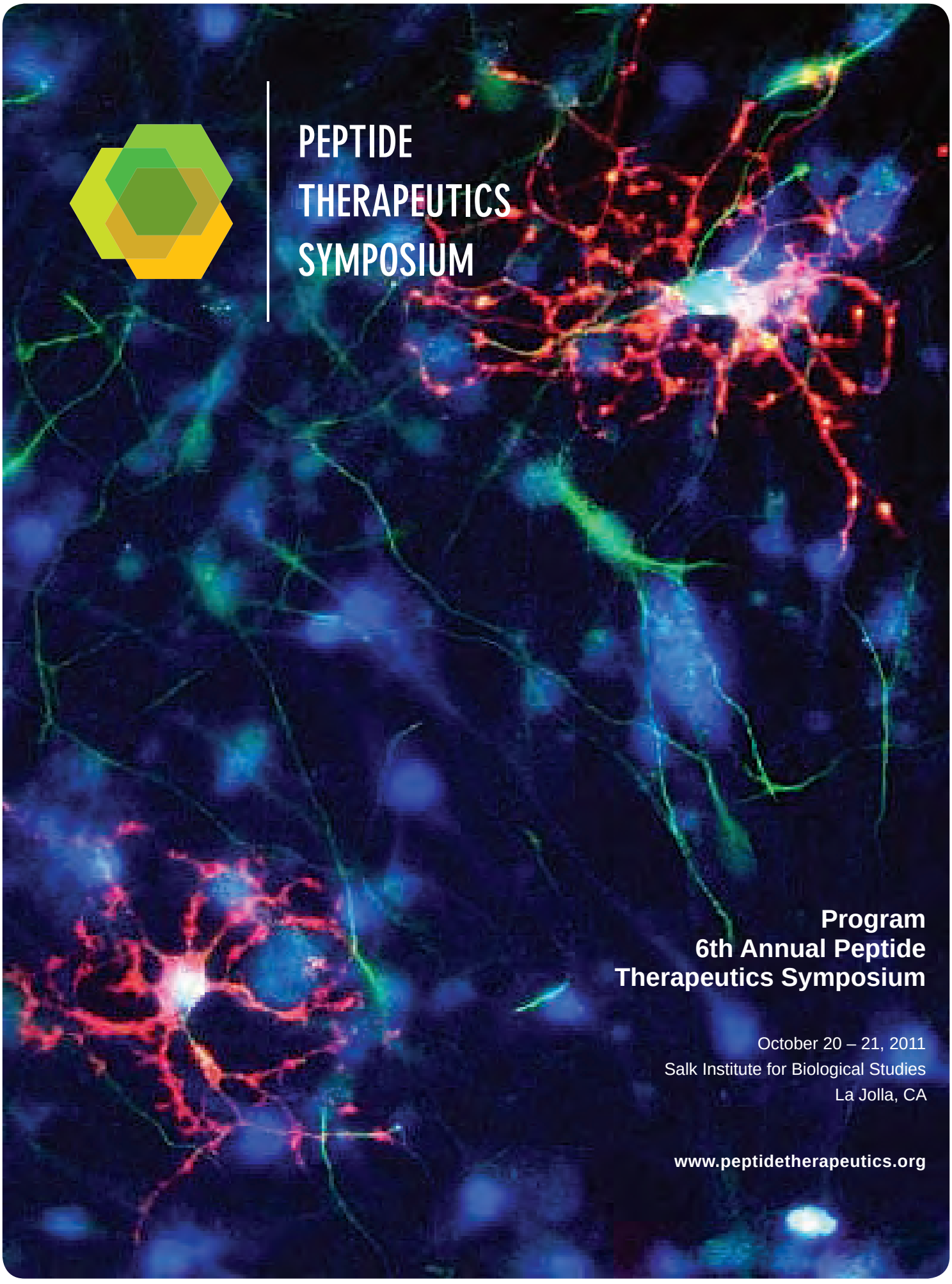
PEPTIDE
THERAPEUTICS
SYMPOSIUM
Program
6th Annual Peptide
Therapeutics Symposium
October 20 – 21, 2011
Salk Institute for Biological Studies
La Jolla, CA
www.peptidetherapeutics.org

