PEPTIDE THERAPEUTICS SYMPOSIUM

Program and Proceedings 9th Annual Peptide Therapeutics Symposium

October 23– 24, 2014
Salk Institute for Biological Studies
La Jolla, CA

www.peptidetherapeutics.org

Table of Contents | 9th Annual Peptide Therapeutics Symposium

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PEPTIDE THERAPEUTICS FOUNDATION

Dear Colleagues,

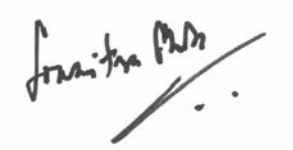
We warmly welcome you to the 9th Annual Peptide Therapeutics Symposium, a scientific meeting sponsored by the Peptide Therapeutics Foundation. The purpose of the Foundation and each annual symposium is to present new discoveries and advances in the field of peptide-based drugs. As in previous years, we have assembled what we believe is a cutting-edge, thought provoking program designed to stimulate questions and conversations.

The Symposium opens on Thursday afternoon with an informative update on leading-edge peptide therapeutics currently in clinical development for cardio-metabolic and neurodegenerative diseases. The Keynote Address by Richard Houghten will follow, detailing breakthrough technology that enables in vivo screening of potential peptide drug candidates. Immediately thereafter we welcome you to join us for the Thursday evening Opening Reception and Poster Session.

The Friday morning program begins with a Plenary Lecture from James Tam describing a unique asparagine-aspartate ligase and its application to the synthesis of cyclic peptides. The program continues with presentations pertaining to biologically-active peptides, clinical studies and core technology that address limitations in pharmacodynamics and delivery of peptide-based drugs.

On behalf of the Peptide Therapeutics Foundation we want to express our thanks for your participation and gratitude to the distinguished faculty that have agreed to present their research.

With kind regards,



Richard DiMarchi
Chairman of the Board
Peptide Therapeutics Foundation

Soumitra Ghosh
President
Peptide Therapeutics Foundation

Sponsors, Peptide Therapeutics Foundation

Ferring Research Institute
Ipsen Biosciences Inc.
MedImmune
PolyPeptide Group
Roche
Zealand Pharma
Zydus Cadila

Ferring Research Institute

Headquartered in San Diego, California, Ferring Research Institute (FRI) is the global peptide therapeutics research center for Ferring Pharmaceuticals. Ferring first established a research group in San Diego in 1996, recognizing the vibrant opportunities in the region. Since establishing a presence in San Diego, Ferring has been able to assemble a world-class peptide research organization and establish collaborations with leading academic scientists. FRI's state-of-the art facility houses research laboratories for peptide medicinal chemistry, biochemistry, bioanalytical, and pharmacology. The small group of researchers working in San Diego has now grown to a staff of more than 70. In recent years the group developed five clinical compounds that have reached human clinical trials. FRI is committed to building a portfolio of novel, innovative peptide therapeutics to address areas of high unmet medical need.

Ferring Pharmaceuticals (Ferring) is a private, research-driven specialty biopharmaceutical company active in global markets. The company identifies, develops and markets innovative products in the fields of endocrinology, gastroenterology, infertility, obstetrics, urology and osteoarthritis. In recent years Ferring has expanded beyond its traditional European base: with over 4,500 employees worldwide, it operates subsidiaries in over 50 countries and makes its products available in more than 90 countries. The company has emerged as a world leader with one of the largest peptide therapeutics portfolios in the industry. 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.

Ipsen Biosciences Inc.

Ipsen (Euronext: IPN; ADR: IPSEY) is a global specialty-driven pharmaceutical company with total sales exceeding €1.1 billion in 2011. Ipsen's ambition is to become a leader in specialty healthcare solutions for targeted debilitating diseases. Its development strategy is supported by four franchises: neurology/Dysport®, endocrinology/Somatuline®, uro-oncology/Decapeptyl® and hemophilia. Moreover, the Group has an active policy of partnerships. R&D is focused on innovative and differentiated technology-driven platforms, peptides and toxins. In 2011, R&D expenditure totaled more than €250 million, above 21% of Group sales. The Group has total worldwide staff of close to 4,500 employees.

MedImmune

MedImmune is the worldwide biologics research and development arm of AstraZeneca with its headquarters in Gaithersburg, Maryland (MD, USA) and large R&D sites in Cambridge (UK) and Mountain View (CA, USA). The company is pioneering innovative research and exploring novel pathways across key therapeutic areas, including respiratory, inflammation and autoimmunity; cardiovascular and metabolic disease; oncology; neuroscience; and infection and vaccines.

The company's robust pipeline includes over 120 biologic compounds in R&D, more than 30 in clinical stage development and several marketed products, Synagis® (palivizumab) and Fluenz® (live attenuated influenza vaccine, LAIV) and others. Peptide drugs are a significant part of both MedImmune's and AstraZeneca's marketed (Zoladex®, Byetta®, Bydureon®) and (pre-)clinical portfolio.

PolyPeptide Group

The PolyPeptide Group is a privately held group of six companies that employs 420 staff worldwide. The PolyPeptide Group focuses exclusively on the manufacture of peptides and related substances and is a leading provider of custom and generic GMP-grade peptides for a range of pharmaceutical and biotechnology applications. With corporate roots that began in the 1950s, the Group was formally launched in 1996. Today, it operates a growing international network of peptide manufacturing facilities. Its world-class chemists and support personnel offer an unparalleled range of services for clients of every size and at every stage of product development. The PolyPeptide Group has been pre-approval inspected by the FDA over fifteen times as well as by other Regulatory Authorities. Altogether, the Group 25 approved APIs.More information about PolyPeptide Group is available at www.PolyPeptide.com.

In addition to large-scale GMP manufacturing, the PolyPeptide Group offers a wide range of other peptide services including radiolabelling, organic synthesis, cosmetic peptides and small-scale custom synthesis. It also has an extensive catalog of peptides and building blocks. The Group's customers range from emerging pharmaceutical companies and biotech organizations through to Big Pharma. The remaining business is primarily linked to the sale of peptide generics, including Calcitonin, Deslorelin, Gonadorelin, Leuprolide, Octreotide, hPTH (1-34), Somatostatin, Triptorelin and Arg-Vasopressin.

Roche

Headquartered in Basel, Switzerland, Roche is a leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics. Roche is the world's largest biotech company with truly differentiated medicines in oncology, virology, inflammation, metabolism and CNS. Roche is also the world leader in in-vitro diagnostics, tissue-based cancer diagnostics and a pioneer in diabetes management. Roche's personalized healthcare strategy aims at providing medicines and diagnostic tools that enable tangible improvements in the health, quality of life and survival of patients. In 2011, Roche had over 80,000 employees worldwide and invested over 8 billion Swiss francs in R&D. The Group posted sales of 42.5 billion Swiss francs. Genentech, United States, is a wholly owned member of the Roche Group. Roche has a majority stake in Chugai Pharmaceutical, Japan. For more information: www.roche.com.

Zealand Pharma

Zealand Pharma A/S (NASDAQ OMX Copenhagen: ZEAL) ("Zealand") is a biotechnology company based in Copenhagen, Denmark. Zealand has world-leading competences in peptide drug innovation, design and development with its main therapeutic expertise in the field of cardio-metabolic diseases — diabetes and obesity in particular. The company has built a broad and mature pipeline of novel drug candidates, which have all been invented based on internal discovery activities. The first Zealand invented drug, Lyxumia® (lixisenatide), a once-daily prandial GLP-1 agonist, is marketed for the treatment of Type 2 diabetes under a global license agreement with Sanofi. Lyxumia® is approved in Europe (March 2013) as well as in Japan, Australia and Mexico, and under regulatory review in a large number of other countries globally, including in the US (NDA submission accepted in Feb 2013).

Zealand has a partnering strategy for the development and commercialization of its products and in addition to the collaboration with Sanofi in Type 2 diabetes, the company has partnerships with Boehringer Ingelheim in diabetes/obesity, Helsinn Healthcare in chemotherapy induced diarrhea and AbbVie in acute kidney injury.

Zydus Cadila

Zydus Cadila is an innovative global pharmaceutical company that discovers, develops, manufactures and markets a broad range of healthcare products. The group's operations range from API to formulations, animal health and wellness products. Headquartered in the city of Ahmedabad in India, the group has global operations in four continents spread across USA, Europe, Japan, Brazil, South Africa and 25 other emerging markets.

In its mission to create healthier communities globally, Zydus Cadila delivers wide ranging healthcare solutions and value to its customers. With over 15,000 employees worldwide, a world-class research and development centre dedicated to discovery research and nine state-of-the-art manufacturing plants, the group is dedicated to improving people's lives.

From a turnover of Rs. 250 crores in 1995, the group posted revenues of Rs. 5200 crores in FY12. The group had posted a turnover of Rs. 4600 crores in FY 11, making it a billion dollar company. The group aims to be a leading global healthcare provider with a robust product pipeline; achieve sales of over $3 bn by 2015 and be a research-based pharmaceutical company by 2020.

Thursday, October 23, 2014

1:00 p.m. – 5:00 p.m.

Registration Check-in
Frederic de Hoffmann Auditorium Reception Area, Lower Level

2:00 p.m. – 5:15 p.m.

9th Annual Peptide Therapeutics Symposium
Frederic de Hoffmann Auditorium

2:00 p.m. – 2:15 p.m.

Opening Remarks
Richard DiMarchi, Ph.D.
Chairman of the Board, Peptide Therapeutics Foundation
Standiford H. Cox Distinguished Professor of Chemistry, Jill & Jack Gill Chair in Biomolecular Sciences, Department of Chemistry, Indiana University

2:15 p.m. – 3:45 p.m.

SESSION I:

Moderator
Maria A. Bednarek, Ph.D.
Director, Peptide Therapeutics Foundation
Fellow and Head of the Peptide Platform, MedImmune/Astra Zeneca

2:15 p.m. – 2:45 p.m.

Multiselective Peptides for the Treatment of Metabolic Diseases
Cristina M. Rondinone, Ph.D.
Vice President, Research and Development; Head Cardiovascular and Metabolic Diseases iMED, MedImunne

2:45 p.m. – 3:15 p.m.

Peptide Agonists of Incretin Receptors Are High Priority Candidates in the Search for the First Effective Treatments of Alzheimer's Disease
Konrad Talbot, Ph.D.
Associate Professor, Department of Neurosurgery, Cedars-Sinai Medical Center

3:15 p.m. – 3:45 p.m.

Continuous Glucose Monitoring: Technology that will Bridge the Gap Until There is a Cure for Type 1 Diabetes
Steven Edelman, M.D.
Professor of Medicine, University of California, San Diego, Veterans Affairs Medical Center; Founder and Director, Taking Control of Your Diabetes 501(c)3

3:45 p.m. – 4:30 p.m.

Break
Frederic de Hoffmann Auditorium Reception Area, Lower Level

4:30 p.m. – 5:15 p.m.

KEYNOTE ADDRESS:

Moderator
Soumitra Ghosh, Ph.D.
President, Peptide Therapeutics Foundation
President, Doon Associates LLC

Peptide Therapeutics: A New Golden Age!
Richard A. Houghten, Ph.D.
Founder, President & CEO, Torrey Pines Institute for Molecular Studies

5:15 p.m. – 7:30 p.m.

Poster Session & Opening Reception
Frederic de Hoffmann Auditorium Reception Area, Lower Level

Friday, October 24, 2014

7:00 a.m. – 11:30 a.m.	**Registration Check-in** Frederic de Hoffmann Auditorium Reception Area, Lower Level
7:30 a.m. – 8:15 a.m.	**Breakfast & Poster Viewing** Frederic de Hoffmann Auditorium Reception Area, Lower Level
8:15 a.m. – 4:45 p.m.	**9th Annual Peptide Therapeutics Symposium** Frederic de Hoffmann Auditorium
8:15 a.m. – 8:30 a.m.	**Welcoming Remarks** Claudio Schteingart, Ph.D. *Director, Peptide Therapeutics Foundation* *Vice President, Science & Technology – Research, Ferring Research Institute Inc.*
8:30 a.m. – 10:00 a.m.	**Plenary Lectures** **Moderator** Hans-Joachim Böhm, Ph.D. *Director, Peptide Therapeutics Foundation* *Global Head of Chemistry, Roche*
8:30 a.m. – 9:15 a.m.	**New Physiology and Pharmacology of the Melanocortin-4 Receptor** Roger D. Cone, Ph.D. *Professor and Chair, Department of Molecular Physiology and Biophysics, Vanderbilt University Medical Center*
9:15 a.m. – 10:00 a.m.	**Chemoenzymatic Approaches in Amide-to-amide Peptide Ligation** James P. Tam, Ph.D. *Professor, Herbalomics and Drug Discovery, School of Biological Sciences, Nanyang Technological University*
10:00 a.m. – 10:30 a.m.	**Break & Poster Viewing** Frederic de Hoffmann Auditorium Reception Area, Lower Level
10:30 a.m. – 12:15 p.m.	**SESSION II:** **Moderator** Torsten Hoffmann, Ph.D. *Director, Peptide Therapeutics Foundation* *Executive Vice President and Chief Scientific Officer, Zealand Pharma A/S*
10:30 a.m. – 11:15 a.m.	**Hepcidin and Minihepcidins: From Mechanistic Studies to Therapeutic Peptides** Tomas Ganz, Ph.D., M.D. *Professor of Medicine and Pathology, University of California, Los Angeles*
11:15 a.m. – 11:45 a.m.	**Discovery of Functional Ligands and Materials from Genetically-encoded Libraries of Chemically-modified Peptides** Ratmir Derda, Ph.D. *Assistant Professor, Department of Chemistry and Alberta Glycomics Centre, University of Alberta*
11:45 a.m. – 12:15 p.m.	**Using the Endosome Escape Trap to Discover Phylomer Peptides which more Efficiently Deliver Cargoes to the Cytoplasm** Paul Watt, D.Phil. *Chief Scientific Officer, Phylogica Ltd*

Friday, October 24, 2014 continued

12:15 p.m. – 1:30 p.m.

