung Han, Ph.D.
Associate Professor at the Salk Institute for Biological Studies

Neuropeptides play a critical role in modulating neural circuits and influencing behavior, yet their precise mechanisms of action remain largely unexplored. In this talk, I will present our latest findings on the role of neuropeptides in neural circuit function, uncovered through the use of novel genetically encoded sensors and silencers designed specifically for peptidergic transmission. By applying these innovative tools, we have identified key pathways and mechanisms by which neuropeptides regulate neuronal activity and orchestrate complex behavioral responses. This presentation will highlight the biological insights gained from these studies, offering a deeper understanding of how neuropeptide signaling shapes brain function and behavior.

Discovery of Amycretin: A CLP-1/amylin Co-agonist for Oral Administration

Thomas Kruse, Ph.D.
Senior Principal Scientist, Novo Nordisk, Denmark

The percentage of the world population that is overweight or obese continues to increase and this leads to a multitude of obesity related complications such as diabetes, cancer, Alzheimer disease, joint problems, and CVD. While these complications may be targeted individually, it may also be valid to treat obesity directly as a root cause to this multitude of conditions that are of great harm to the quality of life of those affected. The most obvious way of treating obesity is to reduce food intake, but the medication must be effective, convenient, and safe. The introduction of pramlintide (amylin) and exendin-4 (GLP-1) on the market by Amylin Pharmaceuticals in 2005 clearly suggested the benefit of these two peptides in the treatment of diabetes but also demonstrated their weight loss potential. It initiated an era of improvement of metabolic peptides that continues to this day. GLP-1 based drugs have seen the rise of liraglutide, semaglutide and tirzepatide with many more in clinical development. The trend appears to be to combine GLP-1 with other anorectic hormones to increase the efficacy, with the goal of becoming as efficacious as bariatric surgery. Prominent examples are the combination of GLP-1 and GIP as in tirzepatide or GLP-1 and glucagon as in survodutide. Pioneered by DiMarchi et al it has also been possible to combine GLP-1, GIP and glucagon in a balanced triagonist. Eli Lilly has progressed this concept to phase 3 with the promising drug retatrutide. While there have been intense efforts within GLP-1 based mono-, co-, and tri-agonists, amylin has for various reasons been less in the spotlight. At Novo Nordisk interest in amylin began in 2004 and an amylin agonist, cagrilintide, is currently in phase 3 in combination with semaglutide. It appears that amylin adds significantly to the efficacy of body weight loss of semaglutide in a safe way and that the combination of GLP-1 and amylin deserve particular interest. This presentation will detail the more recent effort at Novo Nordisk to make a unimolecular format that combine GLP-1 and amylin agonism suitable for oral administration.

Structure Prediction of Cyclic Peptides Via Molecular Dynamics and Machine Learning

Yu-Shan Lin, Ph.D.
Professor, Tufts University

A major obstacle to cyclic peptide development is that little structural information is available for these molecules, making it difficult to perform structure-based design or understand why different cyclic peptide sequences display different binding affinity, membrane permeability, and other properties. The lack of structural information is due to the fact that most cyclic peptides adopt multiple conformations in solution, existing as structural ensembles, which are very difficult to characterize using experimental techniques such as solution NMR spectroscopy. In this talk, I will describe how we develop StrEAMM (Structural Ensembles Achieved by Molecular dynamics and Machine learning) models for cyclic peptides by combining molecular dynamics simulation and machine learning. We can now provide simulation-quality cyclic peptide structure predictions in seconds. We expect such a capability to rapidly predict cyclic peptide structures to enable researchers to understand the structural basis for the diverse properties of different cyclic peptides and greatly accelerate the development of this unique class of molecules.

Advancing Peptide Optimization: Machine Learning-Driven Predictions for Potency, Stability, and Permeability

Ewa Lis, Ph.D.
Founder and CEO, Koliber Biosciences Inc.

Peptide discovery and optimization has traditionally been a sequential, trial-and-error process, focusing on one property at a time — typically starting with potency, then addressing stability or permeability. This can be time-consuming, resource-intensive, and frequently fails to yield optimal compounds. In this presentation we will showcase advancements of the Koliber AI peptide/protein platform in predicting properties such as stability and permeability enabling multi-factor optimization. More importantly we will demonstrate progress in reducing dataset size requirements for training high performing machine learning models to predict peptide potency. We will explore a range of applications, including anti-microbial and immune-modulating peptides, as well as various peptide datasets, such as cyclic peptides and peptides containing non-canonical amino acids. Latest advancements in de novo predictions of potency will be showcased to illustrate the potential future directions in peptide drug optimization. Finally, we will demonstrate a prototype software for peptide design and optimization.

Developing Small Molecule Agonists of GLP-1R and other Peptide-Binding GPCRs

Yingli Ma, Ph.D.
Chief Technology Officer, Structure Therapeutics

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are well established treatments for patients with Type 2 Diabetes Mellitus (T2DM) and obesity with the caveat of the need for injection and cold chain transportation and storage. An oral small molecule GLP-1RA that offers enhanced bioavailability and stability could bring a more convenient alternative resulting in broader accessibility for patients. Here we report the discovery, cryo-EM structure, in vitro and in vivo profiling of GSBR-1290, a highly potent, orally available, novel small molecule GLP-1RA. We also describe data from once daily oral administration of GSBR-1290 in overweight or obese participants as ph2a clinical trial results. Overall, GSBR-1290 is a potentially best-in-class oral GLP-1RA with scalability potentially to serve large unmet needs in patient population globally.

The Discovery of Petrelintide, a Potent, Stable, Long-acting Human Amylin Analog

Henrik Fischer Munch, Ph.D.
Principal Scientist, Department of Medicinal Chemistry, Zealand Pharma, Copenhagen

Petrelintide is a novel amylin analog designed for once weekly (ow) subcutaneous (s.c.) administration in development for weight management.

We will describe the discovery of petrelintide through modifying human amylin into a peptide which is potent, long-acting, chemically and physically stable. Human amylin contains several amino acids which are prone to reduce chemical stability especially around neutral pH. We identified modifications, which have significantly improved the chemical and physical stability whilst retaining biological activity.

A series of optimized lipidated peptides demonstrated excellent pharmacokinetic profiles and were efficacious in reducing food intake and body weight in lean rats. Petrelintide was selected from this group and showed a dose-dependent effect on food intake and body weight reduction in diet-induced obese (DIO) rats.

Petrelintide is currently in clinical development by Zealand Pharma.

Development of Radiopharmaceutical Therapy Agents for Treatment of GPC3-Expressing Tumors

Steven Horton, Ph.D.
Oncology Scientist, RayzeBio

The recent approvals of Lutathera and Pluvicto have highlighted the potential of Radiopharmaceutical Therapy (RPT) as a secure and efficient targeted modality for treating various solid tumors. The successful development of RPT necessitates methodical optimization and a thorough evaluation of the targeting moiety, linker, chelator, and the selection of radioisotopes.

RayzeBio is at the forefront of innovation in this domain, employing a data-driven drug discovery approach to systematically identify optimal RPT agents against clinically validated oncology targets that have yet to be addressed using RPT. In this presentation, we will share the application of this approach to develop and optimization of potential RPT agents for the treatment of GPC3-expressing tumors.

NMR- and Structure-based Design of Novel Reversible and Covalent Therapeutic Peptides

Maurizio Pellecchia, Ph.D.
Professor of Biomedical Sciences, School of Medicine, University of California Riverside

The identification of drug-like antagonists to protein-protein interactions (PPIs) remains a challenging task. The lecture describes the recent strategies developed by the laboratory, including the recently reported HTS by NMR approach, that relies on protein-NMR based screening of combinatorial libraries for identification of short peptide sequences that can be optimized into possible therapeutics. I will report on the approach and its initial applications to the discovery of novel possible therapeutics targeting the receptors tyrosine kinase of the EphA4 and EphA2 subfamilies. Optimization strategies of such peptide mimetics can also rely on the incorporation of mild electrophiles to target not only Cys residues but also other residues such as Lys, His, or Tyr. Hence, I will also report on instances where it is possible to target PPIs with novel electrophiles such as aryl-fluorosulfates that stably and effectively covalently target binding site Lys/His/Tyr residues with examples targeting the anti-apoptotic proteins of the IAP (ML-IAP, XIAP, cIAP1/2) and Bcl-2 families (Mcl-1).