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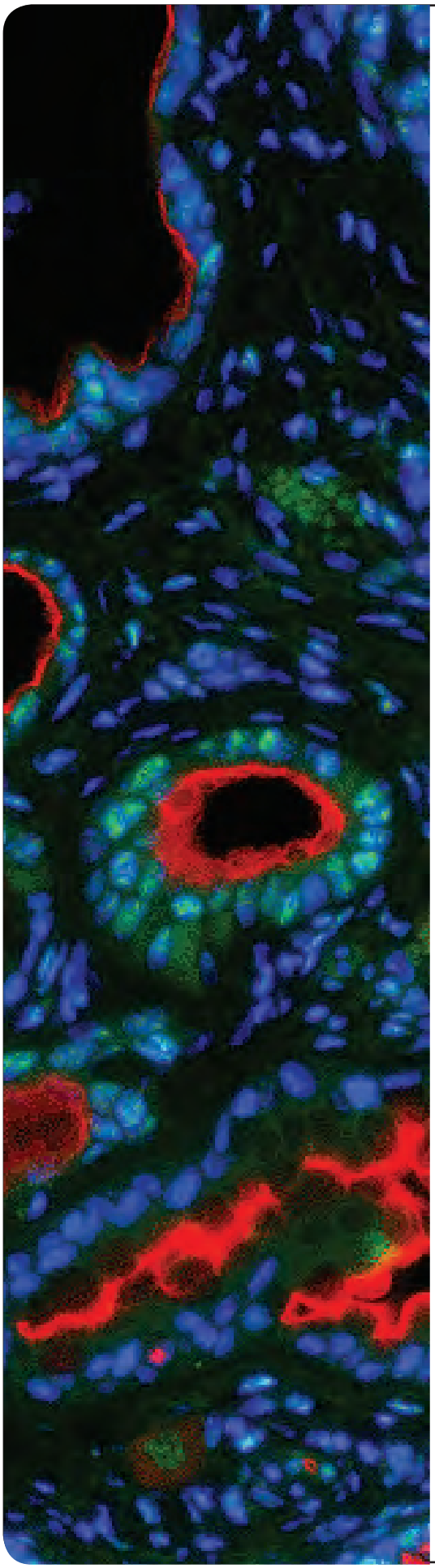
Symposium Sponsors



Dear Colleagues,

Welcome to the 6th Annual Peptide Therapeutics Symposium. We are delighted that you are able to join us for another stimulating meeting dedicated to the research and development of peptide therapeutics and technologies.

This year's program highlights the transition from basic to applied science, from drug discovery to clinical development focusing on the most promising advances within the peptide field.

The meeting begins with a session on *Novel Peptide Therapeutics*, followed by a panel discussion on *What's Driving R&D Today?* We have expanded the program this year by introducing a Poster Session to coincide with the Opening Reception. Please take the time to browse through the posters as you enjoy the company of colleagues and friends.

On Friday morning, the program begins with a keynote address by Peter Schultz and a plenary lecture by William Pardridge addressing exciting new frontiers in peptide research. In the afternoon, lectures and discussions on the latest advances in *Discovery Pharmacology*; *Peptide Transport*; and *Novel Peptide Therapeutics* will conclude the program.

Enjoy the program, poster session, lectures, and the opportunity to network with your peers.

With kind regards,

Richard DiMarchi and Pierre Rivière
On behalf of Peptide Therapeutics Foundation

Sponsors, Peptide Therapeutics Foundation
Amylin Pharmaceuticals
CovX
Ferring Research Institute
Ipsen
PolyPeptide Group
Roche
Zydus Cadila

Photo courtesy of the laboratory of Pamela Itkin-Ansari, Ph.D., Adjunct Assistant Professor, Sanford-Burnham Medical Research Institute/UCSD, La Jolla, CA

Amylin Pharmaceuticals

Amylin Pharmaceuticals is a biopharmaceutical company committed to improving lives through the discovery, development and commercialization of innovative medicines. Amylin has developed and gained approval for two first-in-class medicines for diabetes, SYMLIN® (pramlintide acetate) injection and BYETTA® (exenatide) injection. Amylin's research and development activities leverage the Company's expertise in metabolism to develop potential therapies to treat diabetes and obesity. Amylin is headquartered in San Diego, California. Further information about Amylin Pharmaceuticals is available at www.amylin.com.

CovX

CovX San Diego is one of the Biotech Research Units within Pfizer Worldwide Research & Development. There are R&D sites across the United States, as well as Europe and Asia. CovX contributes to Pfizer's biotherapeutic portfolio by concentrating on the development of novel biotherapeutic conjugates, known as CovX-Bodies. The highly flexible nature of the technology used to efficiently create CovX-Bodies also enables CovX scientists to identify high-value biological targets and to expeditiously move candidates to pre-clinical development and clinical evaluation.

