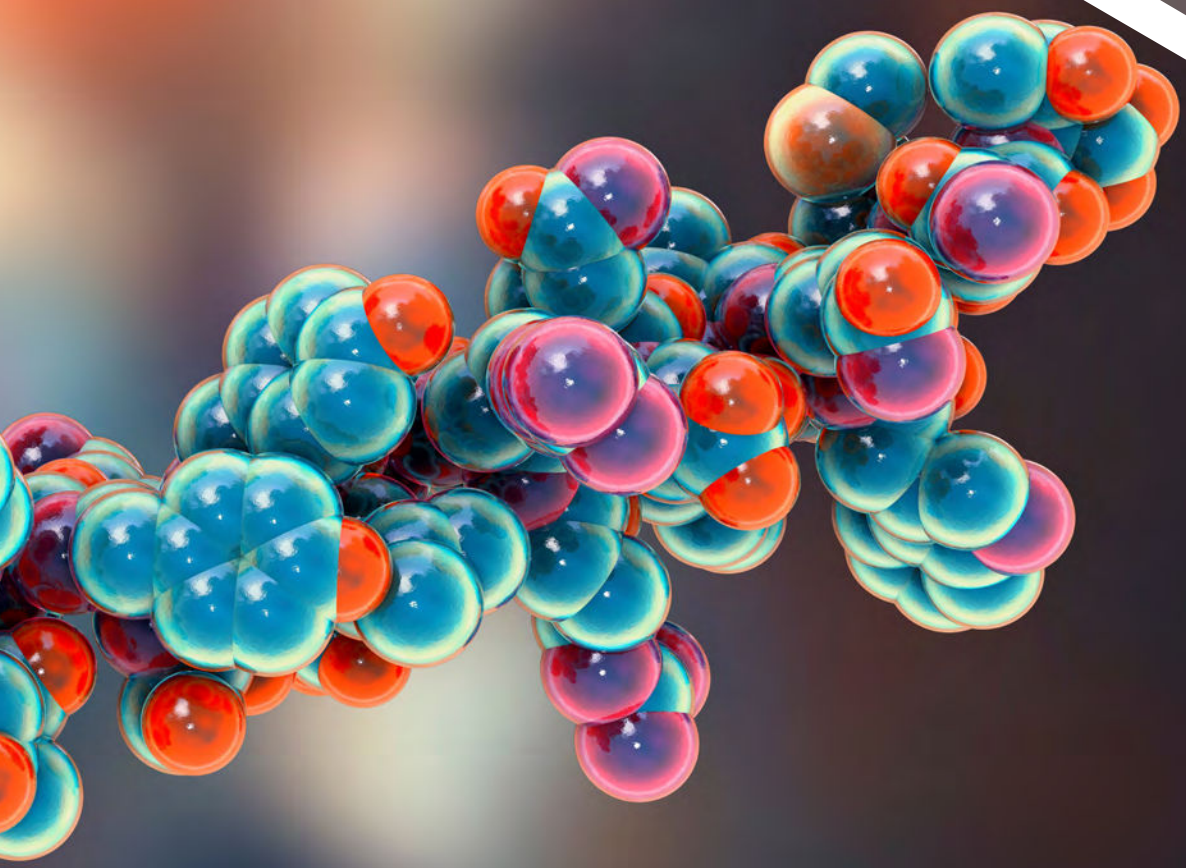
Program and Proceedings

17th Annual
Peptide Therapeutics Symposium

October 20 - 21, 2022
Salk Institute for Biological Sciences
La Jolla, California
www.peptidetherapeutics.org

PEPTIDE
THERAPEUTICS
SYMPOSIUM



17th Annual Peptide Therapeutics Symposium

October 20 - 21, 2022

Salk Institute for Biological Studies, La Jolla, CA

Virtual and In-Person Meeting

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2022 Travel Grant Awardees

Khushbu Bhakta, Chapman University School of Pharmacy
Maj Krumberger, University of California, Irvine
Tahmina Ahmed Milly, Department of Chemistry, University of Nevada
Jonathan Moreno, Chapman University School of Pharmacy
Chelsea Marie Parrocha, University of California, Irvine
Brooke Van Engen, Department of Chemistry, Dordt University
Alexis Verwoert, Philadelphia College of Osteopathic Medicine

Symposium Sponsors

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17th Annual Peptide Therapeutics Symposium

Dear Colleagues,

The Peptide Therapeutics Foundation and its sponsors welcome you to the 17th Annual Peptide Therapeutics Symposium. The hybrid format of the symposium will take place over two days and has been scheduled to align with the time zones of the speakers. Our goal is to present new advances and discoveries in the field of peptide-based 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 Thursday with two plenary lectures. The first from Hiroaki Suga, will discuss the advent of the RaPID in vitro peptide display methodology and the latest advances towards the display of pseudo-natural products. Samir Mitragotri will then present the concept of ionic liquids and how they can be used for the delivery of peptides and proteins across biological barriers. The following session will feature state-of-the-art talks on a long-acting relaxin molecule, and a novel GIP antagonist/GLP-1 agonist for obesity.

After lunch we will celebrate the 70th birthday and lifetime of scientific achievements of Dr. Richard DiMarchi. A session in honor of Richard will include two former colleagues discussing insulin, incretins and other hormones and their impact in the treatment of various medical conditions. We encourage you to join us for the afternoon poster presentations and the opening reception that will immediately follow.

The program continues on Friday morning with plenary lectures from Alan Saghatelian and Roger Cone, highlighting the discovery of novel endogenously expressed peptides and the biology and chemistry surrounding the famous MC3 and MC4 receptors, respectively. The remainder of the day consists of sessions on peptide therapeutic development programs and peptide methodologies.

The Whova interactive meeting platform will allow all attendees to connect directly with colleagues, poster presenters, and speakers. The taped presentations will be available for viewing for 60 days following the close of the meeting. You may use the Q&A function within the virtual platform to ask questions for the speakers, should they not have time to answer them during the live Q&A.

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

Sponsors, Peptide Therapeutics Foundation

AstraZeneca
Ferring Research Institute Inc.
Novo Nordisk
Neurocrine Biosciences
Takeda Pharmaceuticals
The PolyPeptide Group
Zealand Pharma

17th Annual Peptide Therapeutics Symposium

Foundation Sponsors

AstraZeneca

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

Ferring Research Institute, Inc.

Headquartered in San Diego, California, Ferring Research Institute, Inc., (FRI) is the research and ideas incubator of Ferring Pharmaceuticals. Established in 1996, FRI is located in the heart of the Southern California biopharmaceutical community. The center has attracted a diverse group of highly skilled professionals representing over twenty-four countries of origin. FRI is our key research center for early research and development. Here, our scientists work on small molecule and peptide drug discovery, from new target identification up until early drug development phases. FRI is focused on the following key therapeutic areas: reproductive health and maternal health, uro-oncology, gastroenterology and the microbiome. Our state-of-the art facility includes small molecule, peptide and protein drug design, medicinal chemistry, pharmacology, biology, and preclinical ADME capabilities. Historically FRI has focused on the discovery of amino acid-based therapeutics utilizing the body's signaling hormones. Today FRI is committed to building a portfolio of novel, innovative therapeutics using a wide array of modalities in order to address areas of high unmet medical need in our core therapeutic areas. Driving value through personalized medicine.

About Ferring Pharmaceuticals

Ferring is a research-driven, specialty biopharmaceutical group committed to helping people build healthy families and live better lives. Ferring is a leader in reproductive medicine and maternal health, and in specialty areas within gastroenterology and urology. Ferring focuses on developing lifechanging innovations that help people live better lives. Grounded in a 70-year commitment to science and research, we are relentless in our pursuit of therapies that help people build families, stay healthy, and fight disease. Ferring has a strong global profile with offices worldwide and headquartered in Switzerland. We continue to grow through our aim of providing effective treatments for patients. Globally, we reach millions of patients across 110 countries and employ 6,000 employees worldwide. As part of its commitment to developing innovative products to treat diseases with high unmet medical need, Ferring invests heavily in its research infrastructure both in terms of people and technology.

17th Annual Peptide Therapeutics Symposium

Neurocrine Biosciences

Neurocrine Biosciences is a 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, Parkinson's disease, endometriosis* and uterine fibroids*, as well as over a dozen mid- to late-stage clinical programs in multiple 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. (*in collaboration with AbbVie).

Novo Nordisk

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

17th Annual Peptide Therapeutics Symposium

The PolyPeptide Group

The PolyPeptide Group is a privately-held group of manufacturing sites which focus on proprietary and generic GMP-grade peptides for the pharmaceutical and biotechnological market. With more than 60 years of experience, the Group is committed to the highest quality of peptide manufacturing for commercial peptide drug substances, GMP peptides in clinical trials, or small-scale non-GMP custom syntheses. The PolyPeptide Group has grown by selective acquisition of existing expertise, culminating in its position today as a leader in peptide manufacturing. The Group has manufacturing facilities in Sweden (Malmo), France (Strasbourg), India (Ambernath) and two sites in the USA (San Diego CA & Torrance CA). As a multinational company with about 520 employees worldwide, its diversity brings breadth and depth of knowledge and experience to the Group. The Group's long-established core strength in GMP manufacturing and broad range of services supports peptide & peptide-like projects, including conjugation to non-peptide moieties, from the bench through to commercialization. With continually increasing capacity for GMP manufacturing, the PolyPeptide Group is stronger and better equipped to serve the needs of its customers at all stages of pharmaceutical peptide development. With its multinational organization, strict focus on peptides and solid financial base, the Group offers an almost unique security of supply to its customers.

Takeda

Takeda is a global, values-based, R&D-driven biopharmaceutical leader headquartered in Japan, committed to discover and deliver life-transforming treatments, guided by our commitment to patients, our people and the planet. Takeda focuses its R&D efforts on four therapeutic areas: Oncology, Rare Genetics and Hematology, Neuroscience, and Gastroenterology (GI). We also make targeted R&D investments in Plasma-Derived Therapies and Vaccines. We are focusing on developing highly innovative medicines that contribute to making a difference in people's lives by advancing the frontier of new treatment options and leveraging our enhanced collaborative R&D engine and capabilities to create a robust, modality-diverse pipeline. Our employees are committed to improving quality of life for patients and to working with our partners in health care in approximately 80 countries and regions. For more information, visit https://www.takeda.com.

Foundation Sponsors

Zealand Pharma

Zealand Pharma A/S (NASDAQ OMX Copenhagen: ZEAL) ("Zealand") is a biotechnology company specialized in the discovery, design and development of peptide-based therapeutics. The company has a portfolio of medicines and product candidates under license collaborations with Sanofi and Boehringer Ingelheim and a proprietary pipeline of product candidates, which primarily target specialty diseases with significant unmet needs. Zealand is the inventor of lixisenatide, a once-daily prandial GLP-1 analog for the treatment of type 2 diabetes, which is licensed to Sanofi and marketed globally outside the U.S. as Lyxumia® and in the U.S. as Adlyxin®. Sanofi has also developed iGlarLixi, a fixed-ratio combination of lixisenatide and Lantus® (insulin glargine) marketed in U.S. as Soliqua® and Europe as Suliqua®. Zealand's proprietary pipeline includes; glepaglutide*, a GLP-2 analog for the treatment of short bowel syndrome which will initiate Phase III studies in 1H18; dasiglucagon*, a glucagon analog in Phase III as a single-dose rescue therapy for severe hypoglycemia and in Phase II as a multipledose component in a dual-hormone artificial pancreas system; and other earlier stage clinical and preclinical peptide therapeutics. The company has approximately 130 employees and is based in Copenhagen, Denmark. *Glepaglutide and dasiglucagon are proposed International Nonproprietary Names (pINNs)

We continue to grow through our aim of providing effective treatments for patients. Globally, we reach millions of patients across 110 countries and employ 6,000 employees worldwide. As part of its commitment to developing innovative products to treat diseases with high unmet medical need, Ferring invests heavily in its research infrastructure both in terms of people and technology.

Peptide Therapeutics Foundation

Peptide Therapeutics Foundation is a not-for-profit 501C (3), established in 2008 to promote research and development of peptide therapeutics. The Foundation is currently supported by five corporate sponsors; AstraZeneca, Ferring Research Institute, Inc., Novo Nordisk, The PolyPeptide Group, and Zealand Pharma. The Foundation sponsors an annual meeting, Peptide Therapeutics Symposium, which brings together world leaders from academia, the biopharmaceutical industry, CMOs, CROs, and investors interested in all aspects of peptide R&D, including drug discovery, safety and toxicology, clinical development, manufacturing, pharmaceutical development, formulation, drug delivery and regulatory affairs.

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Salk Institute for Biological Studies, La Jolla, CA

Virtual and In-Person Meeting

Thursday, October 20, 2022

7:00 a.m. - 4:15 p.m.	**Registration Check-in** Fritz B. Burns Reception Center, Lower Level
8:00 a.m. – 4:45 p.m.	**17th Annual Peptide Therapeutics Symposium** Conrad T. Prebys Auditorium
8:00 a.m. – 8:15 a.m.	**Opening Remarks** Phil Dawson, Ph.D. *Chairman of the Board, Peptide Therapeutics Foundation* *Professor of Chemistry, Scripps Research*
8:15 a.m. – 10:15 a.m.	**Plenary Lectures** **Moderator:** Tim Culbreth *President, US Operations, PolyPeptide Group*
8:15 a.m. – 9:15 a.m.	**The Next Generation of RaPID System** Hiroaki Suga, Ph.D. *Professor, The University of Tokyo*
9:15 a.m. – 10:15 a.m.	**Ionic Liquids for Delivery of Biologics** Samir Mitragotri, Ph.D. *Professor, Harvard University*
10:15 a.m. – 10:45 a.m.	**Beverage Break** Fritz B. Burns Reception Center, Lower Level
10:45 a.m. – 11:45 a.m.	**Session I** **Moderator:** Antoine Henninot *Associate Director, Takeda Pharmaceuticals*
10:45 a.m. – 11:15 a.m.	**Engineering Long-acting Relaxin ThP - AZD3427** Monika Papworth, Ph.D. *Biologics Engineering, AstraZeneca R&D*
11:15 a.m. – 11:45 a.m.	**Discovery of AMG133, a Novel GIPR Antagonist Antibody/GLP-1 Peptide Bispecific Conjugate for the Treatment of Obesity** Yuan Cheng, Ph.D. *Senior Principal Scientist, Amgen Inc*

Thursday, October 20, 2022 *continued*

11:45 a.m. – 12:30 p.m.

Poster Presentations
Moderator: Sepideh Asfar
Research Advisor and Peptide Discovery Group Leader
Eli Lilly and Company

QPG-1030, Releasable Pegylation of Teduglutide Using Uni-Qleaver® Results in Improved PK/PD Properties in Rats Aiming for Once-Weekly Administration
Supaporn Sawadjoon, *QuiaPEG Pharmaceuticals AB*

Integrated Design of a Membrane-Lytic Peptide-Based Intravenous Nanotherapeutic Suppresses Triple-Negative Breast Cancer
Charles Chen, *Department of Chemistry, King's College London*

Arginine Modifications of Bovine Lactoferricin Peptides with Cytotoxic Effect Against Colon Cancer Cell Lines
Karen Cárdenas-Martínez, *Pharmacy Department, Science Faculty, Universidad Nacional de Colombia*

Synthesis and Stereochemical Determination of Novo29, a New Peptide Antibiotic
Maj Krumberger, *University of California, Irvine*

Discovery of Macrocyclic Peptide Drug Leads by High-Throughput Functional Screening Assays
Rumit Maini, *PepLib*

XeriSol™: A Biocompatible, Non-aqueous Approach to Enhanced Peptide Solubility and Stability
Steven Prestrelski, *Xeris Pharmaceuticals, Inc.*

12:30 p.m. – 1:30 p.m.

Lunch Break
Fritz B. Burns Reception Center, Lower Level

1:30 p.m.– 3:15 p.m.

Session II: Richard DiMarchi Celebration
Moderator: Soumitra Ghosh, Ph.D.
President, Doon Associates LLC

Thursday, October 20, 2022 *continued*

1:30 p.m. – 1:45 p.m.

Introduction
Soumitra Ghosh, Ph.D.

1:45 p.m. – 2:15 p.m.

Chemical Optimization of the Pancreatic Glycemic Hormones
John P. Mayer, Ph.D.
Research Scientist, Department of Molecular, Cellular and Developmental Biology, University of Colorado

2:15 p.m. – 2:45 p.m.

From Serendipity to Rational Design: Multimodality Therapeutics for Multimorbidity Diseases
Brian Finan, Ph.D.
Vice President of Obesity Research, Novo Nordisk

2:45 p.m. - 3:15 p.m.

A Hundred Years Ago Today the Band Began to Play
Richard DiMarchi, Ph.D.
Distinguished Professor of Chemistry, Gill Chair in Biomolecular Sciences, Department of Chemistry, Indiana University

3:15 p.m. – 3:45 p.m.