Empowering Peptide Self-Administration with Needle Free Smart Capsules

Sharat Singh, Ph.D.
Head of Research, Biora Therapeutics

Oral delivery of peptides is extremely challenging as pre-systemic enzymatic degradation and poor membrane permeability of large peptide molecules lead to poor bioavailability. The key issue is to improve the oral bioavailability from less than 1% to at least 30-50%. Painless Liquid-jet oral delivery of peptides to the intestinal tract is an innovative approach that offers several distinct advantages over traditional administration. This technique involves the use of high-velocity liquid jets to penetrate the gastrointestinal mucosa and deliver the therapeutic peptides. My presentation will focus on explaining the mechanism of liquid jet delivery to the small intestine, enabling systemic uptake. Understanding how ingestible Biojet bypass common bioavailability challenges for antibodies, nucleic acids, and peptides.

Identification of Hormonal and Neural Circuits Involved in Gut-Brain Signaling

Nancy Thornberry
Founding CEO, Kallyope

The gut-brain axis, which mediates the bi-directional communication between the gastrointestinal system and the central nervous system (CNS), plays a fundamental role in multiple areas of physiology including regulation of appetite, metabolism, immune response, and gastrointestinal function. The biology of this system is central to the efficacy of incretin-based therapies, which are now leading treatments for type 2 diabetes (T2DM) and obesity. This success, and research to suggest a much broader role for gut-brain circuits in physiology and disease, has led to increasing interest in targeting such circuits for the discovery of new therapeutics. However, our current knowledge of this physiology is limited, largely because the scientific tools have not been available to enable a detailed mechanistic understanding of gut-brain communication.

Fortunately, recent technologies are enabling a better understanding of this system at a molecular level, which is leading to novel insights into gut-brain communication. Such technologies include single cell sequencing, circuit mapping technologies including opto- and chemo-genetics, and gut organoids. This systems biology approach has led to a comprehensive understanding of all the specialized cell types in the major components of the gut-brain axis, and insights into the hormonal and neural communication between these cells and the physiology they modulate. While this work reveals a complexity of signaling even greater than previously appreciated, new insights are now being leveraged for the discovery of new therapeutics.

Preserving Skeletal Muscle Mass and Enhancing Fat Loss by Targeting Activin Type II Receptors in Obesity

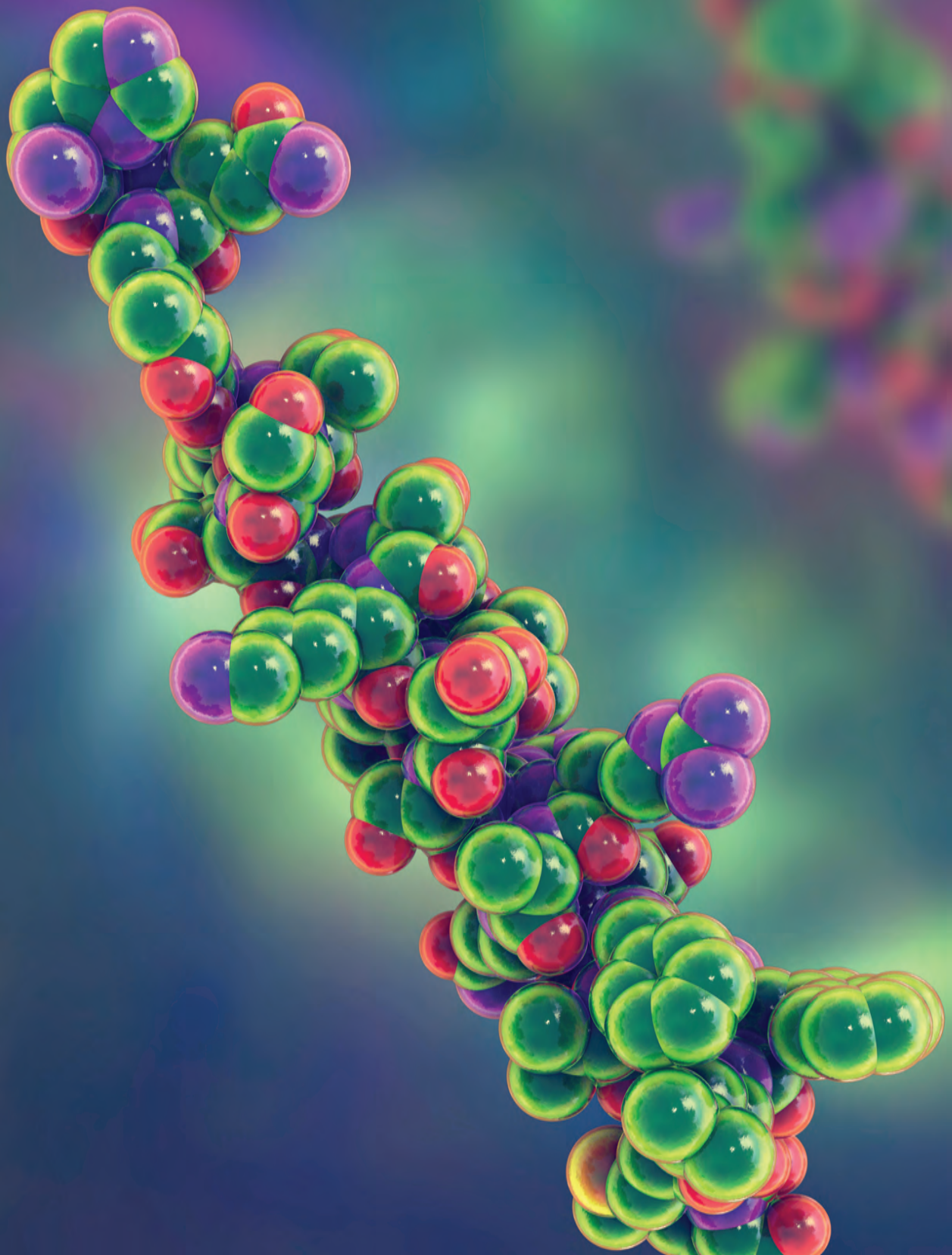
Paul Titchenell, Ph.D.
Department of Physiology, Institute for Diabetes, Obesity and Metabolism; Perelman School of Medicine, university of Pennsylvania

Glucagon-like peptide 1 (GLP-1) receptor agonists reduce food intake, producing remarkable weight loss in overweight and obese individuals. While much of this weight loss is fat mass, there is also a loss of skeletal muscle mass, similar to other approaches that induce calorie deficit. Targeting signaling pathways that regulate skeletal muscle hypertrophy is a promising avenue to preserve lean mass and modulate body composition during weight loss. TGF -like ligands such as myostatin and activin A signal via the activin type II receptors (ActRII) to antagonize muscle growth. Pre-clinical and clinical studies demonstrate that ActRII blockade induces skeletal muscle hypertrophy and reduces fat mass. In this study, we explore the therapeutic potential of bimagrumab, a monoclonal antibody against ActRII, to modify body composition alone and during weight loss induced by GLP-1 receptor agonist semaglutide in diet-induced obese mice. Mechanistically, we define the specific role of the anabolic kinase Akt in mediating the hypertrophic muscle effects of ActRII inhibition in vivo. Treatment of obese mice with bimagrumab induced a 10 % increase in lean mass while simultaneously decreasing fat mass. Daily treatment of obese mice with semaglutide potently decreased body weight; this included a significant decrease in both muscle and fat mass. Combination treatment with bimagrumab and semaglutide led to superior fat mass loss while simultaneously preserving lean mass despite reduced food intake. Treatment with both drugs was associated with improved metabolic outcomes, and increased lean mass was associated with improved exercise performance. Deletion of both Akt isoforms in skeletal muscle modestly reduced, but did not prevent, muscle hypertrophy driven by ActRII inhibition. Collectively, these data demonstrate that blockade of ActRII signaling improves body composition and metabolic parameters alone and during calorie deficit driven by GLP-1 receptor agonism and demonstrate the existence of Akt-independent pathways supporting muscle hypertrophy in the absence of ActRII signaling.

Notes

ABSTRACTS OF POSTER PRESENTATIONS

19th Annual
Peptide Therapeutics Symposium



P01 | Recombinant Synthesis and Structural Characterization of a Peptide Neurotoxin from a Tarantula Venom

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Various neurological diseases such as epilepsy, pain disorders, arrhythmias, and paralysis are caused by mutations in voltage-gated ion channels. Neurotoxins from various venomous animals such as tarantulas, scorpions, snakes, cone snails, sea anemones, insects, and puffer fish are used to probe voltage-gated ion channels because they interact with these channels by either blocking the pore (pore blocker toxins) or by changing the conformation of the channel by binding to the voltage-sending domain (VSD) and modifying its gating properties (gating modifier toxins). Hence, these neurotoxins have the potential to become excellent drug candidates for different conditions arising due to defects in ion channels.