Lunch & Poster Viewing
Frederic de Hoffmann Auditorium Reception Area, Lower Level

1:30 p.m. – 3:00 p.m.

SESSION III:

Moderator
Yvonne M. Angell, Ph.D.
Director, Peptide Therapeutics Foundation
Director of Peptide and Protein Chemistry, Ipsen Biosciences Inc.

1:30 p.m. – 2:00 p.m.

Danegaptide - Potential First and Best in Class Peptide Medicine for Prevention of Myocardial Reperfusion Injury
Rie Schultz Hansen, MSc, Ph.D.
Principal Scientist, Zealand Pharma A/S

2:00 p.m. – 2:30 p.m.

Plecanatide and SP-333, Homologues of Uroguanylin, as Innovative Oral Drugs for Treatment of Gastrointestinal Disorders and Diseases
Kunwar Shailubhai, Ph.D., M.B.A.
Co-Founder and Chief Scientific Officer, Synergy Pharmaceuticals, Inc.

2:30 p.m. – 3:00 p.m.

Novel Peptide Therapeutics Targeting Key Intracellular Signaling Pathways of Cancer Stem Cells
Jörg Vollmer, Ph.D.
Managing Director and Chief Executive Officer, Nexigen GmbH

3:00 p.m. – 3:30 p.m.

Break & Poster Viewing
Frederic de Hoffmann Auditorium Reception Area, Lower Level

3:30 p.m. – 4:30 p.m.

SESSION IV:

Moderator
Claudio Schteingart, Ph.D.
Director, Peptide Therapeutics Foundation
Vice President, Science & Technology – Research, Ferring Research Institute Inc.

3:30 p.m. – 4:00 p.m.

Peptide Antagonists of the Inflammatory Response Enhanced by the Antimicrobial Peptide LL-37
Cheng Kao, Ph.D.
Director of Biotechnology and Professor, Department of Molecular & Cellular Biology, Indiana University

4:00 p.m. – 4:30 p.m.

Integrated Triple Gut Hormone Action Broadens the Therapeutic Potential of Endocrine Biologics for Metabolic Diseases
Brian Finan, Ph.D.
Division Head, Helmholtz Zentrum Munich

4:30 p.m. – 4:45 p.m.

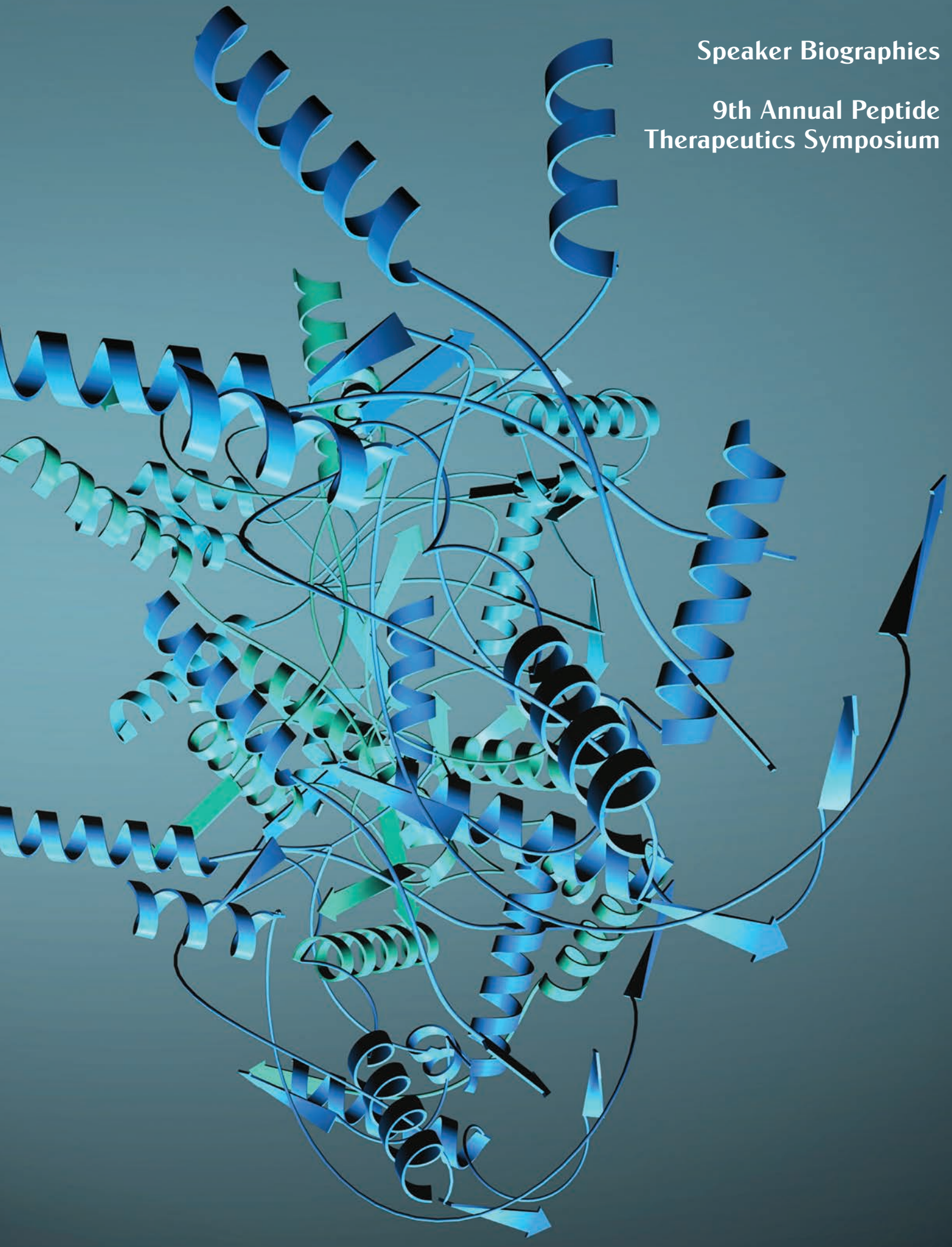
Closing Remarks
Rodney Lax, Ph.D.
Director, Peptide Therapeutics Foundation
Business Development Consultant, PolyPeptide Group

4:45 p.m. – 6:00 p.m.

Networking Reception
Frederic de Hoffmann Auditorium Reception Area, Lower Level

Speaker Biographies

9th Annual Peptide Therapeutics Symposium



Roger D. Cone, Ph.D. | Professor and Chair, Department of Molecular Physiology and Biophysics, Vanderbilt University Medical Center
New Physiology and Pharmacology of the Melanocortin-4 Receptor

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 2003, Cone was selected to be the Director of the Center for the Study of Weight Regulation and Associated Disorders at OHSU, and in 2008 he moved to Vanderbilt to be Professor and Chairman of the Department of Molecular Physiology and Biophysics. 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 important to energy homeostasis. 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 several unique pharmacological findings, including identification of the agouti protein as the first endogenous GPCR antagonist, and the identification of mutations that constitutively activate hormone-binding GPCRs. His discovery and characterization of variant alleles of the MSH receptor 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 demonstrated that blockade of melanocortin signaling was the underlying cause of obesity in the A^{y} agouti mouse. These 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. Based on these findings, defective melanocortin signaling has been identified by the O'Rahilly and Froguel labs as the most common cause of severe obesity in humans. Subsequent studies from the Cone lab demonstrated that the central melanocortin system regulates numerous physiological and pathophysiologic functions including fasting insulin levels, food intake and satiety, diet-induced thermogenesis, and disease cachexia. Cone has received international recognition for this work, including the Ernst Oppenheimer Award (U.S. Endocrine Society), the Berthold Memorial Award (German Endocrine Society), the Freedom to Discover Award for Distinguished Achievement in Metabolic Diseases Research from Bristol-Myers Squibb, the Ipsen Prize, the Berson Award from the American Physiological Society, and election to the US National Academy of Sciences in 2010.

Ratmir Derda, Ph.D. | Assistant Professor, Department of Chemistry and Alberta Glycomics Centre, University of Alberta
Discovery of Functional Ligands and Materials from Genetically-encoded Libraries of Chemically-modified Peptides

Ratmir Derda received his undergraduate degree in Physics from Moscow Institute of Physics and Technology in 2001 and Ph.D. in Chemistry from the University of Wisconsin-Madison in 2008, under the supervision of Laura L. Kiessling. From 2008 to 2011, he was a postdoctoral researcher at Harvard University working under the supervision of George M. Whitesides and Donald E. Ingber. He joined University of Alberta in 2011 as an Assistant Professor in Chemistry. In 2012, he became a principal investigator at the Alberta Glycomics Centre. Derda lab is focused on development of genetically-encoded chemical libraries, selection and evolution of bioactive ligands with dynamic properties and investigation of fundamental mechanism in cell growth and differentiation. His notable awards include Young Investigator Award from the Boulder Peptide Society (2014), Canadian Rising Star in Global Health (2011), National Academies Keck Futures Initiative Award in Synthetic Biology (2010), ACS Excellence in Graduate Polymer Science Research (2007) and Gold Medal at the XXIX International Chemistry Olympiad (1997).

Richard DiMarchi, Ph.D. | Chairman of the Board, Peptide Therapeutics Foundation; Standiford H. Cox Distinguished Professor of Chemistry, Jill & Jack Gill Chair in Biomolecular Sciences, Department of Chemistry, Indiana University
Opening Remarks

Dr. DiMarchi contributions in peptide & protein sciences consists of three decades of work in academia, the pharmaceutical industry and biotechnology companies. He is the Cox Distinguished Professor of Biochemistry and *Gill* Chair in Biomolecular Sciences at Indiana University. He is a co-founder of Ambrx, Marcadia, Assembly and Calibrium Biotechs. He has served as a scientific advisor to multiple pharmaceutical comapnies and three venture funds; 5AM, TMP, and Twilight. He is Chairman of the Peptide Therapeutics Foundation and Board member at Ontarget Therapeutics.

Dr. DiMarchi is a retired Group Vice President at Eli Lilly & Company where for more than two decades he provided leadership in biotechnology, endocrine research and product development. He is readily recognized for discovery and development of rDNAderived Humalog® (LisPro-human insulin). As scientist and executive, Dr. DiMarchi also significantly contributed to the commercial development of Humulin®, Humatrope®, rGlucagon®, Evista®, and Forteo®. His current research is focused on developing macromolecules with enhanced therapeutic properties through biochemical and chemical optimization, an approach he has termed chemical-biotechnology.

Dr. DiMarchi is the recipient of numerous awards including the 2005 AAPS Career Research Achievement Award in Biotechnology, the 2006 ACS Barnes Award for Leadership in Chemical Research Management, the 2006 ACS Esselen Award for Chemistry in the Service of Public Interest, the 2007 Carothers Award for Excellence in Polymer Sciences, the 2009 Watanabe Award for Life Sciences Research, the 2011 Merrifield Award for Career Contributions in Peptide Sciences, the 2012 Phillip Nelson Innovation Award and a 2014 inductee to the National Inventors Hall of Fame.

Steven Edelman, M.D. | Professor of Medicine, University of California, San Diego, Veterans Affairs Medical Center; Founder and Director, Taking Control of Your Diabetes 501(c)3
Continuous Glucose Monitoring: Technology that will Bridge the Gap Until There is a Cure for Type 1 Diabetes

Dr. Edelman is a professor of medicine in the Division of Endocrinology, Diabetes & Metabolism at the University of California at San Diego (UCSD) and the Veterans Affairs (VA) Healthcare System of San Diego and the director of the Diabetes Care Clinic, VA Medical Center. He achieved high honors during his undergraduate studies at the University of California at Los Angeles and was the valedictorian of his medical school class at the University of California Davis Medical School. Dr. Edelman received his internal medicine training at the University of California Los Angeles, and completed his clinical endocrinology fellowship training at the Joslin and Lahey Clinics in Boston, Mass. as well as a research fellowship at UCSD.