Collaborating with other Pfizer sites, CovX scientists combine skills in peptide screening and optimization with state-of-the-art bioconjugation capabilities to provide therapies tailor made for therapeutic areas such as oncology and metabolic disease. Continuing innovation on the part of the approximately 85 scientists and staff has provided multiple new platforms that can be further exploited specifically for bifunctional/multifunctional capability. Since being acquired by Pfizer in 2008, CovX has progressed several molecules into clinical phases of development including CVX-060, an antiangiogenesis agent for cancer into Phase Ib/II trials; CVX-096, a drug for the treatment of diabetes into Phase I; and a novel bifunctional for solid tumors (CVX-241) into Phase I.

Ferring Pharmaceuticals

Ferring Pharmaceuticals (Ferring) is a research-driven, specialty biopharmaceutical company focused on peptides and proteins therapeutics. The company identifies, develops and markets innovative products in the areas of reproductive health, urology, gastroenterology and endocrinology. The company headquartered in Saint-Prex (Switzerland), employs over 3,700 people worldwide, operates subsidiaries in around 50 countries and markets its products in more than 70 countries. Ferring's key products include MINIRIN/DDAVP, PENTASA and MENOPUR. The company's R&D centers are located in Saint-Prex (Switzerland), Copenhagen (Denmark), Mumbai (India), Beer Tuvia (Israel), San Diego and Parsippany (United States) and Tokyo (Japan).

The Ferring Research Institute, Inc. (FRI) was established in San Diego in 1996 as the company's center of excellence for peptide research. Building upon the company's long standing tradition in peptides and "medicines on the body's own terms", FRI has developed a unique expertise in modifying naturally-occurring peptide/hormones to design peptide therapeutics with improved pharmacodynamics, pharmacokinetics and pharmaceutical properties. This has lead in recent years to the discovery of a number of innovative peptidic new chemical entities (NCEs) now at various stages of development, either in house or externally. As a result, Ferring today has the largest portfolio and pipeline of peptide therapeutics.

To learn more about Ferring, its research projects or its products please visit www.ferring.com and http://ferring-research.com.

Ipsen

Ipsen is a global biopharmaceutical group, with sales exceeding €1 billion in 2009. The Group has total worldwide staff of more than 4,400 employees, close to 900 of which contribute to the discovery and development of innovative drugs for patient care. Ipsen's development strategy is based on fast growing specialty care drugs in oncology, endocrinology, neurology and hematology, and on primary care drugs. This strategy is supported by an active policy of partnerships. Ipsen's research & development (R&D) centers and its peptide and protein engineering platform provide the Group with a strong competitive edge. In 2009, R&D expenditure totaled close to €200 million, representing nearly 20% of Group sales. Ipsen's shares are traded on segment A of Euronext Paris (stock code: IPN, ISIN code: FR0010259150). The Group is part of the SBF 120 index. Ipsen has implemented a Sponsored Level I American Depositary Receipt (ADR) program, which trade on the over-the-counter market in the United States under the symbol IPSEY. For more information on Ipsen, visit our website at www.ipsen.com.

The PolyPeptide Group

The PolyPeptide Group 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. More information about the PolyPeptide Group is available at www.PolyPeptide.com.

The Poly Peptide Group is comprised of 6 manufacturing sites that are exclusively focused on the manufacture of active pharmaceutical ingredients (APIs) based on peptides and related substances. The PolyPeptide Group is privately held and employs about 450+ staff worldwide.

The PolyPeptide Laboratories Group has been inspected by the FDA and other Regulatory Authorities numerous times, including more than 15 successful FDA PAI inspections. Altogether, the Group has more than 20 approved APIs.

Since the acquisition of NeoMPS, the service offerings of the PolyPeptide Group have greatly increased. We now can offer radio-labeled peptides, cosmetic peptides, general organic syntheses, an extensive catalog as well as small scale GMP manufacturing in addition to our large-scale GMP manufacturing services. Our 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, Goserelin, GRF (1-29) amide, Leuprolide, Octreotide, PTH (1-34), Somatostatin, Triptorelin and Arg-Vasopressin, in addition to others.

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 personalised healthcare strategy aims at providing medicines and diagnostic tools that enable tangible improvements in the health, quality of life and survival of patients. In 2010, Roche had over 80'000 employees worldwide and invested over 9 billion Swiss francs in R&D. The Group posted sales of 47.5 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.