We have characterized a peptide neurotoxin GsAF2 from the venom of the Chilean rose tarantula Grammostola rosea. This 31-residue peptide is known to have antiarrhythmic and analgesic properties — properties that could make it a potentially useful drug candidate. Although the functional characteristics of the toxin have been studied extensively, its structural characteristics remain a mystery. Understanding both the structural and functional characteristics is essential to studying drug biomolecules. We have recombinantly synthesized GsAF2, tested its bioactivity, and solved its solution structure using solution-state Nuclear Magnetic Resonance (NMR). We have also characterized its interactions with empty bicelles (that excellently mimic cell membranes in which voltage-gated ion channels are embedded) and the VSD of a bacterial voltage-gated sodium channel NaChBac using NMR and computational docking methods. Eventually, investigating the toxin's structural and functional characteristics thoroughly will pave the way toward understanding its value as a drug candidate.

P02 | Enzymatic Platform for Synthesis of Diverse Macrocyclic Peptides

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Cyclic and polycyclic peptides are of considerable interest as therapeutic agents because the conformational restriction resulting from macrocyclization ensures specificity and resistance to proteolytic degradation. However, the assembly of polymacrocyclic structures is often challenging because of the necessity for multi-step syntheses involving orthogonal protecting groups.

In this study, we demonstrate a scalable, radical-mediated, and controllable enzymatic process for catalyzing the formation of thioether crosslinks across a broad spectrum of peptide substrates. The process generates cross-linked macrocycles with atom-level precision of ring size. L- or D- amino acids, β-amino acids, N-methylated residues, and even non-peptidic moieties can exist within in macrocycle or directly participate in the cross-linking. Further, we show that polymacrocyclic peptides with varied numbers of residues between each donor and acceptor residue can be controllably generated in nested or in-line configurations. This logic was extended to generate redox-stable interpeptide cross-links that mimic the complex multi-chain architecture of insulin.

The ability to controllably install multiple thioether cross-links within a single peptide chain without orthogonal protecting group strategies underscores the feasibility of employing the enzyme in synthetic biology and therapeutic peptide development. These findings further establish that this enzymatic method can be utilized as a platform biocatalyst for the discovery and synthesis of diverse peptide macrocycles, allowing for expanded chemical space in peptide-based therapeutic agents.

P03 | Cardiovascular Protection and Functional Recovery: Myristic Acid and Trans Activator of Transcription-Conjugated Protein Kinase C Epsilon and Beta II Peptide Inhibitors Reduce Infarct Size and Enhance Left Ventricular Function in a Porcine Model of Myocardial Ischemia-Reperfusion Injury

Desmond Boakye Tanoh[1], Sindy P. Hernandez[1], Juliet Melnik[1,2], Arjun Nair[1], Sunit G. Singh[1], James Ramsarran[1], Logan Clair[1], Qian Chen[1], Robert Barsotti[1], Lindon Young[1,2]

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Background

Protein Kinase C epsilon (PKC**ε**) and Protein Kinase C beta II (PKC**β**II) signaling is known to activate uncoupled endothelial nitric oxide synthase and NADPH Oxidase respectively, leading to reactive oxygen species (ROS) generation upon restoration of blood flow to previously ischemic myocardium. Both PKC isoforms also induce ROS release from the mitochondria.

Objectives

We hypothesize that inhibiting PKC**ε** or PKC**β**II at the beginning of reperfusion will attenuate ROS induced infarct size and will restore cardiac function compared to controls in an in vivo porcine myocardial ischemia-reperfusion (I/R) model.

Methods

I(1hr)/R(3hrs) induction in male castrated Yorkshire pigs (38-50 kg) was achieved via balloon occlusion of the second branch of the left anterior descending artery (LAD), followed by deflation. At the onset of reperfusion, cell permeable PKC**ε** and PKC**β**II inhibitors individually conjugated with Myristic Acid (Myr) and Trans-Activator of Transcription (Tat) (N-Myr-Tat-CC-EAVSLKPT[PKC**ε**-]; Myr-Tat-PKC**ε**- and N-Myr-Tat-CC-SLNPEWNET[PKC**β**II-]; Myr-Tat-PKC**β**II- respectively),or scrambled peptide (control) were administered through the LAD. Cardiac function was assessed through a comparison of infarct size (area of necrosis (AN)/area at risk (AR)) and ejection fraction between treatment and control. Data was analyzed via student t-test.

Results

Myr-Tat-PKC**ε**- (n=5) and Myr-Tat-PKC**β**II- (n=4) significantly restored EF to 100±1.2% and 98.8±0.9% of baseline, respectively, compared to controls (94.1±2.5%; n=6, $p<0.05$). Myr-Tat--KC**ε**- and Myr-Tat-PKC**β**II- showed significant reduction in infarct size (Myr-Tat-PKC**ε**-: 9.9±2.1%; n=4 and Myr-Tat-PKC**β**II-: 10.0±2.8%; n=4) compared to controls (28.5±8.3%, n=6; $p<0.05$).

Conclusion

Addition of Myr-Tat-PKC**ε**- or Myr-Tat-PKC**β**II- during reperfusion with coronary revascularization post-myocardial infarction (MI) exhibits robust cardioprotection and may reduce incident - heart failure after MI.

P04 | Single Step Peptide Drying of Solvent Applications Using Electrostatic Drying Technology

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Solvents commonly used in peptide synthesis result in the need for solvent removal and concentration steps prior to drying when using traditional drying methods. These drying methods have additional constraints, such as long cycle times and batch processes of lyophilization, or the thermal stresses caused by high temperatures of conventional spray drying. An alternative drying technology, Electrostatic Drying (ESD) can eliminate both solvent removal and concentration steps, and the peptide can be dried in a single step.

ESD is a continuous process that uses electrostatic charge, which enables removal of water and solvents efficiently resulting in dry peptide powders that do not require post processing and the process is scalable. Benefits of ESD include processing low (as low as 1%) or high solids peptide solutions , particle formation and particle engineering and API loading. Additionally, ESD can be an ideal process for sensitive peptides which cannot survive the low temperature and long cycle times of lyophilization and high temperature and physical stress of conventional spray drying.

Case studies conducted on bovine serum albumin (BSA) as a surrogate for peptide, in acetonitrile (ACN) and water mixture showed efficient removal of water and ACN producing dry BSA powders with residual ACN contents below the ICH regulatory limits of 410 ppm. The goals of the studies were to demonstrate that the alternative drying method, ESD, can remove solvent and dry BSA solution in a single step producing powders at both R&D and production scale with high yields at all scales.

This study was funded by Fluid Air, manufacturers of electrostatic dryers and conducted in their pilot labs facility in Naperville, Illinois.

P05 | Quantitative Peptidomics Assays Enabled the Discovery and Validation of Peptides Biomarkers of Immune Cells Infiltrates in the Mouse NASH Liver

