

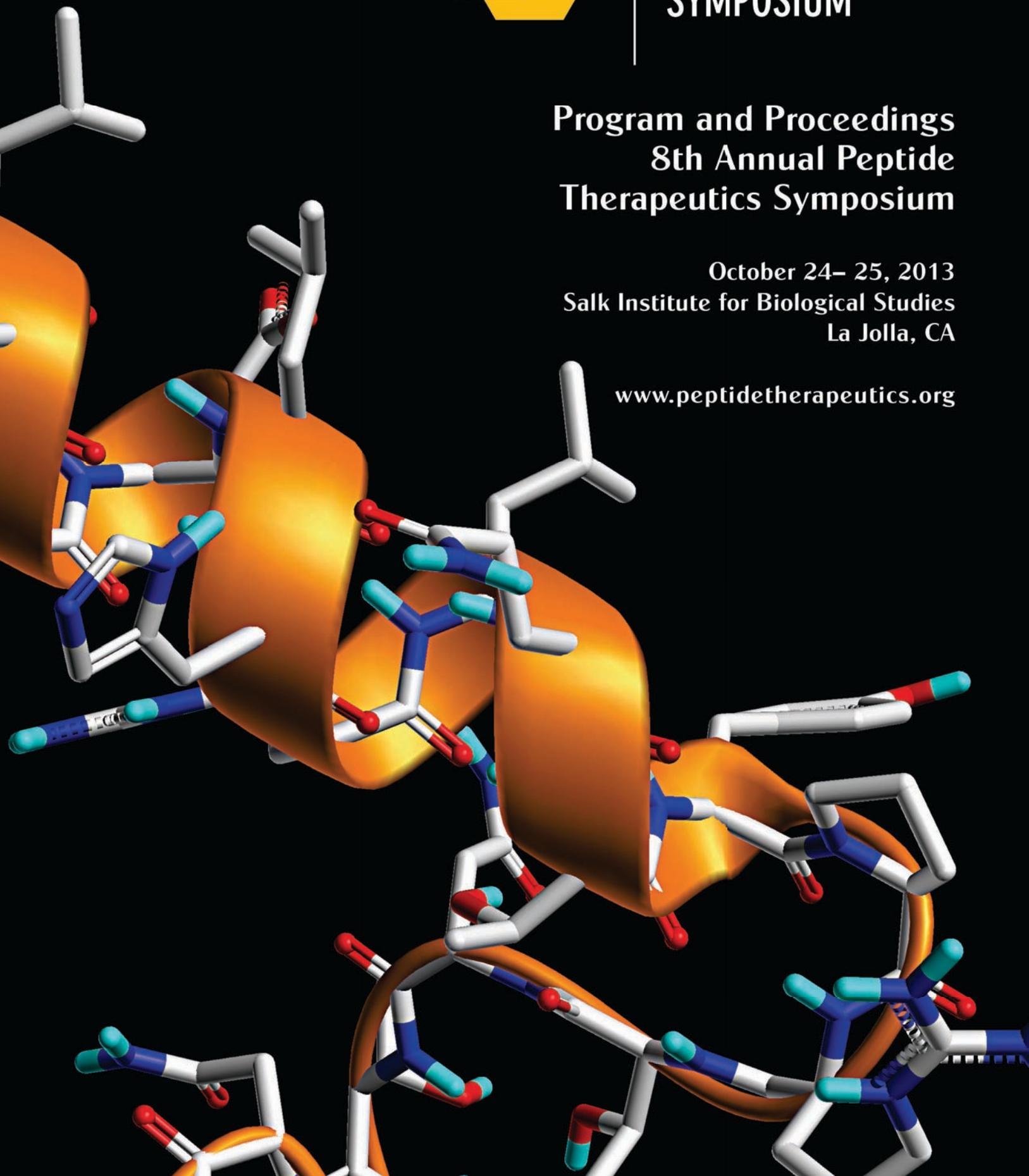


PEPTIDE THERAPEUTICS SYMPOSIUM

Program and Proceedings 8th Annual Peptide Therapeutics Symposium

October 24– 25, 2013
Salk Institute for Biological Studies
La Jolla, CA

www.peptidetherapeutics.org





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Symposium Sponsors



PEPTIDE THERAPEUTICS FOUNDATION



Dear Colleagues,

Welcome to the 8th Annual Peptide Therapeutics Symposium. We are very excited to be able to provide you with another world class program focused on the discovery and development of peptide-based drugs.

We begin with presentations from internationally recognized academic scientists who have pioneered the translation of peptide-oriented discoveries to human studies. Lectures describing interdisciplinary technology advanced in the laboratories of David Clemmer and Ian Wilson will conclude the first day's formal program. The Opening Reception and Poster session follow in a relaxed environment conducive to networking.

The program continues on Friday with an opening lecture by Michael Weiss pertaining to recent advances in insulin structure-function, followed by Samuel Gellman's presentation of beta-peptide based therapeutics. Three subsequent sessions introduce a number of breakthrough therapeutics currently residing between early clinical investigations and regulatory approval. The program also examines approaches to the discovery of novel peptide-based development candidates, in particular new methods in assembly and interrogation of macrocyclic peptide libraries.

We hope that you will enjoy the program and the opportunity to network with a diverse group of international experts who excel in the field of peptide therapeutics

Sincerely,

Richard D. DiMarchi
Symposium Chair & Chairman of the Board, Peptide Therapeutics Foundation

Sponsors, Peptide Therapeutics Foundation

Amylin Pharmaceuticals
Ferring Research Institute
Ipsen
PolyPeptide Group
Roche
Zealand Pharma
Zydus Cadila



Amylin Pharmaceuticals

Amylin Pharmaceuticals LLC is a wholly owned subsidiary of Bristol Myers Squibb, and is committed to improving lives through the discovery, development and commercialization of innovative medicines.

The company was founded in 1987 on the discovery of a hormone, amylin, produced by the same beta cells of the pancreas that make insulin. Since then, Amylin has built a strong foundation on research and development. Amylin's scientists are primarily focused on investigating the potential utility of new peptide hormone candidates. The company has amassed significant research and clinical expertise in metabolic medicine including the areas of diabetes, obesity and cardiovascular disease. By "Challenging Science," Amylin challenges conventional thinking to create innovative approaches to the discovery, development and commercialization of novel therapies for metabolic diseases. Amylin's approach and dedication are rooted in the belief that they will be "Changing Lives" for millions of people - not only with the drugs currently in late-stage development, but also with their pipeline of future therapies. In August 2012, the company was acquired by Bristol Myers Squibb.



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

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.



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

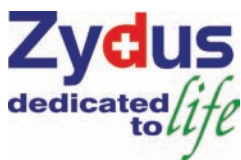
Headquartered in Basel, Switzerland, Roche is a leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics. Roche is the world's largest biotech company with truly differentiated medicines in oncology, virology, inflammation, metabolism and CNS. Roche is also the 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.

The Peptide Therapeutics Foundation would like to acknowledge the generous support of **Bristol-Myers Squibb** for providing funding for registration scholarships for the following individuals:

Joao Arrais
Naila Assem
Joe Chabenne
Cristina Clement
Jeffrey Culhane
Aswini Giri
Shannon Howell
Erika Olson
James Patterson
Darren Thompson
Eng Huan Ung
Naoki Yamamoto

Schedule of Events | 8th Annual Peptide Therapeutics Symposium

Thursday, October 24th, 2013

12:30 p.m. – 5:30 p.m.	Registration Check-in Frederic de Hoffmann Auditorium Reception Area, Lower Level
1:30 p.m. – 5:30 p.m.	8th Annual Peptide Therapeutics Symposium Frederic de Hoffmann Auditorium
1:30 p.m. – 1:40 p.m.	Opening Remarks Adrienne Day, Ph.D. <i>Secretary and Treasurer, Peptide Therapeutics Foundation</i> <i>Director, Business Development, Ferring Research Institute</i>
1:40 p.m. – 3:25 p.m.	SESSION I: Moderator Soumitra Ghosh, Ph.D. <i>Director and President, Peptide Therapeutics Foundation</i> <i>Senior Director, Research, Amylin Pharmaceuticals LLC, A wholly-owned subsidiary of Bristol-Myers Squibb</i>
1:40 p.m. – 2:15 p.m.	The Structural and Energetic Basis of Carbohydrate–Polypeptide Stabilizing Interactions Within Enhanced Aromatic Sequons in Protein Native States Jeffery W. Kelly, Ph.D. <i>Lita Annenberg Hazen Professor of Chemistry, Department of Chemistry;</i> <i>Chairman, Department of Molecular and Experimental Medicine, The Scripps Research Institute</i>
2:15 p.m. – 2:50 p.m.	Developing IMS-MS Techniques as a Means of Following Structural Transitions of Biopolymers in Solution David E. Clemmer, Ph.D. <i>Robert & Marjorie Mann Chair and Professor of Chemistry, Department of Chemistry, Indiana University</i>
2:50 p.m. – 3:25 p.m.	Half-Life Extension Through HESylation® Martin Meyer, Ph.D. <i>Innovation Manager, Innovation & Development Center Carbohydrate Chemistry, Pharmaceuticals Division, Fresenius Kabi Deutschland GmbH</i>
3:25 p.m. – 3:45 p.m.	Break Frederic de Hoffmann Auditorium Reception Area, Lower Level
3:45 p.m. – 4:45 p.m.	SESSION II: Moderator Rodney Lax, Ph.D. <i>Director, Peptide Therapeutics Foundation</i> <i>Senior Director of Business Development, North American for PolyPeptide Laboratories, Inc.</i>
3:45 p.m. – 4:15 p.m.	Long-acting Release of Drug Peptides by <i>in situ</i> Gelling FluidCrystal® Injection Depot Fredrik Tiberg, Ph.D. <i>President and CEO, Camurus AB; Professor Physical Chemistry, Lund University</i>



- 4:15 p.m. – 4:45 p.m. **The Transdermal Delivery of Peptides and other Biotherapeutics**
Frank Tagliaferri, Ph.D.
Vice President, Research & Development, 4P Therapeutics
- 4:45 p.m. – 5:30 p.m. **Translational Lecture**

Structural Insights into HIV, Influenza & HCV Antigen Design
Ian A. Wilson, D.Sc., FRS
Hansen Professor of Structural Biology and Chairman, Department of Integrative Structural and Computational Biology, The Scripps Research Institute
- 5:30 p.m. – 7:30 p.m. **Poster Session & Opening Reception**
Frederic de Hoffmann Auditorium Reception Area, Lower Level

Friday, October 25th, 2013

- 7:00 a.m. – 12:00 p.m. **Registration Check-in**
Frederic de Hoffmann Auditorium Reception Area, Lower Level
- 7:00 a.m. – 8:00 a.m. **Breakfast & Poster Viewing**
Frederic de Hoffmann Auditorium Reception Area, Lower Level
- 8:00 a.m. – 5:00 p.m. **8th Annual Peptide Therapeutics Symposium**
Frederic de Hoffmann Auditorium
- 8:00 a.m. – 8:10 a.m. **Welcoming Remarks**
Pankaj R. Patel
Director, Peptide Therapeutics Foundation
Chairman and Managing Director, Zydus Cadila
- 8:10 a.m. – 9:30 a.m. **Plenary Lectures**

Moderator
Jesse Dong, Ph.D.
Director, Peptide Therapeutics Foundation
Vice President, Compound Discovery, Ipsen
- 8:10 a.m. – 8:50 a.m. **How Insulin Binds: Structure of a Micro-receptor Complex and Implications for Analog Design**
Michael A. Weiss, M.D., Ph.D.
Professor, Departments of Biochemistry, Biomedical Engineering and Medicine (Endocrinology), Case Western Reserve University
- 8:50 a.m. – 9:30 a.m. **Mimicry of Hormone Recognition Surfaces with Peptidic Foldamers**
Samuel H. Gellman, Ph.D.
Ralph F. Hirschmann Professor of Chemistry, Department of Chemistry, University of Wisconsin, Madison
- 9:30 a.m. – 10:00 a.m. **Beverage Break & Poster Viewing**
Frederic de Hoffmann Auditorium Reception Area, Lower Level

Schedule of Events | 8th Annual Peptide Therapeutics Symposium

Friday, October 25th, 2013 continued

10:00 a.m. – 12:00 p.m.

SESSION I:

Moderator

Hans-Joachim Böhm, Ph.D.
Director, Peptide Therapeutics Foundation
Global Head of Chemistry, Roche

10:00 a.m. – 10:30 a.m.

ShK-186, a Peptide Inhibitor of Kv1.3 Potassium Channels as Therapy for Autoimmune Diseases and Metabolic Syndrome

K. George Chandy, Ph.D.
Professor, Department of Physiology and Biophysics, School of Medicine, University of California, Irvine

10:30 a.m. – 11:00 a.m.

The Tale of Two Peptides Rescuing a Company in Distress

Roger J. Garceau, M.D., FAAP
Executive Vice President and Chief Medical Officer, NPS Pharmaceuticals, Inc.

11:00 a.m. – 11:30 a.m.

Towards Optimized Utility of Proteasome Inhibitors with Peptide Epoxyketones

Christopher J. Kirk, Ph.D.
Vice President, Research, Onyx Pharmaceuticals, Inc.

11:30 a.m. – 12:00 p.m.

Direct Selection of Highly Potent Cyclic Peptidomimetics from *In Vitro* Display Libraries

Douglas A. Treco, Ph.D.
President and CEO, Ra Pharmaceuticals, Inc.

12:00 p.m. – 1:15 p.m.

Lunch & Poster Viewing

Frederic de Hoffmann Auditorium Reception Area, Lower Level

1:15 p.m. – 2:45 p.m.

SESSION II:

Moderator

Waleed Danho, Ph.D.
Distinguished Research Leader (Retired), Hoffman-LaRoche, Inc.

1:15 p.m. – 1:45 p.m.

Development of Serelaxin for Acute Heart Failure

Dennis Stewart, Ph.D.
Principal Scientist, Corthera Inc., Novartis Pharmaceuticals Corp.

1:45 p.m. – 2:15 p.m.

SOM230: A New Therapeutic Modality for Cushing's Disease

Ian Lewis, Ph.D.
Investigator III, Peptide Discovery Group, Exploratory Medicinal Chemistry Unit, Novartis Institutes of Biomedical Research

2:15 p.m. – 2:45 p.m.

PeptiDream's PD Platform: Innovative Peptide Discovery Platform

Patrick C. Reid, Ph.D.
CoFounder, Chief Scientific Officer and Member Board of Directors, PeptiDream Inc.

2:45 p.m. – 3:15 p.m.

Beverage Break & Poster Viewing

Frederic de Hoffmann Auditorium Reception Area, Lower Level



Friday, October 25th, 2013 continued

3:15 p.m. – 4:45 p.m.

SESSION III

Moderator

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

3:15 p.m. – 3:45 p.m.

Design of Peptide Therapeutics Exhibiting Dual Pharmacology and Extended Duration of Action

Soumitra Ghosh, Ph.D.
Director and President, Peptide Therapeutics Foundation
Senior Director, Research, Amylin Pharmaceuticals LLC, A wholly-owned subsidiary of Bristol-Myers Squibb

3:45 p.m. – 4:15 p.m.

The Development of BA058, a Novel Peptide, for the Treatment of Osteoporosis

Gary Hattersley, Ph.D.
Senior Vice President, Preclinical Development, Radius Health, Inc.

4:15 p.m. – 4:45 p.m.

^{99m}Tc-Galacto-RGD2: A novel ^{99m}Tc-Labeled Cyclic RGD, Peptide Dimer Useful for Tumor Imaging

Michael Pennington, Ph.D.
President and CEO, Peptides International, Inc.

4:45 p.m. – 5:00 p.m.

Closing Remarks

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

5:00 p.m. – 6:00 p.m.