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 products and cosmeceuticals. 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 13,000 employees worldwide, a world-class research and development centre dedicated to discovery research and eight state-of-the-art manufacturing plants, the group is dedicated to improving people's lives. Recently, Zydus Cadila was declared as the 'Emerging Company of the Year' by the Economic Times for Corporate Excellence in 2010. In keeping with its vision, the group achieved the billion dollar mark in sales in March 2011. It is now set to emerge as one of the leading global healthcare companies with sales of over $3 billion by 2015 and a global research driven company by 2020.

Schedule of Events

Thursday, October 20th

2:30 p.m. – 7:00 p.m.
Registration Check-in
Frederic de Hoffmann Auditorium Reception Area, Lower Level

3:15 p.m. – 6:00 p.m.
6th Annual Peptide Therapeutics Symposium
Frederic de Hoffmann Auditorium

3:15 p.m. – 3:30 p.m.
Welcoming Remarks
Soumitra Ghosh, Ph.D.
Director, Peptide Therapeutics Foundation
Senior Director, Research, Amylin Pharmaceuticals

3:30 p.m. – 4:45 p.m.
Opening Session: Novel Peptide Therapeutics 1

Opening Session Moderator
Soumitra Ghosh, Ph.D.
Director, Peptide Therapeutics Foundation
Senior Director, Research, Amylin Pharmaceuticals

3:30 p.m. – 3:55 p.m.
Development of a Long-acting C-peptide (Ersatta™)
James Callaway, Ph.D.
President and CEO, Cebix Incorporated

3:55 p.m. – 4:20 p.m.
Long Acting Y2R Peptide Mimetic as a New Generation Therapeutic Agent for the Management of T2D
Waleed Danho, Ph.D.
Distinguished Research Leader, Hoffmann-La Roche Inc.

4:20 p.m. – 4:45 p.m.
Somatostatin-Dopamine Chimeric Molecule for Potential Treatment of Pituitary Adenomas and Neuroendocrine Tumors
Jesse Z. Dong, Ph.D.
Director, Peptide Therapeutics Foundation
Vice President, Compound Discovery, Ipsen

4:45 p.m. – 6:00 p.m.
Panel Discussion: What's driving R&D funding today?

Panel Introductions
Michel Pettigrew, MBA
President of the Executive Board & Chief Operating Officer, Ferring Pharmaceuticals

Panel Moderator
Richard DiMarchi, Ph.D.
Symposium Chair & Chairman of the Board, Peptide Therapeutics Foundation
Cox Professor of Biochemistry & Gill Chair in Biomolecular Sciences
Department of Chemistry, Indiana University

Panelists
Hans-Joachim Böhm, Ph.D.
Director, Peptide Therapeutics Foundation
Global Head of Chemistry, Roche; Center Manager, Roche Pharma Research & Early Development Site Basel

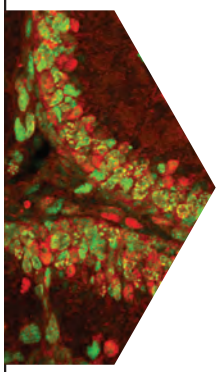


Photo courtesy of the laboratory of Inder Verma, Ph.D., Professor Irwin and Joan Jacobs Chair in Exemplary Life Science Laboratory of Genetics, The Salk Institute for Biological Studies, La Jolla, CA

Schedule of Events

Thursday, October 20th, continued

Stan Crooke, M.D., Ph.D.
Chairman of the Board and CEO, Isis Pharmaceutical, Inc.

Rodney Lappe, Ph.D.
Director, Peptide Therapeutics Foundation
Group Sr. Vice President, Pfizer Worldwide Research & Development;
Chief Scientific Officer, CovX Research

Michel Pettigrew, MBA
President of the Executive Board & Chief Operating Officer,
Ferring Pharmaceuticals

6:00 p.m. – 8:00 p.m. **Opening Reception & Poster Session**
Frederic de Hoffmann Auditorium Reception Area, Lower Level

Friday, October 21st

7:30 a.m. – 6:30 p.m. **6th Annual Peptide Therapeutics Symposium**
Frederic de Hoffmann Auditorium

7:30 a.m. – 12:00 p.m. **Registration Check-in**
Frederic de Hoffmann Auditorium Reception Area, Lower Level

7:30 a.m. – 8:30 a.m. **Breakfast & Poster Viewing**
Frederic de Hoffmann Auditorium Reception Area, Lower Level

8:30 a.m. – 8:45 a.m. **Opening Remarks**
Rodney Lappe, Ph.D.
Director, Peptide Therapeutics Foundation
Group Sr. Vice President, Pfizer Worldwide Research & Development;
Chief Scientific Officer, CovX Research