Beverage Break
Fritz B. Burns Reception Center, Lower Level

3:45 p.m. – 4:45 p.m.

Poster Presentations
Moderator: Ewa Lis, Ph.D.
Founder/CEO, Koliber Biosciences, Inc.

Elucidating the Role of Quorum Sensing (QS) and Developing QS Modulators for *Streptococcus pneumoniae* and Its Close Commensal Relative, *Streptococcus mitis*
Tahmina Ahmed Milly, *Department of Chemistry, University of Nevada*

Docking Peptides into HIV/FIV Protease: A Case Study
Michel Sanner, *Department of Integrated Structural and Computational Biology, Scripps Research*

Benchmarking Peptide Docking: Comparing Deep Learning and Conventional Approaches
Sudhanshu Shanker, *Department of Integrated Structural and Computational Biology, Scripps Research*

Combination of Hybrid Cyclic-Linear Amphipathic Peptides with Chemotherapeutic Agents as a Strategy to Enhance Anticancer Activity
Jonathan Moreno, *Center for Targeted Delivery, Department of Biomedical and Pharmaceutical Sciences, Chapman University School of Pharmacy*

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Thursday, October 20, 2022 *continued*

3:45 p.m. – 4:45 p.m.

Omniligase-1-mediated Ligation for Insulin Analog Synthesis in Solution and On Phage Surface
Yi Zhang, *Department of Pediatrics, Division of Diabetes and Endocrinology, Stanford University*

Rapid Screening of Disulfide-Rich Peptides with Nav1.7 Inhibitory Activity by PERISS Method
Hikaru Taira, *Veneno Technologies Co. Ltd.*

Myristic Acid-Trans-Activator of Transcription Dual Conjugation Facilitates Delivery of Protein Kinase C Beta II Peptide Inhibitor Cargo in Leukocytes
Alexis Verwoert, *Philadelphia College of Osteopathic Medicine*

4:45 p.m. - 6:30 p.m.

Opening Reception
Helen and Morton Adler Memorial Court

Friday, October 21, 2022

7:00 a.m. – 4:15 p.m

Registration Check-in
Fritz B. Burns Reception Center, Lower Level

8:00 a.m. – 4:45 p.m.

17th Annual Peptide Therapeutics Symposium
Conrad T. Prebys Auditorium

8:00 a.m. – 8:15 a.m.

Welcoming Remarks
Nick Cox, Ph.D.
Director, Peptide Therapeutics Foundation
Associate Director, Discovery Chemistry
Novo Nordisk Research Center

8:15 a.m. – 10:15 a.m.

Plenary Lectures
Moderator: Nick Cox, Ph.D.

8:15 a.m. – 9:15 a.m.

Discovery and Characterization of Novel Peptides and Small Proteins
Alan Saghatelian, Ph.D.
Professor, The Salk Institute for Biological Studies

Friday, October 21, 2022 *continued*

9:15 a.m. – 10:15 a.m.

Exploration of Improved MC4R Agonist and Novel MC3R Antagonist Peptides for the Treatment of Obesity
Roger Cone
Director, Life Sciences Institute, University of Michigan

10:15 a.m. – 10:45 a.m.

Beverage Break
Fritz B. Burns Reception Center, Lower Level

10:45 a.m. – 11:45 a.m.

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

10:45 a.m. – 11:15 a.m.

Development of Differentiated Peptide Therapeutic Products Using an Innovative Formulation Technology
Jan Jezek, Ph.D.
Chief Scientific Officer, Arecor

11:15 a.m. – 11:45 a.m.

A New Approach to Cancer Therapy with Documented Clinical Effects
Catharina Svanborg, M.D., Ph.D.
Professor of Clinical Immunology (emeritus), Lund University

11:45 a.m. – 12:30 p.m.

Poster Presentations
Moderator: Ron He
Principal Scientist, RayzeBio

Amino Acids as Heterogenous Soft Template Nucleants in Peptide Crystallisation
Laura Coffey, *University of Limerick*

Evaluation of the Stability and Degradation Profile of Modified Peptides Derived from LfcinB
Isabella Blanco Medina, *Universidad Nacional de Colombia*

Metabolic Stress Mediates Accumulation of Glycation (AGE) PTMs in the Proteomes of Mouse Dendritic Cells and Reshapes the MHC-II Immunopeptidome
Cristina Clement, *Weill Cornell Medicine*

Artificial Intelligence Based Discovery of Novel Peptides with Anti-inflammatory Activity
Ewa Lis, *Koliber Biosciences*

17th Annual Peptide Therapeutics Symposium

Friday, October 21, 2022 *continued*

Antibodies Generated Against an AP-derived Oligomer: Efforts Toward a Novel Alzheimer's Disease Immunotherapy
Chelsea Marie Parrocha, *Department of Pharmaceutical Sciences, University of California, Irvine*

12:30 p.m. – 1:30 p.m.

Lunch Break
Fritz B. Burns Reception Center, Lower Level

1:30 p.m. – 2:30 p.m.

Session IV
Moderator: Johnny Zhu
Director, Peptide Therapeutics Foundation
Vice President of Discovery Chemistry, Ferring Research Institute

1:30 p.m. – 2:00 p.m.

Invention of Oral PCSK9 Inhibitor from mRNA Display Selection
Abbas M. Walji, Ph.D
Director, Discovery Chemistry, Merck & Co. Inc.

2:00 p.m.– 2:30 p.m.

Oral Inhibitors of the SARS-CoV-2 Main Protease for the Treatment of COVID-19
Dafydd Owen, Ph.D.
Senior Scientific Director, Medicinal Chemistry, Pfizer Medicine Design

2:30 p.m. – 3:00 p.m.

Poster Presentations
Moderator: Lindon Young, Ph.D.
Professor of Pharmacology, Philadelphia College of Osteopathic Medicine
Founder & Chief Science Officer, Young Therapeutics, LLC

Dual Myristic Acid and Trans-activator of Transcription Conjugation of PKC Beta II Peptide Inhibitor Enhances Delivery to Mitigate Myocardial Ischemia/Reperfusion Injury
Logan Clair, *Department of Biomedical Sciences, Philadelphia College of Osteopathic Medicine*

Cyclic And Linear Peptides Containing Tryptophan and Arginine Residues as Antifungal Agents
Khushbu Bhakta, *Chapman University School of Pharmacy*

The Thiol-maleimide Reaction Downside: Secrets of an Important By-product Revealed
Jianheng Zhang, *Bachem Americas Inc.*

Friday, October 21, 2022 *continued*

Synthesis of Sulfated and Glycosylated CCR5 N-terminal Peptide
Brooke Van Engen, *Department of Chemistry, Dordt University*

Myristoylated Protein Kinase C Epsilon Peptide Inhibitor Attenuates Acute Kidney Injury in Renal Ischemia Reperfusion
Sunit Singh, *Philadelphia College of Osteopathic Medicine*

3:00 p.m. – 3:30 p.m.

Beverage Break
Fritz B. Burns Reception Center, Lower Level

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

Session V
Moderator: David Parkes, Ph.D.
Chief Scientific Officer, Abvance Therapeutics Inc.

3:30 p.m. – 4:00 p.m.

GLP1 Receptor Bias Agonists: The Long and Short of It
Patricia McDonald, Ph.D.
Associate Professor, Moffitt Cancer Center & Research Institute

4:00 p.m.– 4:30 p.m.

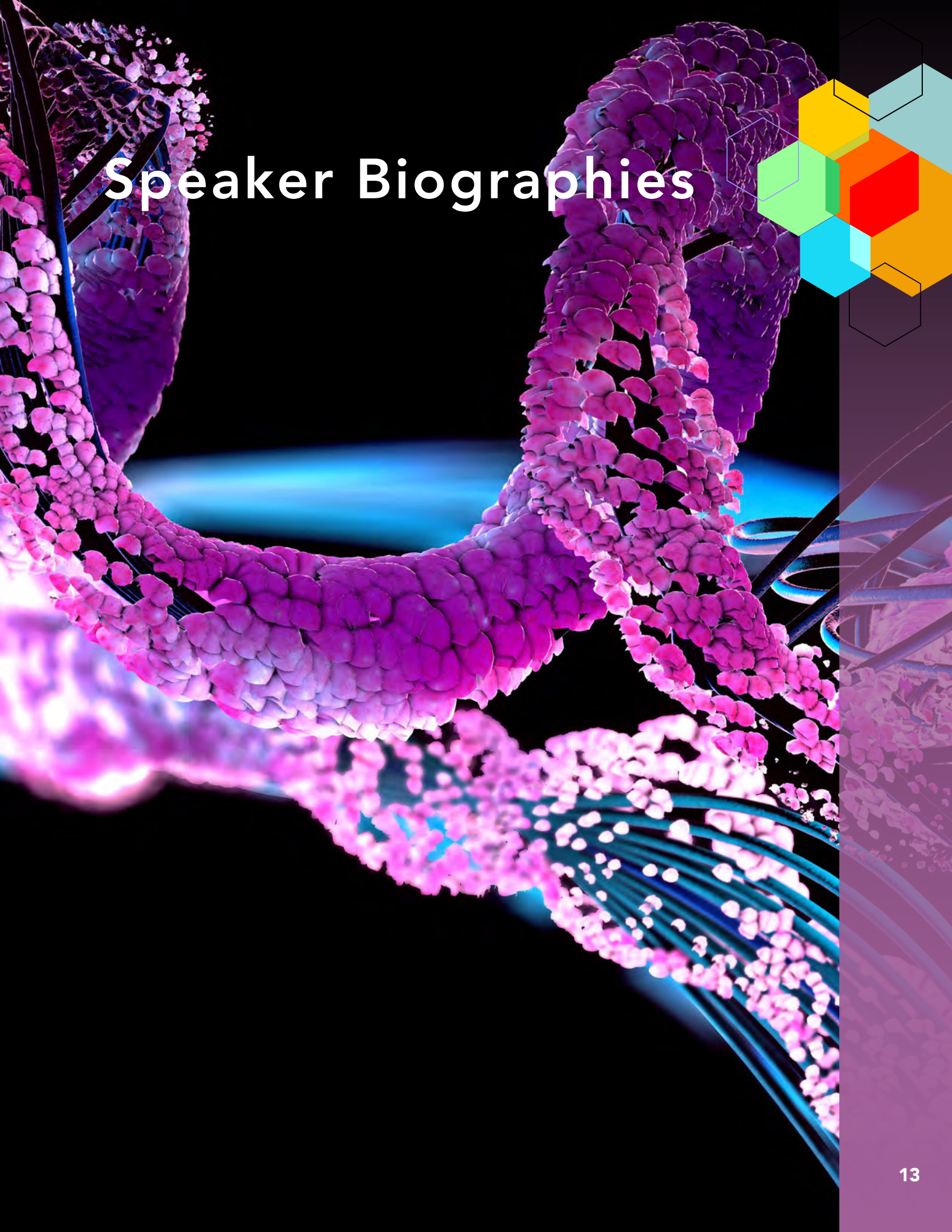
CryoEM After the Resolution Revolution: Achievements, Developments and Challenges
Anette Schneemann, Ph.D.
Senior Staff Scientist, Scripps Research

4:30 p.m. – 4:45 p.m.

Closing Remarks
Adam Mezo, Ph.D.
President, Peptide Therapeutics Foundation
Executive Scientific Director, Discovery Biology Research, Neurocrine Biosciences, Inc.

4:45 p.m. – 6:00 p.m.

Closing Reception
Helen and Morton Adler Memorial Court



Speaker Biographies

Yuan Cheng, Ph.D.

Senior Principal Scientist, Amgen Inc.

Discovery of AMG133, a Novel GIPR Antagonist Antibody/GLP-1 Peptide Bispecific Conjugate for the Treatment of Obesity

Yuan Cheng is a Senior Principal Scientist and leading the Hybrid Modality group for Biologic Therapeutic Discovery at Amgen. She had over 25 years' drug discovery experience with successful track record of advancing challenging drug targets from concept to hit to clinical candidate. Her current research is focused on developing protein conjugation technologies, designing and generation of hybrid modality therapeutics. She is one of the coinventors of AMG 133, a novel GIPR antagonist antibody and GLP-1 peptide conjugate that is in early clinical development. Prior to joining Amgen in 2002, she was a Research Fellow in Medicinal Chemistry at Merck Research Laboratories for seven years.
She received her doctorate degree at Princeton University in Princeton, New Jersey and did postdoctoral research at Columbia University in New York City, NY.

Roger D. Cone, Ph.D.

Director, Life Sciences Institute, University of Michigan

Exploration of Improved MC4R Agonist and Novel MC3R Antagonist Peptides for the Treatment of Obesity

Roger Cone received his B.A. in Biochemistry from Princeton University in 1980, earned his Ph.D. in Biology from the Massachusetts Institute of Technology in 1985, and conducted postdoctoral studies at the Cold Spring Harbor Laboratory. In 1988, he became an assistant professor at the New England Medical Center, and accepted an appointment to the Vollum Institute at Oregon Health & Science University in 1990. In 2008 he moved to Vanderbilt to be Professor and Chairman of the Department of Molecular Physiology and Biophysics. Since 2016, Cone has been Director of the Life Sciences Institute at University of Michigan, and has also served as Vice Provost for the Biosciences since 2017. The Cone lab works on the central control of energy homeostasis, concentrating on the melanocortin system, a complex set of neural circuits demonstrated to regulate a variety of physiological processes critical to the process. These findings resulted from early studies cloning and characterizing a family of five receptors for the melanocortin peptides, and analyzing the pharmacological and physiological functions of these receptors. Cone's studies led to the identification of the agouti protein as the first endogenous GPCR antagonist, and the identification of mutations that constitutively activate a hormone-binding GPCR, the MC1R. His discovery and characterization of variant alleles of the MSH receptor (MC1R) explains much of the coat color variation in domesticated animals and is the molecular basis for over 85% of red hair in humans. After developing the first melanocortin antagonist with Dr. Victor Hruby, Cone used this reagent to demonstrate that blockade of melanocortin signaling stimulated food intake. This, along with the discovery that agouti was an antagonist of the MC4R, and that MC4R deletion caused severe obesity in mice, validated the role of the MC4R in energy homeostasis. In Takahashi and Cone (2005), he discovered that the activity of the AgRP neurons, negative regulators of MC4R neurons, reflected the energy and hunger state of the animal. These and subsequent studies identified the central melanocortin system as a key component of the adipostat, the central circuitry that regulates food intake and energy expenditure to maintain energy stores. Together, these studies led to the development of the first drug for syndromic obesity, the MC4R agonist Imcivree, approved by the

FDA in 2020. Cone has also elucidated the physiological functions of the MC3R, demonstrating that it acts presynaptically on AgRP neurons to negatively regulate the MC4R system and the behavioral and neuroendocrine response to fasting. Cone also demonstrated the MC3R mediates communication between nutritional and reproductive state, and regulates lean mass. Recent work by O'Rahilly confirmed these findings in humans, and also discovered a role for the MC3R in the timing of puberty. Cone has received multiple awards for his work, including election to the National Academy of Sciences, and National Academy of Medicine.

Nick Cox, Ph.D.

Associate Director of Discovery Chemistry, Novo Nordisk

Welcoming Remarks

Dr. Cox is the Associate Director of Discovery Chemistry at the Novo Nordisk Research Center in Seattle, WA. He is leading the chemistry department to drive peptide, protein, and other therapeutic discovery efforts targeting chronic conditions including rare endocrine and blood disorders, obesity, diabetes, and cardiovascular disease. 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.

Professor of Chemistry, Scripps Research

Opening Remarks

Phil Dawson is a Professor in the Department of Chemistry, Scripps Research in La Jolla, CA and Dean of the Skaggs Graduate School of Chemical and Biological Sciences. He received an A.B. (1992) in Chemistry from Washington University, and Ph.D. (1996) from Scripps Research under the guidance of Steve Kent. After pursuing postdoctoral work at Caltech, he returned to Scripps as an Assistant Professor. He has served as President of the American Peptide Society, the Board of Directors for FASEB and cochaired the 22nd American Peptide Symposium and the GRC on Biology and Chemistry of Peptides. He has published over 195 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 and the Akabori Memorial Award from the Japanese Peptide Society. 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.

Richard DiMarchi, Ph.D.

Distinguished Professor of Chemistry, Gill Chair in Biomolecular Sciences, Department of Chemistry, Indiana University

A Hundred Years Ago Today the Band Began to Play

Richard DiMarchi is a Distinguished Professor of Chemistry and Gill Chair in Biomolecular Sciences at Indiana University, where he served as chairman of the Chemistry Department. Dr. DiMarchi is a member of the National Academy of Medicine and the National Inventors Hall of Fame. He is a former Group Vice President at Eli Lilly and later at Novo Nordisk. He is recognized for his contributions to the discovery and development of rDNA-derived Humalog®, rGlucagon®, and Forteo®. His academic research has broadened the understanding of glucagon physiology and the discovery of single molecule multimode agonists for the treatment of diabetes and obesity. He is former decade-long chairman of the Peptide Therapeutics Foundation and is widely recognized as an international spokesperson for macromolecular medicines.