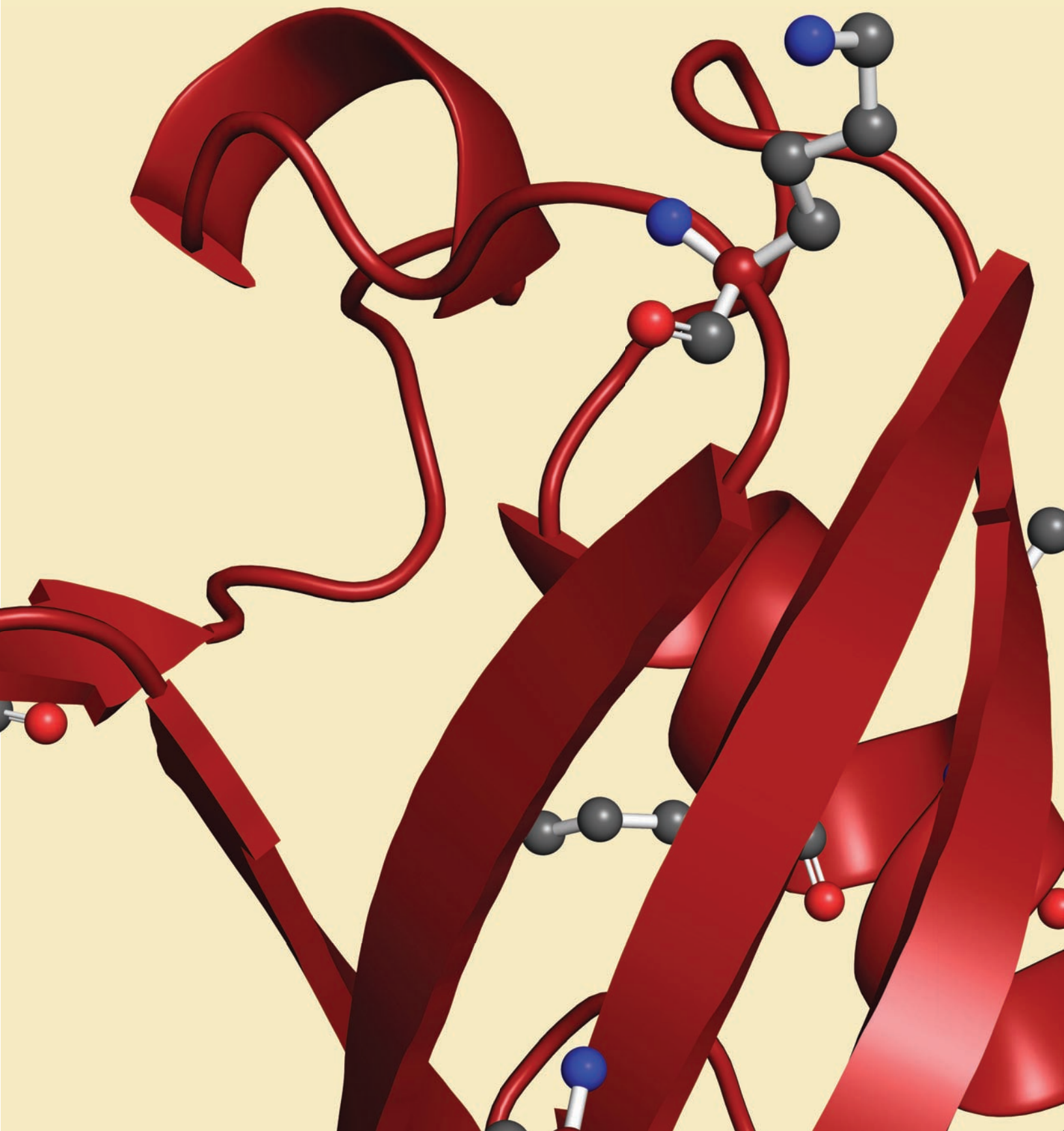
Networking Reception

Frederic de Hoffmann Auditorium Reception Area, Lower Level



Speakers Biographies

8th Annual Peptide Therapeutics Symposium





K. George Chandy, Ph.D. | Professor, Department of Physiology and Biophysics, School of Medicine, University of California, Irvine

ShK-186, a Peptide Inhibitor of Kv1.3 Potassium Channels as Therapy for Autoimmune Diseases and Metabolic Syndrome

Dr. Chandy completed his medical training at the Christian Medical College, Vellore, India, and his Ph.D. at the University of Birmingham, UK. He has been at the University of California Irvine since 1983. For the past three decades, Dr. Chandy has used a multi-disciplinary approach to translate basic science discoveries on potassium channels to therapeutic applications for autoimmune diseases and metabolic syndrome. Dr. Chandy and his collaborators demonstrated the critical role played by potassium channels in cell T lymphocytes and identified the genes (Kv1.3 and KCa3.1) encoding these potassium channels. Guided by molecular modeling and structure-function approaches, they developed the first selective and potent inhibitors (ShK-186 and TRAM-34) of these channels. By using these selective blockers, they defined the important role of KCa3.1 channels in naïve and central memory T cells, and of the Kv1.3 channel in effector memory T cells. These pioneering studies led to a new therapeutic strategy for autoimmune diseases based on targeting Kv1.3 channels in disease-associated effector memory T cells. More recently, they demonstrated the powerful anti-obesity effect of ShK-186 due to novel actions on brown fat-mediated thermogenesis and liver metabolism. ShK-186, a 37-residue peptide, completed human phase 1A trials and has received IND approval from the FDA for phase 1B trials.



David E. Clemmer, Ph.D. | Robert & Marjorie Mann Chair and Professor of Chemistry, Department of Chemistry, Indiana University

Developing IMS-MS Techniques as a Means of Following Structural Transitions of Biopolymers in Solution

Professor Clemmer grew up in the southwest where he received a B.S. in Chemistry from Adams State College (1987) and a Ph.D. from the University of Utah (1992). He was a Japan Society for the Promotion of Science Fellow and did postdoctoral work at the Himeji Institute of Technology in Himeji Japan. He continued his postdoctoral work in Martin Jarrold's laboratory at Northwestern University before joining the Chemistry faculty at Indiana University in 1995. From 2002 to 2006 he served as the chair of the Chemistry Department and he is currently the associate dean for the Natural and Mathematical Sciences.

Clemmer's research involves the development of analytical methods for studying the structures of complex low-symmetry systems. His group is especially interested in measurements that allow rapid characterization of complex mixtures of biological molecules. Some of the methods have been commercialized and now are being used to address a range of scientific problems, including: elucidation of fundamental issues associated with how proteins fold and aggregate; characterization of the human proteome; and, assessment of molecules that may be used as markers for following specific disease states.

Professor Clemmer's research group has published more than 185 papers and their work has been recognized with awards from the Sloan, Dreyfus, and National Science Foundations, the American Chemical Society, and the American Society of Mass Spectrometry. He is an AAAS and FRSC fellow. He was also a member of the Defense Science Study Group.



Adrienne Day, Ph.D. | Secretary and Treasurer, Peptide Therapeutics Foundation; Director, Business Development, Ferring Research Institute

Opening Remarks

Dr. Adrienne Day is the Director of Business Development for Ferring Research Institute. She has more than 15 years of experience in the biotechnology and biopharmaceutical industries, and has worked in the non-profit, for-profit and startup environments.

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

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



Richard DiMarchi, Ph.D. | Symposium Chair and 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

Closing 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. His current research is focused on developing macromolecules with enhanced therapeutic properties through biochemical optimization with non-natural amino acids, an approach termed chemical-biotechnology. He is a co-founder of Ambrx, Inc. and Marcadia Biotech. He is a scientific advisor to Ferring, Merck, Roche and three venture funds; 5AM, TMP, and Twilight.

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 rDNA-derived Humalog® (LisPro-human insulin). This designer insulin represents the first demonstration that structurally altered rDNA-derived biosynthetic proteins can improve pharmacological performance without increasing the risk of an abnormal immunological response. As scientist and manager, Dr. DiMarchi also significantly contributed to the commercial development of Humulin®, Humatrope®, Xigris®, rGlucagon®, Evista®, and Forteo®.

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, and the 2011 Merrifield Award for Career Contributions in Peptide Sciences.



Roger J. Garceau, M.D., FAAP | Executive Vice President and Chief Medical Officer, NPS Pharmaceuticals, Inc.

The Tale of Two Peptides Rescuing a Company in Distress

Roger Garceau, M.D., FAAP, joined NPS in December 2008 and brings over 20 years of broad pharmaceutical industry experience to his position. From 2002 to December 2008, Dr. Garceau served in a number of senior leadership positions at Sanofi and most recently was vice president of the new products group. Previously, Dr. Garceau held various positions, including vice president of clinical operations, interim head of North American medical and regulatory affairs, and head of US medical research, where he led a team of over 200 professionals and oversaw the design and execution of over 50 sponsored clinical trials in 5 different therapeutic areas. Prior to his tenure at Sanofi, Dr. Garceau spent 16 years with Pharmacia Corporation in global development and medical affairs, where he successfully contributed to a number of marketing applications. Dr. Garceau is a board-certified pediatrician. He received a Bachelor of Science in Biology from Fairfield University in Fairfield, Connecticut and his Doctorate of Medicine from the University of Massachusetts Medical School. He is a Fellow of the American Academy of Pediatrics.



Samuel H. Gellman, Ph.D. | Ralph F. Hirschmann Professor of Chemistry, Department of Chemistry, University of Wisconsin, Madison

Mimicry of Hormone Recognition Surfaces with Peptidic Foldamers

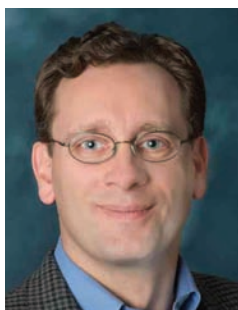
Sam Gellman is the Ralph F. Hirschmann Professor of Chemistry at the University of Wisconsin - Madison. He earned his A.B. from Harvard University in 1981 and his Ph.D. from Columbia University, under Ronald Breslow, in 1986. After an NIH post-doctoral fellowship at the California Institute of Technology, with Peter Dervan, Gellman joined the faculty at the University of Wisconsin - Madison in 1987. Major interests in Gellman's research program have included fundamental studies of non-covalent interactions, elucidation of the origins of peptide and protein folding preferences, development and application of unnatural oligomers that display protein-like conformational behavior ("foldamers"), creation of new amphiphiles for membrane protein manipulation, and development of new biologically active polymers. The work from Gellman's laboratory has been recognized by the Arthur C. Cope Scholar Award from the American Chemical Society (1997), the Vincent du Vigneaud Award from the American Peptide Society (2006), the Ralph F. Hirschmann Award in Peptide Chemistry from the American Chemical Society (2007) and the Rao Makineni Lecture Award from the American Peptide Society (2013). Gellman was elected to the American Academy of Arts & Sciences in 2010. He has served on the National Institutes of Health Medicinal Chemistry Study Section (1999-2002) and several editorial advisory boards (the *Journal of Organic Chemistry*, the *European Journal of Organic Chemistry*, *Biopolymers-Peptide Science*, *Chemical Society Reviews* and *Organic & Biomolecular Chemistry*).



Soumitra Ghosh, Ph.D. | Director and President, Peptide Therapeutics Foundation; Senior Director, Research, Amylin Pharmaceuticals LLC, A wholly-owned subsidiary of Bristol-Myers Squibb

Design of Peptide Therapeutics Exhibiting Dual Pharmacology and Extended Duration of Action

Soumitra Ghosh is Senior Director, Research at Amylin Pharmaceuticals LLC, a wholly owned subsidiary of Bristol Myers Squibb. He joined the company in 2003 and oversees the Research organization's drug discovery programs, pre-clinical support of development programs and its external collaborations. Prior to Amylin, Dr. Ghosh was Senior Director of Chemical Biology at Mitokor, where he directed its mitochondrial proteomics and genetic analysis work, and drug discovery programs for CNS disorders, osteoarthritis and obesity. His work experience also includes development of DNA-based diagnostic tools and peptidase inhibitors at Baxter Diagnostics, Inc. and at the Salk Institute Biotechnology/Industrials Associates (SIBIA). Dr. Ghosh received his undergraduate training at St. Stephen's College, Delhi, and obtained his M.S. and Ph.D. degrees in Chemistry from the Indian Institute of Technology, Kanpur and the University of Chicago, respectively. He conducted his post-doctoral research at the Rockefeller University in New York.



Gary Hattersley, Ph.D. | Senior Vice President, Preclinical Development, Radius Health, Inc.

The Development of BA058, a Novel Peptide, for the Treatment of Osteoporosis

Dr. Hattersley is Senior Vice President, Preclinical Development at Radius, a company focused on developing therapeutics for osteoporosis and other women's health conditions, including, symptoms of menopause and frailty. He has more than 25 years of experience in musculoskeletal research and is the author of numerous scientific publications related to bone biology and physiology. Prior to joining Radius, Dr. Hattersley was a Senior Scientist at Millennium Pharmaceuticals with responsibility for the discovery and development of novel small-molecule agents for the treatment of osteoporosis and other metabolic bone diseases. Dr. Hattersley also held positions at Genetics Institute/Wyeth Research investigating the application of the bone morphogenetic proteins in bone and connective tissue repair and regeneration. Dr. Hattersley received a Ph.D. in Experimental Pathology from St. George's Hospital Medical School in London, UK.



Jeffrey W. Kelly, Ph.D. | Lita Annenberg Hazen Professor of Chemistry, Department of Chemistry; Chairman, Department of Molecular and Experimental Medicine, The Scripps Research Institute

The Structural and Energetic Basis of Carbohydrate–Polypeptide Stabilizing Interactions Within Enhanced Aromatic Sequons in Protein Native States

Jeffery W. Kelly, Ph.D., is the Lita Annenberg Hazen Professor of Chemistry in the Department of Chemistry and the Chairman of the Department of Molecular and Experimental Medicine at the Scripps Research Institute. His research is focused on uncovering protein folding principles and on understanding the etiology of protein misfolding and/or aggregation diseases and using this information to develop novel therapeutic strategies. He has 250+ publications and has received several awards, including The American Chemical Society Ralph F. Hirschmann Award in Peptide Chemistry (2012), The Biopolymers Murray Goodman Memorial Prize (2012), The Protein Society Emil Thomas Kaiser Award (2011), The American Peptide Society Rao Makineni Lectureship (Award; 2011), The American Peptide Society Vincent du Vigneaud Award (2008), The American Chemical Society Arthur C. Cope Scholar Award (2001), State University of New York at Fredonia Alumni Distinguished Achievement Award (2000), The Protein Society–Dupont Young Investigator Award (1999) and The Biophysical Society National Lecturer Award (1999).

Kelly cofounded FoldRx Pharmaceuticals based on his discovery of Tafamidis—approved by the European Medicines Agency in 2011 to treat familial amyloid polyneuropathy. This first-in-class drug is the first pharmacologic agent that halts neurodegeneration in a human amyloid disease. Tafamidis or Vyndaqel also provides the first pharmacologic evidence that the process of amyloidogenesis causes the degeneration of post-mitotic tissue. He also cofounded Proteostasis Therapeutics, a company using small molecules to alter the protein homeostasis network to ameliorate several aggregation-associated degenerative diseases. Kelly also served as Vice President of Academic Affairs and Dean of Graduate Studies at Scripps for nearly a decade.



Christopher J. Kirk, Ph.D. | Vice President, Research, Onyx Pharmaceuticals, Inc.

Towards Optimized Utility of Proteasome Inhibitors with Peptide Epoxyketones

Christopher Kirk received his doctorate at the University of Michigan (US) where he studied T-cell signal transduction in the laboratory of Richard Miller. He remained at Michigan for a postdoctoral fellowship focused on gene-modified dendritic cell cancer vaccines under James Mulé. Since 2001, Christopher has been in the biotechnology industry focused on drug discovery research and drug development in the areas of cancer and inflammation. At Deltagen, Inc., he focused on discovering novel drug targets through high throughput gene knockout technology. In 2004, he became one of the original scientists at Proteolix, Inc. where the cancer drug Kyprolis™ (carfilzomib) was discovered and developed. In 2009, Proteolix was acquired by Onyx Pharmaceuticals, which continues to perform research and development on proteasome inhibitors and protein degradation and homeostasis as a therapeutic strategy to treat cancer and inflammatory diseases.



Ian Lewis, Ph.D. | Investigator III, Peptide Discovery Group, Exploratory Medicinal Chemistry Unit, Novartis Institutes of Biomedical Research

SOM230: A New Therapeutic Modality for Cushing's Disease

Ian Lewis studied chemistry at the University of Edinburgh between 1981– 1985 and then carried out a Ph.D. at the University of Edinburgh between 1985–1988 under the supervision of Professor R. Ramage on the synthesis of polyene teramic acid antibiotics. Subsequently Ian Lewis carried out a Royal Society Post-doctoral Fellowship at ETH Zürich between 1988–1990 in the research group of Professor A. Eschenmoser and then joined Novartis (originally Sandoz) in 1990, researching in the endocrinology and immunology disease areas. Between 2001–2002 Ian Lewis was a Novartis Guest Scientist at the Scripps Research Institute, La Jolla, in the group of Professor K. Barry Sharpless, during the time Professor Sharpless was awarded the Nobel Prize in Chemistry. Since then Ian has carried out research in the Exploratory Medicinal Chemistry Unit of the Oncology Global Discovery Chemistry Organisation. In 2013 Ian received the Senior Investigator Award of the Swiss Chemical Society in recognition of the discovery of SOM230/Pasireotide (Signifor®).



Martin Meyer, Ph.D. | Innovation Manager, Innovation & Development Center Carbohydrate Chemistry, Pharmaceuticals Division, Fresenius Kabi Deutschland GmbH

Half-Life Extension Through HESylation®

Martin Meyer is Innovation Manager at the Innovation & Development Center Carbohydrate Chemistry of Fresenius Kabi Deutschland GmbH with experience in the development of the HESylation half-life extension technology. He graduated with a degree in pharmaceutical sciences from the University of Erlangen in 2004, followed by a half-year research internship at the University of Florida in Gainesville. Martin Meyer earned his Ph.D. in 2009 in the group of Prof. Ernst Wagner at the Ludwig Maximilians University, Munich, where he worked on peptide-assisted polymer-based nucleic acid delivery systems. After obtaining his Ph.D. he joined Coley Pharmaceutical GmbH in Duesseldorf, a part of Pfizer's Oligonucleotide Therapeutics Unit, where he spent three years as scientist working in the field of nucleic acid based therapeutics on the development of carriers for siRNA and antisense oligonucleotides. His current position at Fresenius Kabi focuses on the HESylation half-life extension and drug delivery technology.