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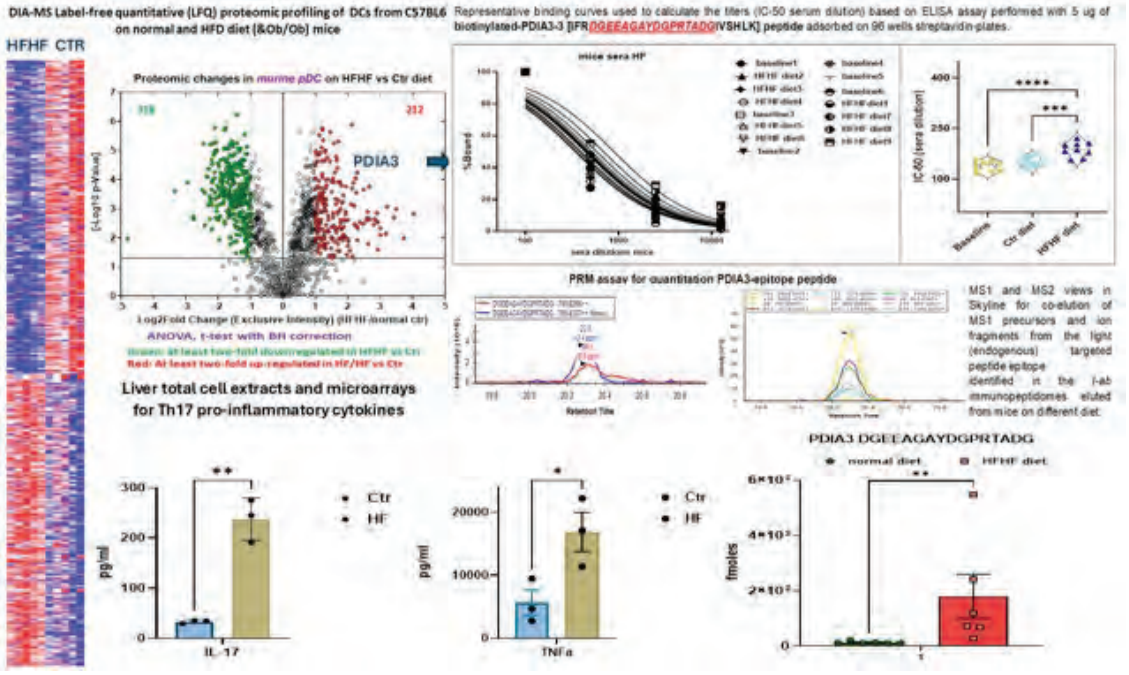
A diet rich in saturated fat and carbohydrates causes a low-grade chronic inflammation in several organs. To investigate the impact of oxidative stress and metabolic syndrome on the whole cellular proteome and peptidome/degradome of professional antigen presenting cells (APCs), we purified the immune cells infiltrates from the NASH liver of mice fed a normal and high fat/high fructose (HF/HF) diet and extracted their total cellular peptidomes (MW<10kDa) using a mild acid (MA) extraction method. The DIA/DDA analysis of the cellular peptidomes lead to the identification of diverse epitopes derived from the glycolytic pathway and ER-stress response, such as PDIA3. We further quantified the amount of PDIA3 peptides, DGEEAGAYDGPRTADG and IFRDGEEAGAYDGPRTADGIVSHLK, presented by the immune infiltrates by performing acid elution followed by PRM using stable isotope–labeled internal standards. As compared with peripheral dendritic cells (DCs), which presented 0.4 and 0.8 fmol of PDIA3 peptides in control and HFHF conditions, respectively, liver-infiltrating cells presented 10 and 400 fmol of PDIA3 peptides in control versus HFHF mice, respectively. This data indicated a 20-fold increase in the potential MHC-II presentation of the PDIA3 peptide in the livers of mice fed HFHF versus control diet, as compared with a twofold increase in the periphery. Because the mouse HFHF diet aims at recapitulating obesity and T2D, we further tested the presence of anti-PDIA3 antibodies in patients with these conditions. Accordingly, we performed ELISA assays against the linear B cell PDIA3 epitope on sera from 48 patients with T2D and quantified increased autoantibodies against PDIA3 protein.



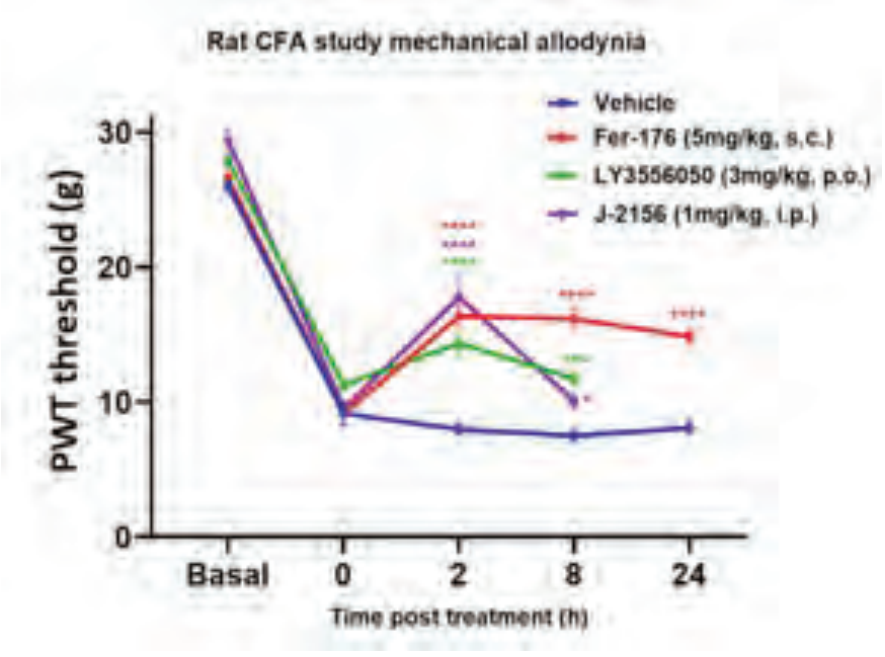
P06 | Long-acting Peripherally Restricted SSTR4 and KOR Agonists as Postoperative Pain Treatments

Derek C. Cole, Richard E. Myers
Ferdia Therapeutics, San Diego, CA

Management of postoperative pain is essential for the 40-50 million US patients undergoing surgical procedures each year. Reliance on opioid medications for pain management has exacerbated an opioid crisis, leading to an urgent need for novel, non-addictive therapies for postoperative pain.

Opioid receptors are central to the pain-killing effects of conventional opioid medications. However, activation of mu- and delta- opioid receptors drive the adverse effects of addiction, constipation, nausea, respiratory depression, and seizures, selective kappa-opioid receptors (KOR) agonism is a promising alternative for safer, non-addictive pain management. The peptidic KOR agonist, difelikefalin, displayed analgesic efficacy in Phase 2 postoperative pain trials but with short duration of efficacy limited by short drug half-life (~2 h). Ferdia Therapeutics is developing novel LA-KOR agonists with extended half-lives to provide improved duration of pain relief in the post-surgical context.

SSTR4 is another powerful anti-nociceptive target expressed on peripheral neurons in the dorsal root ganglia. Selective peptidic SSTR4 agonists are efficacious in reducing pain preclinically (e.g. J-2156) and clinically (LY3556050) but are limited by short half-lives. Ferdia Therapeutics' LA-SSTR4 agonist, Fer-176, has extended duration efficacy >24h in rodent pain models and is being optimized as a potential post-surgical pain relief treatment, with risk for abuse and addiction.



P07 | Enhancing Intracellular Delivery of the Protein Kinase C Beta II Peptide Inhibitor Through N-Terminus Conjugation of Myristic Acid and Trans-Activator of Transcription to Attenuate Rat Polymorphonuclear Leukocyte Superoxide Release

Jennifer Dang[1], Alexandra Barrera[1], Emily Andrews[1], Arjun Nair[1,2], Devani Johnson[1], Juliet Melnik[1], Mai An Le[1], Qian Chen[1], Robert Barsotti[1], Lindon Young[1,2]

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Introduction

Protein kinase C beta II (PKCβII) activation promotes polymorphonuclear (PMN) superoxide (SO) production by phosphorylating NADPH oxidase (NOX-2) at specific amino acid residues. Cell-permeable myristic acid-conjugated PKCβII inhibitor (myr-PKCβII-; SLNPEWNET) (20 μM) significantly attenuated PMA-induced PMN SO release (~35%) compared to controls, suggesting improved intracellular delivery. Similarly, trans-activator of transcription (Tat)-conjugated/NOX-2 inhibitor ([H]- RKKRRQRRR-CSTRRRQQL-NH2) (80 μM) attenuated PMN SO release (~37%). However, the effectiveness of Tat- or dual myr-Tat-conjugated PKCβII- remains unexplored. We hypothesize that dual myr-Tat conjugation will enhance PKCβII- delivery and reduce PMN SO release more effectively than myr-, Tat-, and myr-Tat-PKCβII- scram (WNPESLNTE).

Methods

Sprague-Dawley (SD) male rats (~400g) were anesthetized, administered a 0.5% glycogen injection, and after 16-18 hours, PMNs were harvested and incubated with 5μM myr-Tat-PKCβII-, myr-PKCβII-, Tat-PKCβII-, or myr-Tat-PKCβII- scram. PMN SO release was measured spectrophotometrically by a change is absorbance at 550 nm after PMA stimulation for 420sec. Thereafter, cell viability was determined by trypan blue exclusion (0.2%). Data were analyzed with ANOVA Fisher's PLSD post-hoc analysis.