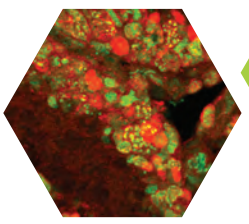
8:45 a.m. – 9:30 a.m. **Keynote Address**

An Expanding Genetic Code
Peter Schultz, Ph.D.
Scripps Family Chair Professor; Department of Chemistry,
The Scripps Research Institute

9:30 a.m. –10:15 a.m. **Plenary Lecture**

Targeting Protein Therapeutics Across the Blood-Brain Barrier with Molecular Trojan Horses
William M. Pardridge, Ph.D.
Distinguished Professor of Medicine, University of California, Los Angeles

10:15 a.m. – 10:45 a.m. **Beverage Break & Poster Viewing**
Frederic de Hoffmann Auditorium Reception Area, Lower Level



Schedule of Events

Friday, October 21st, continued

10:45 a.m. – 12:00 p.m.
Session 1: Discovery Pharmacology

Session 1 Moderators
Binu Philip, MSc, MBA
Business Development, Zydus Cadilla

Jean E. F. Rivier, Ph.D.
Frederik Paulsen Chair in Neurosciences, Clayton Foundation Laboratory of Peptide Biology, Salk Institute for Biological Studies

10:45 a.m. – 11:10 a.m.
Neuropeptidomics: From the Discovery of New Neuropeptides to the Elucidation of their Functions
Jonathan Sweedler, Ph.D.
Professor of Chemistry, James R. Eiszner Family Chair, University of Illinois, Urbana-Champaign

11:10 a.m. – 11:35 a.m.
Comparative Peptidomic Analysis for Functional Discovery of Neuropeptides
Lingjun Li, Ph.D.
Professor, School of Pharmacy and Department of Chemistry, University of Wisconsin

11:35 a.m. – 12:00 p.m.
High Resolution Mass Spectrometry-Based Profiling of Secreted Peptides for Drug Discovery
Steven Taylor, Ph.D.
Director of Chemistry, Amylin Pharmaceuticals; Research Associate, Scripps Institution of Oceanography

12:00 p.m. – 1:30 p.m.
Lunch & Poster Viewing
Frederic de Hoffmann Auditorium Reception Area, Lower Level

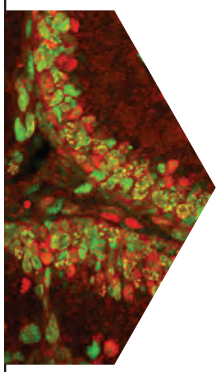
1:30 p.m. – 3:15 p.m.
Session 2: Peptide Transport

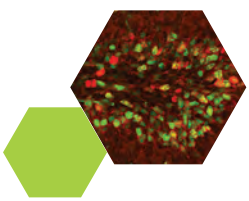
Session 2 Moderators
Jane Salik, Ph.D.
Director, Peptide Therapeutics Foundation
CEO, PolyPeptide Group

Claudio Schteingart, Ph.D.
Vice President, Science & Technology, Ferring Research Institute

1:30 p.m. – 2:05 p.m.
EPiC Technology: Using Peptide to Physiologically Cross the BBB
Jean Paul Castaigne, M.D., MBA
President and CEO, AngioChem

2:05 p.m. – 2:40 p.m.
Endogenous Peptides to Safely Enhance the Delivery of (peptide) Drugs to the Brain
Willem van Werperen, MSc, MBA
CEO, to-BBB