Pankaj R. Patel | Director, Peptide Therapeutics Foundation; Chairman and Managing Director, Zydus Cadila

Welcoming Remarks

Mr. Pankaj Patel has been the guiding force behind the Zydus Cadila's fast tracked growth. With an experience spanning over 30 years in the Indian pharmaceutical industry, Mr. Patel combines both research and techno-commercial expertise and has published 50 research papers. Mr. Patel is on the governing councils of many national industry associations. He is a member of the Advisory council for developing Human Resources for the Pharma Industry, and is also a part of the Task force on R&D and Drug Discovery, Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers, Government of India. Mr. Patel is also an industry representative for the 'Consultative Group on Exports of Pharmaceutical Products' under the Chairmanship of the Minister for Commerce and Industry, Government of India. Mr. Patel is currently the President of the Indian Pharmaceutical Alliance and the Chairman of the Federation of Indian Chamber of Commerce & Industry (FICCI) Gujarat State Council. He is the Executive Chairman, Vice President and Trustee of the Gujarat Cancer Society and Chairman of the Gujarat Cancer and Research Institute. Mr. Patel is also on the Governing Board of The Ahmedabad University and the President of the Ahmedabad Management Association. Mr. Patel was awarded the E&Y Entrepreneur of the Year – Life Sciences Award for the year 2009, the M.L. Schroff Memorial National Award in 2009 and the 'Baroda Sun Lifetime Achievement Award' for the year 2010 by the Bank of Baroda. Recently, Mr. Pankaj Patel was conferred the Indian Pharmaceutical Association's 'Special Recognition Award 2010' in recognition of his contributions to the growth of the Pharmaceutical Industry, Research and the Profession of Pharmacy.



Michael Pennington, Ph.D. | President and CEO, Peptides International, Inc.

^{99m}Tc-Galacto-RGD2: A novel ^{99m}Tc-Labeled Cyclic RGD, Peptide Dimer Useful for Tumor Imaging

Michael Pennington joined Peptides International in December 2010 serving as Chief Technology Officer. In January 2011, he was appointed President and C.O.O. and in January 2013, he was appointed President and C.E.O of the same. After doctoral research at University of Florida, he joined the pharmaceutical industry in the Department of Biotechnology at Schering-Plough in 1988. In late 1989, he joined Bachem Bioscience in King of Prussia, PA as a Principle Scientist in the Peptide Chemistry department. He served as the Group Director for Bachem Bioscience from 1992–2000 before being appointed as President and C.O.O. a position he maintained from 2000–2010. He built and directed an internationally recognized peptide chemistry team focused on producing complex peptides and toxins. Dr. Pennington was a member of Bachem Forschungsausschuss, the International Research and Development from 2000–2010. He has extensive collaborations with both industrial and academic scientists and maintains an extramurally funded research program on several peptide toxins. He is a founder of Airmid Inc, a biotech venture company dedicated to advancing two of his discoveries into clinical development for autoimmune diseases. Dr. Pennington has been awarded five patent and over 90 peer reviewed scientific articles, and serves as an editor of International Journal of Peptide Research and Therapeutics and Current Peptide and Protein Letters. He holds a Bachelors Degree in Chemistry degree from the University of North Carolina - Chapel Hill and a Ph.D. from University of Florida - Gainesville.



Patrick C. Reid, Ph.D. | CoFounder, Chief Scientific Officer and Member Board of Directors, PeptiDream Inc.

PeptiDream's PD Platform: Innovative Peptide Discovery Platform

Dr. Patrick C. Reid is a CoFounder, Chief Scientific Officer (CSO) and a member of the Board of Directors at PeptiDream Inc., a publically listed (TSE: 4587) Tokyo based Biopharmaceutical Company developing peptide-based therapeutics. Prior to the formation of PeptiDream in 2006, Dr. Reid was an Associate Professor of Molecular Biology and Medicine at the University of Tokyo, a position held until 2008, and has published research spanning a variety of research fields, including atherosclerosis, inflammation, metabolism, neurological disease, and cancer research. Dr. Reid also previously served as a member of the scientific advisory board at Perseus Proteomics Inc; a Tokyo based Biopharmaceutical Company developing antibody-based diagnostics and therapeutics, and as the company's Director of International Business Development. Education; Ph.D., Biochemistry, Dartmouth Medical School; Graduate Business Training, Tuck School of Business, Dartmouth College.



Dennis Stewart, Ph.D. | Principal Scientist, Corthera Inc., Novartis Pharmaceuticals Corp.

Development of Serelaxin for Acute Heart Failure

Principal scientist and co-founder of Corthera, which was a privately owned biotech startup principally funded by KPCB and Domain Associated until purchased in 2010 by Novartis. Corthera obtained the relaxin assets from Connetics and continued the development of serelaxin in multiple indications. Dennis lead the preclinical studies for Corthera as well as heading the IP functions for Corthera. Following the acquisition by Novartis, Dennis has continued serelaxin development in acute heart failure and exploring new indications.

From 2000–2003 Dennis was the Principal Scientist at Adiana, a biotech startup developing a transcervical sterilization device.

From 1985 to 2000 Dennis was a faculty member of Ob/Gyn at the University of California at Davis School of Medicine. While there he conducted research in early pregnancy loss and implantation mechanisms, with particular regard to the role of relaxin in these processes. Dennis obtained undergraduate degrees at Iowa State University and obtained a Ph.D. in endocrinology at UC Davis.



Frank Tagliaferri, Ph.D. | Vice President, Research & Development, 4P Therapeutics

The Transdermal Delivery of Peptides and other Biotherapeutics

Frank Tagliaferri is currently Vice President of Research & Development at 4P Therapeutics in Norcross, GA working on the development and commercialization of novel drug delivery products. He received his Bachelor's degree from Franklin & Marshall College in 1987 and his Ph.D. in Chemistry from University of Virginia in 1992. He was a post-doctoral fellow at University of Tennessee, Knoxville from 1992-1995. As Director of Drug Delivery at GeneMedicine (later Valentis) from 1995-2001 his focus was on the development of delivery systems for both DNA and proteins. He later served as Director of Delivery and Preclinical Development at Napro Pharmaceuticals (later Tapestry) from 2001-2003 where he worked on a variety of cell and oligonucleotide therapeutics. He was at Altea Therapeutics in Atlanta, GA from 2003 to 2011 where he most recently served as Vice President of R&D. While at Altea he helped to develop the PassPort® System for the transdermal delivery of small molecules and biologics.



Fredrik Tiberg, Ph.D. | President and CEO, Camurus AB; Professor Physical Chemistry, Lund University

Long-acting Release of Drug Peptides by in situ Gelling FluidCrystal® Injection Depot

Fredrik Tiberg serves as President and Chief Executive Officer of Camurus AB. Prior to assuming this role in 2003, he was Vice President, Head of R&D. He also holds a position as Adjunct Professor of Physical Chemistry, Lund University, and is a member of the Royal Swedish Academy of Engineering Sciences (IVA).

Fredrik received his MSc (Chem Eng) from Lund Institute of Technology, and his PhD in Physical Chemistry from Lund University. During his studies, he was also Research Fellow at Collège de France, Paris under Nobel Laureate Pierre-Gilles de Gennes. In 1994 he became Assistant Professor in Physical Chemistry at Lund University, and in 1996 Section Manager at the Institute for Surface Chemistry, Stockholm, Sweden. Fredrik Tiberg was appointed Associate Professor in Physical Chemistry in 1998 and Professor in 1999. During 2001-2002 he was Visiting Professor at the Physical and Theoretical Chemistry Laboratory, Oxford University, and Special Supernumerary Fellow of University College, Oxford.

Dr. Tiberg has published more than 100 original scientific papers, co-authored several books and is named as inventor on a substantial number of patents.



Douglas A. Treco, Ph.D. | President and CEO, Ra Pharmaceuticals, Inc.

Direct Selection of Highly Potent Cyclic Peptidomimetics from In Vitro Display Libraries

Doug Treco has been the CEO of Ra Pharma™ since its inception and serves on the Company's Board of Directors. In 1988, he co-founded Transkaryotic Therapies Inc. (TKT, acquired in 2005 by Shire plc), a multi-platform biopharmaceutical company developing protein and gene therapy products. In his position as Senior Vice President of Research and Development, Doug established and directed TKT's gene activation and protein production efforts, which led to the approval of the biopharmaceutical products Dynepo™, Replagal®, Elaprase®, and Vpriv™. Previously, he was a Visiting Scientist in the Department of Molecular Biology at Massachusetts General Hospital and a Lecturer in Genetics at Harvard Medical School. He has authored numerous peer-reviewed publications and holds over 35 U.S. and European patents in the areas of protein production, gene mapping, and gene therapy. Doug received his Ph.D. in biochemistry and molecular biology from SUNY at Stony Brook and performed postdoctoral studies at the Salk Institute for Biological Studies and Massachusetts General Hospital.



Michael A. Weiss, M.D., Ph.D. | Professor, Departments of Biochemistry, Biomedical Engineering and Medicine (Endocrinology), Case Western Reserve University

How Insulin Binds: Structure of a Micro-receptor Complex and Implications for Analog Design

Dr. Weiss is the Cowan-Blum Professor and Chair of the Department of Biochemistry at the Case Western Reserve University School of Medicine. He received an A.B. in Physics (1978) and Ph.D. in Biophysics (1986) from Harvard University and M.D. from the Harvard-MIT Program in Health Sciences & Technology (1985). Graduate studies were under the guidance of Prof. Martin Karplus (Department of Chemistry at Harvard University). Prior to assuming his present position in 1999, Dr. Weiss was a Professor of Biochemistry & Molecular Biology, Chemistry and Medicine at the University of Chicago (1994-1999) and Assistant/Associate Professor of Biological Chemistry & Molecular Pharmacology at Harvard Medical School and Clinical Staff Assistant in Medicine (Endocrine Unit) at the Massachusetts General Hospital (1988-1993). Dr. Weiss is Board-Certified in Internal Medicine and a member of the American Society for Clinical Investigation and American Association of Physicians. The research interests of the Weiss laboratory focus on structure-activity relationships in insulin and the insulin receptor with application to human genetics and therapeutic protein design. Dr. Weiss is founder and Chief Scientific Officer of Thermalin Diabetes, LLC and has multiple patents and patent applications describing novel insulin analogs.



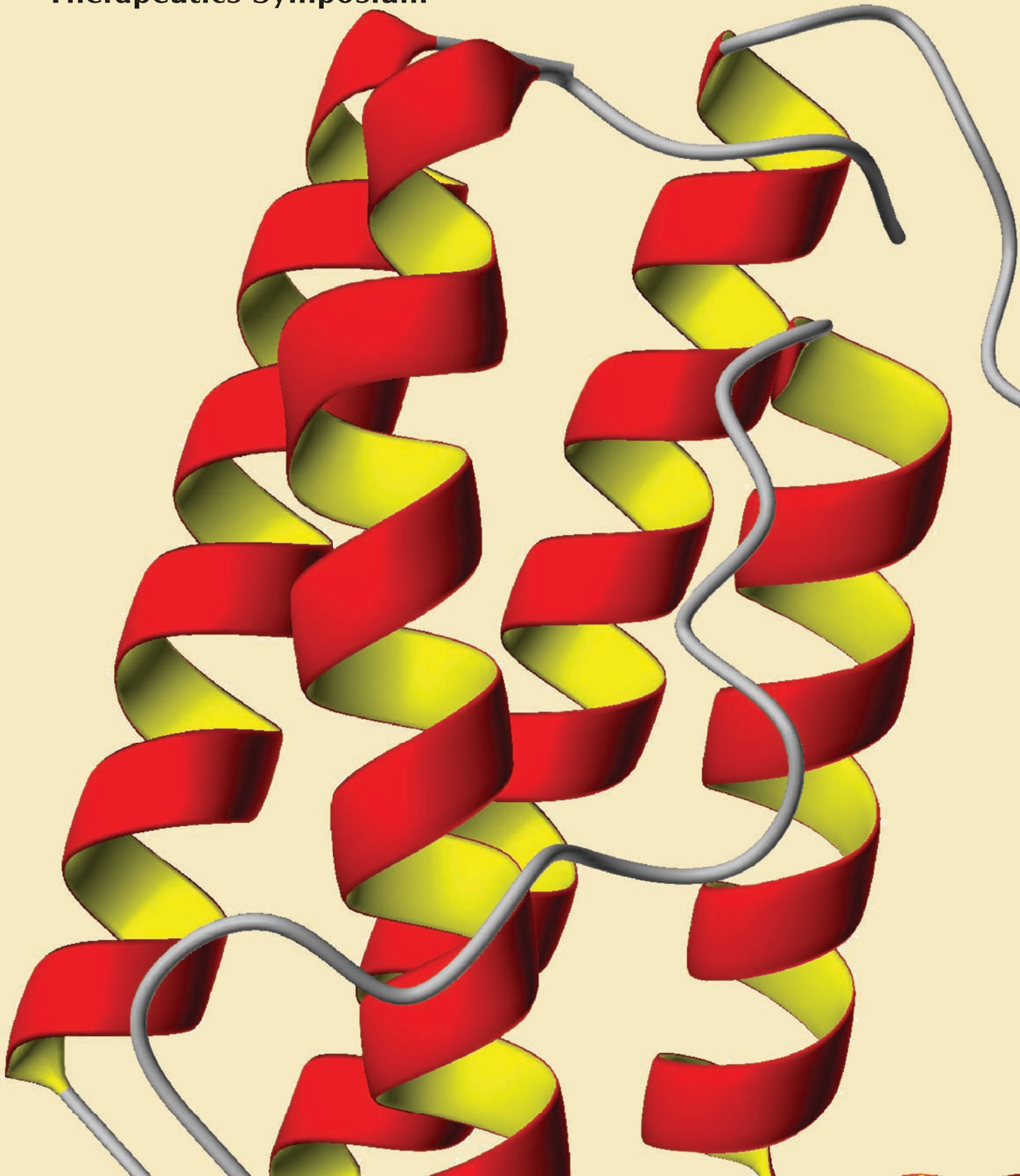
**Ian A. Wilson, D.Sc., FRS | Hansen Professor of Structural Biology and Chairman,
Department of Integrative Structural and Computational Biology, The Scripps
Research Institute**

Structural Insights into HIV, Influenza & HCV Antigen Design

Dr. Ian Wilson received a B.Sc. in Biochemistry from the University of Edinburgh, a D. Phil. degree in Molecular Biophysics from Oxford University, and did postdoctoral research at Harvard University. Dr. Wilson has been a Professor at The Scripps Research Institute since 1982 and is Chair of the Department of Integrative Structural and Computational Biology. His laboratory has focused on immune recognition and, in particular, on how pathogens are recognized by the adaptive and innate immune systems. His laboratory has determined crystal structures of many different antibodies (>150) with a variety of antigens, as well as MHC class I and class II, CD1, T cell receptors, cytokine receptors, Toll-like receptors, and other key pattern recognition receptors. His current focus is on how microbial pathogens are neutralized by the immune system, particularly for influenza virus, HCV and HIV-1. Dr. Wilson also directs the Joint Center for Structural Genomics (JCSG) that has pioneered new methods for high throughput structural studies, including x-ray and NMR. The JCSG has determined over 1450 structures since its inception in 2000, and is one of four production centers in NIH NIGMS PSI:BiologY. Dr. Wilson is a Fellow of the Royal Society, and was awarded a D.Sc. from Oxford University.

Abstracts of Lecture Presentations

8th Annual Peptide Therapeutics Symposium



ShK-186, a Peptide Inhibitor of Kv1.3 Potassium Channels as Therapy for Autoimmune Diseases and Metabolic Syndrome

K. George Chandy, Ph.D. | Professor, Department of Physiology and Biophysics

School of Medicine, University of California, Irvine
291 Irvine Hall, Mail Code: 4560, Irvine, CA 92697 | (949) 824-7435

Overview: The talk will focus on the voltage-gated potassium Kv1.3, a selective picomolar blocker of the channel called ShK-186 (a 37-residue peptide from the sun anemone), and the development of ShK-186 as a therapeutic for autoimmune diseases and metabolic syndrome. ShK-186 exhibits durable pharmacokinetic properties because of slow release from the subcutaneous injection site and long dwell time on the channel once bound; it has completed phase 1A human trials.

Kv1.3 channels as therapeutic target for autoimmune diseases. Of 78 potassium channels in the human genome, human T cells express Kv1.3 and a calcium-activated channel called KCa3.1. Kv1.3 regulates membrane potential and calcium signaling in CD3⁺CCR7⁻ effector T cells, while KCa3.1 plays this role in CD3⁺CCR7⁺ effectors. Disease-associated autoreactive T cells in patients with multiple sclerosis, type-1 diabetes mellitus and rheumatoid are CD3⁺CCR7⁻ effectors with elevated Kv1.3 channels. ShK-186 suppresses calcium signaling, cytokine production and in vivo migration of these cells without impacting CD3⁺CCR7⁺ effectors that express ShK-186-resistant KCa3.1 channels. ShK-186 prevents and treats disease in rat models of multiple sclerosis, rheumatoid arthritis and delayed type hypersensitivity, even when administered once every third day. Several species of parasitic worms secrete homologs of ShK-186; these peptides block Kv1.3, have a structure similar to ShK-186 and their immunomodulatory activity may contribute to their pro-biotic therapeutic effect in autoimmune diseases.