Professor DiMarchi is co-inventor on more than one hundred U.S. patents and co-author to more than two hundred and fifty peer-reviewed scientific publications. He was identified as a top-five translation researcher by Nature Biotechnology for the years 2014 and 2015. Since 2003, he has co-founded five successful biotech companies (Ambrx, Marcadia, Calibrium, MB2, Assembly), with one additional launched in 2019 (MBX). In the last decade Professor DiMarchi has received the 2011 Merrifield Award for career contributions in peptide sciences, the 2014 German National Erwin Schrödinger-Preis, the 2015 Meienhofer Prize, the 2015 Max Bergmann Medal, and the 2016 ACS Alfred Burger career award in medicinal chemistry.

Brian Finan, Ph.D.

Vice President of Obesity Research, Novo Nordisk

From Serendipity to Rational Design: Multimodality Therapeutics for Multimorbidity Diseases

Brian Finan is currently the Vice President of Obesity Research for Novo Nordisk. His responsibilities include driving discovery research and early development within the obesity therapy area, maturing and diversifying the obesity pipeline, and developing portfolio strategies to ensure continued leadership in obesity. His previous role was a leadership position as Site Head and Senior Director of the Transformational Research Unit Chemical Biology at the Novo Nordisk Research Center Indianapolis. Brian started his industry career at Novo Nordisk in 2016 as a scientist and director of biology upon the inception of Novo Nordisk Research Center in Indianapolis, which was established upon the acquisition of biotech companies founded by Dr. Richard DiMarchi. Prior to joining Novo Nordisk, Brian was group leader of the Drug Discovery group at the Helmholtz Diabetes Center in Munich, Germany. Brian's post doc studies focused on Molecular Pharmacology at the Helmholtz Diabetes Center, under the mentorship of Dr. Matthias Tschöp. Brian holds a Ph.D. in Biological Chemistry from Indiana University, under the mentorship of Dr. Richard DiMarchi.

Soumitra S. Ghosh, Ph.D.

President, Doon Associates LLC

Session II Introduction

Soumitra S. Ghosh, Ph.D. is a biopharmaceutical industry consultant and entrepreneur with e xtensive experience in drug development, technology licensing and in formulating and implementing R&D strategy. He is a co-founder of Avexegen Therapeutics, Inc and Abvance Therapeutics, Inc, start-ups focused on GI indications and diabetes, respectively. His experience includes senior R&D leadership positions at Amylin Pharmaceuticals and MitoKor, where he led research programs for the development of small molecule, peptide and protein-based drug candidates for the treatment of metabolic diseases and CNS disorders. He served as the President of the Peptide Therapeutics Foundation for eight years and is a scientific advisor for several biotechnology startups. He has been a recipient of multiple SBIR and California state grants for his work in the industry. He received his MS and Ph.D. degrees in Chemistry from the Indian Institute of Technology and the University of Chicago, respectively, and conducted his post-doctoral work at Rockefeller University.

Jan Jezek, Ph.D.

Chief Scientific Officer, Arecor

Development of Differentiated Peptide Therapeutic Products Using an Innovative Formulation Technology

Dr. Jezek is the Chief Scientific Officer at Arecor. He has been trained as a biophysical chemist and started his professional career developing novel biosensors for a range of analytes. He then switched to medical device development as the principal scientist at Insense, a spin-off company backed by Unilever plc, leading the development of a range of novel medical devices for wound care from the proof-of-concept all the way to market. During his time at Insense, he and his team developed a novel formulation platform to achieve superior stability of proteins and other biological molecules. His inventions related to protein stabilisation led to inception of Arecor Ltd as a separate company focusing on commercialisation and further development of the stabilisation technology. He oversaw expansion of the technology to a number of areas, including therapeutic peptides, as well as its successful application to a range of differentiated products. Dr. Jezek is the author of several papers and a number of patents which underpin Arecor's technology.

John P. Mayer Ph.D.

Research Scientist, Dept. of Molecular, Cellular and Developmental Biology (MCDB), University of Colorado

Chemical Optimization of the Pancreatic Glycemic Hormones

Dr. John Mayer received his undergraduate degree in Biochemistry from Northwestern University in 1979, and his MS (1983) and Ph.D. (1987) degrees in Medicinal Chemistry from Purdue University. This was followed by postdoctoral training in Dr. Richard DiMarchi's group at Lilly Research Laboratories focusing on the total synthesis of insulin and IGF-1 peptides. From 1992 to 1998 he served as head of the peptide chemistry group at Amgen Inc. (Boulder, CO) where he was involved in the total synthesis of growth factors such as NDF, EGF and NGF, and smaller cyclic peptides. In 1998 he rejoined Lilly Research Laboratories to lead the peptide chemistry group which focused on endocrine/diabetes therapeutics including insulin, glucagon, GLP-1. In 2012 he moved to Indiana University, Bloomington where he was involved in the discovery efforts at Calibrium LLC, a diabetes focused startup, acquired by Novo-Nordisk in 2015. In 2017 he joined Prof. Michael Stowell's group at the University of Colorado, Boulder to pursue a number of diabetes related projects. Dr. Mayer has authored, or co-authored over 90 publications and been named as inventor on 6 issued patents and numerous patent applications. He has been a frequent speaker at peptide and drug discovery conferences and served on the American Peptide Society board as an elected council member (2009-2015).

Patricia McDonald, Ph.D.

Associate Professor, Moffitt Cancer Center & Research Institute

GLP-1 Receptor Bias Agonists: The Long and Short of It.

Dr. McDonald received her Ph.D. in 1993 in Molecular Genetics from University of Dundee where her postgraduate studies focused on the role protein phosphatases play in cell cycle progression. Following completion of her Ph. D. she joined the laboratory of Dr. Howard Prentice, Department of Genetics, Glasgow University (1994 -1995) where her focus was on adenoviral-mediated gene transfer in rodent models of cardiac ischemia. As a postdoctoral fellow at Duke University, NC (1996 - 2000) in the laboratory of Dr. Robert Lefkowitz, a world-renowned leader in the G-protein coupled receptor (GPCR) field and recipient of the Nobel Prize for Chemistry (2012), her primary focus was on GPCR function and regulation, and the role(s) played by ß-arrestin in mediating these processes. She identified multiple novel ß-arrestin binding partners that led to several publications including a seminal paper describing ß-arrestin as a novel scaffold for receptor-mediated c-jun N-terminal kinase (JNK) activation. The discovery of ß-arrestin as a signal transducer in its own right made a major contribution to the emerging concept of 'functional selectivity', also known as 'ligand bias'; the phenomenon whereby a GPCR ligand can activate one pathway to the exclusion of others. As a GPCR drug discovery group leader in the pharmaceutical industry (Dupont Pharma, 2000 - 2001; Eli Lilly, 2001 - 2005), she gained significant experience in directing biochemical and cell-based and phenotypic assay development, HTS campaigns, optimization of Lead matter, and *in vitro* and *in vivo* pharmacology, and played a leading role in the introduction of novel technologies to cell-based screening and *in vitro* pharmacology platforms. In 2005, Dr. McDonald transitioned from the pharmaceutical industry to academia where she joined Scripps Research, Florida (2005 - 2018), and

as Associate Director of Drug Discovery Biology continued to lead GPCR-focused drug discovery efforts. In April 2011, she initiated an independent research program and as an Associate Professor in the Dept. of Molecular Medicine (Scripps Research) her laboratory focused on investigating the fundamental molecular mechanisms underlying the regulation, trafficking and activation of GPCRs involved in CNS and metabolic disorders, and cancer. She has continued these efforts since joining the Moffitt Cancer Center & Research Institute, Dept. of Cancer Physiology in Sept 2018. Knowledge gained from these studies may aid in the design of therapeutically useful GPCR modulators. Thus, her major research interests lie in identifying novel, tractable, and anti-diabetes, anti-obesity and anti-cancer targets, developing selective molecular probes of these targets, and where possible optimizing these probes to generate *in vivo* lead molecules for testing in rodent pre-clinical models and human.

Adam Mezo, Ph.D.

President, Peptide Therapeutics Foundation
Executive Scientific Director, Discovery Biology Research, Neurocrine Biosciences Inc.
Closing 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 Executive Scientific Director, Discovery Biology Research 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), Ph.D. 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.

Samir Mitragotri, Ph.D.

Professor, Harvard University
Ionic Liquids for Delivery of Biologics

Samir Mitragotri is the Hiller Professor of Bioengineering and Wyss Professor of Biologically Inspired Engineering at Harvard University. His research is focused on transdermal, oral, and targeted drug delivery systems. He is an elected member of the National Academy of Engineering, National Academy of Medicine and National Academy of Inventors. He is also a foreign member of Indian National Academy of Engineering. He is also an elected fellow of AAAS, CRS, BMES, AIMBE, and AAPS. He is an author of over 400 publications and a Clarivate Highly Cited Researcher. He received his BS in Chemical Engineering from the Institute of Chemical Technology, India and a Ph.D. in Chemical Engineering from the Massachusetts Institute of Technology. He is the Editor-in-Chief of AIChE's journal Bioengineering and Translational Medicine.

Dafydd Owen, Ph.D.

Senior Scientific Director, Medicinal Chemistry, Pfizer Medicine Design

Oral Inhibitors of the SARS-CoV-2 Main Protease for the Treatment of COVID-19

Dafydd Owen has twenty-three years of experience as a medicinal chemist in the design and synthesis of drug-like molecules for Pfizer at its Sandwich UK and Cambridge MA research sites. Heobtained his first degree at Imperial College in 1994 before moving to the University of Cambridge to gain a Ph.D. under the supervision of Professor Steve Ley FRS in 1997. Having won a research fellowship for postdoctoral work, he spent 1998 with Professor Leo Paquette at Ohio State University. During his research career he has delivered over eighty invited lectures and is an author on over seventy research papers and patents. He has made contributions seven clinical candidates during his career at Pfizer. He has been recognized through the Pfizer's Breakthrough Science and innovation Prize, the Pfizer Worldwide R&D People Leader Award and was also selected as an ACS Organic Division Young Industrial Investigator earlier in his career. He serves as a board member of the Structural Genomics Consortium and sits on the editorial advisory board of the Journal of Medicinal Chemistry. He currently works in an outward looking, academically collaborative group for Pfizer looking to better understand protein families and their role in human disease through chemistry. Most recently he led Pfizer's oral protease inhibitor program that ultimately delivered PAXLOVID, the world's first oral anti-viral therapy for the treatment of COVID-19.

Monika A. Papworth, Ph.D.

Biologics Engineering, AstraZeneca R&D

Engineering Long-acting Relaxin ThP - AZD3427

Dr. Monika Papworth is a Principal Scientist at the Department of Biologics Engineering at AstraZeneca Cambridge and an expert in engineering of peptide and antibody-based therapeutics.

After obtaining her master's degree in Biology from the University of Warsaw in Poland in 1991, she gained a Fellowship to study at the Paterson Institute for Cancer Research in Manchester, UK. Her research into glycoproteins of EBV resulted in her being awarded a doctorate by the University of Manchester. In 1995 she took up a post-doctoral position in the Herpes Virus Lab at the Marie Curie Research Institute in Oxted UK, specializing in molecular biology, gene regulation and protein engineering. Later she moved to work with Professor Sir Aaron Klug OM FRS at the MRC Laboratory of Molecular Biology in Cambridge UK, where she worked for 8 years on phage display, DNA-binding zinc-fingers and their use in the therapy of viral and mitochondrial diseases. Since joining AstraZeneca in 2006, Dr. Papworth has worked on various early stage drug discovery programs mainly in the Cardio Vascular, Renal and Metabolic Disease therapy area, leading protein engineering activities and managing projects from target validation to IND. In addition, she is an author of numerous peer-reviewed scientific publications and patents.

17th Annual Peptide Therapeutics Symposium

Alan Saghatelian, Ph.D.

Professor, The Salk Institute for Biological Studies

Discovery and Characterization of Novel Peptides and Small Proteins

Alan Saghatelian is the Dr. Frederick Paulsen Chair, Assistant Director of the Redesigning Biology Initiative and Professor at the Salk Institute in La Jolla, California. He received his BS in Chemistry from UCLA in 1997 and his Ph.D. in Chemistry from the Scripps Research Institute in 2002. He carried out postdoctoral research training at the Scripps Research before joining the faculty at Harvard in 2006. In 2014 Dr. Saghatelian moved his lab to the Salk Institute where it is part of the Peptide Biology Laboratory. He has devoted his career over the past fifteen years to discovering bioactive peptides as a means to improve our understanding of biology and, in doing so, afford new opportunities to treat or cure disease. To do this, he integrates cutting-edge genomics, proteomics, and computational biology that has revealed the existence of hundreds of peptides and small proteins (micropeptides) in human and mouse genomes. In parallel, his lab has demonstrated that several micropeptides have essential biological functions with roles in DNA repair, mRNA stability, and cell stress, leading to the possibility of finding many biologically and biomedically relevant microproteins. Dr. Saghatelian is a chemist and chemical biologist with extensive experience in small molecule design and synthesis, biochemistry, and omics technologies. Dr. Saghatelian's research has been recognized by numerous awards, including the Merck Fellow of the Life Science Research Foundation, the Career Award in Biomedical Sciences from the Burroughs Wellcome Fund, the New Innovator Award from the National Institutes of Health, the Searle Scholars Award from the Searle Foundation, the Sloan Research Fellow from the Alfred P. Sloan Foundation, the Fellow of the American Association for the Advancement of Sciences and the Ono Pharma Foundation Breakthrough Science Initiative Award together with Dr. O'Shea.

Anette Schneemann, Ph.D.

Senior Staff Scientist, Scripps Research

CryoEM After the Resolution Revolution: Achievements, Developments and Challenges

Anette Schneemann is a Senior Staff Scientist at Scripps Research in La Jolla, CA. As a member of the structural biology group of Prof. G. Lander, she participates in overseeing ongoing projects in the laboratory, providing supervision and advice on the design, plan, and execution of the research. Her major focus is on structural analysis of the human mitochondrial proteome by cryoEM.

Before joining Scripps Research, Anette was Chief Scientific Officer and General Manager at NanoImaging Services Inc., a provider of molecular transmission electron microscopy services with specialization in cryoEM and high resolution, 3D structure determination of proteins, viruses and small molecules. At NIS, Anette was responsible for bringing scientific knowledge and leadership to the company. She managed the scientific, research and commercial operations and was instrumental in transforming NIS to a successful firm, leading it to profitability and major growth.

Prior to joining NIS, Anette was Associate Professor in Cell and Molecular Biology at The Scripps Research Institute in La Jolla, CA where her laboratory focused on

structure-function analyses of virus particles. This included studies of particle assembly, genome packaging, and development of virus-like particles as a vaccine platform for multivalent display of foreign antigens. During her academic career, she extensively worked with structural biologists to determine high and low resolution structures of virus particles and proteins by X-ray crystallography, cryo-electron microscopy and electron tomography.

Anette earned a Ph. D. degree in Biochemistry from the University of Wisconsin-Madison and completed a postdoctoral fellowship at UC-Irvine.

Hiroaki Suga, Ph.D.

Professor, The University of Tokyo

The Next Generation of RaPID System

Hiroaki Suga is a Professor of the Department of Chemistry, Graduate School of Science in the University of Tokyo. He is the 121th President of Chemical Society of Japan, and a member of Cabinet Office of Science, Technology and Innovation of Japan. He was born in Okayama City, Japan in 1963. He received his Bachelor of Engineering (1986) and Master of Engineering (1989) from Okayama University, and Ph. D. in Chemistry (1994) from the Massachusetts Institute of Technology. After three years of post-doctoral work in Massachusetts General Hospital, he was appointed as a tenure-track Assistant Professor in the Department of Chemistry in the State University of New York at Buffalo (1997) and promoted to the tenured Associate Professor (2002). In 2003, he moved to the Research Center for Advanced Science and Technology in the University of Tokyo as an Associate Professor, and soon after he was promoted to Full Professor. In 2010, he changed his affiliation to the Department of Chemistry, Graduate School of Science. His research interests are in the field of bioorganic chemistry, chemical biology and biotechnology related to RNA, translation, peptides and pseudo-natural products. He is the recipient of Akabori Memorial Award 2014, Japanese Peptide Society, Max-Bergmann Gold Medal 2016, Nagoya Medal Silver 2017, and Vincent du Vigneaud Award 2019. He is also a founder of PeptiDream Inc. Tokyo, a publicly traded company in the Tokyo First Stock Exchange Market, which has many partnerships with pharmaceutical companies in worldwide. He resigned the Board of Directors of PeptiDream in June, 2018. He is also a founder of MiraBiologics Inc. and the Board of Directors since 2017.

Catharina Svanborg, M.D., Ph.D.