Results

Results showed myr-Tat-PKCβII- ($n=20$, 0.338 ± 0.024, $p<0.05$) and myr-PKCβII- ($n=8$, 0.342 ± 0.041, $p<0.05$) significantly reduced SO release by 28% and 27%, respectively, compared to DMSO control ($n=81$, 0.470 ± 0.013). Tat-PKCβII- ($n=5$, 0.404 ± 0.049) and myr-Tat-PKCβII-scram ($n=3$, 0.542 ± 0.081) was not significantly different compared to controls. Cell viability was >85% in all groups.

Conclusion

Results suggest enhanced intracellular delivery of PKCβII- cargo with myr or myr-Tat when compared to controls. Future studies will use western blotting and immunohistochemistry to further explore PKCβII- translocation and activity.

P08 | Structural Modifications Allow the Removal of Melanocortin Receptor 1 Agonism from Melanocortin Receptor 4 Agonists

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The melanocortin pathway regulates energy balance, and the melanocortin receptor 4 (MC4R) gene is the most commonly associated gene found in childhood obesity. MC4R plays an important role in food intake behavior and energy homeostasis via the binding of its endogenous agonist α-melanocyte–stimulating hormone, whose release is stimulated by leptin. Setmelanotide, an MC4R agonist, is approved by the US FDA for chronic weight management in adults and children ≥6 years of age with genetically linked obesity. Activating the MC4R pathway is potentially a treatment option for general obesity.

Identifying a selective MC4R agonist that minimally activates melanocortin receptor 1 (MC1R) has resulted in the discovery of new MC4R agonists of increasing selectivity as shown in the table below.

Agonist	MC1R EC50 (Emax)	MC4R EC50 (Emax)	MC4R Selectivity[b]
Bremelanotide[a]	0.23 nM (91.8%)	5.01 nM (91.0%)	0.05
1	30.2 nM (78.5%)	4.99 nM (88.3%)	6.05
2	199.6 nM (98.8%)	2.99 nM (107.4%)	66.76
3	69.1 nM (89.9%)	0.74 nM (94.9%)	93.38
4	352.3 nM (32.5%)	9.69 nM (90.5%)	Undefined*

[a]Approved for treatment of acquired, generalized hypoactive sexual desire disorder in premenopausal women. [b]MC1R EC50/MC4R EC50. ccAMP expression was too low to allow the compound to be defined as an MC1R agonist. [c]cAMP, cyclic adenosine monophosphate; EC50, half maximal effective concentration; Emax, maximum effect; MC1R, melanocortin receptor 1; MC4R, melanocortin receptor 4.

The development of these more selective MC4R agonists potentially further improves treatment options for obesity and may help avoid side effects of MC1R stimulation, such as stimulation of eumelanin production.

P09 | The Helminth Defense Molecules: A First-In Class Family of Immue-Regulatory Peptides

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The Helminth Defense Molecules (HDM) are a family of immune regulatory peptides exclusively expressed by trematode worms. We have previously demonstrated that in vivo FhHDM-1, archetypal member of the HDMs, regulated macrophage responses to inflammatory ligands, thereby ameliorating the progression of immune-mediated tissue damage in several murine models of inflammatory disease. Accordingly, we postulated that an understanding of the structure-function relationship of the HDMs would facilitate the design of highly efficacious biotherapeutic peptides. Using a combination of bioinformatics, structural analyses, and cellular assays we have now identified the minimal bioactive peptide (40 amino acids) derivative of FhHDM-1 that regulates macrophage activation. This peptide, termed FhHDM-1.C2, contains a five amino acid motif at its N-terminus, which facilitates cellular interaction and uptake, and an amphipathic □-helix within the C-terminus, which is necessary for lysosomal vATPase inhibitory activity, with both regions linked by a short unstructured segment. A readily synthesisable FhHDM-1.C2 peptide exhibits enhanced regulation of macrophage function, compared to the full-length FhHDM-1, and potent prevention of the progression of relapsing-remitting-experimental autoimmune encephalomyelitis (EAE) when administered prophylactically or therapeutically. The protective effect of FhHDM-1. C2 is not associated with global immune suppression, which places the HDMs peptides as an improved class of biotherapeutics for the treatment of inflammatory diseases. Comparing the HDMs from several zoonotic trematodes revealed a similar capacity for immune regulation. These important new advances into the structure-function relationship of the lead HDM peptide, FhHDM-1, encourages further prospecting and screening of the broader trematode family of peptides for the discovery of novel and potent immune-biotherapeutics.

P10 | A Snake Peptide Toxin for Treatment of Kidney Diseases. From Bench to, Hopefully, Bedside

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The kidney regulates many physiological roles like water homeostasis, expertly managed by the vasopressin type 2 receptor (V2R). Positioned within the kidney's collecting tubule, this membrane receptor responds to the peptide hormone, the vasopressin. The V2R activation triggers the generation of the secondary messenger cyclic adenosine monophosphate (cAMP). cAMP induces urine concentration in alignment with the body's requirements.

Two pathological conditions, hyponatremia and polycystic diseases are addressed by blocking the V2R and since the 1980s, pharmaceutical enterprises developed the "vaptans". Regrettably, the majority of vaptans exhibited hepatotoxicity concerns, and only the tolvaptan (Otsuka Pharma) is used but with many concerns, leaving millions of untreated patients.

Animal venoms are an extraordinary source of potent and natural peptide toxins. A comprehensive screening of venoms against the V2R led to the revelation of a novel cluster of snake toxins within the Kunitz-type peptide family. Among these, the MQ1 toxin emerged as a standout due to its remarkable pharmacological properties. Evaluation within rodent models of hyponatremia and polycystic diseases revealed its promise. Subsequent efforts involved refining the MQ1's characteristics in term of risk of immunogenicity and affinity. The generated MQ232, a 57 residues peptide reticulated by 3 disulfide bridges and produce by solid phase synthesis, boasts a therapeutic window of over 100. With all the hallmarks of a groundbreaking solution, MQ232 is poised to address unmet medical needs.

Embarking on the path to clinical validation, the startup V4Cure, specializing in leveraging animal toxins within the cardio-renal axis, supports MQ232 into human assessment.

P11 | Development of Greener Synthesis and Purification Solutions to Prepare for the New Era of Peptide Therapeutics

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Peptide manufactures have seen massive scale ups in response to the tremendous success of semiglutides in the pharmaceutical sector. Unfortunately, to accommodate the market demand, the production of peptide therapeutics is resulting in a heavy environmental burden. Peptide production is inherently hazardous, with 1) the use of toxic solvents, including N,N-dimethylformamide (DMF), which has recently been banned in the EU, and 2) high volumes of toxic waste, with the majority of solvent usage consumed by HPLC purification. Here we aim to improve the environmental impact of both peptide synthesis and purification, while not compromising on efficiency and purity. In collaboration with Gyros Protein Technologies, the Papini's PeptLab group at the University of Florence validated numerous green solvent alternatives to DMF. These were based on reagent boiling point, solubility, resin swelling and efficiency to mediation amide bond formation. Results of this study demonstrated there was no universal solution, but rather, binary combinations were optimized for a given operation e.g. deprotections vs washes. Additionally, depending on temperature, from 25°C, 50°C and 90°C, different binary combinations were found to produce comparable crude purities to that of challenging peptides made with DMF. Having substituted greener solvents in the first stage of peptide production, we then aimed to reduce solvent consumption during peptide purification. Using our catch and release PurePep Easy Clean purification technology, we could reduce the waste typically generated by iterative HPLC runs, by over 70%. Overall, this work shows we can improve the environmental impact of manufacturing therapeutically relevant peptides, by combining green solvents on the PurePep Chorus and PEC purification.

P12 | Glycopeptide Drugs: CNS Drugs from Endogenous Neurotransmitters

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Glycosylating neuropeptide drugs involves attaching sugar molecules to neuropeptides to enhance their stability, bioavailability, and receptor interaction. This modification can alter the pharmacological properties of the peptides, potentially improving treatment for neurological conditions by increasing drug efficacy and reducing degradation, as seen in research with various glycosylated neuropeptide analogs studied in vitro and in vivo. Here, we present therapeutic glycopeptides related to Pituitary Adenyl Cyclase Activating Peptide (PACAP), Endomorphin I, Oxytocin, and Angiotensin1–7. Endogenous peptide hormones modulate diverse physiological processes, including cell proliferation and development, and may be upregulated after injury to repair neurons and promote neurite extension, or to act on immune cells and modulate inflammatory response. Because of these pleiotropic, protective effects, many groups have evaluated the therapeutic effects of neuropeptides on neurodegenerative diseases such as Parkinson's Disease, Vascular Dementia, as well as injuries related to Traumatic Brain Injury and Stroke. Other peptides act as neurotransmitters and can affect the perception of pain and behavior. Here, we modified each of the peptides and glycosylated (with 3 – 5 different moieties) them and measured their half-life in serum. Additionally, the blood-brain barrier (BBB) penetration as measured by microdialysis with LC-MS was increased with the glycosylation as well. We measured receptor binging for the modified peptides as well. This general strategy of glycosylation of the endogenous peptides causes an increase in half-life and BBB penetration making them potential CNS drugs.