Kv1.3 channels as therapy for metabolic syndrome. In a mouse model of diet-induced obesity, ShK-186 reduced weight gain, adiposity, fatty liver, blood levels of cholesterol, leptin, LDL, HbA1C, fasting blood sugar, and it enhanced peripheral insulin sensitivity. These changes mimic the effects of Kv1.3 gene deletion. ShK-186 did not alter weight gain or change blood chemistry in mice on a chow diet, suggesting that the obesity-inducing diet enhances sensitivity to Kv1.3 blockade. ShK-186 therapy activated brown adipose tissue, which manifested as augmented energy expenditure, with no change in caloric intake, locomotor activity or thyroid hormone levels. The obesity diet induced Kv1.3 expression in the liver, and ShK-186 caused profound alterations in energy and lipid metabolism in the liver. These studies suggest that selective Kv1.3 blockers may have use in obesity and insulin resistance.

Developing IMS-MS Techniques as a Means of Following Structural Transitions of Biopolymers in Solution

David E. Clemmer, Ph.D. | Robert and Marjorie Mann Chair and Professor of Chemistry

Department of Chemistry, Indiana University
800 E. Kirkwood, Bloomington, IN 47405 | (812) 855-8259

It is well accepted that a measurement of an ion's mobility through an inert gas can be compared with calculated mobilities for trial geometries to obtain insight about the abundances and overall shapes of specific ions. In these studies, energy can be added to induce structural transitions and follow changes in the abundances of different conformations that are favored before and after activation. Here, we extend this idea as a means of following structural transitions in solution, examining the well-studied model systems: bradykinin and polyproline. Our approach is to vary the solution composition from which ions are electrosprayed. Overall, we conclude that in some cases it appears that the solution phase structures are more or less preserved in the gas phase; in other cases, new structures are favored in the gas phase –but, these can be mapped back in order to obtain insight about populations of states that were favored in solution. In the case of bradykinin, we find evidence for ~10 different solution phase states that vary in abundance as the solution composition is changed. These populations largely arise from variations in the cis- and trans-configurations of three proline residues in the nonapeptide sequence. The polyproline system provides a chance to study such transitions in detail. When in relatively non-polar solvents such as propanol, polyproline forms a compact type PPI helix; when placed in water the polymer undergoes a series of cis-trans interconversions to produce a type PPII helix, in which water molecules intercalate along the peptide backbone, stabilizing a much more extended structure in solution. We find that although the PPII helix collapses in the gas phase, IMS-MS techniques provide an ideal means of studying the step-by-step transitions that connect these different structures.



The Tale of Two Peptides Rescuing a Company in Distress

Roger J. Garceau, M.D., FAAP | Executive Vice President and Chief Medical Officer

NPS Pharmaceuticals, Inc.

550 Hills Drive, Bedminster, NJ 07921 | (908) 450-5310

In 2006, NPS Pharmaceuticals was facing dire circumstances and an uncertain future. The company had received an approvable letter from the U.S. Food and Drug Administration (FDA) for Preos — a parathyroid hormone for the treatment of osteoporosis and NPS' lead product candidate at the time — and faced a mountain of debt. Thanks to the executive team's foresight, NPS recognized the promise of two peptides in its pipeline and switched its focus from large primary care indications to rare diseases.

The company repurposed Preos, which has since been renamed Natpara, as a treatment for a rare and complex endocrine disorder called hypoparathyroidism. Patients with this condition produce insufficient levels of parathyroid hormone or PTH, the body's principal regulator of calcium and phosphorous. When the body has too little parathyroid hormone, blood calcium levels drop and phosphorus levels increase, which can cause a multitude of nearly 40 physical, emotional and cognitive symptoms. Hypoparathyroidism is the only remaining classic endocrine disorder with no approved replacement therapy. Current supportive approaches aim to reduce the severity of symptoms by raising calcium levels with large doses of oral calcium and active vitamin D supplementation. Over time, calcium may build up in the body and result in serious health risks and irreversible complications like soft tissue calcifications.

Natpara is a bioengineered version of human PTH. Because Natpara is identical in structure to and mimics the action of the 84-amino acid human parathyroid hormone, it has the potential to treat hypoparathyroidism and offer a more physiological treatment outcome than currently available treatments.

In addition to turning its attention to hypoparathyroidism, NPS also decided to accelerate its clinical development program for another rare disease, short bowel syndrome. The drug, called Gattex, is a novel, recombinant analog of human glucagon-like peptide 2 (GLP-2), a peptide involved in normal intestinal function and fluid and nutrient absorption. Patients with short bowel syndrome are unable to absorb enough nutrients and fluids through the gastrointestinal track to sustain life and often require parenteral support to receive the nutrients and fluids they need to live. The long-term use of parenteral support can be associated with serious and sometimes life-threatening complications, as well as reduced quality-of-life.

Fast forward to present day. The FDA and the European Medicines Agency have approved Gattex (EU tradename: Revestive) for the treatment of adult patients with short bowel syndrome. The groundbreaking therapy is the first major treatment advance for adult short bowel syndrome in nearly 40 years. Its unique mechanism of action allows patients to reduce parenteral support volume and infusion days per week. NPS is now exploring Gattex for pediatric patients with short bowel syndrome.

In addition, NPS expects to submit a Biologic License Application to the FDA for Natpara later this year. If approved, Natpara would be the first and only FDA-approved treatment for hypoparathyroidism.

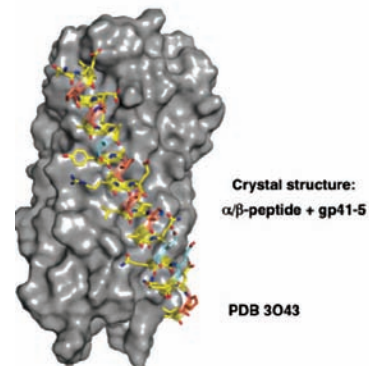
The company that faced a potential disaster not long ago is now a global commercial organization that is thriving financially and poised to be a premier global orphan drug company.

Mimicry of Hormone Recognition Surfaces with Peptidic Foldamers

Samuel H. Gellman, Ph.D. | Ralph F. Hirschmann Professor of Chemistry

Department of Chemistry, University of Wisconsin, Madison
1101 University Avenue, Madison, WI 53706 | (608) 262-3303

Interactions between specific proteins are essential in biology, with key roles in normal physiological signal transduction and disease-related processes. Many such interactions have proven recalcitrant to modulation with small molecules because the protein surface areas involved are large. In these cases, clinical modulation is generally achieved with large peptides or proteins. We are exploring an alternative approach to this challenge, based on peptidic oligomers that contain unnatural backbone elements (i.e., subunits other than alpha-amino acid residues), fold to specific conformations, and display protein-like surfaces ("foldamers"). We have found that informational alpha-helices can be mimicked effectively with oligomers comprised of alpha- and beta-amino acid residues ("alpha/beta-peptides"). Placement of beta residues throughout a sequence can confer substantial resistance to proteolysis. The principles of this approach to alpha-helix mimicry were initially developed in the context of BH3 domain recognition by Bcl-2-family proteins and assembly of CHR+NHR alpha-helical bundles from gp41-derived segments. Current efforts include a focus on peptide hormones that serve as agonists for B-family GPCRs, particularly GLP-1 and PTH, which adopt partially helical conformations when bound to their receptors.



Design of Peptide Therapeutics Exhibiting Dual Pharmacology and Extended Duration of Action

Soumitra Ghosh, Ph.D. | Senior Director, Research

Amylin Pharmaceuticals LLC, A wholly-owned subsidiary of Bristol-Myers Squibb
9625 Towne Centre Drive, San Diego, CA 92121 | (858) 458-8474

Peptide hormones secreted from the gut, adipose tissue and the pancreas, together with nutritional state and neuronal signals, act in concert through central mechanisms to maintain energy and glucose homeostasis. Amylin's drug discovery approach relies on peptide engineering to leverage this neurohormonal basis of glucose and body weight regulation for the design of novel therapeutics. Our peptide hybrid (phybrid) platform is based on fusing bio-active peptides with independent biological activities to generate molecules that display dual pharmacology or enhanced duration of action. These molecular constructs can be made by recombinant expression. As a first example, we have developed phybrids comprised of a glucagon-like peptide-1 receptor agonist covalently linked to an amylinomimetic peptide. The phybrids display the requisite pharmacological actions of their parent peptides, and their metabolic effects in rodent models are equal or superior to the combination of the parent peptides, and superior to either parent peptide alone. As a second example, exendin-4 analogs have been conjugated to small, peptidic domains that non-covalently bind to circulating serum albumin with picomolar affinity. These molecules are potent in their glucose and weight-lowering effects in rodent models, and their long duration of action offer the potential for once-weekly administration for the treatment of diabetes and obesity. The oral delivery of these long-acting molecules has been explored in rodent and primate models.



The Development of BA058, a Novel Peptide, for the Treatment of Osteoporosis

Gary Hattersley, Ph.D. | Senior Vice President, Preclinical Development

Radius Health, Inc.

201 Broadway, 6th Floor, Cambridge, MA 02139 | (617) 551-4703

BA058 is a novel synthetic analog of human PTHrP that is being developed as an anabolic therapy for the treatment of osteoporosis in post-menopausal women. Osteoporosis is a disease characterized by a deterioration of bone structure and quality, resulting in an increased risk of fractures, and represents a leading cause of morbidity in the aging population. Daily BA058 SC injection has produced promising safety and efficacy results in preclinical studies, showing marked reversal of bone mass, restoration of bone micro-architecture and strength and in phase 1 and phase 2 clinical studies demonstrating early and marked increases in bone mineral density. On the basis of these results a large international Phase 3 fracture prevention trial is currently on going. There is also a significant need for an alternative to injection that improves patient convenience and compliance. To accomplish this we have investigated the use of a solid microstructure array technology (sMTS, 3M) for transdermal delivery of BA058. Preclinical and clinical studies to date have shown good tolerance and delivery of BA058 using this short wear time transdermal patch, which potentially represents a new approach for the treatment of osteoporosis.

The Structural and Energetic Basis of Carbohydrate–Polypeptide Stabilizing Interactions Within Enhanced Aromatic Sequons in Protein Native States

Jeffrey W. Kelly, Ph.D. | Lita Annenberg Hazen Professor of Chemistry, Department of Chemistry; Chairman, Department of Molecular and Experimental Medicine

The Scripps Research Institute

10550 North Torrey Pines Road, La Jolla, CA 92037 | (858) 784-9605

Nearly 1/3 of the human proteome traverses the cellular secretory pathway. Most of these proteins are N-glycosylated at Asn within the Asn-Xxx-Thr/Ser sequon. We have demonstrated show that placing an aromatic residue two or three positions prior to a glycosylated Asn in distinct reverse turn structures facilitates stabilizing interactions between the aromatic side chain and the first N-acetylglucosamine (GlcNAc) of the glycan. Glycosylation of a specific “enhanced aromatic sequon” in the appropriate reverse turn type stabilizes the native state of several different proteins by up to $-2.0 \text{ kcal mol}^{-1}$ and slows unfolding. These results enable the engineering of stabilized glycoproteins for research and pharmaceutical applications, especially important for biological drug applications, as glycosylation is known to increase serum half-life, decrease aggregation propensity, and shield immunogenic epitopes, all due in part to a decreased population of the aggregation-prone, protease-sensitive unfolded state resulting from conformational excursions. The structure–energy relationships underpinning carbohydrate–aromatic packing interactions in aqueous solution have been difficult to assess experimentally. We have determined the structures and folding energetics of chemically synthesized glycoproteins to quantify the contributions of the hydrophobic effect and CH– π interactions to carbohydrate–aromatic stabilizing interactions. The hydrophobic effect contributes significantly to protein–carbohydrate stabilizing interactions and is supplemented by CH– π interactions. The strengths of experimentally determined carbohydrate– π interactions do not correlate with the electrostatic properties of the involved aromatic side chains, suggesting that the electrostatic component of CH– π interactions in aqueous solution is small. Thus, energetically important interactions between carbohydrates and aromatic side chains is driven by the hydrophobic effect and CH– π interactions featuring a dominating dispersive component.

Towards Optimized Utility of Proteasome Inhibitors with Peptide Epoxyketones

Christopher J. Kirk, Ph.D. | Vice President, Research

Onyx Pharmaceuticals, Inc.

249 E. Grand Avenue, South San Francisco, CA 94080 | (650) 266-0000

The ubiquitin/proteasome pathway is the primary means by which intracellular protein degradation occurs. The 26S proteasome, a multicatalytic proteolytic machine, plays a central role in regulating most facets of cell physiology and has been the target of drug discovery programs in cancer and inflammatory diseases. Proteasome inhibition is a validated therapeutic strategy for the treatment of B-cell neoplasms. Originating from the natural product epoxomicin, we have generated several peptide epoxyketones, with distinct pharmacologic and pharmacologic profiles as proteasome inhibitors. One of these compounds, carfilzomib, has recently received FDA approval for the treatment of relapsed and refractory myeloma. A second compound, oprozomib, which is an orally bioavailable analog of carfilzomib, has entered clinical trials with encouraging initial results in the treatment of multiple myeloma. Another focus of our research is subunit selective inhibitors of the proteasome. Our discovery of subunit-selective peptide epoxyketones has helped elucidate distinct roles for both the immunoproteasome and constitutive proteasome in immune cell biology. Immunoproteasome selective inhibitors are highly efficacious in mouse models of autoimmunity and represent a new class of therapeutics for the treatment of inflammatory diseases.

SOM230: A New Therapeutic Modality for Cushing's Disease

Ian Lewis, Ph.D. | Investigator III, Peptide Discovery Group, Exploratory Medicinal Chemistry Unit

Novartis Institutes of Biomedical Research

Postfach, CH-4002 Basel, Switzerland | +41 61 3243762

The somatostatin (SRIF, somatotropin release inhibiting factor) field has been a success story in terms of medicinal chemistry and drug discovery offering a variety of therapeutic opportunities, e.g. acromegaly, gastrointestinal neuroendocrine tumors, whole body imaging and radiotherapy. Indeed, a rational medicinal chemistry approach capitalising on structure activity relationships led to the discovery of SOM230, a stable cyclohexapeptide somatostatin mimic which exhibits unique binding to human SRIF receptors (sst1-5). This approach involved transposing functional groups, in the form of unnatural amino acids, from SRIF-14 into the stable, reduced size cyclohexapeptide template. Further, the hydroxyproline urethane extension of SOM230 has been functionalized with the chelators DTPA and DOTA, which is a necessary prerequisite for the possible development of ligands which could be used for whole body imaging. Uniquely, SOM230 exhibits binding with a 30 to 40 times higher affinity than Sandostatin® to the sst1 and sst5 receptors and exhibits higher efficacy in preclinical models in lowering Growth Hormone, Insulin-Like Growth Factor-1, ACTH and corticosterone than Sandostatin®. Recently, phase III clinical studies have established the therapeutic potential of SOM230/Pasireotide (Signifor®), as the first pituitary directed medical therapy for Cushing's disease¹ leading to registration of SOM230 by both EMEA and FDA in 2012.

[1] A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease, Annamaria Colao, Stephan Petersenn, John Newell-Price, James W. Findling, Feng Gu, Mario Maldonado, Ulrike Schoenherr, David Mills, Luiz Roberto Salgado and Beverly M.K. Biller for the Pasireotide B2305 Study Group, N Engl J Med 2012;366:914-24.

Half-Life Extension Through HESylation®

Martin Meyer, Ph.D. | Innovation Manager, Innovation & Development Center Carbohydrate Chemistry, Pharmaceuticals Division

Fresenius Kabi Deutschland GmbH

Pfingstweide 53, D-61169 Friedberg, Germany | +49 6172 686-8406

HESylation® is an innovative half-life extension technology developed by Fresenius Kabi that utilizes hydroxyethyl starch [HES] as biodegradable and versatile polymer for a customized modification of drugs like therapeutic peptides and proteins. This modification leads to an increased in vivo efficacy due to e.g. prolongation of the circulation half-life by reducing the renal clearance or by increasing the stability of the molecule. We present the technology and in vivo data on the performance of biologicals including cytokines and growth factors. Additional data regarding the comparably low viscosity of HES conjugates, which helps to overcome formulation and syringeability issues, will be shown.



^{99m}Tc -Galacto-RGD₂: A novel ^{99m}Tc -Labeled Cyclic RGD, Peptide Dimer Useful for Tumor Imaging

Michael Pennington, Ph.D. | President and CEO

Peptides International, Inc.

11621 Electron Drive, Louisville, KY 40299 | (502) 266-8787

Integrin $\alpha_v\beta_3$ plays a significant role in tumor angiogenesis, and is a receptor for the extracellular matrix proteins (vitronectin, fibronectin, fibrinogen, lamin, collagen, Von Willibrand's factor and osteopontin) with the exposed arginine-glycine-aspartic (RGD) peptide sequence. Integrin $\alpha_v\beta_3$ is expressed at low levels on epithelial cells and mature endothelial cells, but it is overexpressed on the activated endothelial cells of tumor neovasculature and some tumor cells. Thus, integrin $\alpha_v\beta_3$ is considered as an interesting molecular target for early cancer detection.

Cyclic RGD peptides, such as E[c(RGDfK)]₂ (RGD₂) and E[E[c(RGDfK)]₂]₂ (RGD₄), are integrin $\alpha_v\beta_3$ receptor antagonists. Over the last several years, many radiolabeled (^{99m}Tc , ^{18}F , ^{64}Cu , ^{68}Ga and ^{111}In) multimeric cyclic RGD peptides have been evaluated as $\alpha_v\beta_3$ -targeted radiotracers for tumor imaging by single photon emission computed tomography (SPECT) or positron emission tomography (PET). It has been shown that cyclic RGD peptides were able to bind integrin $\alpha_v\beta_3$ with high specificity. Multiple cyclic RGD moieties were utilized to maximize their integrin $\alpha_v\beta_3$ binding affinity and the radiotracer tumor uptake. It was found that multimeric RGD peptides had significantly higher tumor uptake with much longer tumor retention time than their monomeric counterparts.