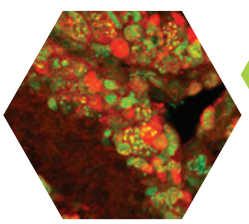




Schedule of Events

Friday, October 21st, continued

2:40 p.m. – 3:15 p.m.	**Enhancing CNS Uptake of Biologics through Molecular Engineering** Ryan Watts, Ph.D. *Associate Director, Head of Neurodegeneration Labs, Department of Neuroscience, Genentech, Inc.*
3:15 p.m. – 3:45 p.m.	**Beverage Break & Poster Viewing** Frederic de Hoffmann Auditorium Reception Area, Lower Level
3:45 p.m. – 5:00 p.m.	**Session 3: Novel Peptide Therapeutics II**
Session 3 Moderators	Janice Reichert, Ph.D. *Director, Peptide Therapeutics Foundation* *Senior Research Fellow, Tufts Center for the Study of Drug Development* Les Miranda, Ph.D. *Director Research, Peptide Research & Discovery, Chemistry Research & Discovery, Amgen*
3:45 p.m. – 4:10 p.m.	**NPY2R Selective Peptide Agonists for the Treatment of Obesity: Balancing Efficacy, Time Action and Cardiovascular Profile** Jordi Alsina, Ph.D. *Senior Research Scientist, Eli Lilly & Company*
4:10 p.m. – 4:35 p.m.	**Development Of CR845, a Novel, Peripherally-Acting Peptidic Kappa Opioid Agonist, for the Treatment of Postoperative Pain** Derek Chalmers, Ph.D., D.Sc. *President & CEO, Cara Therapeutics, Inc.*
4:35 p.m. – 5:00 p.m.	**ZYPH0907: A Novel Orally Active PTH1R Agonist for Treatment of Osteoporosis** Mukul Jain, Ph.D. *Senior Vice President, Zydus Research Center*
5:00 p.m. – 5:15 p.m.	**Closing Remarks** Pierre Rivière, Ph.D. *President & Director, Peptide Therapeutics Foundation* *President, Ferring Research Institute & Senior Vice President, Research*
5:15 p.m. – 6:30 p.m.	**Networking Reception** Frederic de Hoffmann Auditorium Reception Area, Lower Level



Jordi Alsina, Ph.D. | Senior Research Scientist, Eli Lilly & Company
NPY2R Selective Peptide Agonists for the Treatment of Obesity: Balancing Efficacy, Time Action and Cardiovascular Profile

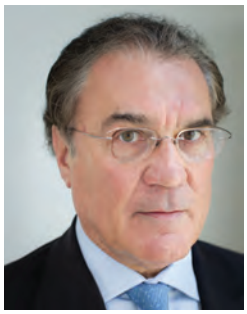
Dr. Alsina graduated in Chemistry from the Universitat de Barcelona, Spain. He received his doctorate in Organic Chemistry from the same institution in 1997 under the supervision of Prof. Fernando Albericio working on the development of new methods for the solid-phase synthesis of C-terminal modified peptides including Backbone Amide Linker (BAL) Strategies. He completed postdoctoral training in peptide chemistry with Prof. George Barany at the University of Minnesota in 2000, followed by three years at Indiana University-Purdue University at Indianapolis focusing on the development of solid-phase organic chemistry methodology. He joined Lilly Research Laboratories in 2004 as Senior Peptide Chemist and was promoted to Senior Research Scientist in 2007. During his time at Lilly Research Laboratories, Dr. Alsina has impacted several important programs in the diabetes and obesity therapeutic areas. He has gained recognition for the exploration and refinement of peptide structure-activity relationships and his peptide synthesis skills. Dr. Alsina has contributed to the scientific community with more than 40 articles in internationally recognized peer-reviewed journals in the solid-phase peptide chemistry and peptide therapeutics areas.

Hans-Joachim Böhm, Ph.D. | Director, Peptide Therapeutics Foundation; Global Head of Chemistry, Roche; Center Manager, Roche Pharma Research & Early Development Site Basel
Panelist

Hans-Joachim Böhm is Global Head of Chemistry at Roche and Center Manager for the Roche Pharma Research and Early Development Site Basel. Prior to this, Hans-Joachim Böhm was President and Research Site Head of Roche Palo Alto from October 2006 to June 2008. Hans-Joachim Böhm also headed Non-clinical development at Roche Basel from January 2005 until September 2006, the Discovery Chemistry Department from 2002–2004, the Discovery Technology Department from 2000-2001 and the Research Informatics Department in Basel. Before joining Roche in 1996, Hans-Joachim Böhm worked for BASF in Ludwigshafen as Computational Chemist from 1988–1996 and for Siemens in Munich in field of Microelectronics from 1985-1987. He obtained his Ph.D. in Theoretical Chemistry at the University of Karlsruhe in 1984.

James Callaway Ph.D. | President and CEO, Cebix Incorporated
Development of a Long-acting C-peptide (Ersatta™)

Dr. James Callaway received his Ph.D. in Biological Chemistry at UCLA and subsequently accumulated over 25 years of experience in the development of biopharmaceutical products at companies such as Ingene (now Xoma), SmithKline Beecham (now GSK), Bayer, and Elan. At Elan he served in several capacities including Head of Development and was intimately involved in the advancement and approval of Tysabri® and Myobloc®. In addition, he served as the lead accountable person in the design, construction, validation, and FDA approval of a biologics manufacturing plant.