P13 | Control Strategies and Method Development for Nitrosamines in Peptide APIs and Drug Products

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Overview

For late-phase drugs, risk assessments for nitrosamines have become an important supplement for filings with both the FDA and EMA, as well as other regulatory agencies. When these assessments propose a potential risk, even if low risk, a robust testing strategy is required to demonstrate compliance with the issued guidance.

- What are the technologies used for nitrosamine testing?
- How do we establish/validate methods for screening and for routine analysis of nitrosamines?
- What are the challenges associated with nitrosamines method development?
- Strategies for establishing test methods for drug-derived nitrosamines
- Case studies for drug-derived nitrosamines

Nitrosamine Control

Nitrosamine impurities Guidance (FDA and EMA) specifies

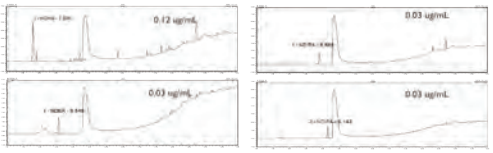
- Very low limits for the typical nitroso impurities individually.
- Total nitrosamines must be no more than the limit for the lowest acceptable intake.
- Product-specific nitroso impurity limits (NDSRIs) can vary, especially if structure-activity-relationship data is available.
- The recommended limit is calculated based on Carcinogenic Potency Categorization Approach (CPCA) risk scoring.

Nitrosamine Impurity	Acceptable Intake Limit	Example Limit for a drug with Max Daily dose (in ppm)	
	(ng/day)	200 mg/day	1,500 mg/day
NDMA (Nitrosodimethylamine)	96	0.48	0.06
NDEA (Nitrosodiethylamine)	26.5	0.13	0.02
NEIPA (Nitrosoethylisopropylamine)	26.5	0.13	0.02
NMBA (Nitrosomethylaminobuytric acid)	96	0.48	0.06
NDIPA (Nitrosodiisopropylamine)	26.5	0.13	0.02
NDBA (Nitrosodibutylamine)	26.5	0.13	0.02
NMPA (Nitrosomethylphenylamine)	26.5	0.13	0.02
Product Specific Nitrosamine	18 – 1500	0.09	0.01

Method Considerations

- Generally, sensitive methods with **limits of quantitation (LOQ) in the parts-per-billion (ppb) range** are needed to meet the low AIs recommended for nitrosamines.
- **Target LOQ** should be 10% of the limit (to justify no routine testing) or 30% of the limit (to justify skip lot testing).
- Testing is typically achieved through **GC-MS or LC-MS/MS**.
- **High-Res Mass-Spec applications** are useful for drug-derived nitroso impurities.
- A robust screening process is created by setting up a set of platform methods by validating orthogonal methods across these technologies.

A platform **GC-MS method** can be a fast and robust option for **smaller nitrosamines** (NDMA, NDEA, NDIPA, NEIPA)



Method Development typically takes ~2 weeks to optimize for accuracy and precision in the specified API matrix and 1-1.5 weeks to validate.

- **Pros**: Minimize sample matrix interference, Flexibility in sample preparation
- **Cons**: Sample concentrations are generally higher as sensitivity is not as low as LC-MS. Potential for *in situ* nitrosamines depending on the sample matrix

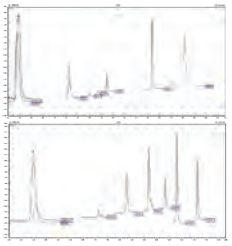
A Platform **LC-MS/MS methods** can be used for the wider complement of nitrosamines

This method is established across two orthogonal columns (Thermo Hybercarb and Hypersil GOLD Phenyl)

Method Development typically takes ~2-4 weeks, as matrix-related effects are challenging to control, and 2-3 weeks to validate.

- **Pros**: Easier to optimize sensitivity and specificity. Lower Sample concentrations
- **Cons**: Sample matrix-related issues can be challenging, (solubility and interference).

LC-MS/MS Sensitivity			
Nitrosamine	Chemical Name	Detection Limit (ng/mL)	Quantitation Range (ng/mL)
NDMA	N-Methyl-N-nitrosomethanamine	0.04	0.08 - 2.0
NDEA	N-Ethyl-N-nitrosoethanamine	0.02	0.04 - 1.0
NMBA	4-[Methyl(nitroso)amino] butanoic acid	0.02	0.04 - 1.0
NDIPA	N-Isopropyl-N-nitrosoisopropylamine	0.02	0.04 - 1.0
NEIPA	N-Ethyl-N-nitroso-2-propanamine	0.02	0.04 - 1.0
NDBA	N-Butyl-N-nitroso-1-butanamine	0.02	0.04 - 1.0
NMPA	N-Methyl-N-nitrosophenylamine	0.02	0.04 - 1.0



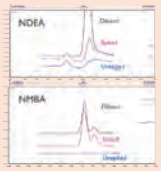
Sensitivity (LOD and LOQ)

Analyte	LOQ	LOQ S/N	LOD	LOD S/N
NDMA	1.5 ng/mL	100	0.75 ng/mL	93
NDEA		42		24
NEIPA		25		8
NDIPA		30		10

Accuracy and Precision

Analysis	Test	Level NDMA, NDEA, NEIPA, NDIPA	API Result	Drug Product Result
Accuracy	%Recovery 50-150%	0.24 / 0.06 ppm	89-139%	79-148%
		2.4 / 0.6 ppm	96-109%	85-89%
		3.6 / 0.9 ppm	100-113%	89-97%
Precision	NMT 25% RSD	0.24 / 0.06 ppm	14-25%	8-10%
		2.4 / 0.6 ppm	1-3%	2-7%
		3.6 / 0.9 ppm	1-3%	3-6%

Case Study 1: Bradykinin, a 9 AA peptide



Orthogonal methods on LC-QQQ

Spiked recoveries from sample matrix as expected for all screened nitrosamines except two, NDEA, and NMBA (using Hypersil method)

- NDEA recovery issues due to coelution with API, resolved using an orthogonal method (Hypercarb)
- NMBA issues are matrix/diluent-related effects. All injections after samples, including bracketing standards, show a ~2x response. Further development for NMBA is needed, specifically evaluating sample prep and diluent additives

Case 1: Bradykinin Screening		
Nitrosamine	Recovery (%) Hypersil	Recovery (%) Hypercarb
NDMA	92	93
NDEA	30	93
NDBA	90	71
NDIPA	94	91
NEIPA	92	92
NMBA	200	170
NMPA	105	83

Case Study 2: Method for API and Drug Product

LCMS

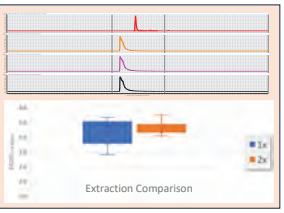
- **Poor DP solubility** due to excipients,
  - Slurry extraction from the excipients matrix is efficient, with good recovery for nitrosamines (in the absence of API).
- API no solubility issues with aqueous/formic acid yet, API coeluted with multiple nitrosamines, impacting recovery
- Various orthogonal LCMS methods were evaluated; coelution continued to be an issue
- Switched to GCMS, dissolved in aqueous, and extracted to DCM;

Matrix-related interference issues were resolved.

Case 2: Screening				
Nitrosamine	Recovery (%) LCMS		Recovery (%) GCMS	
	API	DP	API	DP
NDMA	<50%	<50%	96	89
NDEA	<50%	<50%	96	87
NDIPA	<50%	<50%	109	88
NEIPA	<50%	<50%	109	85

Case Study 3: NDSRI Method for API and Drug Product

- **Tablets don't dissolve** in common diluents, extraction in Methanol/Formate Buffer mixture
- NDSRI coelutes with API, baseline resolution of API from the nitroso impurity failed.
- With **QTOF**, leveraged mass resolution to quantify nitroso API, with relatively narrow mass filter (± 0.0025 m/z). Clean instrument and good tune required for accurate analysis.
- Extraction efficiency was demonstrated through increasing volume studies (1x vs 2x) demonstrating adequate recovery of NDSRI



NDSRI could be quantified

Summary

Nitrosamines present an analytical challenge requiring highly sensitive and robust methods. This can only be achieved via MS techniques, such as GC-MS, High-Resolution LCMS and LC-MS/MS.