We have been interested in radiolabeled multimeric cyclic RGD peptides as PET and SPECT radiotracers for non-invasive imaging of solid tumors. [^{99m}Tc (HYNIC-3P-RGD₂)(tricine)(TPPTS)] (^{99m}Tc -3P-RGD₂; HYNIC = 6-hydrazinonicotinyl; 3P-RGD₂ = PEG₄-E[PEG₄-c(RGDfK)]₂; PEG₄ = 15-amino-4,7,10,13-tetraoxapentadecanoic acid; and TPPTS = trisodium triphenylphosphine-3,3',3''-trisulfonate) is a ^{99m}Tc -labeled dimeric cyclic RGD peptide. ^{99m}Tc -3P-RGD₂ showed very high tumor uptake and rapid renal clearance in glioma-bearing animal model. It is now under clinical investigation as a new SPECT radiotracer for tumor imaging in cancer patients.

Despite its high tumor uptake, ^{99m}Tc -3P-RGD₂ showed high uptake in intestines and spleen. To minimize excess radioactivity accumulation in normal organs, we designed and prepared a new cyclic RGD dimer, Galacto-RGD₂, in which the 7-amino-L-glycero-L-galacto-2,6-anhydro-7-deoxyheptanamide (SAA) linkers were used to bridge two RGD moieties. In this report, we present the synthesis of Galacto-RGD₂, and evaluations of its ^{99m}Tc complex [^{99m}Tc (HYNIC-Galacto-RGD₂)(tricine)(TPPTS)] (Figure 1: ^{99m}Tc -Galacto-RGD₂) as a new SPECT radiotracer for tumor imaging. Integrin $\alpha_v\beta_3$ binding affinity of HYNIC-Galacto-RGD₂ was determined in a whole-cell competition assay. Biodistribution properties of ^{99m}Tc -Galacto-RGD₂ were evaluated and compared to those of ^{99m}Tc -3P-RGD₂ in athymic nude mice bearing U87MG glioma xenografts. The main objective of this study is to demonstrate that SAA and 1,2,3-triazole moieties are indeed able to improve excretion kinetics of ^{99m}Tc radiotracer from non-cancerous organs.

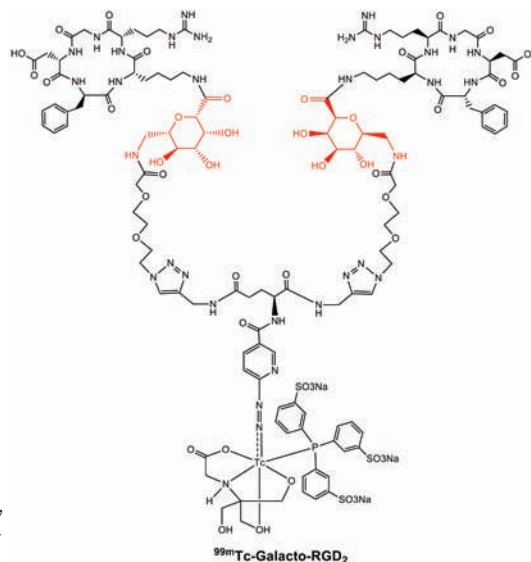


Figure 1. ^{99m}Tc -Galacto-RGD₂

PeptiDream's PD Platform: Innovative Peptide Discovery Platform

Patrick C. Reid, Ph.D. | CoFounder, Chief Scientific Officer and Member Board of Directors

PeptiDream Inc.

4-6-1 Komaba, Meguro-ku, Tokyo, Japan 153-8904 | +81 3 3485 7707

PeptiDream's proprietary PD Platform is a highly versatile peptide generation and selection platform based on three core technologies; 1) Flexizyme, 2) translation, cyclization, and peptide modifying technologies, and 3) PD display. The combination of these 3 technologies into the PD Platform allows PeptiDream to produce libraries of trillions of unique cyclic and helical nonstandard peptides with unparalleled diversity. The PD Platform allows PeptiDream to identify hundreds of novel nonstandard macrocyclic peptides against a target in weeks, covering a wide variety of peptide classes and structures. Researchers can then screen hundreds of hits a week for the desired target binding, selectivity, and biochemical activity by independently expressing each peptide using PeptiDream's PDTs translation system, without the bottleneck of expensive and time consuming chemical synthesis. Leads can then be chemically synthesized and purified for further development.

Development of Serelaxin for Acute Heart Failure

Dennis Stewart, Ph.D. | Principal Scientist

Corthera Inc.

Novartis Pharmaceuticals Corp.

150 Industrial Road, San Carlos, CA 94070 | (650) 622-1671

Serelaxin is the international nonproprietary name for relaxin, an endogenous hormone. Serelaxin has been in clinical development since the early 1990s at Genentech, Connetics, Corthera and finally Novartis.

Relaxin is a peptide hormone produced in both men and women but generally associated with elevated serum concentration during pregnancy. It binds to specific high affinity receptors located in the cardiovascular system and many tissues. It has been found in preclinical studies to have many actions including hemodynamic changes, anti-fibrotic activity, anti-inflammatory actions, and assist in wound healing. It has been evaluated in many clinical studies from cervical ripening, scleroderma, orthodontics and finally cardiovascular indications.

The hemodynamic changes seen in pregnancy are believed to be the result of endogenous relaxin and correspond to desired actions in the treatment of acute heart failure. These include the decreased vascular resistance, increase arterial compliance, and increased renal blood flow. Patients with acute heart failure (AHF) have hypertension and dyspnea (shortness of breath). In Phase 2 and 3 clinical studies conducted by Corthera and then Novartis, serelaxin reduced dyspnea, prevented worsening heart failure and lowered 180 day cardiovascular mortality. Serelaxin was shown to have a good safety profile. These data were supportive of early filing with EU and US regulatory bodies for approval based upon one Phase 3 trial. Novartis is committed to development of serelaxin in AHF and other indications.

The Transdermal Delivery of Peptides and other Biotherapeutics

Frank Tagliaferri, Ph.D. | Vice President, Research & Development

4P Therapeutics

680 Engineering Drive, Suite 150, Norcross, GA 30092 | (770) 263-1900

There is an increasing need for efficacious and patient-friendly delivery systems for the large number of peptides and other biotherapeutics either on the market or in development. A transdermal patch is a convenient, user-applied dosage form which eliminates the need and complexity of an injection. Traditional passive transdermal patches are typically limited to the delivery of small lipid-soluble drugs and are therefore not amenable to larger water-soluble molecules. The development of alternative methods to overcome the barrier imposed by the stratum corneum such as microneedles, microporation, and iontophoresis has expanded the size, water-solubility range, and doses of compounds available for transdermal delivery. It may therefore now be possible to transition many of the current peptide and other biologic drug products into convenient transdermal forms. More importantly, these systems have the potential to allow new biologic candidates to enter the market initially as patient-friendly transdermal patches. Several of these newer approaches will be presented with the emphasis on their applicability to the delivery of peptides and other large molecules.



Long-acting Release of Drug Peptides by *in situ* Gelling FluidCrystal® Injection Depot

Fredrik Tiberg, Ph.D. | President and CEO

Camurus AB

Ideon Science Park, SE-223 70 Lund, Sweden | +46 46 286 5730

Professor Physical Chemistry

Lund University, Box 124, SE-22100 Lund, Sweden | +46 46 222 0000

The successful utilization of therapeutic peptides is often hampered by limited drug stability, short half-lives and poor oral bioavailability. To achieve a desired biological effect, this may necessitate multiple daily injections, which can be painful and inconvenient for the patient. Consequently, significant efforts are being dedicated to extending half-lives of drug peptides through molecular engineering or use of advanced biodegradable sustained release depot technologies, such as polymer microspheres and gels. The advantage of biodegradable depot systems is that they do not require manipulation of the peptide chemistry and consequently the biological activity remains unaltered. However, such technologies typically require more complex manufacturing processes, as well as precise handling and administration procedures by health care providers and patients.

Here we present the FluidCrystal® (FC) Injection depot for long acting release of drug peptides, which facilitates both easy manufacturing and facile administration. The system is described and discussed in terms of its' mode of action and in vivo performance, as well as CMC, primary packaging and in-use aspects.

The principle behind the FC technology is a liquid-to-gel phase transition, occurring immediately as the lipid based FC system is exposed to in vivo conditions, cf (1,2). The phase transition proceeds from the outside towards the centre by absorption of minute quantities of water, which results in an immediate and spontaneous formation of peptide encapsulating nano-domains. The morphology and connectivity of these domains can conveniently be controlled by the lipid ratio of the FC formulation (3), which in turn provides an easy and robust means of controlling the rate and duration of peptide release from the FC depot, ranging from a few days to months.

The dual nature of the FC system, i.e. being a true liquid product and stable gel *in vivo*, enables a ready-to-use product presentation, such as a prefilled syringe, and an easy manufacturing process using standard processing steps, while also providing long-acting release in vivo with a minimum of initial burst release.

The properties of the FC system are exemplified by current clinical projects developing novel long-acting somatostatin, GnRH, and GLP-1 receptor agonist product candidates for treatment of acromegaly/carcinoid syndrome, prostate cancer, and diabetes type 2, respectively. Anticipated significant benefits in terms of manufacturability and patient convenience are discussed together with non-clinical and clinical pharmacokinetic and pharmacodynamic properties.

1. Tiberg F and Johnsson M, *Drug delivery applications of non-lamellar liquid crystalline phases and nanoparticles*, Journal of Drug Delivery Science and Technology, **2011**, 21(1), 101-109
2. Tiberg F, Johnsson M, Nistor C, Joabsson F, in: D. J. Burgess and J. C. Wright (Eds.), Long-Acting Injections and Implants, CRS, Springer, New York, 2012, p. 315.
3. Tiberg F, Johnsson M, Jankunec M and Barauskas J, *Phase Behavior, Functions, and Medical Applications of Soy Phosphatidylcholine and Diglyceride Lipid Compositions*, Chemistry Letters **2012**, 41(10), 1090-1092

Direct Selection of Highly Potent Cyclic Peptidomimetics from In Vitro Display Libraries

Douglas A. Treco, Ph.D. | President and CEO

Ra Pharmaceuticals, Inc.

One Kendall Square, Suite B14301, Cambridge, MA 02139 | (617) 401-4062

Ra's Extreme Diversity™ platform uses in vitro display to rapidly produce and screen extremely large libraries for peptidic macrocycles (Cyclomimetics™) containing modified backbones and unnatural side-chains. The high-affinity and metabolic stability of the “hits” from these libraries are excellent chemical starting points for drug development programs, significantly reducing the lead optimization phase. The synthesis and characterization of products identified from our initial libraries suggest that they may be used for the efficient discovery of intracellular protein-protein interaction inhibitors, highly selective enzyme inhibitors, or synthetic replacements for monoclonal antibodies.

How Insulin Binds: Structure of a Micro-receptor Complex and Implications for Analog Design

Michael A. Weiss, M.D., Ph.D. | Professor, Departments of Biochemistry, Biomedical Engineering and Medicine (Endocrinology)

Case Western Reserve University

2109 Adelbert Road, Cleveland, OH 44106 | (216) 368-5991

How insulin binds to and triggers the insulin receptor has long been the subject of speculation despite decades of investigation. A recent advance by an international team of investigators has led to a low-resolution co-crystal structure of insulin bound to a fragment of the insulin receptor (Menting, J. G., et al. *Nature* **493**:241-5 (2013)). The fragment, containing primary hormone-binding elements L1 and aCT, is designated the “micro-receptor.” Despite its limited resolution (3.9 Å), the structure of the insulin/micro-receptor complex was deciphered based on residue-specific photo-cross-linking studies enabled by extended genetic-code technology (in collaboration with J. Whittaker, CWRU). Structure-function relationships at the level of individual side chains were proposed and tested in relation to high-resolution structures of the isolated hormone and free receptor domains. The relevance of these findings to the holoreceptor was verified by comparative micro-receptor binding studies (in collaboration with S.-J. Chan and D.F. Steiner, University of Chicago). The micro-receptor complex is remarkable for conformational changes in both insulin and in the primary hormone-binding site. Such induced fit leads to a re-interpretation of prior alanine-mutagenesis studies of the receptor ectodomain, but validates long-standing models of a “structural switch” in the C-terminal segment of the B chain of insulin (Hua, Q.X., et al. *Nature* 354:238-41 (1991)). Although the nature of this switch was unclear in the original electron-density map, its localization to residues Phe^{B24} and Phe^{B25} is supported by continuing refinement (in collaboration with M. C. Lawrence; Walter & Eliza Hall Institute, Melbourne, AU) and the anomalous properties of non-standard analogs containing “b-breaker” substitution α,b-dehydro-Phe at these positions (V.S. Chauhan, New Delhi, India). Complementary studies of the folding efficiency of proinsulin analogs in mammalian cell lines (in collaboration with P. Arvan (University of Michigan) and S.B. Kent (Chicago)) imply that the B-chain switch enables potential structural trade-offs between requirements of foldability and function to be circumvented. Implications of our results for the design of therapeutic insulin analogs will be discussed with potential application to the engineering of ultra-temperature-stable single-chain insulin analog formulations of humanitarian utility in the developing world.



Structural Insights into HIV, Influenza & HCV Antigen Design

Ian A. Wilson, D.Sc., FRS. | Hansen Professor of Structural Biology and Chairman

Department of Integrative Structural and Computational Biology

The Scripps Research Institute

10550 North Torrey Pines Road, La Jolla, CA 92037 | (858) 784-9706

Influenza, Hepatitis C, and HIV-1 continue to constitute significant threats to global health. We have structurally and functionally characterized several potent, broadly neutralizing antibodies (bnAbs) against HIV-1, influenza and Hepatitis C viruses. The major surface antigen, the hemagglutinin (HA), of influenza virus is the main target of neutralizing antibodies. However, most antibodies are strain-specific and protect only against highly related strains within the same subtype.

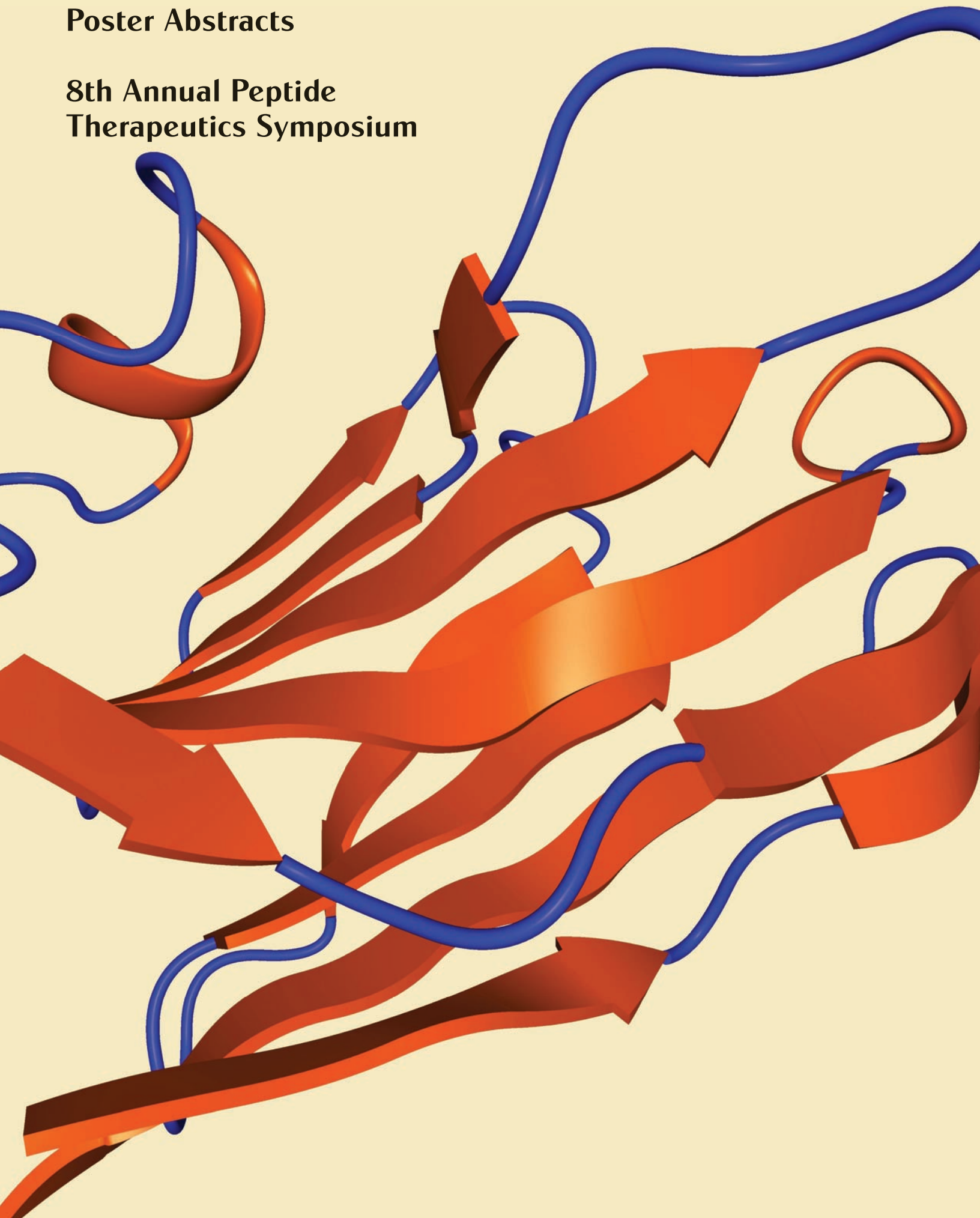
Recently, a number of antibodies have been found that are much broader and neutralize across subtypes and groups of influenza A viruses, as well as influenza B, through binding to functionally conserved sites. We have determined co-crystal structures of antibodies with the HA and identified highly conserved sites in the fusion domain (stem) and in the receptor binding site (head). Circulating HCV is genetically diverse, but antibodies HCV1 and AP33 have potent neutralizing activity against many isolates across most genotypes of the virus. The antibodies target a conserved antigenic site on the virus E2 envelope glycoprotein that overlaps with the CD81 receptor-binding site. We have determined crystal structures of both antibodies in complex with a peptide spanning the conserved epitope. The structures reveal the peptide adopts the same conformation when bound to both antibodies, which can be stabilized and optimally presented in immunogen design.