Dr. Edelman has strong interests in education and patient advocacy. He is the founder and director of Taking Control of Your Diabetes (TCOYD), a not-for-profit organization with the goal of teaching and motivating patients in diabetes self-care. Since 1995, TCOYD has reached hundreds of thousands of people living with diabetes through a variety of education portals including national conferences, publications, television, and community programs.

Dr. Edelman's has written more than 200 articles and five books. He has won numerous awards for teaching and humanitarianism and was recognized by San Diego Magazine as a Top Doctor eight of the last nine years, an honor only achieved by a handful of physicians. He was chosen as the teacher of the year amongst the over 400 faculty members at UCSD numerous times. He was awarded the Diabetes Educator of the year by the American Diabetes Association in 2009, the Distinction in Endocrinology award by the American Association of Clinical Endocrinologists in 2011 and recently named in US News and World Report amongst the top 1% of endocrinologists in the US. Of all his accomplishments, Dr. Edelman is most proud of his compassionate, smart and successful daughters, Talia and Carina.

Brian Finan, Ph.D. | Division Head, Helmholtz Zentrum Munich
Integrated Triple Gut Hormone Action Broadens the Therapeutic Potential of Endocrine Biologics for Metabolic Diseases

Brian Finan is the Head of the Division of Drug Discovery within the Institute for Diabetes and Obesity at the Helmholtz Zentrum. Brian received his Ph.D. in 2011 from Indiana University under the mentorship of Dr. Richard DiMarchi. During his graduate work, Brian Finan specialized in building multifunctional single molecules that simultaneously target multiple receptors involved in the control of energy metabolism and glucose homeostasis. Such peptides include co- and tri-agonists with integrated, highly potent, and balanced activity at the glucagon superfamily of receptors. Additionally, Brian developed a novel peptide-mediated approach to deliver nuclear hormone action selectively to specific cell subpopulations, as highlighted by conjugates of GLP-1 and estrogen, which offers synergistic metabolic benefits while avoiding the hallmark toxicities that otherwise plague estrogen pharmacology. During his postdoctoral training, Brian continued the pre-clinical development of these compounds under the guidance of Dr. Matthias Tschöp and Dr. Timo Müller in Munich. His current work aims to dissect the molecular underpinnings governing the synergistic behavior of some of the aforementioned compounds while simultaneously continuing the translational pursuit of these compounds. Furthermore, Brian is exploring other molecular combinations in his pursuit of finding a poly-pharmacology that more closely replicates the massive metabolic benefits of bariatric surgeries.

Tomas Ganz, Ph.D., M.D. | Professor of Medicine and Pathology, University of California, Los Angeles
Hepcidin and Minihepcidins: From Mechanistic Studies to Therapeutic Peptides

Tomas Ganz is a Professor of Medicine and Pathology at the David Geffen School of Medicine at University of California, Los Angeles (UCLA). He received his BS in Physics from UCLA, PhD from the California Institute of Technology in Applied Physics and MD from UCLA. He then trained in Internal Medicine and Pulmonary/Critical Care Medicine at the UCLA Medical Center, and did his post-doctoral training there with Prof. Harvey Herschman. His major focus was on research on the biological role of peptide mediators in innate immunity and iron metabolism. More recently, he has investigated the pathogenesis of anemia of inflammation and iron overload states, and worked on the development of hepcidin agonists and antagonists. His laboratory at UCLA has been continuously supported by grant funding from the National Institutes of Health, as well as from private foundation and biotechnology firms. He has authored more than 250 publications in refereed journals and more than 30 book chapters. Dr. Ganz has served as an Associate Editor of Blood (1998-2007), President of the International Bioiron Society (2009-2011) and has been a member of the Erythrocyte and Leukocyte Biology (ELB) Study Section of the National Institutes of Health. His work resulted in the founding of three biotechnology enterprises, Intrinsic LifeSciences, Merganser Biotech and Silarus Therapeutics, focused on the diagnostic and therapeutic applications of iron-regualtory hormones hepcidin and erythroferrone, and has been a scientific advisor to the leading pharmaceutical and biotechnology companies worldwide. He received the Marcel Simon Award of the International Bioiron Society in 2005 and the E. Donnall Thomas Prize of the American Society of Hematology in 2014, for the discovery of hepcidin and related advances in understanding iron homeostasis.

Rie Schultz Hansen, MSc, Ph.D. | Principal Scientist, Zealand Pharma A/S
Danegaptide - Potential First and Best in Class Peptide Medicine for Prevention of Myocardial Reperfusion Injury

Rie Schultz Hansen holds a Ph.D. in medicinal research and is Principal Scientist for cardiovascular research at Zealand Pharma, Denmark. For the last 14 years, the focus of Rie Schultz Hansen's research and industrial work has been to discover and develop innovative new medicines for the treatment of cardiovascular diseases such as atrial fibrillation, ventricular fibrillation and acute myocardial infarction and she is the author of more than 50 publications, published conference reports and patent applications.

During the last 4 years Rie Schultz Hansen has been leading the effort of investigating the effects of treatment with anti-arrhythmic peptides on myocardial salvage. This has included instigating external research collaborations as well as establishing cardiovascular capabilities at Zealand with state-of the art in vivo and ex vivo models of cardiovascular disease.

In addition to her industrial work, Rie Schultz Hansen is an associate of the Danish Arrhythmia Research Center (DARC) and the Danish Cardiovascular Research Academy (DACRA), and a member of the steering committee for Cardiovascular Research at the SUND PhD School of University of Copenhagen.

Richard A. Houghten, Ph.D. | Founder, President & CEO, Torrey Pines Institute for Molecular Studies
Peptide Therapeutics: A New Golden Age!

Richard A. Houghten, Ph.D. is the Founder, CEO & President of the Torrey Pines Institute for Molecular Studies, a not-for-profit, San Diego and Florida bi-coastal medical research organization. Now in its 26th year, it has become internationally recognized for its scientific contributions and innovations in the use of peptide libraries made up of millions to literally trillions peptides as powerful tools for basic research and drug discovery. Dr. Houghten has founded three commercial businesses, including a publicly-traded biotechnology company. His many awards include the 2004 Ralph Hirschmann Award in Peptide Chemistry by the American Chemical Society, and the 2005 Bruce Merrifield Award by the American Peptide Society. He has authored/co-author over 571 publications and has been issued 75 US and 47 International patents. Richard Houghten is a Fellow of the American Association of Pharmaceutical Sciences and American Association for the Advancement of Science.

Cheng Kao, Ph.D. | Director of Biotechnology and Professor, Department of Molecular & Cellular Biology, Indiana University
Peptide Antagonists of the Inflammatory Response Enhanced by the Antimicrobial Peptide LL-37

Cheng Kao received his bachelor's degree in Biology and Microbiology from the University of Michigan, where he did research on cloning of the human cholinesterase receptor. He obtained his Ph.D. at Michigan State University, studying how mobile genetic elements can prevent viral infection. He was an American Cancer Society Postdoctoral fellow at UCLA where he studied how a virus can alter transcription of the host cell and a National Science Foundation Plant Biology postdoctoral fellow studying RNA virus replication. The research in the Kao lab seeks to: 1) understand how RNA viruses can infect cells and make copies of themselves; 2) determine the rules for the recognition of RNA by proteins, and 3) elucidate how the infected cells detect viral RNA molecules and trigger inflammatory responses. The latter area of studies led the lab to study fascinating antimicrobial peptides that can inhibit anti-bacteria inflammatory responses but activate anti-viral responses. These research areas impact human diseases such as Hepatitis C, viral gastroenteritis, psoriasis, lupus, and asthma. Dr. Kao's research had been supported by the National Institute of Health, the National Science Foundation, and several pharmaceutical and biotechnology companies. Dr. Kao has published over 170 peer-reviewed papers and has five patents. Most importantly, Dr. Kao has trained over twenty postdocs, fifteen graduate students, and 60 undergraduate researchers.

Rodney Lax, Ph.D. | Director, Peptide Therapeutics Foundation; Business Development Consultant, PolyPeptide Group
Closing Remarks

Rodney Lax studied Biochemistry at the University of Birmingham (UK) and the Chester Beatty Institute in London (UK) before moving to Germany in 1970. In Germany he worked in the field of steroid endocrinology at the University of Ulm from 1970– 975 and from 1975–1986 at the University of Essen, where he lectured in Physiological Chemistry and became an associate professor in 1985. Starting in 1986, he worked for a number of small biotech companies in Northern Germany involved in peptide-based pharmaceuticals, including Bissendorf Peptides GmbH, Pharma Biotechnology Hannover GmbH, Saxon Biochemicals GmbH and WHERL GmbH, which was later acquired by the PolyPeptide Group. In 2003, he moved to PolyPeptide Laboratories in Torrance, where he became Senior Director of Business Development, North America. After retiring from that position in 2014, he now works as a business development consultant. He has published over 50 full papers, mainly related to steroid endocrinology. More recently he has written articles on peptides for technical journals distributed to the pharmaceutical industry. He has been a member of the German Endocrinological Society and German Society for Biological Chemistry. He was a member of the TIDES Advisory Committee between 2008 and 2013. Since 2013 he is a member of the Peptide Therapeutics Foundation Avisory Board.

Cristina M. Rondinone, Ph.D. | Vice President, Research & Development; Head Cardiovascular and Metabolic Diseases iMED, MedImmune
Multiselective Peptides for the Treatment of Metabolic Diseases

Dr. Cristina Rondinone received her Ph.D. in Biochemistry from University of Buenos Aires. Her postdoctoral training was at the Laboratory of Cellular and Developmental Biology, NIDDK, NIH, USA as a Visiting Fellow. In 1995, she moved to Sweden where she was first Senior Scientist for the Lundberg Laboratory for Diabetes Research, Department of Internal Medicine, University of Gothenburg and then she was appointed as (Docent) Associate Professor in Molecular Medicine, University of Gothenburg. From 1998 to 2005, she worked at Abbott Laboratories, where she became first Associate Research Fellow of the Volwiler Society and then Group Leader in the metabolic disease research area. In 2005 she moved to Hoffmann-La Roche as Research Director of Metabolic Diseases and in 2007 became Senior Director and Therapeutic Area Head overseeing drug discovery programs in metabolic and vascular diseases, including target identification, lead optimization and advancement of preclinical candidates into clinical development. In 2011 she moved to MedImmune, Inc., as Vice President Research and Development and Head Cardiovascular and Metabolic Diseases, leading the portfolio of biologics in this therapeutic area. She has published more than 65 academic publications in the field of diabetes, insulin resistance and obesity, and coinventor of 4 patents. She was also Editor of the book Therapeutic Aplications of RNAi. She has also has been invited speaker in numerous national and international symposiums as well as Chairman of numerous sessions at the Keystone Symposia, American Diabetes Association and European Diabetes Association. She was member of the Editorial Board of the journal Endocrinology and Associate Editor of Archives of Physiology and Biochemistry as well as reviewer for the American Diabetes Association, NAASO, National Institutes of Health (NIH), National Science Foundation (US), Institut Curie, French Ministry of the Research and Education, Czech Science Foundation, Israel Science Foundation and the Australian Science Foundation. She is also member of the Scientific Advisory Board for the Keystone Symposia and she recently was inducted as a member of the Real National Academy of Pharmacy in Spain.

Claudio Schteingart, Ph.D. | Director, Peptide Therapeutics Foundation; Vice President, Science & Technology – Research, Ferring Research Institute
Welcoming Remarks

Dr. Schteingart is Vice President, Science & Technology – Research at Ferring Research Institute Inc. His current responsibilities are the evaluation of new technologies for the discovery and development of novel peptide therapeutics and to provide guidance to drug discovery programs at the Institute as well as supporting drug candidates in Development at Ferring Pharmaceuticals. He joined the Institute in 1996 as a research chemist and participated in the discovery of the peptidic GnRH antagonist degarelix, launched in 2009, and eight other peptidic drug candidates in various stages of clinical development for women's health, critical care medicine, and gastroenterology.

Dr. Schteingart received a Ph.D. in Chemistry at the University of Buenos Aires, Argentina. After postdoctoral studies in the Department of Chemistry at the University of California, San Diego, he moved to the Department of Medicine where he carried out research in the chemistry, physiology, metabolism, and physicochemical properties of biliary components and lipids.

Kunwar Shailubhai, Ph.D., M.B.A. | Co-Founder and Chief Scientific Officer, Synergy Pharmaceuticals, Inc.