Professor (emeritus) of Clinical Immunology, Lund University

A New Approach to Cancer Therapy with Documented Clinical Effects

Professor Svanborg is an award-winning Emeritus Professor of Clinical Immunology at Lund University, Sweden and Fellow of the Royal Swedish Academy of Science. She is the Founder and Chairman of Hamlet Pharma and Linnane Pharma. Professor Svanborg is highly respected scientist, particularly in the study of the pathogenesis of infectious diseases, with over 500 published papers to her credit. The Svanborg group has pioneered research in two main areas; innate immunotherapy for bacterial infections and novel approaches to cancer therapy. The later includes the

use of tumoricidal complexes formed by partially unfolded peptides and oleic acid which are under development by Hamlet primarily for bladder cancer and a novel MYC inhibitor. Her awards include Kennedy Visiting Professorship Award at Imperial College, London, the Domagk award, the non-restricted grant award (BMS), the Edwin H. Beachey Distinguished Visiting Professorship Award at the University of Tennessee, the Jubilee award of the Swedish Medical Society, the Nordic Söderberg award and the Scientist of the Year Award in 2014 from the independent foundation Research Sweden.

Abbas M. Walji, Ph.D.

Director, Discovery Chemistry, Merck & Co. Inc.

Invention of Oral PCSK9 Inhibitor from mRNA Display Selection

Abbas received his Ph.D. from University at Buffalo working with Professor Huw M. L. Davies, and completed his Post-Doctoral studies working in the laboratories of Professor David W. C. MacMillan first at the California Institute of Technology then at Princeton University. He joined Merck Discovery Chemistry in 2007 at the West Point, PA site working on several discovery programs across the infectious disease and neuroscience therapeutic areas. Notably, he co-led the discovery team in the design and development of 18F[MK-6240] a Tau PET imaging agent to enable the discovery of new therapeutics for Alzheimer's disease. In 2016, he was a founding member of the Discovery Chemistry Modality organization in Kenilworth, NJ, and has led the effort to integrate larger chemical modalities to the medicinal chemistry tool-box. During this time he co-led the discovery team to the invention of MK-0616, an oral PCSK9 cyclic peptide inhibitor for lowering LDL cholesterol. Currently, Abbas leads a Discovery chemistry team in West Point, PA working across therapeutic areas, applying established and novel chemical modalities (small molecule, macrocyclic peptides, and protein domain mimics), and novel screening technologies (DEL and mRNA display) to challenging biological targets.

Notes

Speaker Abstracts

Discovery of AMG133, a Novel GIPR Antagonist Antibody/GLP-1 Peptide Bispecific Conjugate for the Treatment of Obesity

Yuan Cheng, Ph.D.
Senior Principal Scientist
Amgen Inc.

Yuan Cheng, Bin Wu, James R. Falsey, Jelly Netirojjanakul, Brad Herberich, Jerry Ryan Holder, Kelvin Sham, Les P. Miranda, Todd Hager, Shu-Chen Lu, Shanaka Stainislaus, Renee Komorowski, Dohan Weeraratne, Larissa Atangan, Joan Helmering, Renee Komorowski and Murielle M. Veniant

We describe the discovery and development of AMG113; a novel GIPR antibody, GLP-1 peptide conjugate.

Obesity and its comorbidities, such as type 2 diabetes and cardiovascular diseases, represent a serious threat to public health. Glucose-dependent insulinotropic polypeptide receptor (GIPR) plays a role in regulation of body weight and glucagon-like-peptide-1 (GLP-1) receptor agonists are known to control blood glucose levels and induce satiety. In this presentation, we describe the discovery of AMG133, a novel antibody and peptide conjugates comprising a GLP-1 receptor agonist tethered to specific engineered cysteines in a GIPR antagonistic antibody. A range of GLP-1 potency was explored by selective chemical modification to GLP-1 peptide to maximize weight reduction. Antibody conjugation sites and linkers impacted *in vivo* activity and were evaluated to optimize the pharmacokinetic profile and weight loss efficacy *in vivo*. AMG 133 demonstrated robust body weight reduction and significant improvement of metabolic parameters in preclinical models. AMG133 demonstrated efficacy and tolerability with desired pharmacokinetic profiles in the phase 1 clinical trial and has potential to be an effective agent for treatment of obesity.

Exploration of Improved MC4R Agonist and Novel MC3R Antagonist Peptides for the Treatment of Obesity

Roger D. Cone, Ph.D.
Director, Life Sciences Institute
University of Michigan

R.D. Cone[1], P. Sweeney[2], C.C. Hernandez[1] and L.E. Gimenez[1], N. Dahir[1], Y. Gui[1], and T.S. Sawyer[3]

[1]University of Michigan, MI; [2]University of Illinois, IL; [3]Courage Therapeutics , MA

Variations in melanocortin peptide signaling are responsible for some of the most observable human phenotypes, including red hair and early onset obesity. In the nervous system, study of melanocortin and agouti signaling, and their GPCRs, have elucidated many novel aspects of neuropeptidergic signaling. Examples include the first discovery of an endogenous GPCR antagonist (AgRP - possibly also a biased agonist), one of the rare examples of a neuropeptidergic GPCR exhibiting a gene dosage effect fundamental to the mechanics of energy homeostasis, and one of the rare examples of a GPCR capable of G-protein independent coupling to an ion channel.

These novel signaling modalities all play an important role in the regulation of energy homeostasis, however much remains to be understood. While much is known about the role of the MC4R in energy homeostasis, the MC3R has been an enigma. Recent work has begun to provide a framework: the MC3R is a negative regulator of MC4R neurons[1], and is also critical for the sensing of energy deficits by the AgRP neurons, and the resulting behavioral and neuroendocrine responses to fasting. This may help explain the observation that inhibition of the MC3R hypersensitizes animals to a wide variety of anorexigenic agents. This suggests that MC3R antagonists may provide a therapeutic opportunity for both enhancing existing agents, and as well as for the maintenance of weight loss. Lastly, the recently reported case of a patient with homozygous loss of the MC3R demonstrates the conserved role of the MC3R in mouse models and human[2].
Three melanocortin peptide drugs have now been approved by the FDA for syndromic obesity (Imcivree), erythropoietic protoporphyria (Scenesse), and female hyposexual disorder (Vyleesi), however all these compounds are pan-agonists of the melanocortin receptors. Further, existing MC4R agonists lack sufficient potency to treat the most common genetic obesity syndrome, MC4R haploinsufficiency. In order to advance melanocortin pharmacology, we have sought to create potent, receptor subtype-specific MC3R and MC4R compounds[3]. After 8 rounds of SAR, and synthesis and pharmacological characterization of close to 500 different peptides, we are now able to report compounds with sub-nanomolar EC_{50} values and 1000X specificity for the hMC4R, and low nanomolar EC50 values and 1000X specificity for the hMC3R.

References
1. M. Ghamari-Langroudi et al., Science Advances, (2018), 4, DOI: 10.1126/sciadv.aat0866
2. B. Lam et al., Nature (2021), 599, 436.
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A Hundred Years Ago Today the Band Began to Play

Richard DiMarchi, Ph.D.
Distinguished Professor of Chemistry
Linda & Jack Gill Chair in Biomolecular Sciences
Indiana University, Department of Chemistry

The discovery and subsequent therapeutic application of insulin a century ago represented a groundbreaking event in physiology, biochemistry, and medicine. Remarkably, its introduction into medical practice preceded its structural determination by more than three decades. Among peptide-based therapeutics insulin represents the granddaddy of them all as a substance capable of miraculous pharmacology, although one hampered by a narrow therapeutic index. In our pursuit of structurally optimized macromolecules for management of diabetes, obesity, and other endocrine diseases we have focused on minimizing the need for insulin therapy while simultaneously optimizing the peptide for use as a therapeutic agent.

One cannot overstate the essential role of biotechnology to the discovery and development of peptide and protein therapeutics. Our earliest contributions to the biosynthesis of human insulin and IGF-1 established a foundation to the subsequent discovery and registration of lispro-insulin for diabetes, and later teriparatide for osteoporosis. The more recent discoveries of single molecule, incretin agonists with multiple mechanisms of action reflect our long-standing interest in glucagon as a life-saving medicine and the realization of its full pharmacology.

The term "chemical biotechnology" was introduced to reflect the integration of classical small and large molecule-based pharmacology, while advancing chemical methodology for synthesis of complex macromolecules. To further this goal, we have developed novel chemistry that utilizes a non-canonical linkage of the A- and B-chain N-termini which enables unrestricted

access to insulin-like peptides. We have recently applied this method to the synthesis of virus-derived insulin-like peptides to reveal unique biochemical characteristics. Separately, we have championed the use of peptides to target multiple nuclear hormone receptors thereby minimizing their off-target activities that have historically limited their therapeutic potential.

We have benefited from both great timing and multiple advances in core biotechnologies that have revolutionized life sciences research.

This is the century of biology, and chemistry as an enabling science remains a vital ingredient to its realization and progress. We have benefited from both great timing and multiple advances in core biotechnologies that have revolutionized life sciences research. I am hugely appreciative of the many, many individuals that have contributed to the work with which I have been associated. There is much to collectively celebrate but in a relative sense what remains to be accomplished dwarfs what has been achieved. While the technologies, molecules and personal awards are meaningful, it is unquestionably the individuals that have mentored us and those which we pass the responsibility for the future that are of greatest importance.

From Serendipity to Rational Design: Multimodality Therapeutics for Multimorbidity Diseases

Brian Finan, Ph.D.
Vice President of Obesity Research
Novo Nordisk

Combinatorial strategies that harness the therapeutic benefits of multiple hormonal mechanisms, oftentimes with a multi-valent unimolecular format, are now widespread in industrial drug discovery and development programs for cardiometabolic diseases. Poly-agonists at two or more receptors for the endocrine hormones glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), glucagon, amylin, and fibroblast growth factor 21 (FGF21) have shown enormous pre-clinical potential to provide cardiometabolic disease normalization. Emerging clinical data are now showing the translational virtue of the multi-modal concept, but more importantly, the transformative impact on human diseases and multimorbidity. Various therapeutic programs will be summarized, which will highlight of the rational design, preclinical exploration, and clinical validation of peptide-based multi-agonists, while celebrating the visionary ideas and impact that Richard DiMarchi has made to research scientists within his orbit, to the pursuit of unconventional scientific theories, and to the vast health benefits brought to patients.

Emerging clinical data are now showing the transformative impact of a multi-modal approach to human disease.

Development of Differentiated Peptide Therapeutic Products Using an Innovative Formulation Technology

Jan Jezek, Ph.D.
Chief Scientific Officer
Arecor

The competition in the peptide therapeutic market is increasing and successful product development requires a number of good decisions to be made with respect to the target product profile, formulation, delivery device and intellectual property. Convenience of administration and consequent patient adherence have become a major driving force toward improved products, both for new peptide therapeutic entities and for life cycle management of existing ones. Innovative formulation is becoming key to achieving such differentiation. For example, there is an increasing number of intravenously administered specialty hospital products in Ready-to-Administer or Ready-to-Dilute liquid formats that are much easier to use and reduce the probability of dosing errors compared with lyophilized alternatives. Similarly, convenient dosage forms have been developed for subcutaneously administered products, particularly those that can be self-administered by the patient. Lastly, innovative formulation can also be used to affect the pharmacokinetic profile of a peptide drug to improve the treatment outcomes. This talk will present several case studies demonstrating how innovative formulation of selected peptide therapeutics can achieve superior product profiles, enabling products with improved storage stability, convenience of use and desirable *in vivo* properties. The case studies will focus on peptides used in the treatment of diabetes as well as other conditions. Basic scientific principles of the molecular interactions behind the improved product profiles will also be discussed.

Chemical Optimization of the Pancreatic Glycemic Hormones

John P. Mayer, Ph.D.
Research Scientist Dept. of Molecular, Cellular and Developmental Biology (MCDB)
University of Colorado

Insulin and glucagon are the two pancreatic hormones responsible for maintaining glucose homeostasis. Their integrated physiological action tightly maintains plasma glucose at low millimolar concentrations. Insulin lowers glucose by stimulating peripheral tissue uptake and suppressing hepatic glucose release, while glucagon counteracts insulin action by promoting hepatic glycogenolysis and gluconeogenesis. Insulin has a rich medicinal history over the last forty years, as rDNA-technology has enabled commercial production of analogs that offer enhanced therapeutic efficacy, safety, and convenience. In contrast, glucagon as an agonist has received relatively less attention with its role limited to the emergency treatment of life-threatening hypoglycemia.

The DiMarchi lab has been at the forefront in establishing direction for improved T1D management through pioneering inventions pertaining to insulin and glucagon that stand separate from the more recent and highly visible contributions to the incretins and multimode pharmacology directed at T2D and obesity. The research group developed synthetic methodologies enabling the synthesis of other members of the insulin family including IGFs, relaxins and most recently the structurally related viral insulins. These chemical approaches include the biomimetic single-chain routes, directed disulfide-bond formation, and chemically labile non-native surrogates of the native connecting peptide. These recent contributions stand upon the foundation of achievements associated with the initial commercial biosynthesis of human insulin and the first chemically optimized analog approved for human use. Glucagon has received only fraction of the attention devoted to insulin, and paradoxically most of it devoted to the pursuit of glucagon antagonists. Nonetheless, it is every bit as much of a life-saving drug as insulin, but

its potential has been largely underappreciated. From a chemical perspective, native glucagon is a problematic peptide that suffers from biophysical and chemical instability. DiMarchi and associates have addressed these limitations and delivered a comprehensive set of chemical approaches that have relevance to not only glucagon, but to the broader field of therapeutic peptides. In the context of the chemical optimization of glucagon came the rediscovery of glucagon's potential as a thermogenic agent and the novel concept of GLP-1/glucagon co-agonism.

A tranformative impact on diabetes care resulted from key chemical technology innovations

This presentation will cover key chemical technologies contributed by Prof DiMarchi and his research colleagues that have had transformational impact on diabetes care.

GLP-1 Receptor Bias Agonists: The Long and Short of It.

Patricia McDonald, Ph.D.
Associate Professor
Moffitt Cancer Center & Research Institute

E Sturchler[1] A Nieto[1,3], J Xia[1], P Cistrone[1], L Rinaman[2], P Dawson[1], R Lerner[1] and P McDonald[1,3]

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Glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) agonist mimetics are now commonly used as treatment options for type 2 diabetes mellitus (T2DM). GLP-1R signals through G-protein-dependent, and G-protein-independent pathways by engaging the scaffold protein ß-arrestin. Preferential signaling of ligands through one or the other of these pathways is known as 'ligand bias'. We previously reported the discovery of the first, potent and selective GLP-1R G-protein-biased agonist, namely P5; identified using an innovative strategy that involved the high-throughput autocrine-based functional screening of large combinatorial Exendin-4 derived peptide libraries. Preclinical studies in mouse models of T2DM demonstrated that P5 is a weak insulin secretagogue. Nonetheless, chronic, daily dosing of diabetic mice with P5 resulted in increased adipogenesis, reduced adipose tissue inflammation as well as hepatic steatosis, and was more effective at correcting hyperglycaemia and lowering haemoglobin A1c levels than Exendin-4. Moreover, P5 treatment increased circulating concentrations of incretin hormone glucose-dependent insulinotropic polypeptide/gastric inhibitory polypeptide (GIP). Collectively, these data suggest that GLP-1R G-protein-biased agonists may provide a novel therapeutic approach to T2DM (Zhang et al., 2015). As common adverse effects of GLP-1 therapies in humans include nausea/emesis, more recently, we performed a conditioned taste aversion (CTA) test in rodents to compare the aversive effects of administering P5 versus Exendin-4 at glucose lowering doses. A very robust aversive response to Exendin-4 was observed whereas P5 showed no difference to vehicle control suggesting that P5 elicits glycemic benefits in rodents without concomitant signs of nausea. Furthermore, as most of the current developments in the

Our data suggest that a GLP-R1 G-protein-biased agonists may provide a novel therapeutic approach to Type

field of incretin mimetics aim to increase half-lives to extend intervals between injections, we have also generated a modified version of P5 with a significantly improved half-life (P5-L). We show that while it retains G protein bias *in vitro* (notably with a virtually undetectable ß-arrestin response), and weak insulin secretagogue activity yet anti-hyperglycemic properties *in vivo*, unlike P5 which is weight neutral in diet-induced obese animals, once weekly administration of P5-L promotes significant weight loss compared to the FDA-approved, long-acting GLP-1 mimetic, dulaglutide. Herein, we compare and contrast the short- and long-acting versions of the GLP-1R G protein bias agonist P5.

Ionic Liquids for Delivery of Biologics

Samir Mitragotri, Ph.D.
Professor
Harvard University

Ionic liquids, the liquid salts comprising organic anions and cations, offer exciting opportunities for several therapeutic applications. Their tunable properties offer control over their design and function. Starting with biocompatible ions, we synthesized a library of ionic liquids and explored them for various drug delivery applications. Ionic liquids provided unique advantages including overcoming the biological transport barriers of skin, buccal mucosa and the intestinal epithelium, among others. At the same time, they also stabilized peptides and proteins and enabled the delivery of biologics across these barriers. Ionic liquids also provided unique biological functions including adjuvancy towards vaccines. I will present an overview of the design features of ionic liquids and their ability to facilitate biologics delivery.