A number of exciting new human monoclonal antibodies have also been recently isolated that potently neutralize HIV-1 isolates across all clades. Structural and functional characterization of these bnAbs has led to the identification of novel epitopes on HIV-1 Env, many of which involve glycans. These glycan-dependent Abs have unique features that enable them to penetrate the glycan shield and bind complex epitopes that consist of sugars and underlying protein segments on gp120. This information is now being used to aid in structure-assisted vaccine design for HIV-1 and for a more universal flu vaccine. This work was carried out in collaboration with the Burton, Ward and Law labs at TSRI, Moore lab at Weill Medical College, Crowe lab at Vanderbilt, the International AIDS Vaccine Initiative (IAVI) Neutralizing Antibody Consortium at TSRI, the Scripps Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID), and Crucell Vaccine Institute. IAW is supported by NIH grants AI100663, AI082362, AI84817, AI099275 and GM094586.



Poster Abstracts

8th Annual Peptide Therapeutics Symposium



P01 Towards the Design and Synthesis of Antiviral Proteins

Naila Assem, Anette Schneemann, Philip E. Dawson

Department of Chemistry and Molecular Biology and Cell Biology, The Scripps Research Institute,
10550 N. Torrey Pines Road, La Jolla, CA 92037 USA

The influenza virus is the cause of yearly epidemics and periodic pandemics. Currently, effective prophylactic treatments are necessary to combat infectivity. In an attempt to combat this virus we have turned to a highly conserved hemagglutinin (HA) epitope where broad spectrum human neutralizing antibodies bind. Our goal was to synthesis an epitope mimic effective at eliciting an immune response against a wide spectrum of the influenza virus. To mimic the highly conserved helical epitope on HA, we have grafted the epitope on to a coiled coil scaffold. The binding affinity of the coiled coils to neutralizing antibodies has been tested and will be discussed. In addition, we were successful at conjugating these coiled coil mimics onto flockhouse virus particles to achieve multivalent display of our HA mimics. In parallel, we have turned to Baker and coworkers who have designed HA-binding proteins that inhibit the H1 and H5 strains of virus with low nanomolar affinity. We were successful at the total synthesis of the HA binding protein HB80.4 and are currently exploring alterations to further stabilize its secondary structure.

P02 Development of Injectable IL-6 Antagonists for the Treatment of IL-6-driven Pathologies: A Novel Drug Discovery Platform Utilizing Drug-Like Characteristics of Disulfide-Rich Peptides

Ashok Bhandari, Jaimee McMahon, Jenny Zhang, Tran Trung Tran, Dion Celino Jr., Gregory T. Bourne, Katie E. Glen, Mark L. Smythe, Dinesh V. Patel, Craig A. Murphy
Protagonist Therapeutics Inc., 1455 Adams Drive, Menlo Park, CA 94025 USA

Protagonist Therapeutics' technology platform selects and optimizes constrained scaffolds such as disulfide-rich peptides (DRPs) for drug discovery. DRPs overcome the fundamental 'instability' disadvantage of linear peptides and provide a means to exploit the desired attributes of both small molecules and biologics while limiting the acknowledged deficiencies of these approaches. Importantly, DRPs are not new to the market; recent examples include Linzess (linaclotide acetate), Prialt (ziconotide) and Omontys (peginesatide). Whereas the majority of these drugs are derivatives of naturally occurring peptides, Protagonist's de novo approach engineers new functionality onto peptide scaffolds for selected targets. The engineering undertaken is an integrated and corroborative approach utilizing molecular design, phage display, peptide and medicinal chemistry. We will present work showcasing the discovery and rapid optimization of peptide antagonists against IL-6, a target involving protein-protein interactions not inhibitable with small molecules. Data presented will highlight the activity of the antagonists in cell-based assays and an in vivo model setting the foundation for achieving our goal of nominating a novel new chemical entity (NCE) for the treatment of IL-6 driven pathologies.

P03 Novel Vasopressin 1a Receptor (V1A-R) Partial Agonists Induce Vasoconstriction Without The Risk Of Ischemia: Comparison With V1a-R Full Agonists

Edward Cable¹, Geoffrey Harris¹, Kazimierz Wisniewski¹, Hiroe, Tariga¹, Susan Song¹, Jeannine Toy¹, Halina Wisniewska¹, Mark Lu¹, Steven Hoffmaster¹

¹ Ferring Research Institute, San Diego, CA 92121 USA

Purpose: Vasopressin (AVP) and terlipressin have been used to treat cardiovascular complications in portal hypertensive patients. Vasopressin analogs are thought to act by causing specific vasoconstriction of the splanchnic circulation (and skin) via V1a receptor activation. Reduction in splanchnic blood flow reduces portal pressure. Although terlipressin and AVP have been used clinically, both agents have a narrow therapeutic index that limits their use to hospitalized patients. The aim was to design V1a partial agonists with capped vasoconstrictive activity that provide clinically meaningful vasoconstriction over a broad dose range without the risk of causing tissue hypoxia.

Methods: a) In vitro, recombinant cell lines expressing human and rat V1A-R and V2R; b) Ex vivo, human and rat mesenteric resistance arteries; and c) In vivo, skin blood flow (SBF) and lactate in normal rats and portal pressure measurements in portal hypertensive rats.

Results: A series of V1a-R partial agonist compounds were identified. In in vitro assays at the V1a-R, compounds demonstrated a significantly reduced Emax over a broad concentration range compared to AVP and other full agonists. Partial agonists were tested in vivo in a rat skin blood flow model (SBF) to assess if the reduction in in vitro Emax translated into reduced maximal vasoconstriction. Compounds that maximally decreased SBF < 60% (compared to V1a-R full



agonists) demonstrated no evidence of tissue hypoxia, while those >60% increased blood lactate. Partial agonists also decreased the diameter of human resistance arteries, with an Emax significantly lower than full agonists. When tested in portal hypertensive rats, a significant decrease in portal pressure was observed that hit a plateau that could be maintained over a broad dose range.

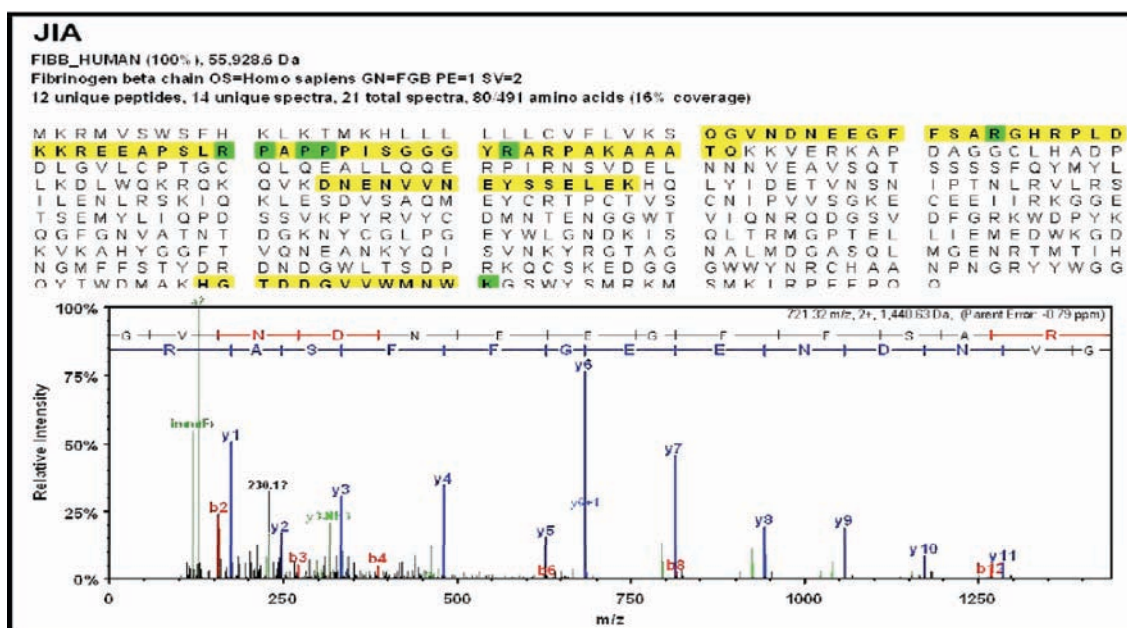
Conclusions: A novel series of V1a-R partial agonists have been discovered that produce moderate vasoconstriction without ischemia over a broad dose range. In patients with portal hypertension, such agents could be used to decrease portal pressure and treat or prevent many cardiovascular complications, such as HRS-1&2, ascites, refractory ascites and post paracentesis induced circulatory dysfunction and the intrinsic safety of such agents could expand the use of vasoconstriction therapy in these patients potentially outside of the hospital.

P04 Development of Peptidomics Assays for Discovery of Endogenously Processed Peptides from Healthy and Juvenile Idiopathic Arthritis (JIA) Human Synovial Fluid

Cristina C. Clement Ph.D. and Laura Santambrogio Ph.D. MD

Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461 USA

Juvenile idiopathic arthritis (JIA) is the most common chronic condition seen by pediatric rheumatologists. We and others hypothesized that joint destruction could be partly due to an adaptive immune response mediated by antibodies, and that the characterization of the peptidome (together with the degradome) found in arthritic synovial fluid (SF) (from children with JIA) will help to advance the present studies and shed new molecular mechanisms on the pathogenesis of JIA. Herein, we present the development of peptidomics assays coupled with high resolution nanoLC-MS/MS on LTQ/Orbitrap Velos mass spectrometer aimed to characterize the endogenously processed peptides from the SF of children with JIA and control patients. The SF peptidome was fractionated by ultrafiltration and peptides with MW<5 kDa were sequenced by HCD/ETD nanoLC Orbitrap-ESI-MS/MS or CID nanoLC LTQ-ESI-MS/MS. The peptidome analysis revealed the breakdown products of the fibrinogen alpha and beta chains and cartilage, mainly proteoglycan 4, fibronectins (1 and 6), lumicans, periostin, and multiple collagen subtypes (I, II, III, IV, V, among others). The peptidome found in the JIA-SF suggests a mechanism for the amplification of the autoimmune process during inflammation. To our knowledge this is the first analysis of the peptidome from JIA SF. The preliminary findings on the breakdown products of the structural cartilage components suggests a mechanism for amplification of the autoimmune process during inflammation. Moreover, the peptidomics assays described herein could be applied to other biological samples of biomedical interest and further used to investigate the proteases (the degradome) responsible for regulating the bioactive peptides.



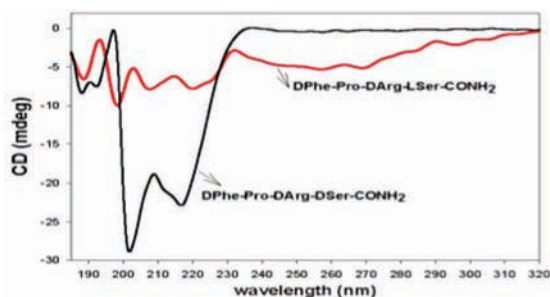
P05 Structure-based Design, Secondary Structure Analysis and Kinetics Evaluation of New [D-(Phe)-Pro-D-Arg-P1'-CONH₂] Derived Direct Thrombin Inhibitors

Cristina C. Clement, Janet Gonzalez and Manfred Philipp

Department of Chemistry, Lehman College & Biochemistry Program, CUNY Graduate School, New York, NY 10036 USA

Recently, our research group described the biochemical and structural characterization of three non-covalent direct thrombin inhibitors (DTI) that contain the common sequence D-Phe(P3)-Pro-(P2)-D-Arg(P1)-P1'-CONH₂ [1]. The three-dimensional structures of three complexes of human alpha-thrombin with the three lead peptidic inhibitors (with L-isoleucine, L-cysteine or D-threonine at the P1' position) highlighted all inhibitors adopting a substrate-like orientation in the active site of thrombin [1]. Herein, we report the further development of new peptidic DTI and perform an optimization for P3 position by replacing D-Phe with different un-natural Phe-analogs (such as D-3,3-di-Phenylalanine, D-3,5-difluorophenylalanine, trans and dihydrocinnamic acids, (L)/(D)-Tic [1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid], (L)/(D)-Thi [Thienylalanine], D-Naphthylalanine (D-Nal) and 1,2,3,4-tetrahydronorharman-3-carboxylic acid (D-Tpi) among others). The SAR (structure-activity relationship) at P3 position showed that the compounds with D-3,3-di-Phenylalanine are the new lead DTIs with inhibitory constant in the lowest 50 nM range. Circular dichroism studies showed that the D-Arg- at *i*+2 position followed by D-amino acids (polar and neutral or small hydrophobics like D-Thr, D-Gln, D-Ser and D-Ala, respectively) in *i*+3 position favors beta turn and beta hairpin structures in solution at low and neutral pH. Replacement of D- with L-amino acids at *i*+3 position was accompanied by a significant lost in the beta turn structure. In addition, the aromatics (L-Phe, L-Tyr and L-Trp) at *i*+3 position are disturbing the beta structure while the replacement of D-Phe with L/D-Tic is accompanied by a shift towards beta-strand-like structure. SAR studies showed that tetrapeptides which adopt beta turn or beta hairpin conformation in solution are more potent DTIs.

- 1 Figueiredo AC, Clement CC, Zakia S, Gingold J, Philipp M, Pereira PJ. Rational design and characterization of D-Phe-Pro-D-Arg-derived direct thrombin inhibitors. PLoS One. 2012;7(3):e34354. doi: 10.1371/journal.pone.0034354.

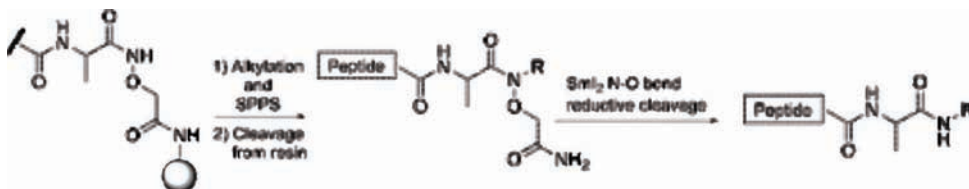


P06 C-terminal N-alkyl Amide Peptides via Hydroxamic Ester Alkylation and SmI₂ Reductive N-O Bond Cleavage

Jeffrey Culhane, Philip Dawson, The Scripps Research Institute, La Jolla, CA 92037 USA

Modifications at the C-terminus of synthetic peptides are desirable in that they can impart enhanced stability toward peptidases and other endogenous metabolic enzymes. Additionally, C-terminal N-alkyl amides can be advantageous in facilitating peptide targeting and membrane penetration. Methods for modifications of the C-terminus have only sparingly been reported; the challenge being the ability to conveniently and efficiently modify the peptide at its point of attachment to the solid-phase while not affecting the lability of the bound peptide during the standard cycles of either Fmoc or Boc synthesis or at the time of peptide cleavage.

A simple and robust method for the installation of unnatural modifications at the C-terminus of synthetic peptides is described. Coupling Fmoc-aminoxyacetic acid (Aoa) to the resin provides a chemoselective handle towards alkylation in the context of protected peptides under mildly basic conditions in the presence of alkyl halides. After cleavage and universal deprotection, these C-terminal peptide hydroxamic esters are reductively cleaved with SmI₂, furnishing C-terminal N-alkyl amides in high yields and purities.





P07 P07 CMDpeptideSM: A Physics Driven Strategy for Predicting Peptide and Macrocycle Structure

D.J. Diller, D.G. Sprous, J.T. Swanson, S. Ponomarev and J. Audie
CMD Bioscience Inc., Science Park, New Haven, CT 06511 USA

Peptides combine many of the virtues of small molecules and proteins and minimize many of their vices. Organisms exploit peptides to solve numerous physiological and pharmacological problems, from cell and hormonal signaling, to the use of toxins for prey capture and assorted other functions. Pharmaceutical researchers, especially when confronted with “undruggable” targets, are beginning to build on nature and exploit the pharmacological potential of peptides. As these “undruggable” targets are particularly common players in the transformations leading to cancer, understanding how peptides can be used to increase the space of “druggable” targets is essential.