Platform Methods for typical nitrosamines can be established based on current FDA/USP methods

- Once an accurate and sensitive method is established, chromatography development can be minimal.
- Challenges remain for individual sample matrices as composition of API and Drug Product, solubility, structural similarities to impurities will all play a factor.
- Having orthogonal separations pre-developed can assist in rapid screening for impurities and accelerate the development and validation process.
- Nitrosamine Drug Substance Related Impurities (NDSRI) need high-res MS and MS/MS as a primary testing strategy
- Single Reaction Monitoring and Fragmentation can provide clarity on the identity of impurity peaks observed with masses consistent with NDSRIs.

P14 | Novel Approach in the Treatment of Anaplastic Thyroid Cancer Using EGFR- and PIP3-Targeted Synthetic Peptides to Inhibit the PI3K/AKT/mTOR Signaling Pathway

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Although rare, anaplastic thyroid carcinoma (ATC) represents the most aggressive and deadliest TC in humans. The overall survival of patients with ATC is about 4 months following diagnosis. Nowadays, this malignancy has no known effective cure. With a high morbidity rate and the paucity of treatment options, it is crucial to investigate novel therapeutic approaches. Mainly dysregulated signaling pathways in ATC are those of MAP kinase and PI3K/AKT/mTOR (PAM).

The proposed peptide-based targeted therapy is developed in our lab and aims to inhibit the aberrant PAM pathway, essentially responsible of cell division, growth and survival. EGFR overexpression and overactivation in oncologic processes and its endocytosis represent a driving element in our strategy, whereas phosphatidylinositol (3,4,5)-trisphosphate (PIP3) represents the therapeutic target due to its involvement in PAM triggering and cell survival.

In this context, an EGFR-targeted peptide (vector peptide, VP) was coupled to a PIP3targeted therapeutic peptide (TP) via a scaffold molecule in a peptide complex (PC) to enable specific drug delivery to ATC cells. Once associated with EGFR, PT is endocytosed and induces apoptosis specifically in cancer cells by targeting intracellular PIP3.

The molecular mechanism of PV binding to EGFR has been analyzed *in silico* by peptide-protein docking studies using the HPEPDOCK web server. VP has a long half-life and binds to the interface between domains I and III of EGFR, in the large hydrophobic pocket exposing the binding sites to EGF. VP is endocytosed independently of the EGF presence and without activating the EGFR. Within cells, VP is colocalized with EGFR, following its trafficking pathway. Moreover, 10 µM of PC induces cell apoptosis after 1h of incubation. To conclude, our studies confirmed that VP is a good EGFR-targeting candidate to deliver TP to cancer cells.

P15 | Harnessing the Melanocortin System to Heal Inflammatory Diseases

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Palatin Technologies, Inc., Cranbury, NJ

The melanocortin receptor 1 (MC1R) is key to the innate system that returns tissue-based cells and the immune system to homeostasis from the inflamed state. To create therapeutic candidates to exploit this, 3 peptides were designed to agonize MC1R. Two are in clinical trials (PL9643 for dry eye disease [DED] and PL8177 for ulcerative colitis [UC]). The third (PL9654) has been characterized in multiple retinal disease models.

In a pivotal phase 3 study (MELODY-1) of an ophthalmic solution of PL9643 in participants with DED, the efficacy results were statistically significant vs vehicle for the coprimary endpoint of pain ($P<0.025$) and 7 of 11 exploratory endpoints ($P<0.05$), including eye dryness, as early as 2 weeks. Importantly, PL9643 has an excellent safety and tolerability profile.

Oral PL8177 is currently in a double-blind, placebo-controlled phase 2 study evaluating its safety, tolerability, and efficacy for UC, with intermediate readout expected 4Q2024. In a rat model, oral PL8177 significantly improved the total colitis index. Histopathology showed PL8177 maintained colon structure and barrier and reduced immune cell infiltration. snRNAseq analysis demonstrated changes consistent with disease modification following treatment, including a shift in macrophage state from the pro-inflammatory M1 phenotype to an anti-inflammatory M2 state.

Subcutaneously and topically administered PL9654 was investigated in rat models of diabetic retinopathy and showed significant efficacy in reducing contrast vision loss vs vehicle. Histopathology showed less photoreceptor degeneration, improved retinal thickness, and maintenance of the blood-retinal barrier. snRNAseq showed molecular-level changes consistent with disease modification, including negative enrichment of inflammatory pathways.

P16 | Protein Kinase C Delta Peptide Activator Provides Protection During Hypoxia/Reoxygenation and Elicits Significant Anti-Cancer Effects in Vitro

Juliet Melnik[1]; Qian Chen[1], Robert Barsotti[1], Lindon Young[1,2]

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Introduction

Protein kinase C delta (PKCδ) activation is known to inhibit NOX-2/superoxide (SO) release in polymorphonuclear leukocytes (PMNs) and elicit cardioprotective effects in ischemia-reperfusion (I/R) injury. Augmenting PKCδ activity also promotes tumor suppressive effects via apoptosis. This study examined the cardioprotective and anticancer effects of PKCδ peptide activator (PKCδ+) in endothelial cells and cardiomyocytes, cardiovascular cells susceptible to oxidative damage.

Methods

Hypoxia/Reoxygenation(H/R): Human umbilical vein endothelial cells (HUVECs) and rat cardiomyocytes (H9C2 cells), were pretreated with PKCδ+ (N-Myristic acid+MRAAEDPM) (0.25-5μM) or untreated control for 37 mins, prior to H(24hr)/R(24hr). Anti-Cancer: Human breast cancer (MCF7) cells were treated with PKCδ+ (0.5-20μM) or untreated control for 37 mins. Cell viability was assessed by light microscopy and spectrophotometric analysis using a cell counting kit. Absorbance data were analyzed using student t-test.

Results

Pretreatment with PKCδ+ (0.25-4 μM) improved H9C2 and HUVECs cell viability, with significant improvement of HUVEC viability (1μM, 0.4±0.03; n=5, $p<0.05$) vs control (0.26.±0.04, n=5). PKCδ+ dose-dependently promoted MCF7 cell death at 20μM 0.33±0.03; n=5, $p<0.05$ compared to controls (0.49±0.02, n=5).

Conclusions

Lower doses of PKCδ+ provide cardioprotection during H/R, while higher doses are more effective at providing anti-cancer effects. Optimizing dosing for tumor suppression and I/R tissue preservation could make PKCδ+ an attractive clinical drug.

P17 | Making Waves in GLP-1 Characterization: Solving Isomer Challenges with High Resolution Ion Mobility

Ashli R. Simone, Greg Kilby
MOBILion Systems

Isomeric GLP-1 impurities such as D-amino acid substitutions or isomerization of Asp to isoAsp are difficult to resolve or missed by conventional LC-UV or MS characterization due chemical similarity. They often exhibit limited shifts in retention time and are undetectable by mass shifts unsuspectingly presenting as pure peaks. High resolution ion mobility-MS (HRIM) is used with LC to provide an orthogonal separation improving the specificity of detection by separating based on the shape of the peptide permitting isomeric discrimination. The GLP-1 market is expected to surpass $100 billion dollars in revenue by 2030 and demands for these materials are ever increasing. Strategies must be employed to keep up with the demands. A sub-3 min HRIM-MS screening method permits the separation of the GLP-1 API, semaglutide, from isobaric impurities reducing the burden of lengthy LC methods. The limit of detection, linearity of response, and identification by collision cross section of semaglutide are also demonstrated.