Oral Inhibitors of the SARS-CoV-2 Main Protease for the Treatment of COVID-19

Dafydd Owen, Ph.D.
Senior Scientific Director, Medicinal Chemistry
Pfizer Medicine Design

Small molecule inhibition of viral proteases has been a successful anti-viral therapeutic strategy in HIV and HCV. Structural insight on the SARS-CoV-2 Mpro and previous small molecule experience with intravenous SARS-CoV-1 inhibitors gave a starting point for an oral Mpro inhibitor program in response to the COVID-19 outbreak. Working in a peptidomimetic chemotype, the team investigated a number of cysteine traps in reversibly covalent inhibitors, while looking to confer sufficient metabolic stability and permeability to attain oral bioavailability. This presentation will contrast the use of benzothiazole ketones and nitriles as reversible, cysteine reactive warheads. Systematically challenging the need for hydrogen bond donors throughout the pharmacophore proved a successful strategy for enhancing permeability. This resulted in the discovery of PF-7321332, the first oral SARS-CoV-2 Mpro inhibitor to reach clinical development. PF-7321332 showed pan-human coronavirus activity, selectivity against human proteases and *in vivo* efficacy in a mouse adapted model of SARS-CoV-2 infection. Dose responsive *in vivo* efficacy was observed against both lung histopathology and viral load end points in mouse studies upon oral dosing of PF-7321332. Phase 1 healthy volunteer studies will be described, with and without combination with low dose ritonavir as a pharmacokinetic enhancer. The preclinical work to identify PF-7321332 (now known as nirmatrelvir) and the resulting Ph1 study was the basis for a combined Ph2/3 study in high-risk patients. Nirmatrelvir/ritonavir went on to receive emergency use authorization for the treatment of high risk COVID-19 patients in the United States in December of 2021, just 17 months after nirmatrelvir was first synthesized.

Engineering Long-acting Relaxin ThP -AZD3427

Monika A Papworth, Ph.D.
Biologics Engineering
AstraZeneca R&D

AZD3427 enables investigation of the therapeutic potential of a long acting Relaxin-2 heterodimer

Relaxin-2 is a human hormone which is structurally related to insulin and best known for its role in pregnancy. Relaxin was previously shown to have various cardiovascular benefits in pre-clinical models and in clinical trials, where recombinant human Relaxin-2 peptide, called Serelaxin, has been pursued as a potential therapy for acute decompensated HF, demonstrating improvement in acute bio-markers after 48h iv infusion. However, a wider therapeutic potential associated with prolonged exposure to relaxin has not been realised yet because of limited treatment duration with Serelaxin and its short circulating half-life.

AZD3427 is a novel therapeutic protein (ThP) fusion of half-life extending Fc and Relaxin-2 heterodimer, which is engineered to closely resemble the structure of the natural hormone. AZD3427 is designed to improve pharmacokinetics and stability of human Relaxin-2, while maintaining its *in vitro* and *in vivo* pharmacology profile. AZD3427 is currently in clinical development.

Discovery and Characterization of Novel Peptides and Small Proteins

Alan Saghatelian, Ph.D.
Professor
The Salk Institute for Biological Studies

Determining the number and understanding the function of protein-coding genes in the human genome is one of the most important challenges in biology. Using a combination of cutting-edge proteomics and genomics tools we have found thousands of new protein-coding genes in the human genome. These protein-coding genes were initially missed because they encode peptides and small proteins of less than hundred amino acids (microproteins), revealing a blind spot in gene finding algorithms for small ORFs (smORFs). The functional characterization of several smORFs has led to the discovery of new pathways that regulate diverse cellular processes and physiological processes. These results highlight the existence of a large new class of understudied protein-coding genes that may contain many additional bioactive microproteins.

CryoEM After the Resolution Revolution: Achievements, Developments and Challenges

Anette Schneemann, Ph.D.
Senior Staff Scientist
Scripps Research

CryoEM has undergone a spectacular rise to the forefront of structural biology since the resolution revolution several years ago. Following major improvements in electron microscopes,

breakthroughs in camera technology and new image processing algorithms, cryoEM is now a go to method for high resolution protein structure determination. Technological advancement continues at a breathtaking speed and ability to solve structures at near atomic resolution has become increasingly routine, efficient and cost-effective. This presentation will provide a brief overview of the three modalities in cryoEM (single particle analysis, tomography and micro electron diffraction) and highlight some of the dazzling achievements that have occurred in the field. Current trends and strategies for further innovation will be introduced and explained. Lastly, despite the many exciting improvements in cryoEM, significant challenges remain, particularly with regard to sample preparation and throughput. Solving these stubborn bottlenecks represents a major effort in the field and potential solutions will be presented and discussed.

The Next Generation of RaPID System

Hiroaki Suga, Ph.D.
Professor
The University of Tokyo

Macrocyclic peptides possess a number of pharmacological characteristics distinct from other well-established therapeutic molecular classes, resulting in a versatile drug modality with a unique profile of advantages. Macrocyclic peptides are accessible by not only chemical synthesis but also ribosomal synthesis. Particularly, recent inventions of the genetic code reprogramming integrated with an *in vitro* display format, referred to as RaPID (Random non-standard Peptides Integrated Discovery) system, have enabled us to screen mass libraries (>1 trillion members) of non-standard peptides containing multiple non-proteinogenic amino acids, giving unique properties of peptides distinct from conventional peptides, e.g. greater proteolytic stability, higher affinity (low nM to sub nM dissociation constants similar to antibodies), and superior pharmacokinetics. The field is rapidly growing evidenced by increasing interests from industrial sectors, including small start-ups as well as mega-pharmas, toward drug development efforts on macrocyclic peptides, which has led to several *de novo* discovered peptides entering clinical trials. This lecture discusses the aforementioned screening technology, the RaPID system, and several showcases of therapeutic potentials of macrocyclic peptides. This lecture also discusses the most recent advance in the display of pseudo-natural products generated by thiopeptide post-translationally modifying enzymes.

A New Approach to Cancer Therapy with Documented Clinical Effects

Catharina Svanborg, M.D., Ph.D.
Professor (emeritus) Clinical Immunology
Lund University

Controlling cancer cell proliferation and death is a long-term goal of science and cancer therapy. Inducing apoptosis exclusively in cancer cells would, in theory, achieve treatment without side effects, but such solutions have proven elusive. Silencing oncogenes would prevent tumor progression and restore tissue homeostasis. Two approaches are discussed here.

1. *A new group of protein-lipid complexes that preferentially kill tumor cells in cancer models and clinical studies*. We have identified a peptide-based molecular approach for targeting and killing tumor cells and evidence of its clinical potential. A 39-residue alpha-helical peptide from alpha-lactalbumin gains lethality for tumor cells by forming oleic acid complexes (alpha1-oleate). NMR measurements and computational simulations define a lipid core surrounded by conformationally fluid, alpha-helical peptide motifs, essential to trigger tumor cell death. In a

placebo-controlled clinical trial of non-muscle invasive bladder cancer, primary end points of safety and efficacy of alpha1-oleate treatment were reached. Intra-vesical instillations of alpha1-oleate triggered massive shedding of tumor cells and tissue fragments into the urine, treated tumors showed evidence of apoptosis and the tumor size was reduced. Drug-related side effects were not detected, supporting a lack of toxicity. The results are especially encouraging for bladder cancer, where therapeutic failures and high recurrence rates create a great, unmet medical need.

Presenting two novel approaches to silencing oncogenes

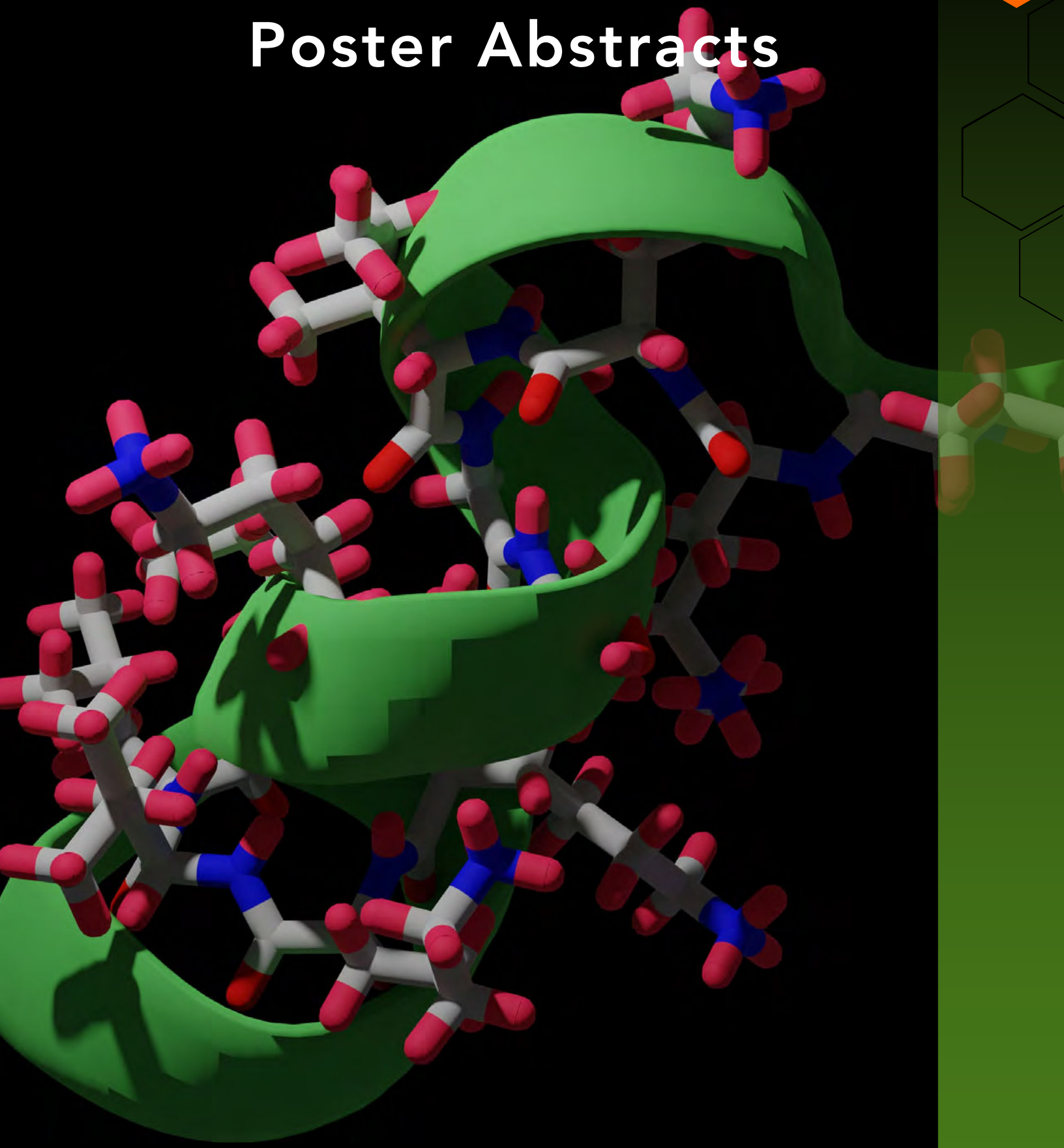
2. *A new approach for targeting the MYC oncogene, using a bacterial protease.* While MYC has been named ''the quintessential oncogene'' and is deregulated in the majority of human cancers, finding c-MYC inhibitors for therapeutic use has been problematic. MYC has long been viewed as "undruggable". We made the surprising observation that uropathogenic *E. coli* activate c-MYC degradation and attenuate MYC expression in host cells and tissues. We further identified effector molecules responsible for this effect. The bacterial Lon protease degraded c-MYC and showed therapeutic efficacy in bladder and colon cancer models. Long-term protection, defined by delayed tumor progression, increased survival and low toxicity further supported the therapeutic potential of Lon. These results suggest that bacteria have evolved strategies to control c-MYC tissue levels, which can be exploited to target c-MYC therapeutically in different cancers.

Invention of Oral PCSK9 Inhibitor from mRNA Display Selection

Abbas M. Walji, Ph.D.
Director, Discovery Chemistry
Merck & Co. Inc.

Proprotein convertase subtilisin/ kexin type 9 (PCSK9) is a secreted serine protease implicated in the progression of hypercholesterolemia. Inhibitors of the PCSK9 : LDL (low-density lipoprotein) receptor (protein : protein interaction (PPI)) have demonstrated clinical benefit in the reduction of LDL cholesterol and are currently used in the treatment of dyslipidemia. However, the current approved therapies which include two monoclonal antibodies and one siRNA, are limited due to administration by injection. Our goal has been to elevate the medical benefit of PCSK9 inhibition through an oral therapeutic agent that would provide patients with a more accessible and convenient route of administration. Herein we will share our success in identifying high affinity cyclic peptides from mRNA display selections and how we leveraged our institutional strength in structure-based drug design and innovative medicinal chemistry to overcome the chemical and pharmacokinetic challenges and yield a clinical candidate.

Poster Abstracts



Withdrawn

P01 In Vitro Cytotoxicity of Hybrid Peptides on CaSki Cervical Cancer Cells

Ardila-Chantré, N.[1], Fierro-Medina, R. [1], Parra-Giraldo, C. M.[2], Rivera-Monroy, Z. Y. [1], García-Castañeda, J.E. [1]

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Hybrid peptides are non-natural constructs that contain at least two different bioactive sequences and can be obtained by the chemical union of these sequences (1). These hybrid peptides are designed to achieve molecules with improved properties or to confer a specific biological activity. In this research hybrid peptides containing the RRWQWR sequence together with functional peptide sequences such as anticancer peptides, targeting peptides to cervical cancer cells, and cell penetrating peptides, were synthesized using solid phase peptide synthesis and Fmoc/tBu strategy (2). Hybrid peptides were purified by solid phase extraction and the purity of the peptides was between 85 and 99%. They were also characterized by reverse phase high performance liquid chromatography (RP-HPLC) and MALDI-TOF mass spectrometry. The cytotoxic effect of the peptides was evaluated in vitro on human cell lines derived from cervical cancer CaSki (3). The results show that the hybrid peptides RRWQWR-Ahx-RWQWRWQWR and RRWQWR-Ahx-RLLRRLLR showed the greatest cytotoxicity on the cell line evaluated. It was observed that the cytotoxic effect occurs in a short time and was dependent on the concentration of the hybrid peptide. In this way, it is verified that hybrid peptides can be a useful tool for the design of cytotoxic agents.

Acknowledgements

MTT: (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)

Precursor peptide	IC_{50} (μM) CaSki
RRWQWR	> 202
RWQWRWQWR	> 134,5
RLLRRLLR	> 182,7
QQLPSSSTSTYP	> 154,5
GDALFSVPLEVY	> 152,8
KQNLAEG	> 263,9
QVNGLGERSQQM	> 148,6
YGRKKRRQRRR	> 124,0
RRRRRRRR	> 145,0

Functional Peptide	Hybrid peptide sequence	IC_{50} (μM) CaSki
Anticancer peptides	RRWQWR-*Ahx*-RWQWRWQWR	49
	RRWQWR-*Ahx*-RLLRRLLR	9,2
Targeting peptides to cervical cancer cells	RRWQWR-*Ahx*-QQLPSSSTSTYP	>84,2
	RRWQWR-*Ahx*-GDALFSVPLEVY	> 83,7
	RRWQWR-*Ahx*-KQNLAEG	> 108,7
	RRWQWR-*Ahx*-QVNGLGERSQQM	> 82,4
Cell penetrating peptides	RRWQWR-*Ahx*-YGRKKRPQRRR	> 77,5
	RRWQWR-*Ahx*-RRRRRRRR	> 85,1

Table 1. IC_{50} values obtained for the peptides against the cervical cancer cell line CaSki.

To the Universidad Nacional de Colombia and the MinCiencias for the financing of the project: "Obtención de un prototipo peptídico promisorio para el desarrollo de un medicamento de amplio espectro para el tratamiento del cáncer de colon, cuello uterino y próstata". Project code 110180762973, contract RC No. 706–2018.