Whether used as input for understanding target binding or ADME predictions, knowledge of ligand 3D structure is a critical first step. In the past we have shown that using a Multiple Start Monte Carlo (MSMC) sampling protocol we are able to consistently generate near native conformers for linear peptides. Here we discuss the extension of CMDpeptideSM to cyclic peptides including peptides with multiple disulfide bonds, N-C cyclization and non-natural cyclizations. Preliminary results indicate that our extended MSMC work-flow can be used to consistently sample near native conformations for diverse cyclic peptides. Finally, we show encouraging preliminary results on general macrocycles.

P08 Enhancing the Efficacy of Biotherapeutics by Affibody Technology

Lindvi Gudmundsdóttir¹, Ingmarie Höidén-Guthenberg¹, Andreas Jonsson¹, Joachim Feldwisch¹,
Jörgen Carlsson², Fredrik Frejd¹, Caroline Ekblad¹

¹Affibody AB, Sweden, www.affibody.com; ²Rudbeck Laboratory, Uppsala University, Sweden

Affibody[®] molecules are small engineered scaffold proteins with high specificity, tunable kinetics and biodistribution, making them ideal for targeted therapy and molecular imaging. Their high structural stability enables flexible engineering into multivalent and multispecific formats to further enhance the efficacy of therapeutic or biotechnological products. A recent approach includes potentiation of antibodies by creating AffiMabs, in which Affibody[®] molecules are fused to antibodies to provide additional functionalities for developing therapeutics with superior efficacy.

The half-life of Affibody[®] molecules and other biotherapeutics can be extended up to several weeks by applying Affibody's Albumod[™] technology. The core of the Albumod[™] technology is the Albumin Binding Domain (ABD), a 5 kDa protein engineered to bind human serum albumin (HSA) with an exceptionally high affinity. Improved pharmacokinetic and pharmacodynamic properties of ABD-fusion proteins have been demonstrated in vivo. The Albumod[™] technology has been optimized for human use, through extensive engineering to remove potential immunogenic epitopes. Successful deimmunization was confirmed in a CD4⁺ T-cell proliferation assay. The lead ABD variant is in development for clinical use.

P09 Targeting Schizophrenia: Direct Animal Studies of Neurotensin(8-13) Peptidomimetics

Noam S. Freeman^a, Gilia Melendez^b, David Feifel^b, Yitzhak Tor^a.

^aDepartment of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0358, USA; ^bDepartment of Psychiatry, University of California, San Diego Medical Center, 200 West Arbor Drive, San Diego, CA 92103-8218 USA

Neurotensin (NT) is a tridecapeptide (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-OH) neurotransmitter found in the central nervous system (CNS) and in the gastrointestinal tract. Interest in NT as a possible antipsychotic arose in the 1980s when it was found that NT is produced and released from the same brain cells that contain dopamine. To date, it has been suggested that a NT agonist can be a potential therapeutic for treatment of multiple CNS disorders including schizophrenia, Parkinson's disease, pain and drug abuse as well as for blood pressure, eating disorders, obesity, cancer, neurodegenerative disorders and inflammation. NT and NT(8-13), the minimal structural sequence required for displaying its full biological activity, are readily degraded in the gastrointestinal system and the blood and do not effectively cross the blood brain barrier (BBB). Countless attempts to identify NT(8-13) peptidomimetic agonists as drug leads have met little success due to inconsistency between receptor binding affinity and biological activity and to the inability of most compounds to cross the BBB. We present a direct in-vivo SAR approach to identify potential drug leads by specifically screening for the desired antipsychotic effect. Peptidomimetics of NT(8-13) were evaluated in rodents after peripheral injection by two independent assays indicative of NTR1 receptor activation: 1) The desired antipsychotic activity of the compounds was evaluated by their potency in reversing the prepulse inhibition of startle reflex deficits; 2) The ability of the compounds to reduce core body temperature. This approach has led to the discovery of a novel, highly potent and long lasting orally bioavailable NT(8-13) peptidomimetic.

P10 Design and Synthesis of Novel Ligands for the Treatment of Pain

Aswini Kumar Giri¹, Srinivas Deekonda¹, Todd W. Vanderah², Frank Porreca², Victor J. Hruby¹

¹Departments of Chemistry and Biochemistry, ²Department of Pharmacology, University of Arizona, Tucson, AZ 85721 USA

The management of pain, mainly sustained and neuropathic pain, is a major challenge and millions of people all over the world suffer from such kind of pain every day. Opioids continue to be the backbone for the treatment of these pain states. However, constant opioid treatment is accompanied with serious undesirable effects including drowsiness and mental clouding, nausea and emesis, and constipation. Sustained use of opioid therapy also develops analgesic tolerance in many patients. These unwanted effects significantly diminish the patients' quality of life.

Opioids, which activate MOR and DOR, have been found to be more effective as analgesics than those activating only MOR or DOR. Promising analgesic effects have also been observed when NK-1 antagonist activity is introduced with the opioid activities. In this poster, we will be discussing some of our designing principles, synthesis of few selective novel ligands along with their in vitro biological profiles.

P11 Novel Treatment for Bacterial Sepsis-Augmented Passive Immunotherapy

¹Gore, S.; ^{1,2}Bangert, M.; ³Rajam, G.; ³Ades, E.W.; ²Gordon, S.B.; ¹Kadioglu, A.

¹Institute of Infection and Global Health, University of Liverpool, UK; ²Respiratory Infection Group, Liverpool School of Tropical Medicine, UK; ³Division of Bacterial Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333 USA

Antibacterial resistance is increasing and with the pipeline for new antibiotics drying up, novel therapeutic strategies are needed for the treatment of severe bacterial infections. One strategy that has shown much promise against *Streptococcus pneumoniae* infection is P4 peptide therapy (Bangert et al., *J. Infect. Dis.* 2012;205(9):1399-407). The administration of the P4 peptide results in the increased expression of Fcγ receptors on phagocytic cells. When coupled with IVIG (pooled human IgG) this leads to a significant increase in opsonophagocytosis of the pathogen. In animal models of pneumococcal pneumonia, treatment with P4 peptide therapy resulted in increased survival during invasive pneumococcal pneumonia and prevention of the development of sepsis. IVIG is assumed to contain the entire panoply of anti-pathogen antibodies which, in theory, would make P4 therapy an immensely broad-spectrum therapeutic. This project goes on to look at the efficacy of P4 treatment against Gram-negative infections, namely *E. coli* and *Klebsiella pneumoniae*, as well as the pharmacokinetics and pharmacodynamics of P4 therapy.

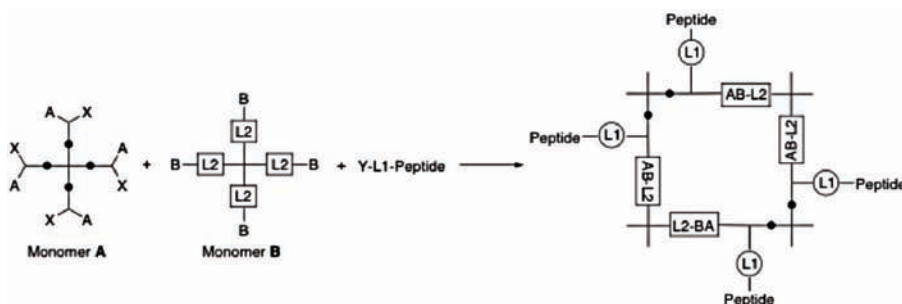
Animal infection models will then be used to ascertain whether any enhancement in phagocytosis translates to improved survival during a disseminating *E. coli* peritonitis model.

The P4 peptide has already shown much promise in the treatment of pneumococcal infections and has the potential to become an essential tool in the treatment of severe infections especially where a diagnosis has not yet been confirmed.

P12 An Optimized Hydrogel Offers Tunable Half-life Extension for Peptides and Proteins

Jeff Henise, Brian R. Hearn, Louise Robinson, Gary W. Ashley, and Daniel V. Santi
ProLynx LLC, San Francisco, CA 94158 USA

We recently reported a first-generation Tetra-PEG hydrogel system for peptide half-life extension. Our strategy involves using two β-eliminative linkers having distinct and predictable elimination rates. One cleavable linker is used to covalently tether a peptide drug to the hydrogel allowing release of the native peptide with a tunable half-life, and the second linker, having a slower cleavage rate, is used to crosslink the hydrogel. The synthesis of these hydrogel-peptide conjugates involves attaching the drug to an average of four arms of an 8-arm PEG monomer; the remaining arms are crosslinked with a 4-arm PEG to form a hydrogel. Because of the random drug coupling and crosslinking, the first-generation gels contain significant heterogeneities and entanglements contributing to the premature release of PEG-drug fragments upon biodegradation. In the present work, we describe the synthesis and properties of a second-generation hydrogel in which exactly 4 arms of each PEG monomer are crosslinked to form a more-ideal Tetra-PEG diamond lattice, with improved degradation kinetics. We report variations on this approach to hydrogel-peptide conjugates and describe peptide release and degradation properties of such gels.



Second-generation hydrogel-peptide conjugates. Monomer A contains eight end-groups: four X end-groups, that couple with Y groups for peptide attachment and four A end-groups that react with the B groups of monomer B to form polymer crosslinks. The hydrogel formed on mixing these three components has cleavable L1 groups to control release of the peptide drug and cleavable L2 linkers that control gel degradation. All couplings used biorthogonal reactions.

P13 Directed Evolution of High Affinity, Cyclic, Protease Resistant Peptides Using mRNA Display

Shannon Howell, Stephen Fiacco, Richard Roberts, Terry Takahashi, Lan Huong Lai
University of Southern California, Los Angeles, CA 90089 USA

Short peptides constructed with the 20 natural amino acids are generally considered to have little therapeutic potential because they are unstable to proteolysis and devoid of regular secondary structure. However, proteolysis sites are often idiosyncratic arguing that there may be sequences that are highly resistant to cleavage. Here, we have explored this idea in the context of peptides that bind to the signaling protein Gia1. To do this, we used a two-step *in vitro* selection process—degradation of the starting library with protease (chymotrypsin), followed by positive selection for binding via mRNA display. These experiments resulted in a series of peptides with >100 fold increase in protease resistance compared to the parental library. Surprisingly, selection for chymotrypsin resistance also resulted in similarly improved stability in human serum (~100 fold) and enabled an *in vivo* half-life of ~15 minutes in the mouse. Mechanistically, the decreases in cleavage result from both a lower rate of cleavage (k_{cat}) and weaker interaction with the enzyme (K_m). One origin of these changes appears to be folding, as the molecules show both a remarkable level of secondary structure in free solution and excellent binding affinity ($K_d \sim 8$ nM) given their small size of twelve amino acids. Overall, our results demonstrate that the hydrolytic stability of natural peptide sequences can be readily improved by two orders of magnitude simply by optimizing the primary sequence by directed evolution.

P14 Evaluation and Performance comparison of new Core-Shell Media vs. Fully Porous Media for Preparative Purifications

Marc Jacob, Wayne Daneker, JT Presley III, Simon Lomas and Jeff Layne
Phenomenex, Inc., 411 Madrid Avenue, Torrance, CA 90501 USA

High performance HPLC/UHPLC core-shell material is the latest technological advancement in chromatographic media. When used under analytical conditions, core-shell particles show improved efficiency and performance over fully porous particles of equivalent particle size.

With the recent commercialization of a low pressure 5 μ m core-shell media, it is now possible to offer core-shell media in a preparative format (>20 mm ID) that's compatible with standard prep LC systems.

In this poster, we will demonstrate that this new 5 μ m core-shell particle size, available in a variety of bonded phases, can be packed efficiently in a preparative format with internal diameter greater than 2 centimeters. Additionally, we will highlight the advantage of such product and discuss applications that are pertinent for small scale drug discovery and peptide purification.

P15 HPLC Enantioseparation of N-Fluorenylmethoxycarbonyl α -Amino Acids Using Polysaccharide Based Chiral Stationary Phase Under Reversed Phase Mode

L. Peng, M. Jacob, B. Wayne Daneker and T. Farkas
Phenomenex, Inc., 411 Madrid Avenue, Torrance, CA 90501 USA

N-Fluorenylmethoxycarbonyl (Fmoc) α -amino acids are important building blocks for the solid phase synthesis of peptides.¹ After the development of Fmoc/tBu strategy² for solid phase peptide syntheses, Fmoc α -amino acids have become the raw materials of choice for the preparation of synthetic peptides.

Using this methodology, long peptides (up to 100 amino acids residues) can be prepared in a few days with high yield from micro molar (mg) up to molar scale (kg). As the number of amino acids residues increases the final purity and overall yield of the peptide produced is directly affected by the chemical and chiral purity of the protected amino acids used.

Currently, for the most common commercially available Fmoc protected α -amino acids, the expected enantiomeric purity is > 99.0% enantiomeric excess (ee) for the L form and sometimes the purity required must be \geq 99.8% ee. This level of precision can only be achieved by very few analytical techniques, chiral HPLC being one of them. The main advantages of chiral HPLC analysis over other techniques are speed, detection level and ease of use. HPLC is also used on a regular basis by the peptide chemists to analyze purified fractions as well as peptide purity.

In this presentation, we will report the chiral separation of the most common 19 Fmoc protected α -amino acids derivatives under reversed phase separation mode using polysaccharide-based chiral stationary phases.³ All Fmoc α -amino acids analyzed in this study are baseline resolved with an analysis time below 25 min in isocratic conditions. The order of elution as well as the enantiomer identification are also reported.

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P16 Protein Interactions as Drug Targets: a Combined Computational and Experimental Approach

Joan Teyra, Satra Nim, Jouhyun Jeon and Philip M. Kim
The Donnelly Centre, University of Toronto, Toronto, ON, Canada

Protein interactions and their networks have been at the focus of recent biomedical science. In particular, there is growing interest in targeting protein interactions with future therapeutic agents. I will outline our efforts to combine advances in structure modeling, machine learning and state-of-the-art combinatorial chemistry to target protein interactions using synthetic peptides. Our integrated pipeline covers everything from the identification of particular protein interactions important in different cancer types to the validation of candidate compounds *in vivo*. Specifically, we first utilize modern machine learning techniques to integrate a large variety of cancer genomic datasets to identify suitable drug targets. We then use structural modeling to find the subset of targets that can be inhibited using peptides. Using peptide phage display, we obtain high-affinity binders that inhibit the protein-protein interaction in question. Finally, we use lenti-viral delivery to verify the efficacy of our peptides in cell lines. Thus far, we have obtained peptide binders for about a hundred high-value protein domains.

P17 Targeted Ablation of Adipocyte Progenitors with Peptides Derived from a Combinatorial Library

Mikhail Kolonin, Alexes Daquinag, Chieh Tseng, Ahmad Salameh, University of Texas, Houston, TX 77030 USA

There is a lack of effective pharmacological treatments against obesity, a risk and complicating factor for a number of life-threatening diseases. Overgrowth of white adipose tissue (WAT), hallmarking obesity, relies on proliferation and differentiation of adipose stromal/stem cells (ASC). By merging phage display technology with fluorescence activated cell sorting (FACS), we screened a combinatorial library for peptides that target mouse ASC *in vivo* and isolated peptide CSWKYWFGE that specifically homes to ASC. We used this peptide as bait to purify the corresponding ASC surface receptor: a previously unreported cleavage product of decorin (termed Δ DCN), which is differentially expressed on ASC surface. Here we hypothesized that inactivation of adipocyte progenitors could be used to prevent WAT expansion. We have used the CSWKYWFGE peptide to induce adipocyte progenitor apoptosis in the mouse diet-induced obesity model. Targeted adipocyte progenitor cytoablation was sustained upon treatment discontinuation and resulted in compromised WAT expansion despite increased food consumption. Our findings introduce a new approach to obesity intervention.



P18 Hypothesized Mechanism of Action for the Pulmonary Hypertensive Homing Peptide CARSKNKDC (CAR)

Mann D¹, Scheenstra J¹, Rothman A²

¹Vascular BioSciences, Goleta, CA, ²Children's Heart Center Nevada, Las Vegas, NV 89109 USA

Recent experiments^{1,2} have demonstrated the ability of the pulmonary hypertensive homing, cellpenetrating peptide CARSKNKDC (CAR) to enhance the effects of co-administered vasodilators (fasudil, Y-27632, imatimib, and sildenafil) in selectively lowering pulmonary pressure in animal models of pulmonary arterial hypertension (PAH). Here we provide a hypothesis for CAR's mechanism of action.

In previous experiments, cell-surface heparan sulfate (HS) was shown to be necessary for both CAR binding and internalization³. When treated with heparinase I and III, binding of CAR to Chinese hamster ovary cells was greatly reduced. This suggested that CAR's specific binding and internalization is mediated by the presence of HS moieties on the surface of the target cell.

One possible mechanism by which CAR could facilitate the selective uptake of co-administered drugs is through heparan sulfate-mediated macropinocytosis. Macropinocytosis is a non-clathrin, non-caveolin, lipid raft-dependent form of endocytosis that allows for the regulated internalization of extracellular solute molecules. Studies have described the role of heparan sulfate as the receptor for lipid raft-dependent macropinocytotic internalization⁴, and macropinocytosis has also been shown to underly the internalization of other cationic cell-penetrating peptides^{5,6,7}. Heparan sulfate mediated macropinocytosis could explain CAR's ability to increase the localized concentration of co-administered drugs without requiring the drugs to be conjugated to CAR.