Jean Paul Castaigne, M.D., MBA | President and CEO, AngioChem
EPiC Technology: Using Peptide to Physiologically Cross the BBB

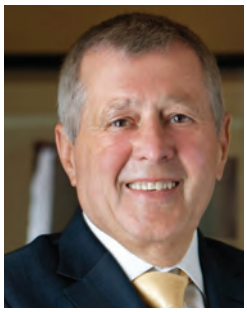
Dr. Castaigne is a senior executive with extensive international experience in the pharmaceutical and biotech industry. Prior to joining AngioChem as CEO, he was COO and CSO of Conjuchem, and previously he was Vice President, Head of Global R&D at the Fournier Group in France. In addition, Dr. Castaigne spent eleven years with Novartis in a variety of management positions, including Corporate Vice President for Canada, President and Managing Director in the Philippines and Director of Medical and R&D in France. Dr. Castaigne has also worked with CILAG (J&J) and Sanofi in France. He received his MD from Paris University in 1975 and held the position of Associate Professor of oncology and pneumology in 1978. Dr. Castaigne received an MBA from HEC Paris in 1987. Dr. Castaigne is member of the board of the following biotech companies: Tranzyme Pharma and Asmacure.

Derek Chalmers, Ph.D., D.Sc. | President & CEO, Cara Therapeutics, Inc.
Development of CR845, a Novel, Peripherally-Acting Peptidic Kappa Opioid Agonist, for the Treatment of Postoperative Pain

Dr. Chalmers has been the Co-Founder, President and CEO and Executive Director, Cara Therapeutics since 2004, a Clinical-stage, biotechnology company focused on discovering and developing novel, superior therapeutics to treat pain and inflammation. Lead kappa agonist in Phase II studies.

Additionally, from 1997-2004 Dr. Chalmers was the Co-Founder, Vice President and Executive Director of Arena Pharmaceuticals (NASDAQ: ARNA), a Publicly traded biopharmaceutical company developing a broad pipeline of compounds that act on G protein-coupled receptors, or GPCRs. The company currently has two drug candidates in clinical development. From 1994-1997 he was the Principal Investigator at Neurocrine Biosciences (NASDAQ: NBIX), a publicly traded product-based biopharmaceutical company focused on neurological and endocrine diseases and disorders. And from 1990-1994 he was a Research Fellow/ NARSAD Fellow/ Fogerty International Fellow at the University of Michigan.

Dr. Chalmers received his Ph.D. from the University of Glasgow, Faculty of Medicine in 1990 and his B.Sc. (Hons) – University of Glasgow, Faculty of Science in 1986.



Stan Crooke, M.D., Ph.D. | Chairman of the Board and CEO, Isis Pharmaceutical, Inc.
Panelist

Dr. Crooke is Founder, Chairman and Chief Executive Officer of Isis Pharmaceuticals. Isis is a development stage biopharmaceutical company that is focused on a new paradigm in drug discovery, antisense oligonucleotides. Since Dr. Crooke and his colleagues founded Isis in 1989. The Company has completed its initial public offering in May 1991, and has reported broad progress in antisense technology and its rapid conversion to therapeutic product opportunities. Isis was the first company to commercialize an antisense drug and has achieved a number of important corporate collaborative relationships. In 2006, Dr. Crooke was named in Nature Biotechnology as one of biotechnology's influential individuals.

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Prior to founding Isis, Dr. Crooke was President of Research and Development for SmithKline Beckman Corporation (SKB). He also coordinated the research and development activities of SKB including its instruments, diagnostics, animal health and clinical laboratory businesses. Prior to joining SKB, Dr. Crooke helped establish the anticancer drug discovery and development program at Bristol Myers, which succeeded in bringing to market a significant number of drugs.

During his career, Dr. Crooke has supervised the development of 19 drugs currently on the market and others in development. Dr. Crooke has won a number of teaching awards and has been a professor of pharmacology at Baylor Medical School and the University of Pennsylvania. He has trained a number of graduate students and numerous post doctoral fellows. He has authored over 400 publications, has edited 21 books, and has been granted many patents. Dr. Crooke is active in molecular and cellular biology and pharmacology of antisense oligonucleotides. Dr Crooke has served on numerous boards of directors and various editorial boards, and has won a number of awards.

Dr. Crooke received his M.D. and Ph.D. from Baylor College of Medicine, Houston, Texas and his B.S. in Pharmacy from Butler University, Indianapolis, Indiana.

Waleed Danho, Ph.D. | Distinguished Research Leader, Hoffmann-La Roche Inc.