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P02 Cyclic And Linear Peptides Containing Tryptophan and Arginine Residues as Antifungal Agents

Khushbu Bhakta (presenter), Naiera Mohamed Helmy, Jonathan Moreno, Keykavous Parang
Chapman University School of Pharmacy

Pathogenic fungi are responsible for several human infections. Antibiotic resistance development, the increasing number of immunodeficiency and/or immunosuppression-related diseases, and limited therapeutic selections trigger the search for novel alternative antifungal agents. Herein, we report the synthesis of peptides containing positive and hydrophobic amino acids, namely linear peptides, $(R_3W_3)_2$, $(RWRW_3)_2$, $(R_3WRW)_2$, $(RWW)_4$, and $(WRR)_4$ and their cyclic peptides counterparts, $[R_3W_3]_2$, $[RWRW_3]_2$, $[R_3WRW]_2$, $[RWW]_4$, and $[WRR]_4$. The peptides were screened against *candida albicans* (ATCC 60193), *candida pararsilosis* (ATCC 23019), and *aspergillus fumigatus* (Af-BP, clinical isolate) for the antifungal activity. Linear and cyclic peptides showed minimum inhibitory concentration (MIC) ranging from 6.25 to 50 µg/ml. Minimum Fungicidal concentration (MFC) values were between 25 to 50 µg/ml against *candida albicans* and *candida pararsilosis*. Among linear peptides, (WRR)4 showed the lowest MIC of 6.25 µg/ml against Candida pararsilosis and 12.5 µg/ml against *candida albicans* and *aspergillus fumigatus*. cyclic $[R_3W_3]^2$ showed a MIC of 12.5 µg/ml in three isolates, and cyclic $[WRR]_4$ showed MIC values of 12.5, 6.25, and 25 µg/ml against *candida albicans*, *candida pararsilosis*, and *aspergillus fumigatus*, respectively. In the case of *aspergillus*, cyclic $[R_3W_3]_2$ showed the highest inhibition (80%) in biofilm generation when compared to $(WRR)_4$ and $[WRR]_4$ with 41.9 and 53% inhibition, respectively. Time-kinetics assay showed the effect of the peptides on inhibiting antifungal growth from 3-9 hours. The effect of peptides on the constructions of fungal growth of three isolates was demonstrated using confocal microscopy, indicating the inhibitory effect of the peptides upon the remarkable decrease in the number of treated cells.

P03 Evaluation of the Stability and Degradation Profile of Modified Peptides Derived from LfcinB

Blanco-Medina Isabella, Guerra-Acero-Turizo Luisa Maria, Cardenas-Martínez Karen Johana, González-López Nicolás Mateo, García-Castañeda Javier Eduardo, Rivera-Monroy Zuly Jenny

Peptides derived from the protein Bovine Lactoferricin and their modifications have shown antibacterial, antifungal and antineoplastic activity and selectivity, thus, they are candidates for further development. Although they have shown exceptional results, there are problems related to their stability, considering their peptidic structure they are likely to be targets of several proteases found in human tissue. This might arise as a challenge in their development as their pharmacokinetic properties might not be appropriate for drug development. Taking all of this into account, it is important to preliminarily assess the pharmacokinetic properties of these peptides. In this work 8 peptides, monomeric, dimeric and functionalized with RGD motif, were analyzed using RP-HPLC. Peptides were evaluated: (I) in a 25% human serum solution, (II) in a complex biological system of cellular culture medium with 10% of fetal bovine serum, and (III) against trypsin and chymotrypsin. All of the 8 peptides were successfully evaluated for their stability in different complex biological systems. These peptides were found to bind to plasma proteins, possibly due to their positive charge and amphiphilicity. Monomeric peptide proved to be more stable than its dimeric analog in human serum. RGD modifications were proven to diminish plasma protein binding percentage. Furthermore, they showed high susceptibility to proteases. The analytical method and pretreatment process proved to be useful for the analysis of peptides in complex biological matrices. Half life time and protein binding were established for each peptide in their respective matrix.

Acknowledgements
To the Universidad Nacional de Colombia and the MinCiencias for the financing of the project: "Obtención de un prototipo peptídico promisorio para el desarrollo de un

medicamento de amplio espectro para el tratamiento del cáncer de colon, cuello uterino y próstata". Project code 110180762973, contract RC No. 706–2018.

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P04 Arginine Modifications of Bovine Lactoferricin Peptides with Cytotoxic Effect Against Colon Cancer Cell Lines

Karen J. Cárdenas- Martínez[1], Andrea C. Barragán-Cárdenas[2], Claudia M. Parra-Giraldo[3], Alejandra Ochoa-Zarzosa[5], Joel E. Lopez-Meza[5], Zuly J. Rivera- Monroy[4], Javier E. García- Castañeda[1]
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There is an increasing need for novel anticancer agents as drug resistance arises, leading to remission and difficulties in curing patients with cancer. Among this burden, in the United States in 2022 colon cancer is expected to be the third more common and lethal cancer in both sexes. Anticancer peptides are considered new treatment alternatives and Bovine lactoferricin-derived peptides, precisely ^{26}[F] LfcinB (20-30)2 previously presented cytotoxicity against Caco-2 cells (IC_{50}: 17μM). As an interesting molecule for colon cancer treatment, we developed some modifications which include: Orn/Arg changes and N-terminal substitutions of D-Arg by L-Arg. We tested the cytotoxic effect of these peptides against Caco-2 and HT-29 colon cancer cell lines and HEK 293, fibroblast, and Vero noncancer cell lines. We found that ^{20}[Arg] plays an important role in the activity and selectivity of these molecules and that ^{25}[Arg] can be changed for ornithine with overall improvements in selectivity. All molecules presented low hemolytic activity (<10%) at concentrations of 62 μM. We analyzed by flow cytometry the cell dead type induced by peptide ^{25}[Orn]^{26}[F] LfcinB (20-30)2; the cellular dead was mainly associated to late apoptosis in all cases, like what was found with the parent peptide. These molecules were affected by trypsin and chymotrypsin treatment, for which further stability optimization might be needed. Overall, the peptide ^{25}[Orn]^{26}[F] LfcinB (20-30)2 compared to 26[F]LfcinB (20-30)2 has similar potency against cancer cell lines and higher selectivity against noncancer cell lines, these peptides can be considered promissory to develop future therapies against colon cancer.

Key words: Bovine lactoferricin, arginine, ornithine, colon cancer.

P05 Integrated Design of a Membrane-Lytic Peptide-Based Intravenous Nanotherapeutic Suppresses Triple-Negative Breast Cancer

Charles H. Chen[1,2], Yu-Han Liu[3], Arvin Eskandari[1], Jenisha Ghimire[4], Leon Chien-Wei Lin[3], Zih-Syun Fang[3], William C. Wimley[4], Jakob P. Ulmschneider[5], Kogularamanan Suntharalingam[6], Che-Ming Jack Hu[3], Martin B. Ulmschneider[1]

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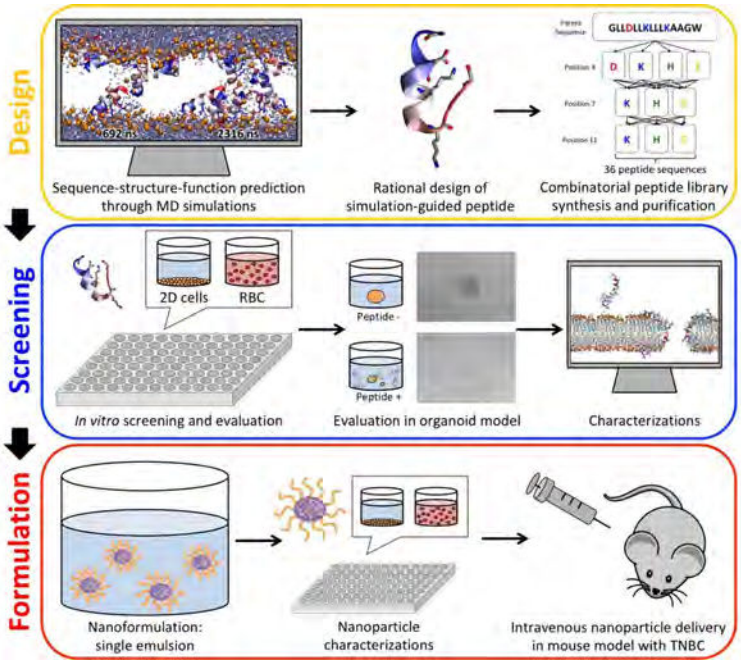
Membrane-lytic peptides offer broad synthetic flexibilities and design potential to the arsenal of anticancer therapeutics, which can be limited by cytotoxicity to noncancerous cells and induction of drug resistance via stress-induced mutagenesis. Despite continued research efforts on membrane-perforating peptides for antimicrobial applications, success in anticancer peptide therapeutics remains elusive given the muted distinction between cancerous and normal cell membranes and the challenge of peptide degradation and neutralization upon intravenous delivery. Using triple-negative breast cancer as a model, the authors report the development of a new class of anticancer peptides. Through function-conserving mutations, the authors achieved cancer cell selective membrane perforation, with leads exhibiting a 200-fold selectivity over non-cancerogenic cells and superior cytotoxicity over doxorubicin against breast cancer tumorspheres. Upon continuous exposure to the anticancer peptides at growth-arresting concentrations, cancer cells do not exhibit resistance phenotype, frequently observed under chemotherapeutic treatment. The authors further demonstrate efficient encapsulation of the anticancer peptides in 20 nm polymeric nanocarriers, which possess high tolerability and lead to effective tumor growth inhibition in a mouse model of MDA-MB-231 triple-negative breast cancer. This work demonstrates a multidisciplinary approach for enabling translationally relevant membrane-lytic peptides in oncology, opening up a vast chemical repertoire to the arms race against cancer.

Fig 1.Schematic diagram of integrated design of peptide-based nanomedicine in cancer treatment. The process of nanomedicine development involves peptide drug design, evaluation against both 2D and 3D cell cultures, and nanomedicine formulation for animal study.



P06 Dual Myristic Acid and Trans-activator of Transcription Conjugation of PKC Beta II Peptide Inhibitor Enhances Delivery to Mitigate Myocardial Ischemia/ Reperfusion Injury

Logan Clair, James Ramsarran, Taurai Augustin, Emily Andrews, Tameka Dean, Qian Chen, Robert Barsotti, and Lindon Young

Philadelphia College of Osteopathic Medicine, Department of Biomedical Sciences

Dual conjugation of PKC Beta II peptide inhibitor (PKCßII-) with myristic acid (myr) and trans-activator of transcription (Tat) (Myr-Tat-CC-SLNPEWNET) has been shown to enhance intracellular delivery and attenuate myocardial ischemia/reperfusion (I/R) injury in an ex-vivo rat model. Previously, myr-Tat-PKCßII- demonstrated significant cardioprotective effects from 100nM to the 1pM concentration. However, the lowest concentration at which myr-Tat-PKCßII- is still cardioprotective has yet to be determined; this study investigates the 100fM concentration.

Isolated rat hearts underwent global I(30-min)/R(50-min). Cardiac function was recorded via a pressure transducer. Treatments were infused during the first 5 min of R. Following R, infarct size was determined by excising infarcted tissue stained with 1% triphenyltetrazolium chloride (i.e. infarct tissue weight/ total tissue weight). Data were analyzed using ANOVA Fisher's LSD analysis.

For both infarct size and final +dP/dt Max, myr-Tat-PKCßII- 100fM (12.1±0.9%, 401±60mmHg/s, n=3) was not significantly different compared to untreated controls (21.9±2.8%, 783±92mmHg/s, n=20). Compared to the 1pM concentration (1095±433mmHg/s, n=4), final +dP/dt Max at 100fM was significantly depressed ($p<0.05$).

Myr-Tat-PKCßII- 100fM demonstrated a reduction in infarct size accompanied with cardiac depression. Although this reduction in infarct size was not significant compared to untreated controls, further testing is required. Myr-Tat-PKCßII- has continually exhibited concentration-independent reduction in infarct size, mechanism unknown. However, thus far in our ongoing experiments, cardiac function has been concentration-dependent with optimal function at 1pM and depressed function at both extremes (i.e. 100nM and 100fM).

P07 Metabolic Stress Mediates Accumulation of Glycation (AGE) PTMs in the Proteomes of Mouse Dendritic Cells and Reshapes the MHC-II Immunopeptidome

Cristina C Clement[1]; Rajesh Kumar Soni[2]; Laura Santambrogio[1]
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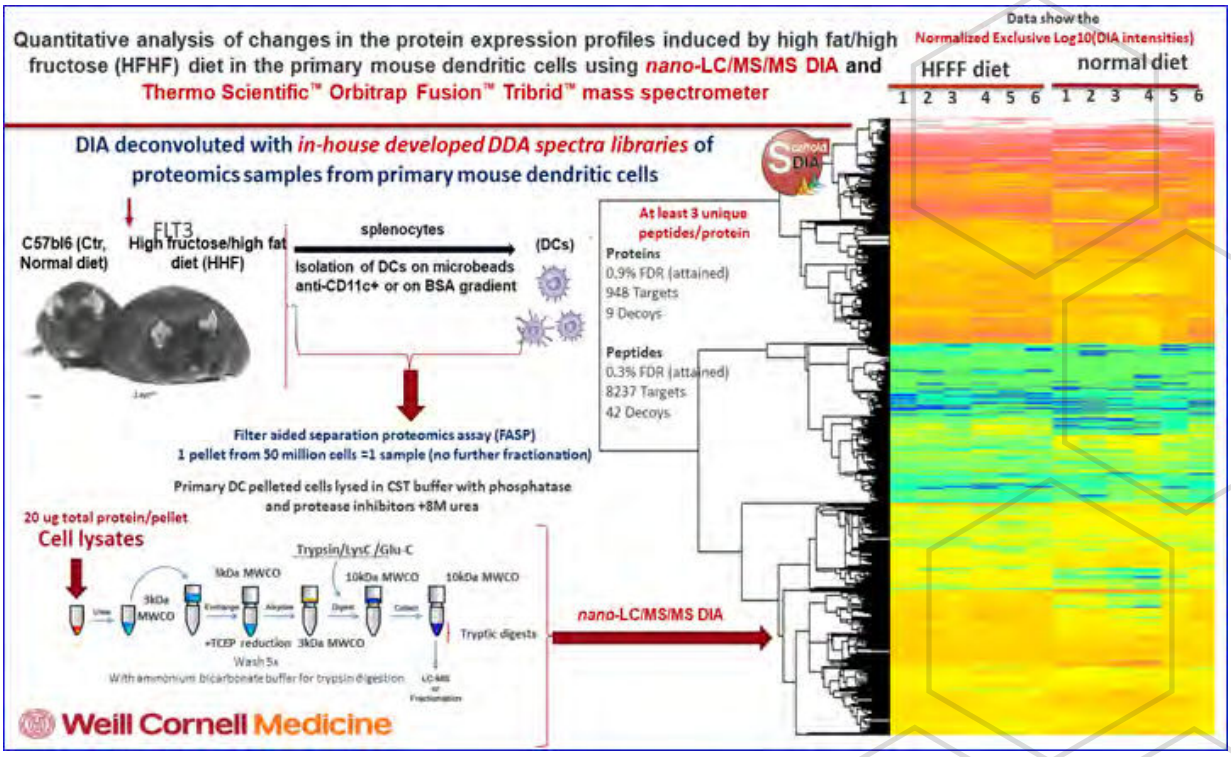
A diet rich in saturated fat and carbohydrates causes a low-grade chronic inflammation in several organs. To investigate the impact of oxidative stress and metabolic syndrome on the whole cellular proteomes of professional antigen presenting cells (APCs), we isolated biological replicates consisted of total proteomic extracts of dendritic cells (DCs) from B6 mice on normal diet, high fructose/high fat (HFHF) diet and Ob/Ob mice. We developed and optimized quantitative label-free (LFQ) data independent (DIA) and data dependent (DDA) nano LC-MS/MS analytical platforms for monitoring the protein expression profiles. Bioinformatics and GO annotations mapped quantitative changes in energy and stress related proteins associated with several metabolic pathways including glycolysis, fatty acids oxidation and mitochondrial oxidative phosphorylation. Analysis of the cellular proteome PTMs ranked formyl-lysine and carboxymethyl lysine (CML) as the most abundant AGEs found in Ob/Ob DCs. An additional proteomic analysis, performed on gradient purified late endosomes also confirmed the increased number of glycated proteins in the Ob/Ob vs B6 organelles. We further obtained the immunopeptidomes by immunoaffinity-purification of MHC-II proteins from the DCs of Ob/Ob mice, as well as B6 mice on Ctr or HF diets, followed by peptides elution and analysis using (LFQ) DDA and DIA assays. The immunopeptidomes were enriched in peptides and neoepitopes derived from proteins involved in many branches of redox metabolism and cellular responses to oxidative stress. The qualitative and quantitative changes in the DC proteomes elicited by metabolic insults were mirrored in the landscape of immunopeptidomes eluted from I-Ab MHC-II molecules on mouse DCs.