Plecanatide and SP-333, Homologues of Uroguanylin, as Innovative Oral Drugs for Treatment of Gastrointestinal Disorders and Diseases

Dr. Shailubhai is a Co-Founder and Chief Scientific Officer of Synergy Pharmaceuticals, Inc., a NASDAQ-listed biotechnology company focusing on innovative therapeutics for treatment of GI disorders and diseases. Dr. Shailubhai has held leadership positions at Monsanto Life Sciences Company (St. Louis, MO), Callisto Pharmaceuticals, and Synergy Pharmaceuticals Inc. At Monsanto Company Dr. Shailubhai worked on a number of projects in inflammatory diseases, and eventually headed the cancer prevention group where he initiated research programs focusing on prevention of breast, prostate, and colon cancer in humans. He also initiated discovery projects to explore the therapeutic potential of uroguanylin, a physiological agonist of guanylate cyclase-C (GC-C), in GI diseases and colon cancer. One of these projects was to explore the potential of uroguanylin for treatment of chronic constipation. These pioneering research efforts opened a novel avenue for therapeutic applications of uroguanylin and other GC-C agonists, not only in colon cancer but also in other GI diseases such as irritable bowel syndrome-constipation (IBS-C), chronic idiopathic constipation (CIC), and inflammatory bowel disease (IBD).

In 2000, Dr. Shailubhai joined Synergy Pharmaceuticals Inc. to explore and develop therapeutic applications of GC-C agonists, and to identify superior analogs of uroguanylin more suitable to drug development. In 2002 Dr. Shailubhai's research led to the discovery of plecanatide (aka SP-304), which is currently in Phase III clinical trials for treatment of CIC and IBS-C. He is also chiefly responsible for discovery of SP-333, which is being developed for treatment of ulcerative colitis and opioid-induced constipation. SP-333 currently represents proteolytically the most stable and potent analog of uroguanylin, an ideal property for its potential use in treating ulcerative colitis. In vitro studies on the anti-inflammatory mechanism of SP-333 suggest that this activity is likely through inhibition of NF-kappa B signaling, leading to the suppression of pro-inflammatory cytokines. Oral administration of SP-333 has been shown to ameliorate colitis in a number of experimental models. In addition, Dr. Shailubhai has identified several other proprietary GC-C agonists as part of the development of Synergy's discovery portfolio. Dr. Shailubhai has 17 issued patents, several pending patent applications, and 40 research publications in journals of international repute.

Konrad Talbot, Ph.D. | Associate Professor, Department of Neurosurgery, Cedars-Sinai Medical Center

Peptide Agonists of Incretin Receptors Are High Priority Candidates in the Search for the First Effective Treatments of Alzheimer's Disease

Dr. Konrad Talbot received his Ph.D. in behavioral neuroscience from UCLA in 1989. After teaching behavioral neuroscience as an assistant professor at Mount St. Mary's College in California (1990-1995) and St. Olaf College in Minnesota (1995-1997), he pursued a different career as a postmortem Alzheimer's disease (AD) investigator. This began with a postdoctoral fellowship in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania (Penn, 1997-2001) and continued at the same university with appointments as a senior research investigator (2001-2007) and subsequently as a research assistant professor in the Department of Psychiatry. In that department, Dr. Talbot helped identify novel molecular pathologies contributing to cognitive deficits in both schizophrenia and AD.

Seeking the molecular basis for those disorders, Dr. Talbot discovered in 2003 the first reductions of a protein genetically associated with schizophrenia in the brains of such cases and later showed that this could help explain their profound cognitive deficits. In the same period, Dr. Talbot also discovered the first clear evidence of impaired insulin signaling in brains of AD cases. For the first stage of that research, he and Dr. Arnold shared a T.L.L. Temple Foundation Discovery Award from the Alzheimer's Association. With a novel ex vivo stimulation paradigm, Dr. Talbot and Dr. Hoau-Yan Wang at CUNY reported in 2012 the first direct evidence of brain insulin (and IGF-1) resistance in AD and showed its likely molecular causes and cognitive effects.

Now an associate professor in the Department of Neurosurgery at Cedars-Sinai Medical Center in Los Angeles, Dr. Talbot has focused his research on testing the hypothesis that AD can be effectively treated using peptide agonists of incretin receptors to reduce brain insulin resistance. His talk will summarize the rationale of that hypothesis and the results of experiments testing it.

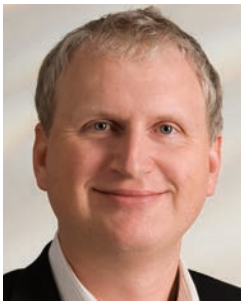
James P. Tam, Ph.D. | Professor, Herbalomics and Drug Discovery, School of Biological Sciences, Nanyang Technological University

Chemoenzymatic Approaches in Amide-to-Amide Peptide Ligation

James P. Tam is the Director of the Herbalomics and Drug Discovery Laboratory. He served as the Founding Dean of the School of Biological Sciences, the Founding Director of Biological Research Center and the Founding director of the double-degree program in Biomedical Science and Chinese Medicine at Nanyang Technological University, Singapore.

He received his Ph.D. in Medicinal Chemistry from the University of Wisconsin, Madison, USA and held appointments as Associate Professor at The Rockefeller University, USA (1982-1991), Professor at Vanderbilt University, USA (1991-2004) and The Scripps Research Institute, USA (2004-2008). His research work focuses on the discovery, design and development of therapeutics, particularly orally active biologics, immunologics, anti-infectives, anti-proliferatives and synthetic vaccines.

Professor Tam has published more than 330 papers in these areas of research. He received the Vincent du Vigneaud Award in 1986, the Rao Makineni Award by American Peptide Society in 2003, the Ralph F. Hirschmann Award by the American Chemical Society (ACS) in 2005, and the Merrifield Award by American Peptide Society in 2013 for his outstanding contributions to peptide and protein sciences. The Merrifield and Hirschmann Awards, administered by the APS and ACS respectively, recognize the highest achievements in the chemistry, biochemistry and biophysics of peptides at an international level. In addition to his scientific research, he has also been active in the peptide community. Besides serving on many editorial boards, he organizes international peptide and protein symposia and was co-founder of the past ten International Chinese Peptide Symposia. He received the Cathay Award from the Chinese Peptide Society, China in 1996. He was also honored as Honorary Professor by Peking University and Peking Union Medical College.



Jörg Vollmer, Ph.D. | Managing Director and Chief Executive Officer, Nexigen GmbH

Novel Peptide Therapeutics Targeting Key Intracellular Signaling Pathways of Cancer Stem Cells

Dr. Jörg Vollmer joined Nexigen in October 2011. He has more than sixteen years of experience in scientific research and drug development, and holds a diploma and doctorate from the Max-Planck-Institute for Immunobiology. Dr. Vollmer started his career in 1999 at Coley Pharmaceutical developing Nucleic Acid-based immune modulatory therapeutics. Working for Coley until 2007, latest in the position as Vice President Discovery & Development, he was responsible for the discovery of novel nucleic acid and small molecule product candidates in Oncology and Autoimmune Diseases. Between 2008 and 2011 Coley Pharmaceutical's site in Germany did belong to Pfizer's Global Research and Dr. Vollmer was in his role as Site Head and Managing Director involved in the discovery.

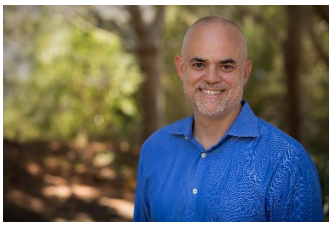
Paul Watt, D.Phil. | Chief Scientific Officer, Phylogica Ltd

Using the Endosome Escape Trap to Discover Phylomer Peptides which more Efficiently Deliver Cargoes to the Cytoplasm

A leading graduate from The University of Western Australia, Paul Watt completed his doctorate in Molecular Biology at Oxford University before taking up postdoctoral appointments at Harvard and Oxford in the genome stability field. As a Research Fellow at the Telethon Kids Institute, he was appointed Adjunct Professor at the University for Western Australia. Professor Watt has published 50 peer reviewed scientific papers and is primary inventor on 24 patent applications, many of which have been granted in the US and Europe. He has held the roles of CEO, CSO and Director of two public biotechnology companies: Professor Watt founded InfaMed Ltd., now owned by Avita Medical, which is commercialising a drug delivery device he invented, which is marketed internationally. Professor Watt is currently CSO of Phylogica, a drug discovery company which he founded to commercialise a novel, structure-rich class of peptide known as Phylomers.

ERRATA

Friday, October 24, 2014
Session III:
2:00 p.m. – 2:30 p.m.



Arylomycin Antibiotics

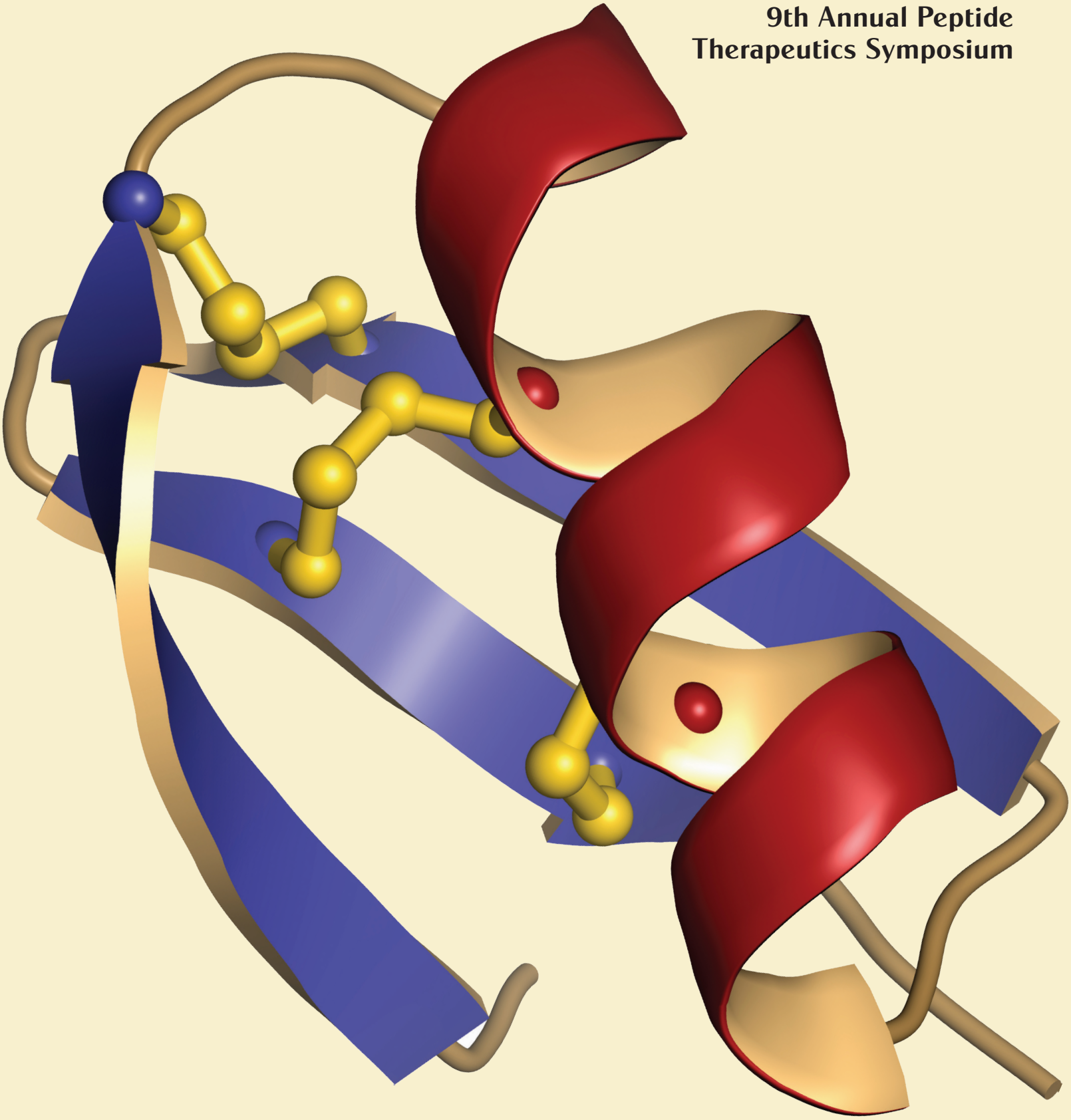
Floyd E. Romesberg, Ph.D. | Associate Professor, Department of Chemistry
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 | (858) 784-7290

Speaker Biography
Floyd Romesberg's research combines the tools of bio/organic chemistry, molecular biology, microbiology, genetics, and modern spectroscopy to study different aspects of evolution. Projects include the identification and development of novel antibiotics, the development of tools to apply steady-state and time-resolved UV/vis and IR spectroscopy to understand how proteins are evolved for biological function, the investigation of the cellular response to DNA damage in prokaryotic and eukaryotic cells, and the development of unnatural base pairs with which to expand the genetic alphabet and thereby increase the chemical and functional potential of DNA and RNA. Recently Floyd's lab succeeded in generating a semi-synthetic organism that stably propagates six-letter DNA, paving the way to living factories to produce novel proteins for biotechnological and medical applications. Floyd is also a co-founder of Achaogen, Inc. and RQx, Inc., two companies working to develop novel antibiotics, as well as Synthorx, Inc., a new synthetic biology company.