We hypothesize that heparan sulfate-mediated macropinocytosis could be a plausible mechanism by which CAR binding could promote the internalization of co-administered compounds. Experiments are currently underway to test these hypotheses, while CAR is being developed as a therapeutic adjuvant for PAH.

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P19 Cardioprotective Actions of Recombinant Annexin A-1 Peptide Analogs

Nozer Mehta¹, Jesmond Dalli², Angelo Consalvo¹, Mauro Perretti²

¹Enteris BioPharma, Boonton, New Jersey, USA; ²Queen Mary University of London, UK

Annexin A1 (AnxA1), a 37-kDa glucocorticoid regulated protein, possesses anti-inflammatory and proresolving actions reducing human and murine neutrophil–endothelial interactions, accelerating neutrophil apoptosis, stimulating macrophage efferocytosis and neuroprotection. These homeostatic functions of AnxA1 are mediated by formyl peptide receptor 2/Lipoxin A4 receptor (FPR2/ALX). Upon calcium binding, AnxA1 undergoes conformational change with exposure of the N-terminal domain. The anti-inflammatory response is limited by neutrophil-derived serine proteases, such as elastase (HNE) and proteinase 3 (PR3), which cleave the N-terminal region. Peptides modeled on the N-terminal sequence of AnxA1 possess anti-inflammatory properties in murine models of inflammation and ischemia/reperfusion injury.

We assessed the cleavage of Annexin A1 derived peptides that span the full N-terminal region along with an amide group at the C-terminus [AnxA1(2–50)NH₂], which increased the potency of the peptides. In vitro digests with HNE and PR3 demonstrated that cleavage at the C-terminal side of Val25 was prominent and a common recognition site for both enzymes. This is a variance from full length AnxA1, which in similar experimental settings is cleaved at positions 11, 22, and 36. Substitution of Val25 with leucine [Leu25-AnxA1(2–50)NH₂] conferred greater resistance to HNE and PR3, and higher stability to digestion by activated human neutrophils. Cleavage at a second valine residue at position 48 by HNE and PR3 was also shown to be significant, and hence peptide AnxA1(2–48)NH₂ was also tested. All three peptides were recombinantly expressed in *E. coli* and enzymatically amidated. In a murine model of myocardial ischemia/reperfusion injury, all three peptide analogs potently attenuated myocardial damage as demonstrated by reduced necrotic tissue and circulating Troponin I. These actions were coupled with a reduction in systemic inflammatory markers. When Leu25-AnxA1(2–50)NH₂ was administered 1 h following reperfusion, it afforded a potent cardioprotective action and marked reduction in 24-h mortality. Further pre-clinical and clinical development of these stable N-terminal peptide analogs is ongoing.

P20 Sulfone Reagents for Generating Thiol Conjugates with Improved Serum Stability

James T. Patterson, Shigehiro Asano, Narihiro Toda, and Carlos F. Barbas, III

Departments of Chemistry and Cell & Molecular Biology, The Scripps Research Institute, 10550 N. Torrey Pines Rd., La Jolla, CA 92037 USA

Conjugation strategies dictate factors such as loading and stability which can greatly influence therapeutic outcomes. We recently synthesized a panel of hetero aryl methylsulfone derivatives to compare their reactivity with thiols to standard maleimide conjugation. Such maleimide-thiol linkages are susceptible to non-specific hydrolysis as well as thioether exchange with free cysteine, glutathione, and the serum protein albumin. Methylsulfonyl phenyloxadiazole compounds proved to be highly reactive under a variety of conditions allowing for conjugation with cysteine. Furthermore, the half-life of benzothiazole and phenyloxadiazole sulfone conjugates were at least doubled relative to maleimide conjugates in human serum. The application of our sulfone labeling chemistry to peptides/proteins is thus a viable route for making conjugates with improved serum stability.



P21 Improved PK Properties of Albumin Fusion Proteins Through the Modulation of FcRn Mediated Recycling

Mark Perkins and Randall Engler, Novozymes Biopharma, Castle Court, 59 Castle Boulevard, Nottingham, UK

The attachment of a therapeutic molecule to recombinant human albumin is becoming an increasingly attractive half-life extension strategy for biological drugs. This approach seeks to combine the naturally long plasma half-life of human albumin with the therapeutic effect of the peptide or protein. This technology has been employed with a diverse range of molecules that are currently undergoing clinical development, with the most advanced being GSK's Abiglutide. In general the pharmacokinetic properties of an albumin fusion or conjugate are dominated by the albumin part of the construct. Therefore, the ability to modulate the pharmacokinetic properties of the albumin component will have distinct advantages both in terms of expanding the dosing regimens possible with albumin therapeutics (two weekly and monthly) and allowing greater control of dose.

The *in vivo* half-life of human albumin is modulated by the FcRn receptor. Through protein engineering we have developed a range of human albumin variants with modified binding to the FcRn Receptor. The result is series of albumin variants with both increased and decreased plasma half-life, compared to the native albumin molecule. Here we present data that explores the pharmacokinetic properties of these albumin variants in both wild-type and transgenic mouse models. In addition, the application of these variants to controlling the half-life of model and therapeutic proteins will be discussed.

P22 Self-administered Long-acting Octreotide Conjugates

Eric Schneider, Gary Ashley, Ralph Reid, Daniel Santi
ProLynx LLC, San Francisco, CA 94158 USA

Three synthetic peptidic Somatostatin agonists — Octreotide, Lanreotide and Pasireotide — are approved by the FDA to treat one or more of the following: Gastroenteropancreatic Neuroendocrine Tumors, acromegaly, and Cushing's disease. Because the half-lives of the agonists are short (i.e. hours) and require twice daily injections, each has been formulated as a long-acting release (LAR) form that is administered once every 4 weeks. However, the LAR forms suffer certain deficiencies. A) They all require painful intra-gluteal i.m. (Octreotide, Pasireotide) or “deep” s.c. injection (Lanreotide) using a large bore needle, requiring or usually administered by a health professional. B) Octreotide LAR and Pasireotide LAR show a burst-effect that may contribute to certain adverse events; C) in PLGA formulations, octreotide drug is extensively N-acylated by components of the polymer; and D) there is significant “wasted” AUC that could contribute to certain adverse events.

Here, we describe a releasable PEG-Octreotide conjugate using b-eliminative releasable linkers that A) can be self-administered s.c. by the patient once a week; B) administered through a small gauge needle, C) shows no burst effect; D) shows a low C_{max} and flat C vs t profile with little “wasted” AUC. Simulations indicate that use of an analogous s.c. Tetra-PEG hydrogel carrier could provide formulations that require once every two week or monthly administrations. Overall, these conjugates should be more economical and time-saving thus leading to increased compliance and decreased adverse side effects associated with initial burst and high C_{max} effects.

P23 NextGen Venomics: Natural, Virtual and Synthetic Venoms for Peptide Drug Discovery, Target Deorphanization and Lead Optimization

Reto Stöcklin, Atheris Laboratories, Case postale 314, CH-1233 Bernex-Geneva, Switzerland

The animal kingdom includes 200'000 venomous species that developed over several hundred million years of evolution. Each venom typically consist of a unique cocktail of hundreds different molecules, mostly highly potent and selective bioactive ingredients falling within the class of well-structured medium-sized peptides. They are a proven source for screening pharmaceutical targets that are difficult to address using standard medicinal chemistry approaches such as ion channels, transmembrane or circulating proteins. Dozens of venom-derived mini-protein drug candidates have been taken into drug development and six of these made it to clinical use.

Usually, the first step in the search for new compounds is a bioassay, which is followed by a deconvolution process leading to isolation and characterization of the bioactive substance. Today, the "Venomics" strategy that we pioneered combines state-of-the-art peptide synthesis, proteomics, transcriptomics and post-genomics technologies with specialized bioinformatics tools. This generates an abundance of valuable data in a very short period of time and using much smaller amounts of natural products.

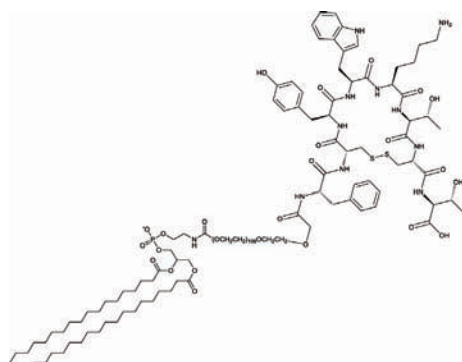
We will present an innovative NextGen Venomics platform that is aimed at providing access to yet impossible to explore samples in an unprecedented manner through a combination of natural, synthetic and virtual venoms:

- Pre-fractionation of venoms to produce libraries of **natural venoms** for HTS
- Massive venom gland NextGen mRNA sequencing
- Bioinformatics to extract sequences and produce the **first virtual venoms**
- Original software to streamline the transcriptomics-assisted deconvolution process
- An integrated in silico platform to screen virtual venoms and design optimized leads
- Large-scale multiplex synthesis of peptides as **first synthetic venoms libraries**

P24 Manufacture of a Peptide Conjugate for the Targeted Delivery of Chemotherapeutic Agents in Liposomes

Daniel R. Studelska, Zhiyong Tao, Miranda Steele, James R. Wheatley, Eric A. Burge, Debbie Brame, Claire E. Brook, Alex Micka, Christie Belles, Todd Osiek
Mallinckrodt Pharmaceuticals, St. Louis, MO 63042 USA

Tyr³-Octreotate binds the SSTR2 receptor, overexpressed in some neuroendocrine cancers. DSPE-PEG₅₀₀₀ conjugation to Tyr³-Octreotate enables the decoration of liposomes with this targeting moiety. Tyr³-Octreotate has an N-terminal and lysine amine available for conjugation with DSPE-PEG₅₀₀₀-NHS. The amine on lysine is important for the binding of the peptide to the SSTR2 receptor and needs to be protected during conjugation. We developed a successful method using ivDde for protection of the lysine side-chain enabling correct solution phase conjugation with the peptide N-terminus. We describe the solid phase synthesis of cyclic ^{2,7} Tyr³ Lys(ivDde)-Octreotate, its solution phase conjugation with DSPE-PEG₅₀₀₀ and the removal of the ivDde protecting group from the lysine. The major DSPE-PEG₅₀₀₀-NHS peak is consumed during solution phase conjugation. Removal of ivDde from the lysine of DSPE-PEG₅₀₀₀-Tyr³ Lys(ivDde)-Octreotate by 1% hydrazine/DMF requires nucleophilic attack; unchecked, the deprotection proceeds to cleave lipid from the desired product. Lysine protection of Tyr³-Octreotate by ivDde efficiently directs conjugation of DSPE-PEG₅₀₀₀-NHS to the N-terminus of the peptide. Analytical monitoring during solution phase conjugation and ivDde removal by hydrazine entails reverse phase chromatography. Conjugates cannot be eluted from C18 columns with acetonitrile. They require at least the eluent strength of IPA/MeOH. The LC-MS assay to determine N-terminal or side-chain functionalization of Tyr³-Octreotate by DSPE-PEG₅₀₀₀ is presented.





P25 Adapter Molecules for Protein Site Specific Dye Labeling

Darren A. Thompson, Eric G.B. Evans, Tomas Kasza, Glenn L. Millhauser, and Philip E. Dawson
The Scripps Research Institute, La Jolla, CA 92037 USA

Chemoselective protein labeling remains a significant challenge in chemical biology. Although many selective labeling chemistries have been reported, the details of matching the reaction with appropriately functionalized proteins and labeling reagents is often a challenge. Here we have site specifically labeled the cellular form of the Prion protein with a fluorescent dye under mild non-denaturing buffer conditions at near neutral pH through ketoxime conjugation. To facilitate this labeling, a protein was expressed with site specific acetylphenylalanine and conjugated to commercially available maleimido-fluorophores mediated by a water soluble adapter molecule. A general strategy for the efficient solid phase synthesis of adapter molecules capable of converting maleimido-labels into aminooxy or azide functional groups and their application to protein and peptide labeling is presented.

P26 Making Orally Administered Chimeric Antimicrobial Peptides (ChAMPs) with Antiviral Properties

Eng Huan Ung, BioValence Sendirian Berhad, Selangor, Malaysia

RetroMAD1 is a unique 'proof-of-concept' Chimeric Antimicrobial Peptide (ChAMP) that is designed for oral administration as a naked protein. It can withstand proteolytic activity with Pepsin at pH2 and Trypsin at pH8 and detectable by ELISA in the serum of mice fed RetroMAD1 within 30 minutes post-oral-gavage. It retains full bioactivity even after exposure to 70C for 15minutes followed by 55C for another 45minutes in a thermocycler. Using 'Super-Critical-Fluid-Drying' a free-flowing micronized powder may be formed that retains antiviral activity. For Dengue Virus, RetroMAD1 completely inhibited the NS2B-NS3 serine endo-protease at 20 μ M at 37C and 10 μ M at 40C. The IC50 value of 4.99 μ M and Ki value of 2.49 μ M were superior to results reported for other peptide drugs published in 2011-2012. RetroMAD1 significantly reduces viral titers in all 4 serotypes of Dengue as well as in HSV1 and HSV2 in Vero cells confirmed by Real Time PCR. Multi-centre Vet administered trials involving over 200 client-pets in Malaysia, Singapore and the Philippines gave promising results for FIV and FeLV in cats and CPV2 in puppies. Aquarium studies with 3 species of shrimp against 3 different unrelated viruses (MBV, HPV and WSSV) also showed broad-spectrum antiviral activity. Asian Seabass fingerling fishes infected with VNN gave 78% survival 4-weeks post challenge when fed RetroMAD1 and an adjuvant while the untreated control fishes all died by day 6. Experimental monkeys infected with Simian Rotavirus A also showed markedly increased survivorship when treated with RetroMAD1.

P27 Peptidic Antagonists to Target Dysregulated Wnt Signaling in Cancer

Jörg Vollmer, Nexigen GmbH, Nattermannallee 1, 50829 Cologne, Germany

The intracellular Wnt pathway is often mutated in cancer and in cancer stem cells that are responsible for treatment resistance. Although generally recognised as high-potential target for treatment of many tumors, thus far direct targeting of Wnt signaling has been difficult also owing to the lack of druggable pathway-specific targets. Intracellular cell-permeable peptide modulators targeting the Wnt pathway were identified by using our proprietary next generation peptide screening platform in living eukaryotic cells. This screening system has been tested successfully with various protein classes, like transcription factors, kinases, and multifunctional proteins. The most advanced peptide candidate demonstrates strong inhibition of cellular phenotypes, which are characteristic for the Wnt-pathway, like inhibition of migration, proliferation, or colony formation *in vitro* and *ex vivo*. In *in vivo* tumor models significant inhibition of tumor growth is observed. Our data support that Nexigen's platform delivers cell-permeable peptides with target-specific activity and *in vivo* anti-tumor efficacy upon systemic exposure.

P28 Human type N-glycan Conjugation to Therapeutic Peptides and Proteins

Naoki Yamamoto, GlyTech, Inc. Kyoto, JP

GlyTech, Inc. has been focusing on human type asparagine linked glycans (N-glycans), and has established a large-scale manufacturing process to prepare highly purified and characterized human type N-glycan libraries. Furthermore, GlyTech has developed glycosylation technologies which can be applied for not only producing homogeneous glycoproteins, but also creating value-added glycopeptide/glycoprotein therapeutics. For example, attaching several glycans to peptides and proteins leads to generation of homogeneous glycopeptides and glycoproteins with optimized glycan structures at desired glycosylation positions. GlyTech is now offering custom synthesis services of glycosylated compounds and contract research & development services, and also developing own pipelines including several therapeutic glycopeptide/glycoprotein candidates. Through this poster presentation, GlyTech's platform technologies and recent progresses will be introduced.

P29 Optimization of Single-chain Insulin Folding with Demonstrated Superiority of B28-A1 Analogs

A.N. Zaykov, J. P. Mayer and R.D. DiMarchi

Indiana University, Department of Chemistry, Bloomington, IN 47405 USA

The chemical synthesis of insulin presents a long-standing challenge due to the difficulties involved in the assembly of its primary sequence and native disulfide bond formation. Insulin contains three disulfides and formation of the correct pattern is critical to achieving high potency, and is well-documented to be problematic. Two general strategies in chemical synthesis have emerged. A two-chain combination method based on chemically-directed disulfide bond formation and a single-chain insulin (SCI) method where the disulfide bonds are formed under equilibrium and directed conditions have been reported. The SCI method is more physiological where insulin folding is assisted by a C-peptide, much like proinsulin. Several SCI analogues with various connecting peptides have been developed but with limited emphasis on the efficiency in folding.

Insulin structure reveals close proximity of Gly^{A1} to the C-terminus of B-chain, making direct amide bond formation a driving force for correct folding. In this work we explored the folding efficiency of SCI analogs where the A-chain Gly^{A1} was linked to B-chains of variable, shortened length. We observed high sensitivity in SCI folding dependent upon the specific position of the connection, with B28 and 29 as the only two sites that demonstrated efficient folding. In a comparative sense B28-A1 analogs exhibited superior folding efficiency with higher tolerance to the changes around B-chain terminus. An enzymatic cleavage site was installed at the fusion site to enable conversion to two-chain hormones. In conclusion, we show that SCIs with amide bond linkage between residues B28 and Gly^{A1} are easily folded to native insulin structure and enzymatically converted to biologically active peptides.