P08 Amino Acids as Heterogenous Soft Template Nucleants in Peptide Crystallisation

Laura Coffey, Prof. Sarah Hudson, Prof. Tewfik Soulimane
University of Limerick

A soft template is a species that is dissolved in a crystallisation liquor and works to facilitate and control nucleation. Amino acids have been shown to act as heterogenous soft templates for insulin crystallisation (Link and Heng 2021). This study aims to investigate this soft templating behaviour in peptide crystallisation using L-histidine and L-arginine as soft templates.
The majority of protein and peptide crystallisation studies reported are concerned with elucidating crystal structure (Spencer and Nowick 2015). This has provided valuable information about the function of many biological peptides and proteins but more research is needed on the physiochemical properties that govern their crystallisation. This study aims to add to this research and to determine how the crystallisation of proteins and peptides can be enhanced and potentially controlled.
Methodology: Sitting drop vapour diffusion crystallisation of peptides (approx. 10 amino acid chain) will be carried out in the presence of varying concentrations of L-histidine and L-arginine. Mean crystal number and size will be trended over time from micrographs.

Link, F.J. and Heng, J.Y.Y. (2021) 'Enhancing the crystallisation of insulin using amino acids as softtemplates to control nucleation', CrystEngComm, 23(22), 3951-3960, available: http://dx.doi.org/10.1039/D1CE00026H.
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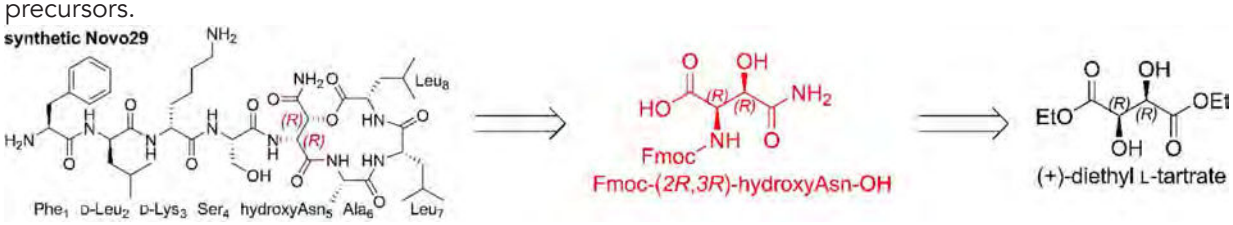
P09 Synthesis and Stereochemical Determination of Novo29, a New Peptide Antibiotic

Maj Krumberger, Xingyue Li, Adam G. Kreutzer, Aaron J. Peoples, Anthony G. Nitti, Andrew M. Cunningham, Chelsea R. Jones, Dallas E. Hughes, James S. Nowick

Novo29, a new antibiotic from a soil bacterium closely related to *E. terrae* was recently reported. Novo29 is an eight-residue depsipeptide comprising a macrolactone ring and a linear tail. It is active against Gram positive bacteria, including drug-resistant human pathogens, such as MRSA and VRE. Novo29 kills bacteria by inhibiting bacterial cell wall synthesis, with no detectable resistance occurring upon serial passaging. Although the amino acid sequence of Novo29 has been reported, the stereochemistry of the rare noncanonical amino acid hydroxyasparagine at position 5 was not able to be determined. Neither NMR spectroscopic analysis nor correlation with authentic hydroxyasparagine of known stereochemistry was feasible, leaving open the question of which hydroxyasparagine stereoisomer constituted the natural product.

Novo29 is related in structure to teixobactin, which is produced by *E. terrae*, but it is smaller, containing 8 residues instead of 11. Like teixobactin, Novo29 exhibits good activity against Grampositive bacteria and targets the prenyl-pyrophosphate-saccharide regions of lipid II and related membrane-bound cell wall precursors.

Novo29 is a promising antibiotic drug candidate because it shares structural similarities with teixobactin, binds to similar lipid II cell-wall precursors, and does not exhibit gelation at high concentrations. In the current study, we establish the stereochemistry of hydroxyasparagine residue at position 5 and confirm the structure of Novo29 through chemical synthesis and spectroscopic and functional correlation. We also report the X-ray crystallographic structure of a hydroxyasparagine epimer of Novo29, which may provide insights into how Novo29 may bind bacterial cell wall precursors.



P10 Artificial Intelligence Based Discovery of Novel Peptides with Anti-inflammatory Activity

Lis Ewa, Lindmeier Lily
Koliber Biosciences

Artificial Intelligence (AI) is becoming widely adopted for small molecule drug discovery, yet the methods for leveraging AI for peptide drug discovery are lagging far behind. These challenges are primarily driven by limited availability of peptide datasets, high dimensionality of the design space as well as poorly developed methods for encoding peptides for deep learning algorithms. Koliber has developed a unique biologically inspired AI peptide platform that enables training of high-performance machine learning models even on small datasets. The models enable in silico prioritization of new variants and provide deep insights into key drivers enabling hypothesis generation. The AI platform has been validated on peptide datasets in several application areas including immunology, metabolic disease and antimicrobials. The peptides included cyclic peptides and peptides containing unnatural amino acids and ranged from 6 to 45 residues in length. In this presentation we will discuss how the AI platform was utilized to build T cell activation models and discover novel peptides with anti-inflammatory cytokine releasing activity. The in vitro validation in human immune cells including development of novel immunogenicity assays will be discussed as well.

P11 Discovery of Macrocyclic Peptide Drug Leads by High-Throughput Functional Screening Assays

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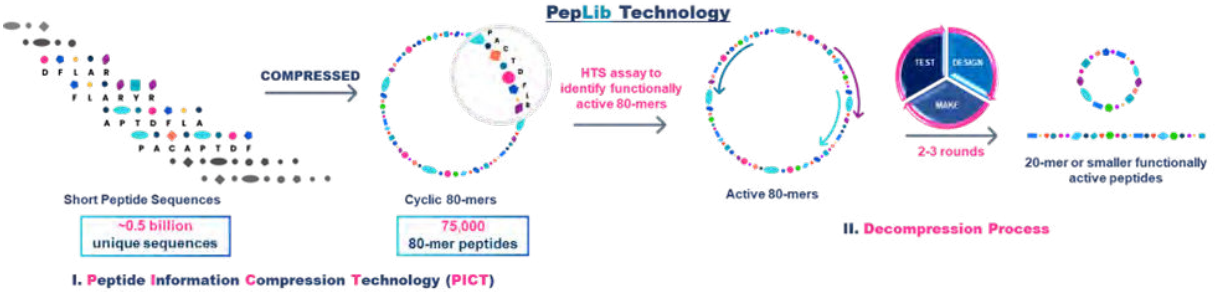
PepLib has developed a peptide discovery platform capable of the discovery of functionally active peptide hits directly from a screen. Based on PepLib's proprietary Peptide Information Compression Technology (PICT), a library of cyclic peptides containing half a billion unique sequences has been designed and synthesized. Each member is individually expressed, head-to-tail cyclized, and purified in a genetic tag-free manner to build a one-well one-peptide library. The capabilities of the PepLib discovery platform extend beyond just binding assays to biochemical and cell-based functional assays making it suitable for difficult-to-drug membrane proteins including GPCRs, ion channels and other cell-surface receptors.



To highlight the success of this platform, results from two functional screens are presented: 1) discovery of a 10-mer head-to-tail cyclized peptide antagonist (IC50 ~ 460 nM) against a GPCR and 2) discovery of a 16-mer head-to-tail cyclized peptide inhibitor (IC50 ~ 500 nM) of a receptor-ligand interaction.
** Lead and corresponding author*

P12 Elucidating the Role of Quorum Sensing (QS) and Developing QS Modulators for *Streptococcus pneumoniae* and Its Close Commensal Relative, *Streptococcus mitis*

Tahmina Ahmed Milly, Yftah Tal-Gan
Department of Chemistry, University of Nevada

Quorum sensing (QS) is a ubiquitous communication mechanism in bacteria that controls bacterial group behavior phenotypes, such as competence, biofilm formation, and virulence factor production.[1] *Streptococcus pneumoniae*, an opportunistic pathogen, and *Streptococcus mitis* are prototypes of commensal bacteria in the mitis group and share >80% of their genes.[2] Both *S. mitis* and *S. pneumoniae* utilize a peptide pheromone (competence stimulating peptide, CSP), which binds to its membrane bound ComD receptor to induce QS responses and different pathogenic phenotypes. Our goal is to target this nonessential bacterial communication pathway through impediment of the peptide-receptor interaction by using synthetic CSP analogs, thereby circumventing a key issue with traditional antibiotics, the introduction of selective pressure for resistance development.[3, 4] To this end, we conducted comprehensive structure activity relationship (SAR) analyses of both *S. pneumoniae* and *S. mitis* CSPs to gain a deeper understanding of the molecular mechanisms that drive these QS circuitries. Our SAR results revealed several interesting activity trends and uncovered several CSP-based QS modulators with distinct activity profiles. We then performed structural analysis of mutated CSP analogs to determine the correlation between the CSP secondary structure and QS activation. Additionally, we evaluated several phenotypes that can be utilized to assess the effect of lead peptide analogs on the expression of group behavior genes. In addition to yielding a series of new

QS activators and inhibitors, our key SAR knowledge of the CSP pheromones can be utilized for the rational design of highly potent, pharmacologically stable CSP-based QS modulators with therapeutic potential.

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P13 Combination of Hybrid Cyclic-Linear Amphipathic Peptides with Chemotherapeutic Agents as a Strategy to Enhance Anticancer Activity

Presenting Author Moreno, J.[1] Contributing author(s) El-Aarag, B.[1, 2], Tiwari, R., Mentor or PI Parang, K.[1]

[1] Center for Targeted Delivery, Department of Biomedical and Pharmaceutical Sciences, Chapman University School of Pharmacy

[2] Biochemistry Division, Chemistry Department, Faculty of Science, Menoufia University

We have previously shown that peptides containing hydrophobic and positively charged residues are efficient molecular transporters of doxorubicin. Herein, we report the synthesis and biological evaluation of two hybrid peptides containing cyclic peptides composed of alternate arginine (R) as positively charged residues and tryptophan (W) as hydrophobic residues ($[RW]_5K$ and $[R_5W_4]K$) conjugated to the linear peptide AH-135 with the sequence of (Ac)NH-R-W-L-R-R-W-L-R-W-W-R-R-COOH. The synthesized hybrid peptides were $[RW]_5K$-(AH-135) and $[R_5W_4]K$-(AH-135). $[RW]_5$ and $[R_5W_4]$ have been previously reported by our laboratory as molecular transporter Cell Penetrating Peptide (CPP) and antimicrobial agents, respectively. The hybrid peptides were purified by reverse-phase HPLC and characterized by MALDI-TOF. The antiproliferative activities of several anticancer drugs: Clofarabine, Gemcitabine, Etoposide, Dasatinib, Camptothecin, Fludarabine, Cabazitaxel, and Doxorubicin, were improved in the presence of 8 μM of $[R_5W_4]K$-(AH-135) by (47%, 2-fold), (44%, 1.8 fold), (39%, 1.4 fold), (32%, 1.4 fold), (24%, 1.3 fold), (22%, 1.3 fold), (21%, 1.3 fold), and (15%, 2 fold), respectively, after 72 h incubation in MDA-MB-231 cells. Similarly, Gemcitabine (33%, 1.8 fold), Etoposide (31%, 1.4 fold), Chlofarabine (27%, 1.5 fold), Dasatinib (22%, 1.3 fold), Camptothecin (17%, 1.3 fold), and Cabazitaxel (15%, 1.3 fold) improved the antiproliferative activity of the parent drug in SK-OV-3 cells. Additionally, $[R_5W_4]K$-(AH-135) (8 μM) improved Doxorubicin activity by 5-fold in the Doxorubicin-resistant cell line MES-SA after 72 h of incubation. Indicating the potential of the hybrid peptide to be used as a delivery tool for chemotherapy drugs. This strategy may benefit from covalently linking the anticancer drugs to the hybrid peptide.

P14 Antibodies Generated Against an AP-derived Oligomer: Efforts Toward a Novel Alzheimer's Disease Immunotherapy

Chelsea Marie T. Parrocha,[1] Adam G. Kreutzer,[2] Jesse Pascual,[3] Cherie Stringer,[3] Jennifer T. Nguyen,[1] Ashley L. Ith,[1] Elizabeth Head,[3] and James S. Nowick*[1,2]

[1]Department of Pharmaceutical Sciences, University of California, Irvine

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ß-Amyloid (Aß) peptide vaccines are promising therapeutics against Alzheimer's disease (AD) which rely on the generation of antibodies after an endogenously administered Aß antigen. These newly generated anti-Aß antibodies neutralize endogenous targets of interest that are similar to the antigen. Current Aß peptide vaccine clinical candidates rely on nonconformationally defined fragments of full-length Aß as the antigen. However, these fragments could self-aggregate into heterogeneous higher orders of assembly which may lead to inconsistent treatments and potentially harmful side effects. Using a conformationally defined and biophysically characterized Aß-derived oligomer generated in our lab, 4AT-L, we sought to generate a novel peptide vaccine that ameliorates AD pathology in the 5xF AD transgenic AD mouse model and could serve as a potential new therapeutic against AD.
We hypothesized that 4AT-L could stimulate the production of antibodies that target endogenous Aß and may lead to amelioration of cognitive impairment and pathology in the 5xF AD mice. As a proof of concept, rabbit polyclonal antibodies were generated against 4AT-L creating the 4AT-L polyclonal antibody to determine if these antibodies can recognize AP in human brain tissue by immunohistochemistry and immunofluorescent microscopy. This investigation has shown that the polyclonal antibody recognizes disease relevant pathology in the of people with AD and people with Down Syndrome and AD. 5xFAD mice immunized with the 4AT-L peptide vaccine have thus far generated literature precedent antibody titers which may infer an amelioration of AD pathology and behavior impairment in 5xF AD mice. Final results will be presented at the Peptide Therapeutics Symposium.

P15 Xerisol™: A Biocompatible, Non-Aqueous Approach To Enhanced Peptide Solubility And Stability.

Steven J. Prestrelski
Xeris Pharmaceuticals, Inc.

Peptide drug formulations are prone to degradation and aggregation/fibrillation in aqueous environments. Our proprietary XeriSol™ non-aqueous formulation technology platform is designed to address the limitations of aqueous formulations for peptide drugs. The solutions are formulated using biocompatible, non-aqueous solvents that have high stability and solubility. The solvent prevents degradation and aggregation/fibrillation of the peptide and allows for development of room-temperature stable, ready-to-use peptide formulations. When a ready-to-use XeriSol formulation is injected into a patient, it is effectively placed back into a water environment where it displays high bioavailability. This presentation will showcase the technology platform including clinical data from the Gvoke® (glucagon injection) product which has been approved and is being commercialized globally. In addition, results will be presented for a pramlintide-insulin co-formulation currently in clinical studies.

P16 Docking Peptides into HIV/FIV Protease: A Case Study

Dayna Olson[1,2], Katherine Ge[1,3] and Michel Sanner[1]
[1]Department of Integrated Structural and Computational Biology
The Scripps Research Institute
[2]Michigan State University
[3]Bishops High School

Peptide docking software has been rapidly improving over the past few years with state-of-the art techniques now rivaling docking accuracy of small molecule docking which has been refine for decades. Notably, deep learning techniques such as AlphaFold2 and OmegaFold are showing promising results for predicting the interaction mode of peptides with their binding partners. Here we compare deep learning and conventional peptide docking methods' ability to recognize native

peptide sequences for HIV and FIV protease. We identified a set of native peptides from the gag pol polyprotein chain cleaved by the protease and designed sets of peptides unlikely to be cleaved. We then docked these peptides with AlphaFold2, OmegaFold and AutoDock CrankPep. Surprisingly, the deep learning methods, which usually outperform conventional methods performed poorly for this particular target, while the conventional docking program AutoDock CrankPep mostly docked the native peptides correctly, while incorrectly predicting half the non-native peptides to be cleaved. These results suggest that better prediction accuracy is achieve when both conventional and deep learning docking methods are used jointly. They highlight the pressing need for post-docking re-ranking computational methods to select the most likely correct predictions.