Lecture Abstract
We are taking a unique approach to broad-spectrum antibiotic discovery based on the simple principle that the same bacterial arms race that drove the evolution of antibiotics in nature must also have selected for specific mechanisms of resistance. In fact, the competitive co-evolution of producer and susceptible strains likely bestows all natural product antibiotics with a life cycle that oscillates between broad-spectrum potent activity and more narrow-spectrum reduced activity. Nonetheless, and unlike the scaffolds identified from typical screening libraries, all scaffolds selected for the arms race benefit from eons of optimization, and many may once have had broad-spectrum activity. Just as medicinal chemists have had success in the optimization of validated antibiotics to overcome specific mechanisms of resistance that arose during clinical development ("next generation" variants have been the most successful aspect of recent discovery efforts), we predict that such naturally or evolutionarily validated, "latent" antibiotics would be excellent scaffolds for optimization. As our first candidate latent antibiotic we have examined the arylomycin lipopeptide natural products, which target type I signal peptidase (SPase), the endopeptidase required to release proteins from their N-terminal leader sequences during secretion. We demonstrate that the spectrum of the arylomycins is limited by mutations in SPase that reduce the affinity with which the arylomycins bind and that analogs that overcome this reduction in affinity have the potential for broad-spectrum activity. Moreover, the availability of the arylomycins has allowed us to demonstrate that SPase has important and previously unknown roles outside of secretion, with important implications for our understanding of bacterial physiology and the potential of the arylomycins as therapeutics.

Abstracts of Lecture Presentations

9th Annual Peptide Therapeutics Symposium



New Physiology and Pharmacology of the Melanocortin-4 Receptor

Roger D. Cone, Ph.D. | Professor and Chair, Department of Molecular Physiology and Biophysics
Vanderbilt University Medical Center
702 Light Hall, Nashville, TN 37232 | (615) 936-7085

The Melanocortin-4 receptor (MC4R) is a well-validated target for the treatment of common obesity, and cachexia. Other studies suggest potential applications in diabetes and metabolic syndrome, depression related anorexia and anhedonia, and obsessive-compulsive disorder. The MC4R appears to be at the heart of the adipostat, in that administration of melanocortin agonists inhibits food intake and increases energy expenditure. Chronic administration of potent small molecule and peptide melanocortin agonists has produced significant weight loss in models systems from rodents to primates. However, clinical trials of potent orthosteric agonists of the MC4R have failed due to target-mediated pressor effects. Despite the target-mediated pressor response, two different peptide analogues of the native α-MSH ligand, RM-493 and MC4-NN2-0453 have been demonstrated to cause weight loss without a pressor response. Thus, a better understanding of the mode(s) and site(s) of MC4R activation in both weight loss and cardiovascular regulation is needed for the development of useful MC4R-specific therapeutics. We have recently identified several new aspects of MC4R function that may be applied to this problem. First, the pharmacological activity of MC4R is regulated in vivo by an accessory protein, MRAP2, that is not highly expressed in cell lines classically used for pharmacological analysis (Sebag et al., Science 278, 2013).

While the MC4R couples to $G\alpha_S$ in all cells tested, we have also recently determined that α-MSH and AgRP regulate neurons in the PVN via a novel G-protein independent signaling pathway coupling the receptor to the activity of the inward rectifier Kir7.1. Thus, AgRP is actually a biased agonist of the MC4R, and we have also identified α-MSH analogues that act as biased agonists preferentially coupling the MC4R to Kir7.1 over $G\alpha_S$. Of course, another potential explanation for absence of pressor activity in the new generation of α-MSH peptides may be the differential penetration of peptides into the CNS. In this regard, while MC4R has been considered primarily a central neuropeptide receptor, we have now identified a novel physiological pathway for MC4R in the periphery that may also play a role in the regulation of food intake and energy homeostasis. We show that MC4R is expressed in peptide YY (PYY) and glucagon-like peptide one (GLP-1) expressing enteroendocrine L cells. When vectorial ion transport is measured across mouse or human intestinal mucosa, administration of α-MSH induces a MC4R-specific PYY-dependent anti-secretory response consistent with a role for the MC4R in paracrine inhibition of electrolyte secretion. Finally, MC4R-dependent acute PYY and GLP-1 release from L cells can be stimulated in vivo by intraperitoneal administration of melanocortin peptides to mice. This suggests physiological significance for MC4R in L cells, and indicates a previously unrecognized peripheral role for the MC4R, complementing vagal and central receptor functions. These new physiological and pharmacological aspects of MC4R function suggest additional options for the development of melanocortin-based peptide therapeutics.

Masoud Ghamari-Langroudi[1], Brandon L. Panaro[1], Julien A. Sebag[1], Gregory J. Digby[1], Savannah Y. Williams[1], Iain R. Tough[2], Thue W. Schwartz[3], Helen M. Cox[2] and Roger D. Cone[1]

[1] Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, TN 37232 USA

[2] King's College London, Wolfson Centre for Age-Related Diseases, Guy's Campus, London SE1 1UL, UK

[3] Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Medical and Health Sciences, University of Copenhagen, 2200 Denmark

Discovery of Functional Ligands and Materials from Genetically-encoded Libraries of Chemically-modified Peptides

Ratmir Derda, Ph.D. | Assistant Professor, Department of Chemistry and Alberta Glycomics Centre
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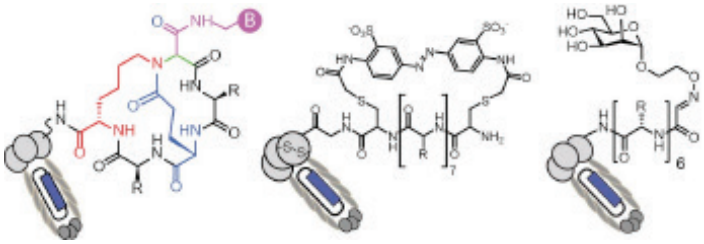
Identification of synthetic ligands for proteins is the basis for the development of therapeutic compounds, and functional biomaterials [1,2]. Selection and evolution of ligands from genetically encoded libraries is an attractive strategy for the identification of such ligands. We combine organic synthesis and natural peptide libraries to yield genetically-encoded libraries of vast structural complexity [3, 4]. This method, for example, can produce libraries of glycosylated ligands that could serve as a source of discovery of inhibitors for therapeutically-important carbohydrate-binding protein [3] or light-responsive macrocycles that can be turned "on" or "off" by light [5]. These billion-scale ligand libraries serve as starting material for biomaterial design. We will describe strategies for integration of the selection and biomaterial screening using arrays of three-dimensional porous material (paper) modified by peptides [6].



1. R Derda, S Musah, BP Orner, JR Klim, L Li, LL Kiessling "High-throughput Discovery of Synthetic Surfaces that Support Proliferation of Pluripotent Cells," *JACS*. **2010**, 132, 1289.

2. L Li, JR Klim, R Derda, AH Courtney, LL Kiessling, "Spatial control of cell fate using synthetic surfaces to potentiate TGF-beta signaling," *PNAS*, **2011**, 108, 11745.

3. S Ng, MR Jafari, W Matochko, R Derda "Quantitative Synthesis of Genetically Encoded Glycopeptide Libraries Displayed on M13 Phage," *ACS Chem. Biol.*, **2012**, 7, 1482.

4. P Kitov, D F Vinals , S Ng , K F Tjhung , and R Derda "Rapid, Hydrolytically Stable Modification of Aldehyde-terminated Proteins and Phage Libraries," *J. Am. Chem. Soc.*, **2014**, DOI: 10.1021/ja5023909

5. MR Jafari, Lu Deng, S Ng, W Matochko, A Zeberof, A Elias, John S. Klassen, R Derda* "Discovery of light-responsive ligands through screening of light-responsive genetically-encoded library," *ACS Chem. Biol.*, **2014**, 9, 443.

Continuous Glucose Monitoring: Technology that will Bridge the Gap Until There is a Cure for Type 1 Diabetes

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Many diabetes specialists strongly feel that the development of accurate continuous glucose monitory (CGM) devices represent one of the most significant advancements in the treatment of patients with type 1 diabetes (T1D) since the discovery of insulin, which was over 90 years ago. With these devices, patients are able to know what their blood glucose readings are 24 hours per day. They can see where their blood glucose values are coming from, what it is now and what direction it is going. However, equally important to the actual blood glucose number itself is the glucose trend. Patients can react sooner to rising or falling blood glucose values to prevent extreme hyperglycemia and potentially fatal hypoglycemia. Subcutaneously injected insulin is not physiologic and consistently unpredictable making treatment of type 1 diabetes very unpredictable and CGM can help tremendously. CGM is also playing an important role in basic and clinical research and in the development of the artificial pancreas, which will bridge the gap until there is a real cure. Collectively, the use of these CGM devices have shown to improve glucose control with lower A1C values, more time in target blood glucose range, less hypoglycemia, and improved quality of life. As more evidence accumulates confirming their role in diabetes management, insurance coverage is improving and higher numbers of patients are using these devices. People with diabetes and the health care practitioner needs to be aware of the technology and its limitations and advantages, as well as being able to identify which patients will likely benefit from its use.

Integrated Triple Gut Hormone Action Broadens the Therapeutic Potential of Endocrine Biologics for Metabolic Diseases

Brian Finan, Ph.D. | Division Head
Helmholtz Zentrum Munich
Business Campus Garching-Hochbruck, Parkring 13, 85748 Garching, Germany | +49 89 3187 2172

We report the discovery of a novel peptide that aims to mimic endocrine effects of bariatric surgeries by bundling enhanced agonism at the GLP-1-, GIP-, and glucagon receptors, resulting in unprecedented potential to medicinally address the metabolic syndrome. The tri-agonist is composed of intermixed residues selective to each native ligand, which were selected from judicious structure/function analysis, and integrated with features that also impart optimized *in vivo* pharmacokinetics. This balanced unimolecular tri-agonist proved superior to reciprocal co-agonists and best-in-class mono-agonists to reduce body weight, enhance glycemic control, and reverse hepatic steatosis in rodent models of obesity and diabetes, independent from differences in pharmacokinetics. The tri-agonist capitalizes on the benefits of high potency and coordinated mixed agonism, allowing more aggressive dosing with less risk of adverse effects. Various loss-of-function rodent models, including genetic, pharmacological blockade, and chemical knockout, confirm each constituent activity and demonstrate the individual contributions of each component to the overall metabolic efficacy of the tri-agonist. The enhanced efficacy results from synergistic glucagon action to increase energy expenditure, GLP-1 action to reduce caloric intake and improve glucose control, and GIP action to potentiate the incretin effect and buffer against the diabetogenic effect of inherent glucagon activity. Reduction of glucagon agonism through selective chemical modifications reduced the weight-lowering capacity but positively influenced glycemia. Accordingly, these individually balance-adjusted tri-agonists with laddered relative glucagon activity may provide unprecedented opportunities in the personalized treatment of heterogeneous metabolic diseases such as obesity and type 2 diabetes.

Hepcidin and Minihepcidins: From Mechanistic Studies to Therapeutic Peptides

Tomas Ganz, Ph.D., M.D. | Professor of Medicine and Pathology
David Geffen School of Medicine, University of California, Los Angeles
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The deficiency of hepcidin, the 25-amino acid peptide hormone that controls iron absorption and its tissue distribution, is the cause of iron overload in nearly all forms of hereditary hemochromatosis and in untransfused iron-loading anemias. Hepcidin acts by binding to its cellular receptor/iron transporter ferroportin and causing its endocytosis and proteolysis, thereby decreasing intestinal absorption of iron and iron delivery to plasma. We showed that the interaction between hepcidin and ferroportin depends on a small ferroportin pocket including a thiol cysteine interacting with the N-terminal 9-amino acid segment of hepcidin. Based on these studies we rationally designed minihepcidins, small drug-like hepcidin agonists. Optimized minihepcidins were developed that had superior potency and duration of action compared to natural hepcidin or other minihepcidins, and favorable cost of synthesis. Minihepcidin PR65 was administered by subcutaneous injection daily for 2 weeks to iron-depleted or iron-loaded hepcidin knockout mice. PR65 administration to iron-depleted mice prevented liver iron loading, decreased heart iron levels and caused the expected iron retention in the spleen and duodenum. PR65 administration to hepcidin knockout mice with pre-existing iron overload caused redistribution of iron from the liver to the spleen. In a mouse model of β-thalassemia intermedia a related minihepcidin improved anemia and reduced tissue iron burden. Minihepcidins should be beneficial in genetic iron overload disorders and iron-loading anemias.