P18 | Hydrophobic Modifications to a Cationic Amphiphilic Polyproline Helix (CAPH) Scaffold Improves Cell Uptake and Targeting of Intracellular Pathogenic Bacteria

Zachary St. John[1], Thomas Dietsche[1], Nader Abutaleb[2], Mohamed Seleem[2], Jean Chmielewski[1]

[1]Purdue University, Department of Chemistry

[2] Virginia Tech, Department of Biomedical Sciences and Pathobiology

With the rise of resistant strains, it is projected that bacterial infections will become a leading cause of death worldwide by the year 2050.1 Thus, there is an urgent need to develop new antibiotics that aim to overcome acquired resistance mechanisms. One manner by which bacterial pathogens can evade drug treatment is by forming intracellular reservoirs, thereby limiting the efficacy of antibiotics that lack cell permeability.2 In this study, hydrophobic modifications to a cationic amphiphilic polyproline helix (CAPH) were introduced to determine their effects on cell uptake and bacterial clearance. Flow cytometry and confocal imaging were performed on HeLa cells to compare uptake efficiency and subcellular localization of the synthesized CAPHs. The peptides along with control antibiotics were screened against a variety of bacterial strains and MIC values were determined. Lastly, the hydrophobically modified CAPHs were tested in an infection model with murine macrophage J774A cells that were infected with either MRSA or S. enterica. In comparison to the control antibiotics and CAPH peptide lacking hydrophobic modification, the newly synthesized CAPHs showed superior cell uptake and ability to eliminate intracellular pathogens, highlighting the benefit of this structural optimization campaign. Considering the unique design and activity of these CAPHs, this work will inspire further efforts in the development of peptide-based antibiotics capable of circumventing bacterial resistance.

References:

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2. Kuriakose, J.; Hernandez-Gordillo, V.; Nepal, M.; Brezden, A.; Pozzi, V.; Seleem, M. N.; Chmielewski, J. Targeting Intracellular Pathogenic Bacteria with Unnatural Proline-Rich Peptides: Coupling Antibacterial Activity with Macrophage Penetration. Angew. Chem. Int. Ed. 2013, 52 (37), 9664–9667.

P19 | Feasibility of an Electrochemiluminescence Assay to Detect Antibodies Against Therapeutic Peptides

Ruoxuan Sun, Janey Ronxhi, Xuemei Yang, Mark G. Qian, Xiaobin Zhang
Global Drug Metabolism, Pharmacokinetics & Modeling, Preclinical & Translational Sciences, Takeda Development Center Americas, Inc., Cambridge, MA, USA 02139

The emergence of anti-drug antibodies (ADAs) elicit significant impacts to the bioactivity and toxicity of biotherapeutics. Developing reliable assays to monitor the magnitudes of ADAs in blood samples, therefore, represents a crucial task in animal and human studies throughout the development of biotherapeutics. Peptides represent a significant and fast-growing category of biotherapeutics for the management of a variety of disorders. While peptides generally exhibit lower immunogenicity compared to large molecules, drug developers are still required to conduct the risk-based immunogenicity assessment as mandated by the regulatory authorities. To streamline the development and validation of ADA assay for peptide therapeutics, we hereby developed and qualified an electrochemiluminescence immune assay (ECLIA) based on direct binding strategy to detect ADAs against peptides. Our assay demonstrates its effectiveness across various peptide therapeutics ranging from marketed product semaglutide to our internal investigated candidates T1 and T2. The sensitivity estimated according to a provisional screening cut point at 2.00 was under 100 ng/ml which meets FDA's requirement. In addition, we identified key factors such as buffer, detection reagent and plate type which collectively defines the assay performance. We managed to present a valuable tool to expedite the development and validation of ADA assays for peptide-based therapeutics, and it can be converted, without major modifications, to adapt various matrices as needed.

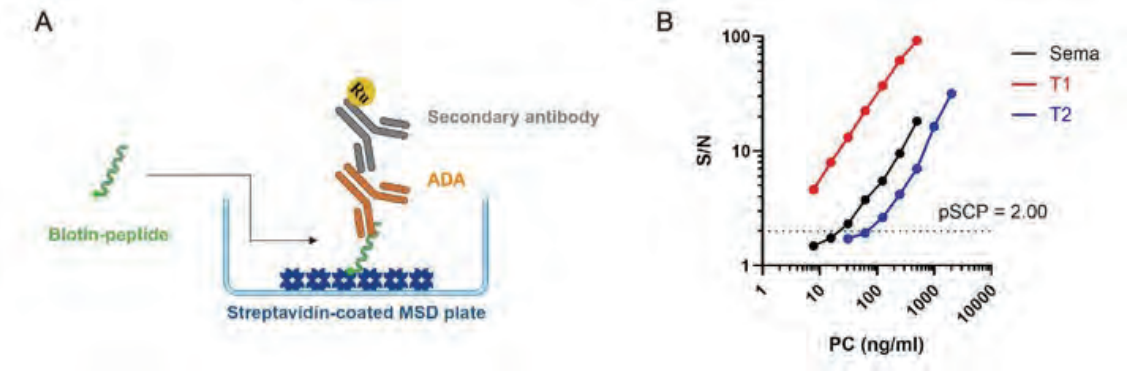

Figure. The overview of assay design and performance. (A) The schematic flow of the direct binding assay format. (B) The sensitivity curve of semaglutide (Sema), T1 and T2 in human plasma. Designated positive control antibodies were used for each drug. A provisional cut point factor (pSCP) at 2.00 was applied to estimate the assay sensitivity.

P20 | DNA-Encoded Librairies and Display Technologies Empower Early Discovery of Peptide Drugs and Peptide-Based Delivery Tools

Rhys Taylor
WuXi AppTec

Peptide therapeutic discovery is experiencing a resurgence, particularly for challenging, historically “undruggable” targets. WuXi AppTec is leading the way in this field with cutting-edge technologies and platforms. Traditional phage display, while cost-effective and providing substantial library diversity, is limited by its reliance on only the 20 natural amino acids, resulting in restricted chemical diversity. In response, we have developed our mRNA display capabilities, which surpasses phage display in robustness with macrocycles up to 15 amino acids long. Currently, this service uses only natural amino acids, but we plan to incorporate unnatural amino acids starting in 2025.

Additionally, our peptide DNA-encoded library (DEL) service provides an alternative approach, leveraging unnatural amino acids to generate hundreds of billions of linear and cyclic peptide-like molecules. These DEL macrocycles offer broader chemical diversity and improved physicochemical properties compared to traditional peptide libraries, with smaller ring sizes (6-9 amino acids) and innovative cyclization strategies, including the ‘click’ reaction. Conversely, we can also design a focused peptide-DEL library based on an initial phage or mRNA-Display screen with up to 4 sites to include any of our 1400+ validated natural and unnatural amino acids. The DEL platform also enables the use of diverse cyclization strategies beyond disulfide and thiol-ether bonds, such as the ‘click’ reaction, which we used to produce our current libraries. In our poster we demonstrate the effectiveness of our DEL technology for discovering macrocyclic peptides.

P21 | Combining Advanced Peptide Screening Methods to Identify Candidates for PDC/RDC/POC Development

Dr. Weiliang (Timo) Xu, Dr. Jin Zhang
PepLib, One Beacon St., 15th Floor, Boston, MA 02108

Peptide-based therapeutics, including peptide-drug conjugates (PDCs), peptide-radionuclide conjugates (RDCs), and peptide oligonucleotides (POCs), are gaining recognition as highly promising targeted treatment options due to their exceptional specificity, low toxicity, and flexible pharmacokinetic profiles. To expedite the identification of effective peptide candidates, we have developed an advanced peptide discovery platform that combines Peptide Information Compression Technology (PICT), Disulfide-Rich Peptides (DRPs) phage display, animal toxin libraries, nano macrocyclic peptides, and virtual peptide libraries. This cutting-edge platform efficiently discovers multicyclic peptide hits with antibody-like binding affinity (sub-nM to pM), enhanced serum stability (lasting from hours to days), and bi-functional properties optimized to engage multiple receptor targets within a six-month timeframe.

Our integrated screening approach employs high-throughput techniques to swiftly identify peptide leads that meet the stringent criteria required for PDC, RDC, and POC development. We have successfully discovered peptide leads with high binding affinity and endocytosis on over 40 targets, including FAP, Nectin-4, Trop2, GRPR, FGFR2, GPC3, DLL3 and TSLPR. The platform's combination of diverse peptide libraries and sophisticated computational modeling enhances the selection of candidates with superior binding affinities, structural stability, and functional adaptability. By leveraging these advanced screening technologies, we address the limitations of traditional peptide discovery methods, shortening development timelines and reducing the reliance on extensive medicinal chemistry optimization.

Our findings illustrate that this platform significantly streamlines the discovery process for peptide-based therapeutics, establishing a powerful pipeline for the development of next-generation bi-functional peptides with broad applications in oncology, inflammation, and other therapeutic areas.

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