P17 QPG-1030, Releasable Pegylation of Teduglutide Using Uni-Qleaver® Results in Improved PK/PD Properties in Rats Aiming for Once-Weekly Administration

Supaporn Sawadjoon, Marcus Bosson, Achim Orzechowski, Christian Sund, and Vidar Wendel-Hansen
QuiaPEG Pharmaceuticals AB

The Glucagon-like peptide 2 (GLP-2) analogue, teduglutide (Gattex®), indicated for the treatment of patients with short bowel syndrome (SBS) has an increased half-life (2-3 hrs) and stability as compared to the native GLP-2 (7 min), but still requires daily dosing. To further extend the half-life of teduglutide, a prodrug approach employing a releasable polyethylene glycol (PEG) linker has recently been developed. QPG-1030 was produced by conjugation of teduglutide to PEG using the releasable linker platform, Uni-Qleaver®, and showed improved pharmacokinetic (PK) and pharmacodynamic (PD) properties compared to teduglutide, similar to the properties of apraglutide, a GLP-2 analogue in clinical development aimed to be administered once weekly. An in vitro bioactivity assay for GLP-2 confirmed that the PEG-teduglutide conjugate has low agonist activity on the receptor and thus functions as a prodrug. Following a single subcutaneous dose of 400 nmol/kg of QPG-1030 to rats, a mean elimination half-life of 18 hours was observed for teduglutide. Following 5 days of repeated daily subcutaneous dosing of QPG-1030 to rats, a significant and dose-dependent increase in small intestinal weight was observed, indicative of potent GLP-2 agonist activity. The effect was significantly enhanced compared to that of teduglutide at comparable dose levels and comparable to equimolar daily doses of apraglutide. These results indicate that QPG-1030 has the potential to be developed as

P18 Benchmarking Peptide Docking: Comparing Deep Learning and Conventional Approaches

Sudhanshu Shanker and Michel Sanner
Department of Integrated Structural and Computational Biology
The Scripps Research Institute

Deep neural networks such as AlphaFold2 and OmegaFold were originally developed for the computational prediction of the structure of protein monomers starting from their sequence. Recently these methods have been shown to also perform well for predicting interactions of peptides with their binding partners. We benchmarked AlphaFold2 and the newly released OmegaFold against the state-of-the-art conventional peptide docking engine AutoDock CrankPep (ADCP) on various datasets. We provide a head-to-head comparison performance of these peptide docking software using the same success metric for all of them and discuss their respective merits. We show that, while the deep learning methods predictive models perform very well, ADCP successfully handles some cases where these other methods fall short, suggesting that a combination of these methods can achieve the best predictive accuracy.

P19 Myristoylated Protein Kinase C Epsilon Peptide Inhibitor Attenuates Acute Kidney Injury in Renal Ischemia Reperfusion

Sunit G. Singh[1], Alexis B. Verwoert[1], Tameka C. Dean[1], Devani Johnson[1], Lisa Shah[1], Shino Sleeper[1], Qian Chen[1], Robert Barsotti[1], Yanlin Jiang[2], James George[2], Anupam Agarwal[2], and Lindon Young[1,3]
[1]Philadelphia College of Osteopathic Medicine; [2] University of Alabama at Birmingham School of Medicine; [3] Young Therapeutics, LLC

Ischemia-reperfusion (I/R) is a major cause of acute kidney injury, resulting in decreased renal function due to reactive oxygen species (ROS) generated by tissue cytokines. Activation of cytokine receptors augment activation of protein kinase C epsilon (PKCε). Activated PKCε increases endothelial nitric oxide synthase (eNOS) activity during I/R. eNOS is uncoupled during I/R and principally produces ROS. We aim to evaluate the effects of cell permeable, myristoylated PKCε peptide inhibitor (N-myr-EAVSLKPT; myr-PKCε-) on renal function and PKCε translocation compared to scrambled peptide control (N-myr-LSETKPAV; myr-PKCε-scram) in murine renal I/R. We hypothesize that myr-PKCε- will recover glomerular filtration rate (GFR), attenuate serum creatinine (Cr) and PKCε translocation to vascular endothelium compared to myr-PKCε-scram.

Renal pedicles of male C57BL/6J mice (25–30g) were clamped bilaterally for 19 min. Myr-PKCε- or myr-PKCε-scram (1.6 mg/kg; 20 μM blood) were administered into the tail vein one min before unclamping. GFR and Cr were measured at baseline, 24h, 72h, and 96h post-injury. PKCε immunohistochemistry (IHC) was conducted on kidney sections. Data were evaluated by unpaired Student's t-test.

Myr-PKCε- (n=6) significantly improved both GFR and Cr throughout the 96h reperfusion period compared to myr-PKCε-scram control (n=7, $p<0.05$). Myr-PKCε- restored final GFR and Cr to 52% and 54% vs. myr-PKCε-scram 29% and 18% respectively, compared to initial baseline values. Qualitative IHC analysis shows that PKCε localization to vascular endothelium was attenuated by myr-PKCε- vs myr-PKCε-scram.

Results suggest myr-PKCε- improves kidney function and attenuates PKCε localization to vascular endothelium following I/R injury. Quantitative analysis of IHC is pending.

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P20 Rapid Screening of Disulfide-Rich Peptides with Nav1.7 Inhibitory Activity by PERISS Method

Hikaru Taira[1], Toshiaki Okada[1], Lu Zhibo[1], and Tadashi Kimura[1]
[1]Veneno Technologies Co. Ltd.

Disulfide-rich peptides (DRP) in the venom of spiders are highly active and selective against various ion channels. Besides, they have high resistance to digestive enzymes, making them a promising basic scaffold for peptide drugs. The PERISS (intra periplasm secretion and selection) is a peptide selection method based on evolutionary molecular engineering using periplasmic display technology, which enables rapid screening of DRPs that bind to an ion channel (Figure 1.).
In this study, we conducted to discover novel DRPs that inhibit a human voltage-gated sodium channel Nav1.7, which plays a key role in regulating peripheral pain.
To conduct the PERISS screening, gene constructs of a chimeric human potassium channel Kv2.1 in

which each voltage-sensing domain of Nav1.7 was transferred to Kv2.1 were prepared and expressed on the inner membrane of *E. coli*. The disulfide-rich peptide GTx1-15 derived from tarantula venom was used as the scaffold of the DRP library, and its genetic library was constructed using in silico calculation based on the three-dimensional structural model. Next, we performed the PERISS screening to identify Nav1.7-binding DRP sequences using these gene constructs. Then, the activity of the hit DRPs identified by the PERISS method was measured by the two-electrode voltage fixation method using an oocyte system of *Xenopus laevis*, then we identified the DRPs with Nav1.7 inhibitory activity. The PERISS method we have developed could provide novel active DRPs against various ion channels shorter than the conventional peptide screening method.

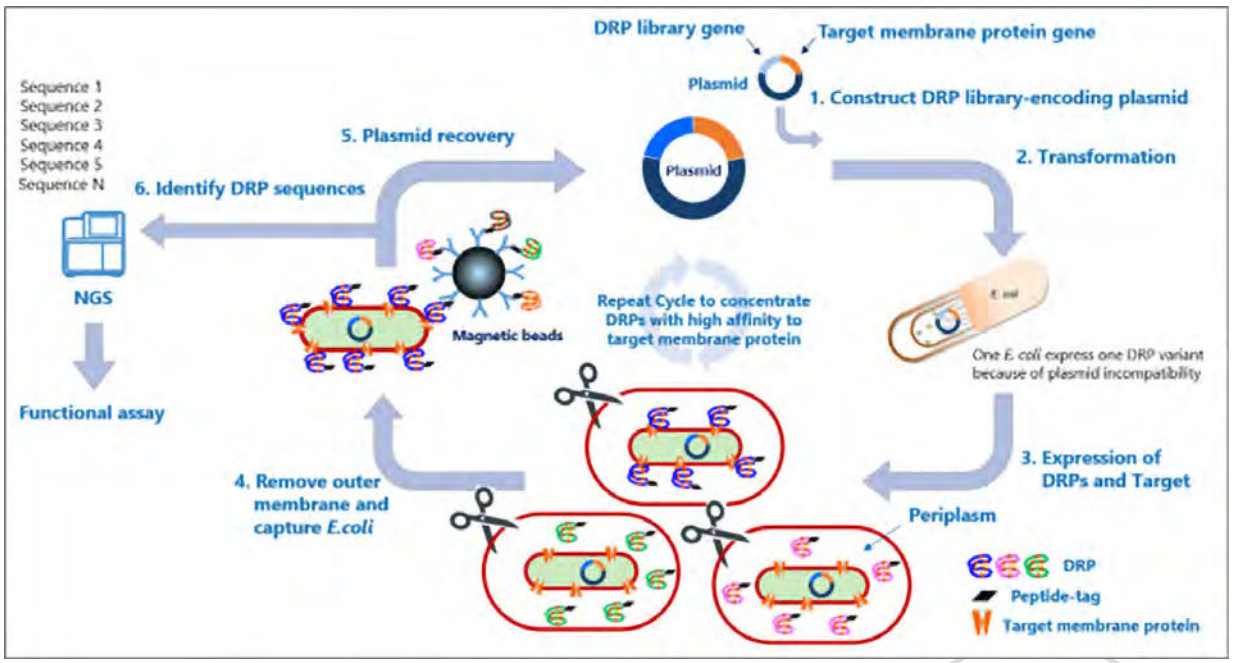
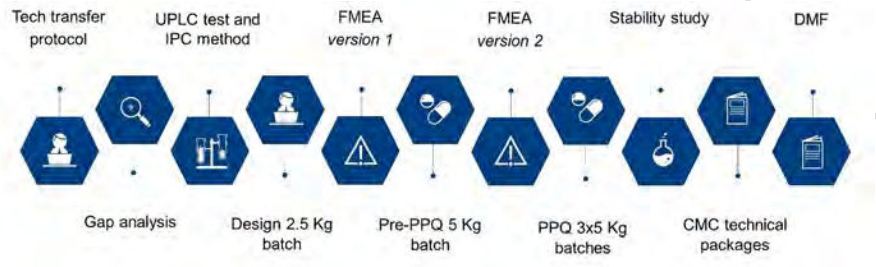


Figure 1. Schematic diagram of PERISS screening

P21 CMC Development Activities During Technology Transfer of Peptide Drugs

Jyothi Thundimadathil, Ph.D.
Director CMC Development, Bachem Inc.

Careful evaluation and execution of various CMC (Chemistry, Manufacturing and Control) activities is critical during process transfer of a peptide API from one site to another. The CMC aspects will be highlighted for technology transfer of a peptide drug, Lanreotide. In this case, technology transfer is planned to accommodate future scale up needs for the API. Parameters such as process change, scale, and modifications, equipment changes and revalidation requirements will be evaluated. Various CMC activities include preparation of tech transfer protocol, gap analysis, development of improved test methods, transfer of validated test methods, process challenge studies, FMEA (Failure mode effect analysis) version 1 and 2, preparation of pre-validation batch, manufacturing of 3 PPQ batches, ICH stability study of API, compilation of tech transfer report, and documentation for DMF filing.



P22 Synthesis of Sulfated and Glycosylated CCR5 N-terminal Peptide

Brooke Van Engen‖, Lisa Nicholson‖, Anna Rediger‖, Hailiang Joshua Zhu
Department of Chemistry, Dordt University

CC chemokine receptors play an important role in the mediation of physiological functions of immune cells and contain active binding sites on the N-terminal peptide.[1] CC chemokine receptor 5 (CCR5) mediates leukocyte activity via sulfation and glycosylation,[2] and previous research indicates that these post-translational modifications contribute to high binding affinity for chemokines.[1] Structure-defined CCR5 N-terminal peptides are needed to understand the effects of different forms of O-glycosylation and tyrosine sulfation on the binding affinity of CCR5. The synthesis of the O-glycosylated and sulfated N-terminal peptide is a challenge due to the instability of sulfation groups and the synthesis of the O-glycosylated amino acids. In our work, an azide-containing galactosyl chloride donor was synthesized in a large-scale from per-acetylated galactose with only one column purification needed at the last step of synthesis, and silver oxide was used for the first time in coupling the sugar donor with an Fmoc-Ser-OAll acceptor resulting in a 2.6:1 alpha/beta ratio. Notably, the Fmoc-Ser-OAll was synthesized in a more than 20-gram scale without column purification. Commercially available 2-chloro-trityl protected Fmoc-tyrosine was used for solid-phase sulfation as the 2-chloro-trityl group can be removed under mild acidic conditions without cleavage of the peptide from the resin, and a CCR5 N-terminal peptide with per-acetylated GalNAc and a sulfation group was synthesized with our strategy. Future work involves including four different protecting groups for Fmoc-tyrosine and incorporating Core 2 O-glycans in the N-terminal peptide.

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‖These authors contributed to this work equally

P23 Myristic Acid-Trans-Activator of Transcription Dual Conjugation Facilitates Delivery of Protein Kinase C Beta II Peptide Inhibitor Cargo in Leukocytes

Alexis Verwoert, Sunit Singh, Emily Andrews, Arjun Nair, Devani Johnson, Taylor DiLisi, Alexandra Barrera, Denise Pinto, Annam Humayun, Zinya Talukder, Tameka Dean, Qian Chen, Robert Barsotti, Lindon Young

Protein kinase C beta II (PKCßII) activation promotes polymorphonuclear (PMN) superoxide (SO) production by phosphorylating serine and threonine amino acid residues on NADPH oxidase (NOX-2).

Previously, myristic acid-conjugated (myr) PKCßII inhibitor (PKCßII-; N-SLNPEWNET) attenuated phorbol 12-myristate 13-acetate (PMA) induced SO release compared to PMA alone. Myr-conjugation to peptides is known to facilitate intracellular delivery of cargo via simple diffusion, while trans-activator of transcription (Tat; YGRKKRRQRRR) conjugation acts via an endocytotic mechanism. However, dual myr-Tat-conjugation is a new development in intracellular cargo delivery.

We hypothesize myr-Tat-conjugation will exhibit superior attenuation of SO release compared to myr- or Tat-conjugation alone.

This study compared the effects of myr-PKCßII-, Tat-PKCßII-, myr-Tat-PKCßII-, and control group. Rat PMNs were incubated for 15min at 37oC with either myr-PKCßII-, Tat-PKCßII-, or myr-Tat-PKCßII- (all 5µM). SO release was measured by the change in absorbance at 550nm over 360sec via ferricytochrome c reduction after PMA stimulation (100nM). Data were analyzed with ANOVA Fisher's PLSD post-hoc analysis.

Myr-Tat-PKCßII- significantly attenuated SO release by 43% (n=5, 0.27±0.06) compared to control (n=8, 0.48±0.04). Myr-PKCßII- (n=4, 0.33±0.07) and Tat-PKCßII- (n=4, 0.40±0.06, all $p<0.05$) attenuated SO release by 32% and 16%, respectively. Cell viabilities were > 85% in all groups.

Preliminary results suggest that myr-Tat dual conjugation improves PKCßII- delivery compared to myr- or Tat-conjugation alone. Myr- was also more effective than Tat-conjugation.

Future studies will investigate the effects of myr-, Tat-, or myr-Tat-PKCßII- peptides on PKCßII- translocation or activity using immunohistochemistry and western blot analysis.

P24 The Thiol-Maleimide Reaction Downside: Secrets Of An Important By-Product Revealed

(Sequence Sensitivity And Ph Dependence Of Maleimide Conjugated N-Terminal Cysteine Peptides To Thiazine Rearrangement)

Jianheng Zhang (Presenter), Isaiah N. Gober[1], Alexander J. Riemen[1], Matteo Villain[2]
[1] Research and Development Department, Bachem Americas, Inc.
[2] CMC Development Group, Bachem Americas, Inc.

Thiazine formation during the conjugation of N-terminal cysteine peptides to maleimides is an underreported side reaction in the peptide literature. When the conjugation was performed at neutral and basic pH, we observed the thiazine isomer as a significant by product. Nuclear magnetic resonance (NMR) spectroscopy confirmed the structure of the six-membered thiazine and ultra-high performance liquid chromatography (UHPLC) combined with tandem mass spectrometry (MS/MS) allowed for facile, unambiguous detection due to a unique thiazine mass fragment. Furthermore, substitution of various amino acids adjacent to the N-terminal cysteine in a tripeptide model system resulted in different rates of thiazine formation, albeit within the same order of magnitude. We also determined that varying the N-substitution of the maleimide affects the thiazine conversion rate. Altogether, our findings suggest that thiazine rearrangement for N-terminal cysteine-maleimide adducts is a general side reaction that is applicable to other peptide or protein systems. Performing the conjugation reaction under acidic conditions or avoiding the use of an N-terminal cysteine with a free amino group prevents the formation of the thiazine impurity.

P25 Omniligase-1-mediated Ligation for Insulin Analog Synthesis in Solution and On Phage Surface

Yi Wolf Zhang[1,2,3], Nai-Pin Lin[1,2,3], Danny Hung-Chieh Chou[1,2]
[1]Department of Pediatrics, Division of Diabetes and Endocrinology, Stanford University
[2]Department of Biochemistry, University of Utah
[3]These authors contributed equally

The B-chain C-terminal region of insulin has been mutated or modified to achieve improved therapeutic efficacies. For example, all FDA-approved insulin analogs have altered C-terminal segments, leading to improved pharmacokinetic properties and significant clinical benefits on blood sugar regulation. Nonetheless, there is still no efficient method to synthesize insulin analogs with the

altered C-terminal region. Herein, we report a facile synthesis using omniligase-1 to ligate an insulin core with a peptide segment in high conversion. We further apply this ligation to M13 phage surface modifications and demonstrate that the phage-displayed insulin molecules can bind to insulin receptor ectodomain in an insulin-dependent manner. More interestingly, omniligase-1 could only selectively mediate the ligation to phage PIII protein, and we showed that insulin phage libraries could be generated with commercially available phage libraries. These results pave the way for engineering new insulin analogs from phage display with therapeutic properties and demonstrate the feasibility of using omniligase-1 to display and screen disulfide-rich peptides and proteins on phage, which traditional methods cannot achieve.

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