Tomas Ganz[1], Elizabeta Nemeth[1], Peter Ruchala[1], Stefano Rivella[2] and Brian MacDonald[3]

[1] UCLA School of Medicine, Los Angeles, CA
[2] Weill Cornell Medical College, New York, NY
[3] Merganser Biotech LLC, Philadelphia, PA

Danegaptide - Potential First and Best in Class Peptide Medicine for Prevention of Myocardial Reperfusion Injury

Rie Schultz Hansen, MSc, Ph.D. | Principal Scientist
Zealand Pharma A/S
Smedeland 36, 2600 Copenhagen, Denmark | +45 88 77 36 00

Danegaptide (ZP1609) is a modified di-peptide that belongs to a novel class of anti-arrhythmic peptide mimetics with both anti-arrhythmic and cytoprotective properties. Zealand Pharma A/S ("Zealand") is currently evaluating danegaptide in a Phase II clinical Proof-of-Concept study for its protective effects against reperfusion injury in patients with myocardial infarction (NCT01977755). The chemical structure of danegaptide is inspired by the native anti-arrhythmic peptide (AAP: H2N-Gly-Pro-Hyp-Gly-Ala-Gly-CONH2) which was originally isolated from bovine atria and was shown to synchronize chick cardiomyocyte beating *in vitro* Following the discovery of AAP, several synthetic AAPs — such as the hexapeptide AAP10 (H2N- Gly-Ala-Gly-Hyp-Pro-Tyr-CONH2) — were discovered. The exact molecular target for the native peptide as well as the synthetic AAPs is not currently unknown. AAP10 has been widely used for *in vitro* experiments but enzymatic instability limits its clinical usefulness. To increase stability, Zealand designed several molecules from a pharmacophore model which led to the invention of danegaptide — a stable peptide mimetic of AAP10. The present talk will focus on the invention of danegaptide and its preclinical profile, giving insights also into some of our molecular target identification work, and conclude with a brief discussion of the considerable clinical Phase I data available for this peptide as well as the design of the ongoing clinical Phase II study.

Peptide Therapeutics: A New Golden Age!

Richard A. Houghten, Ph.D. | Founder, President & CEO
Torrey Pines Institute for Molecular Studies
11350 SW Village Parkway, Port St. Lucie, FL 34987 | (772) 345-4800

Peptides are the major information trafficking agents in mammalian biological systems. Advances over the past 10-20 years have transformed peptide basic research and drug discovery. As powerful discovery approaches, now routinely available, are combined with powerful and practical delivery systems, peptides will play an ever increasing role as effective therapeutic agents.

A short historical review will be presented. Current strategies for small molecule screening in drug discovery typically involve the screening of 250,000 to 1,000,000 individual compounds in robot-assisted high throughput *in vitro* biochemical or cell-based assays. However, this approach is not typically used when screening peptides for effective hits/leads. A confluence of powerful advances using peptide based *in vitro* discovery methodologies as well as recent unique phenotypic screening approaches will be discussed with an emphasis on the ability to identify peptides with uniquely desirable and enhanced properties.

Peptide Antagonists of the Inflammatory Response Enhanced by the Antimicrobial Peptide LL-37

Cheng Kao, Ph.D. | Director of Biotechnology and Professor, Department of Molecular & Cellular Biology
Indiana University
212 S. Hawthorne St., 201A Simon Hall, Bloomington, IN 47405 | (812) 855-7583

LL-37 is a multifunctional peptide secreted by human epithelial cells to lyse bacteria and suppress the inflammatory response initiated by endotoxin-sensing Toll-like Receptor 4 (TLR4). LL-37 can also enhance signal transduction by the nucleic acid-sensing TLR3 and TLR9. How LL-37 interacts with ligands and affect signal transduction by the various TLRs is not fully understood. We determined that LL-37 complexed with TLR4 and TLR3 ligands uses different receptors to enter cells. Furthermore, double-stranded (ds) RNA complexed to LL-37 enters cells by endocytosis and acidification of the endosomes triggers LL-37 to release the dsRNA in these endosomes and make the dsRNA available to TLR3. We mapped LL-37 binding to various TLR ligands and identified a region required for LL-37 oligomerization. A truncated peptide named LL-29 that contains the LL-37 oligomerization region was found to inhibit LL-37 enhancement of signal transduction by TLR3 and TLR9 in cultured cells. LL-29 retained antimicrobial activity and the suppression of signal transduction by TLR4. LL-29 also prevented the dsRNA/LL-37 complex from localizing to endosomes that contain TLR3. These results shed light on the requirements for LL-37 modulation of TLR signaling. LL-29 could also serve as the prototype to generate antagonists of signal transduction by nucleic acid-sensing TLRs.

C. Cheng Kao, Robert Vaughan, and Divyendu Singh

Multiselective Peptides for the Treatment of Metabolic Diseases

Cristina M. Rondinone, Ph.D. | Vice President, Research & Development; Head Cardiovascular and Metabolic Diseases iMED
MedImmune
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The rapid increase in the prevalence of obesity in the world is becoming an important health problem. Obesity may cause several metabolic complications, including type 2 diabetes mellitus, hyperlipidemia, high cholesterol, NASH, coronary artery disease as well as hypertension. Current strategies for treatment of obesity and diabetes are not adequately effective and are frequently companied with many side effects. Thus, new ways to treat metabolic diseases are urgently needed. Over the last few years more biologics, including peptides, are being developed as new targets for these diseases, including different types of insulins and incretins like GLP-1. Recent scientific discoveries related to the "cure of diabetes/obesity" with bariatric surgery, pancreatic regeneration, and differentiation of brown fat in humans, lead to an explosion of new peptide targets that have the potential to make a difference. We have developed different dual peptides targeting the GLP-1 and glucagon receptors that showed profound effects in body weight and metabolic control in animal models of diabesity. In addition, we found a novel role of these types of dual peptides in alleviating fatty liver and improving liver regeneration in a NASH animal model. Moreover, several parameters that assessed hepatic inflammation, oxidative stress, fibrosis and apoptosis were ameliorated by co-agonist treatment. The development of multiselective peptides that will stop or reverse these diseases will have a great impact in the patients and the society.

Plecanatide and SP-333, Homologues of Uroguanylin, as Innovative Oral Drugs for Treatment of Gastrointestinal Disorders and Diseases

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Agonists of guanylate cyclase-C (GC-C) are emerging as a new class of drugs for the treatment of gastrointestinal (GI) disorders and diseases. Uroguanylin (UG) and guanylin (GN) are endogenous natriuretic peptides that bind and activate GC-C receptors located on the luminal side of the GI tract to stimulate cGMP synthesis, a second messenger maintaining electrolytes and fluid transport, homeostasis of epithelial cells, and barrier function in the GI tract. In addition, the heat-stable enterotoxin (ST peptide) produced by *Escherichia coli* is also a GC-C agonist that exploits GC-C signaling to produce uncontrolled traveler's diarrhea. GC-C agonists represent a new class of drugs effective in the treatment of chronic idiopathic constipation (CIC) and irritable bowel syndrome-constipation (IBS-C). We and our collaborators have been specifically exploring the therapeutic potential of analogues of UG as a unique sub-class of GC-C agonists for the treatment of CIC, IBS-C, opioid-induced constipation (OIC), inflammatory bowel diseases (IBD) and prevention of colon cancer. UG is a 16 amino acid peptide which exists in several distinct topological isomers in aqueous solution, only one of which is biologically active. This and other inherent features of UG make it unsuitable for clinical development. Based on results from thermal bond energy calculations, 3-D structure modeling, structure activity relationship and molecular simulation studies, we developed plecanatide and SP-333 as novel homologues of UG that bind and activate GC-C receptors in a pH-dependent manner, and are expected to mimic functions of UG in the GI tract. SP-333 is relatively more resistant to proteolysis in simulated intestinal fluid than plecanatide. Results from animal studies demonstrate that oral treatment with either plecanatide or SP-333 is efficacious in promoting GI motility, overcoming opioid-induced inhibition of GI motility, suppressing visceral hyperalgesia, and in ameliorating colitis via a cGMP-mediated mechanism. Plecanatide has successfully completed Phase II clinical trials in CIC and IBS-C patients, and the drug is presently in two Phase III clinical trials in CIC patients and is being readied for registration trials in IBS-C as well. SP-333 is presently concluding a Phase II clinical trial in patients with OIC, and there are additional plans to explore its potential in patients with ulcerative colitis. The seminar will also discuss physiological mechanisms underlying the pharmacology and mode-of-action of GC-C agonists for the treatment of GI diseases and disorders.

Peptide Agonists of Incretin Receptors Are High Priority Candidates in the Search for the First Effective Treatments of Alzheimer's Disease

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Among the greatest challenges in 21st century medicine is the development of effective treatments for Alzheimer's disease (AD), an incapacitating disorder whose prevalence is reaching epidemic levels worldwide. Despite intensive efforts, treatments tested to date have either proven ineffective or only modestly effective for no more than a year early in the disorder. A very promising new target for treatment has emerged, however, from our discovery that the AD brain is markedly insulin resistant even in the absence of diabetes and even at an early stage called mild cognitive impairment (MCI) (Talbot et al., Journal of Clinical Investigation 122: 1316-1338, 2012). Because brain insulin signaling protects against many core pathologies and symptoms of AD, brain insulin resistance may play a central role in the pathogenesis of AD.

Effective treatments of brain insulin resistance in AD may thus be effective treatments of the disorder itself. AD might be treatable, then, with antidiabetics safe for human use that cross the blood-brain barrier. Yet only one class of such drugs consistently show promise as AD therapeutics: receptor agonists of the incretins, glucagon-like peptide -1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These include the FDA-approved GLP-1 agonist liraglutide (Victoza), which has been studied extensively in the APP/PS1 mouse model of AD. This model develops severe brain insulin resistance by 7.5 months based on ex vivo stimulation tests. Liraglutide (25 nmol/kg) given ip daily for 2 months virtually eliminates brain insulin resistance in APP/PS1 mice. Perhaps for that reason, the same drug regimen also restores their synaptic plasticity and reduces their AD-like pathologies (Aβ plaque load, microglial activation, synaptic loss, and vascular damage) and AD-like symptoms (poor object recognition and spatial memory).

Liraglutide is likely to have the same therapeutic effects in AD cases given our findings that such cases have severely diminished brain levels of GLP-1 and that exposure of this drug (100 nM) to brain tissue from MCI and AD dementia cases for just one hour significantly reduces insulin resistance in that tissue. In MCI tissue, the drug elevates insulin responsiveness 60-75%. Even greater elevations are expected using peptides activating both GLP-1 and GIP incretin receptors, because the therapeutic effects noted with liraglutide on the AD mouse model are also exerted by GIP agonists alone. As that predicts, dual GLP-1/GIP agonists are 1.5 - 2.0 times more potent than liraglutide in reducing Aβ plaque loads in the mouse model.

Apart from their beneficial actions in the brain, incretin agonists offer the added benefit of treating peripheral resistance, which can exacerbate AD pathology. These agonists are also among the few promising AD therapeutics sufficiently tested in humans to meet the goal of the *National Plan to Address Alzheimer's Disease* to prevent and effectively treat this disorder by 2025.

For the reasons summarized here, incretin peptide agonists, especially dual GLP-1/GIP agonists, are emerging as high priority candidates for the first effective treatment of AD.

Chemoenzymatic Approaches in Amide-to-amide Peptide Ligation

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The amide-to-amide approaches for peptide ligation and macrocyclization through transpeptidation have been realized both chemically and enzymatically. Both approaches bear striking similarity and employ a series of acyl shifts to break and make amide bonds. Here we report the discovery of a new peptide ligase that displays a broad specificity for the N-terminal amino acids and is C-terminal amino-acid-specific. Importantly, it enables peptide ligation with high efficiency. We have also developed an efficient chemical scheme based on the amide-to-amide approach, and which is N-terminal amino-acid-specific. In this presentation, we will illustrate their applications and highlight their similarities in our synthesis of peptides and peptide macrocycles.

Novel Peptide Therapeutics Targeting Key Intracellular Signaling Pathways of Cancer Stem Cells

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One of the challenges in today's treatment of cancer is tumor recurrence and spread occurring despite therapeutic intervention. One of the ground lying causes is the existence of subpopulations within a tumor with distinct tumor-initiating powers, the cancer stem cells. There is a great need for specific molecular therapies to target key signaling pathways supporting these cells. However, most intracellular key components of these pathways are difficult to access for conventional anti-cancer therapies. Peptide therapeutics targeting protein-protein interactions with the ability to reach intracellular compartments appear an attractive alternative to conventional therapies to inactivate signaling pathways such as WNT, Notch and Hedgehog, and to allow for the elimination of cancer stem cells. Nexigen's Nexi*Screen* platform identifies potent intracellular peptides (the Nexi*Tides*) targeting these pathways. These *NexiTides* have powerful *in vitro* anti-cancer stemness activity and are effective in xenografted and orthotopic models of tumor growth and metastases.

Using the Endosome Escape Trap to Discover Phylomer Peptides which more Efficiently Deliver Cargoes to the Cytoplasm

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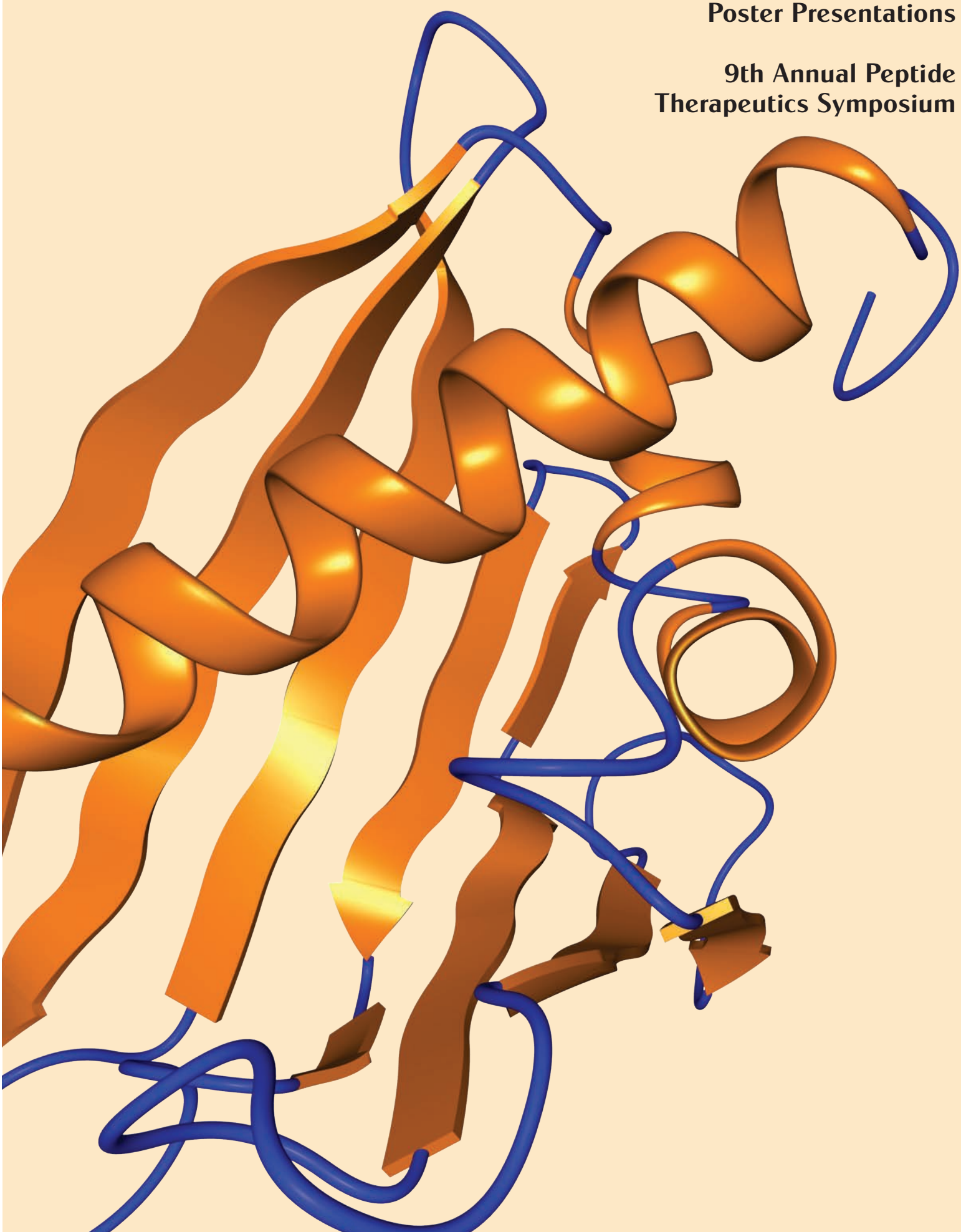
Phylomers are a new class of peptide, derived from fragments of biodiverse microbial genomes. Phylomer libraries can also be used to identify new cell penetrating peptides for delivery of macromolecules and nanoparticles into cells. Some of these cell penetrating Phylomers are specific for particular cell types. Phylomers themselves can be active against intracellular targets in vivo and can be used to discover and validate new targets. Phylogica is using its technology including the novel 'endosome escape trap' to isolate CPP's which more efficiently deliver their cargoes to the cytoplasm. The activity of these Functional Penetrating Peptides (FPPs) can then be determined using cargoes such as toxins and blockers of intracellular PPI's which have no activity in endosome, being only functional in the cytoplasm. The ability to deliver biologics more efficiently into cells offers the potential to open up the intracellular target landscape to protein and peptide therapeutics.

Abstracts of Poster Presentations

9th Annual Peptide Therapeutics Symposium



P01 A Novel Aspartate Protection Minimizing Aspartimide Derived By-products

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Despite recent advances in stepwise Fmoc SPPS, base-mediated aspartimide formation remains problematic, particularly for the synthesis of long peptides because of the repeated exposure to piperidine [R. Subiros-Funosas, A. El-Faham, F. Albericio, Tetrahedron, 67, 8595 (2011]. There is, therefore, a need for simple methods for the efficient suppression of this side reaction. To address this issue, we investigated the effects of increasing the steric bulk of the standard t-butyl group by linear homologation. Our rational was that an analog of the t-butyl group in which the methyl groups were substituted for longer alkyl chains would help shield the aspartyl b-carboxyl group and thereby reduce the formation of aspartimide derived by-products.

To this end we prepared Fmoc-Asp(OEpe)-OH, where OEpe is 3-ethylpentan-3-yloxy, Fmoc-Asp(OPhp)-OH, where OPhp is 4-n-propyl-4-yloxy, and compared the effectiveness of this derivative against that of Fmoc-Asp(OtBu)-OH and Fmoc-Asp(OMpe)-OH [2] in the synthesis of the well established model peptide scorpion toxin II (H-Val-Lys-Asp-Gly-Tyr-Ile-OH) and the Asn variant (H-Val-Lys-Asp-Asn-Tyr-Ile-OH) [4]. Following Fmoc SPPS, these peptide resins were treated for 18 h with 20 % piperidine commonly used for Fmoc removal, resembling the exposure received during 100 cycles.

The symmetrical homologs of the tert-butyl protecting group are an interesting new class of compounds with superior properties in the minimization of aspartimide derived by-products reducing aspartimide to < 0.1 % per cycle. Therefore we are convinced that these compounds will significantly facilitate Fmoc SPPS as well as peptide purification and in doing so increase peptide purity and overall yields.

P02 The Development, Validation and Application of Various Biophysical Modules in CMDInventus to Enable Structure-based Peptide Drug Design and Discovery

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Recently, peptides have regained favor within drug discovery circles because there is mounting evidence that peptides, unlike small molecules and antibodies, can be used to significantly increase the space of druggable targets to include intracellular protein-protein interactions and agonists of class B GPCRs. In order to fill this biological gap, peptides must exhibit complex pharmacological behaviors, typically by binding to shallow and relatively featureless binding surfaces to modulate protein-protein interactions. The daunting task of designing novel peptides to modulate protein-protein interactions can be ameliorated by harnessing the vast amount of scientific information and knowledge of proteins that has accrued over the last two decades. Importantly, in an age variously referred to as the “computer” and “information” age, computation provides the ideal framework for harnessing and applying disparate sources of information to the problem of identifying therapeutic peptides to modulate protein-protein interactions. Here we describe a suite of computational, structure-based modules — implemented in our proprietary computational peptide drug discovery platform, CMDInventus — that can be used to solve a range of peptide lead discovery and optimization problems, from novel peptide binding site identification, to peptide structure prediction and high resolution protein-peptide complex prediction.

P03 Evolution or Revolution: Veltis® Technology Demonstrates Significantly Improved Drug Half-life beyond Wild-type Albumin — Proof of Concept Study

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Many promising protein and peptide drug candidates fail to produce the desired effect in vivo because of their short serum half-life. The half-life of drug candidates can be increased by conjugation or fusion to albumin owing to an increase in size, which prevents renal clearance and recycling of the molecules via the neonatal Fc receptor (FcRn). Interaction with FcRn rescues albumin, and attached therapeutic agents, from lysosomal degradation. Enhancing the interaction between albumin and FcRn was postulated to result in improved serum half-life. Using rational engineering strategies we have developed a new generation of safe, stable and efficacious albumins with significantly prolonged serum half-life in several animal models including cynomolgus macaques. The ability to modulate albumin half-life enables an opportunity to optimize the dose frequency, drug tolerability and dose quantity their drug candidate.

As proof of principle, Exenatide, a drug used for the treatment of type II diabetes with a short serum half-life, was conjugated to the engineered albumins by maleimide-thiol conjugation chemistry using the free thiol group at Cys-34 of the engineered albumins. Conjugates were stabilized by performing a hydrolysis of the succinimide ring. The conjugates were assessed in pharmacokinetic and pharmacodynamic studies in mice to demonstrate the potential of the Veltis technology for extension of half-life of an active therapeutic. The data presented here show that the engineered albumin-exenatide conjugate exhibits improved serum half-life beyond that achieved with a wild-type albumin-exenatide conjugate and demonstrates the potential benefits of the Veltis technology for optimising drug dose frequency and efficacy.

P04 Novel, Long Acting Analogs of Astressin B, a Corticotropin Releasing Factor (CRF) Antagonist

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CRF is the key neuro-regulator of the hypothalamic-pituitary-adrenal cortical axis and mediates numerous stress-related endocrine, autonomic, metabolic and behavioral responses. Since the discovery of CRF, many biologically active agonists and antagonists have been synthesized. The introduction of non-natural amino acids, and peptide cyclization are the most common strategies to increase peptide stability and duration of action. Astressin B {(cyclo(30-33)[DPhe^{12},Nle^{21,38},Leu(Me)^{27,40},Glu^{30},Lys^{33}]-Acetyl-h/r-CRF$_{(9-41)}$}, a CRF antagonist developed in our laboratory earlier, has been employed by a number of investigators to study the biological actions of the CRF system. Astressin B blocked a variety of stress-induced responses, including stress-induced inhibition of the reproductive system in rhesus monkeys, gastrointestinal function in rats, and pain-related sensitization. Despite its effective inhibition of ACTH release, Astressin B resulted in no clear side effects in rats and monkeys. It had no effect by itself on postprandial gastric emptying or colonic activity. Astressin B produced a long lasting blockade of stress-induced hair loss through an action on the skin. Here, we present the synthesis, solubility, receptor binding and in vivo ability to reduce ACTH release of novel analogs of Astressin B.

P05 Multi-step Peptide Purification Using a Single Stationary Phase

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Peptide synthesis technology has developed sufficiently to allow for large scale manufacturing of peptides. The interest in using peptides as therapeutic agents has been a significant driver of this technology. Isolation and purification of the desired peptide product has also been developing with the synthesis technology.

The typical process for purifying a crude synthetic peptide mixture is to employ a multi step purification process. The first step is to remove most of the undesired components by one methodology. Followed by, one of more different chromatographic steps to “polish” the material to the desired purity level. These different steps are typically complimentary forms of chromatography such as ion exchange, gel permeation, affinity, and reverse phase.

The work presented here, follows the basic multi step concept but they are accomplished with the same stationary phase in each step. The steps are differentiated by pH and sometimes organic solvent composition. This strategy has been applied to crude samples of Bivalirudin and other commercially significant synthetic peptides.

P06 Peptides Displayed as High Density Brush Polymers Resist Proteolysis, Penetrate Cells, and Retain Bioactivity

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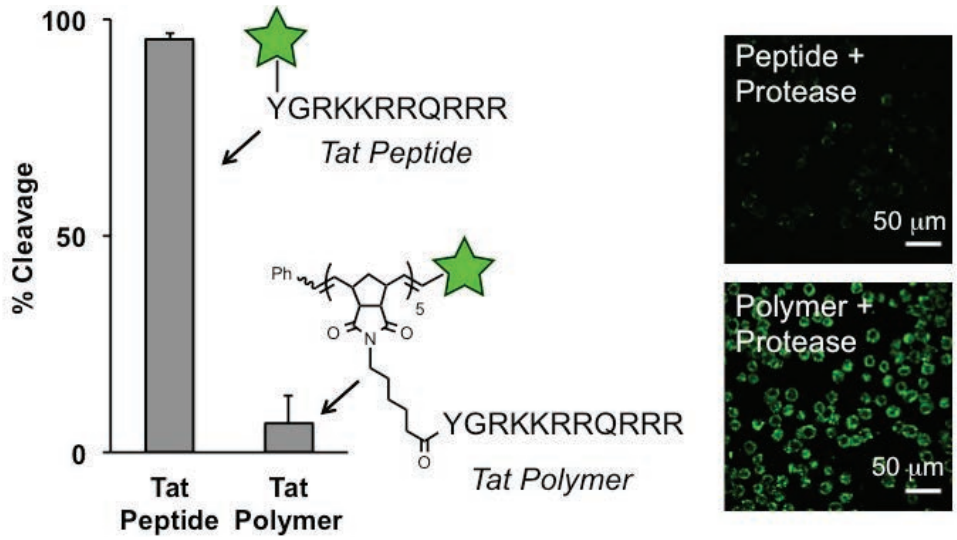
Peptides have been developed as highly specific and efficacious tools for treating and diagnosing disease. However, the utility of most peptides is severely hampered in vivo by inefficiencies in cellular uptake and by rapid digestion endogenous proteases that are abundant in circulation. Here we present an easy-to-access strategy for packaging active peptides as high-density brush polymers to render them resistant to proteolysis in a tunable fashion. Moreover, the polymerized peptides are readily taken up by cells if at least one Arg or Lys is present in the parent sequence. The utility of our strategy is demonstrated by showing a wide scope of peptide sequences that are resistant to digestion by myriad proteases when packaged in this manner, including two popular cell penetrating peptides and a therapeutic peptide whose activities are each maintained when polymerized. Furthermore, we demonstrate that the proteolytic susceptibility of the polymers can be tuned by adjusting the density of the polymer brush. We envision that the general strategy of preparing peptides as high-density brush polymers will greatly increase the in vivo efficacy and widen the therapeutic window of a wide range of peptide-based therapeutics and diagnostics.



P07 Semienzymatic Formation of Cyclic Cystine Knot (CCK)

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Conopeptides, toxins from marine cone snails, have attracted much interest as drug candidates because they possess high specificity for their physiological targets such as ion channels and receptors. Although they are often found disulfide-rich, their low stability against proteases in vivo has been a bottleneck to drug development. To improve their stability, cyclization has been one of the promising methods by reducing their susceptibility to proteolysis. In this study, we have successfully cyclized κ-conotoxin PVIIA that possesses a cystine knot formed by three disulfide bonds, and blocks the Drosophila shaker potassium channel. Based on successful production of a cyclotide, kalata B1, which also has a cystine knot core, κ-PVIIA was cyclized by a modified sortase A using a seven amino acid linker (LPETGGG). Here, we present a three-dimensional structure of cyclic-PVIIA determined by NMR experiments and its activity against shaker potassium channel in comparison with the wild-type. Cyclisation of κ-PVIIA implies possibility of the same application to other conotoxins sharing the same cysteine framework (I-IV, II-V, III-VI) forming a knotted core, such as the currently marketed peptide drug, ω-MVIIA.

P08 Peptides Targeting EGFL7 as Anti-Angiogenic Agents

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Epidermal growth factor-like domain 7 (EGFL7) is a protein that is up-regulated in actively remodeling endothelium and in endothelial progenitor cells, components which are involved in angiogenesis. Inhibition of EGFL7 in zebrafish disrupts vascular tube formation during vasculogenesis [1]. EGFL7 expression correlates with poor prognosis in malignant glioma, hepatocellular carcinoma and non-small cell lung cancer, and therefore represents a potentially valuable therapeutic target for anti-cancer strategies. Pre-clinical models have demonstrated (Roche/Genentech) that anti-EGFL7 antibody enhances the inhibition of tumor neovascularization. We hypothesized that peptides could be discovered that bind and block the function of EGFL7, leading to the inhibition of angiogenesis. Here, we describe the identification and characterization of novel anti-EGFL7 peptides using a combinatorial 'beads on a bead' approach for ligand discovery [2]. An on-bead cell binding assay was used to validate the peptide hits using an EGFL7-expressing HT1080 fibrosarcoma cell line. Hit peptides were then sequenced using a MALDI-TOF technique [3], and their binding affinity to EGFL7 was quantified. Two high-affinity ligands, LCE71 and LCE72, inhibited sprouting and tube formation of human endothelial cells in vitro. A F-18 PET imaging agent was developed based upon LCE72 and demonstrated in vivo EGFL7 targeting in a xenograft murine model. These peptides also inhibited angiogenesis induced by tumour cells in vivo, in avian embryo and murine models. Efforts to evaluate the mechanism of action and the efficacy of these peptides in treating tumors are currently underway.

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P09 CAR Peptide: A Novel Peptide Adjuvant to Ameliorate Cachexia

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Cachexia, the loss of body mass that cannot be reversed nutritionally, is a positive risk factor for death that is frequently seen in patients with cancer, AIDS, chronic obstructive pulmonary disease, chronic kidney disease, multiple sclerosis, congestive heart failure and other conditions. Cachexia is difficult to treat and the response to standard treatment is poor.

In the process of developing a 9 amino acid cyclic peptide, CARSKNKDC (CAR), as a therapeutic adjuvant for the treatment of pulmonary arterial hypertension (PAH) we came across an unexpected benefit of CAR administration: the amelioration of bodyweight loss in the animals that received CAR.

In our experiment, PAH was induced by a single s.c. injection of 60 mg/kg monocrotaline. After 28 days, treatment was initiated with imatinib 10 mg/kg with or without CAR 3 mg/kg for 14 days. Animals were fed ad libitum. After 14 days of treatment, animals that received CAR with imatinib weighed more than those receiving imatinib alone (Figure 1).

Similarly, in a pilot study of CAR's adjuvant properties in a mouse model of triple negative breast cancer (TNBC), the animals that received 3 mg/kg CAR along with 3 mg/kg paclitaxel gained more bodyweight than animals that received just 3mg/kg paclitaxel or saline vehicle (Figure 2).

Taken together, these results suggest that CAR peptide, when co-administered with other therapeutics, may offer unexpected potential benefits in maintaining body weight for those patients at risk for cachexia in addition to CAR's previously demonstrated ability to enhance the therapeutic benefits of co-administered therapies.

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Figure 1. Bodyweight changes during the treatment period. N=5 animals in each group.
Blue triangles = CAR treated animals

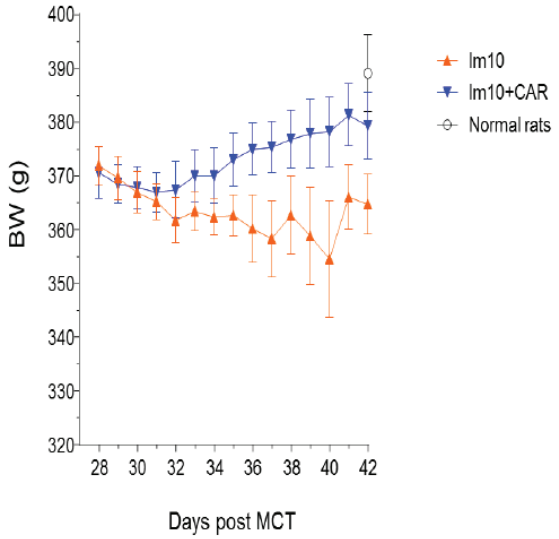
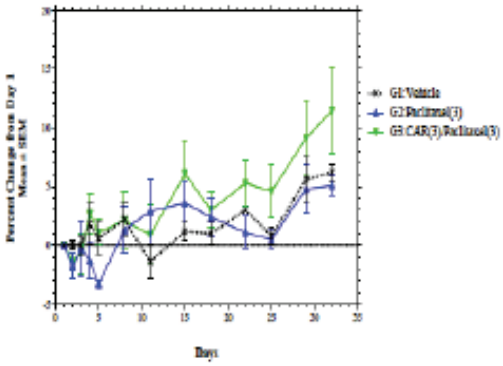


Figure 2. Percent mean bodyweight changes from Day 1 in triple negative breast cancer animals. N=3 animals in each group.
Green triangles= CAR treated animals



P10 Pellicon® 3 TFF Devices with 3 kDa Ultracel® Regenerated Cellulose Composite Membrane for Processing Insulin and Similar Peptide Therapeutics

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Global demand for insulin production is ever growing. Processing of small molecules such as insulin, antibody fragments and oligonucleotides demands a filtration system that can operate at higher pressures and temperatures and in aggressive chemical environments. There is a need for more robust filtration systems having composite membranes and thermoplastic modules. EMD Millipore aims to extend current solutions to Pellicon 3 TFF (Tangential Flow Filtration) system with enhanced product features to meet demanding filtration needs with ease of installation and use.

The Pellicon 3 cassettes with 3 kDa regenerated cellulose composite membrane provide superior capability with rugged and reliable performance over multiple production runs of insulin. Particularly, 3 kDa Pellicon 3 cassettes can operate at high TMP (trans-membrane pressure up to 80 psi) without concentration polarization effect to render high flux capability. Pellicon 3 TFF systems present a compact system footprint due to high mass transfer capability. In addition it offers robust solvent compatibility and an excellent scaling tool for processes ranging from 0.2 L and higher.

P11 BiotinPEG4TPG Hydrate: A Novel Reagent for the Bioconjugation of Arginine Residues in Peptides and Proteins

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Biotin is an extremely useful molecule in basic biochemistry research. Reagents for intrinsic cysteine and lysine modification exist and represent a multimillion dollar market. The side chain of arginine is typically found on the protein surface and its directed conjugation is an attractive alternative site for derivatization. Using a high yielding click / CuAAC approach, biotinPEG4alkyne and azidophenylglyoxal were combined to create a novel biotinylation reagent. Examples of the ease of use and broad utility of this approach in biotechnology are given with enzyme, antibody and peptide ligations.

P12 Effects of Cargo Molecules on Membrane Perturbation Caused by Transportan10 Based Cell-Penetrating Peptides

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Cell-penetrating peptides with the ability to escape endosomes and reach the target are of great value as delivery vectors for different bioactive cargoes and future treatment of human diseases. We have studied two such peptides, NickFect1 and NickFect51, both originated from stearylated transportan10 (PF3). To obtain more insight into the mechanism(s) of peptide delivery and the biophysical properties of an efficient vector system, we investigated the effect of different bioactive oligonucleotide cargoes on peptide-membrane perturbation and peptide structural induction. We studied the membrane interactions of the peptides with large unilamellar vesicles and compared their effects with parent peptides transportan10 and PF3. In addition, cellular uptake and peptide-mediated oligonucleotide delivery were analyzed. Calcein leakage experiments showed that similar to transportan10, NickFect51 caused significant degree of membrane leakage, whereas NickFect1, similar to PF3, was less membrane perturbing. The results are in agreement with previously published results indicating that NickFect51 is a more efficient endosomal escaper. However, the presence of a large cargo like plasmid DNA inhibited NickFect's membrane perturbation and cellular uptake efficiency of the peptide was reduced. We conclude that the pathway for cellular uptake of peptide complexes is cargo dependent, whereas the endosomal escape efficacy depends on peptide hydrophobicity and chemical structure. For small interfering RNA delivery, NickFect51 appears to be optimal. The biophysical signature shows that the peptide alone causes membrane perturbation, but the cargo complex does not. These two biophysical characteristics of the peptide and its cargo complex may be the signature of an efficient delivery vector system.

P13 Synthesis and Pharmacological Profile of Peptidic V1a Receptor Partial Agonists

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Cirrhosis is a clinical condition predominantly caused by excessive alcohol consumption or hepatitis. The most prominent manifestations of this circulatory dysfunction are marked splanchnic vasodilation and portal hypertension. There are numerous clinical and experimental studies indicating that V1a receptor agonists such as terlipressin are effective in treating complications of cirrosis. It has been demonstrated that terlipressin causes a significant reduction in portal hypertension [1].

However, fully efficacious V1aR agonists cause excessive vasoconstriction at higher plasma concentrations and therefore have a narrow therapeutic index. We hypothesized that V1a receptor agonists with reduced efficacy would be safer than maximally efficacious agonists and could be used at much higher doses while not causing side effects associated with undesired excessive vasoconstriction.

In the present study we identified a series of vasotocin analogues which are potent V1aR agonists and exhibit selectivity versus the related oxytocin/vasopressin receptors. As compared to AVP, the novel compounds displayed reduced Emax (30-70%) at the V1a receptor in vitro and showed a better selectivity profile versus related receptors. The reduced efficacy was also demonstrated in vivo in a rat skin blood flow model.

Structures and pharmacological profiles of new analogues will be presented in the context of their potential utility as novel treatments for complications of cirrhosis.

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P14 Selection of Biased GLP-1 Receptor Agonists from Intracellular Combinatorial Peptide Libraries

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Generating drugs with selective outcomes can be difficult for GPCRs because, when engaged, multiple signaling pathways may be activated. To solve this problem, we developed an autocrine-based system for selection of biased agonists from large combinatorial peptide libraries. One hundred million unique peptides and a GPCR receptor are co-localized in the plasma membrane of reporter cells and activated cells are selected.

Here we report the selection of biased agonists (in relative to nature ligand exendin-4) for the glucagon like peptide-1 receptor with the aid of deep sequencing technology. One peptide, P6, increased cAMP production, intracellular calcium mobilization and ERK1/2 activation as potent as exendin-4 but without activation of beta arrestin-1 and arrestin-2. When peptide P6 was tested in mice by acute GTT, it showed 10-fold higher potency to lower glucose levels than exendin-4. Complete loss of glucose lowering activity in GLP-1R KO C57BL/6J mice confirmed that the peptide's mechanism of action was mediated by GLP1R. More interestingly, P6 can lower plasma glucose levels without significant increase of insulin levels in C57BL/6J mice, ob/ob mice and DIO mice model. Measuring ITT indicated that peptide P6 had stronger insulin sensitizing effect.

This approach is highly efficient in generating of GPCR biased agonists that are more specific in their mode of action which may translate into drugs with a desired physiological effect.

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