Long Acting Y2R Peptide Mimetic as a New Generation Therapeutic Agent for the Management of T2D

Dr. Waleed Danho holds the position of Distinguished Research Leader at Hoffmann-La Roche Inc. in Nutley, New Jersey, USA. (till April 1 2011). Dr. Danho completed his Ph.D. in 1967 at the University of Aachen, Aachen, Germany in the laboratories of Professor Dr. mult. Helmut Zahn. He went on to do post doctoral training at the Hormone Research Laboratory, University of California, San Francisco in the laboratories of Professor Dr. Choh Hao Li. His research interests are in drug discovery of peptide-based drugs, peptide mimetics, and conformationally restricted peptides.

Dr. Danho also serves as an adjunct professor at the University of Medicine and Dentistry of New Jersey, Department of Biochemistry (1996-Present). He is reviewer for the *Journal of Peptide Research*, *QSAR & Combinatorial Science*, as well as for the *Journal of Medicinal Chemistry*; he is a member of the editorial board of The International Journal of Peptide Research and Therapeutics. Dr. Danho authored and co-authored over 250 scientific articles and 21 patents in the field of peptides. He has presented and chaired various sections of the American, European and International Peptide Symposia since 1972. He is the winner of the Wilhelm Borches Medal (1968) of The University of Aachen for Summa cum in the PhD Program. In 2009 Dr. Danho was awarded the “Lifetime Achievement Award” from the North Jersey section of the American Chemical Society.

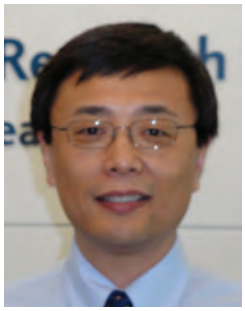
Last September, Dr. Danho was awarded the “2009 Meienhofer Award” at Roche Colorado Corporation Peptide Symposium “RCCPS 09.”

Richard DiMarchi, Ph.D. | Symposium Chair & Chairman of the Board, Peptide Therapeutics Foundation; Cox Professor of Biochemistry & Gill Chair in Biomolecular Sciences; Department of Chemistry, Indiana University
Panel Moderator

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 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 rDNAderived 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.



Jesse Z. Dong, Ph.D. | Director, Peptide Therapeutics Foundation; Vice President, Compound Discovery, Ipsen
Somatostatin-Dopamine Chimeric Molecule for Potential Treatment of Pituitary Adenomas and Neuroendocrine Tumors

Dr. Dong has served as Vice President of Compound Discovery at Ipsen since 2009 overseeing peptide and toxin drug discovery research. He joined Ipsen/Biomeasure, Incorporated in 1993 as a scientist in the medicinal chemistry department. He is the inventor of four drug candidates that are currently in development: Taspoglutide in phase III clinical trials for treatment of type II diabetes, BA058 in phase III clinical development for treatment of postmenopausal osteoporosis, RM-131 in phase I clinical trial for GI disorders, and RM-493 in preclinical stage for treatment of obesity. During his distinguished scientific career to date, he has published over 130 scientific articles and has been awarded 27 U.S. patents. Prior to joining Ipsen/Biomeasure, Dr. Dong was a Research Fellow in the Unit for Rational Drug Design, Department of Medicine, Boston University Medical Center. He holds a Ph.D. in Organic Chemistry from Ohio University, Athens, Ohio and M.S. and B.S. degrees from Peking University, Beijing, China.

Soumitra Ghosh, Ph.D. | Director, Peptide Therapeutics Foundation; Senior Director, Research, Amylin Pharmaceuticals
Welcoming Remarks

Soumitra Ghosh is Senior Director, Research at Amylin Pharmaceuticals, Inc. and joined the company in 2003. He oversees the chemistry and biology research groups and leads a joint clinical development program of a diabetes drug candidate with Biocon, India. Prior to Amylin, Dr. Ghosh was Senior Director of Chemical Biology at Mitokor for ten years, where he directed its 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.

Mukul Jain, Ph.D. | Senior Vice President, Zydus Research Center
ZYPH0907: A Novel Orally Active PTH1R Agonist for Treatment of Osteoporosis

Dr. Mukul Jain is leading the New Chemical Entities (NCE) program at Zydus Research Centre (ZRC), the R&D wing of Zydus Cadila Group. Dr. Jain obtained his B.Pharm., M.Pharm. and Ph.D. degrees plus a diploma in Business Management from Nagpur University, Nagpur, India. He also has a certificate in Executive Management Program from IIM-Ahmedabad. After completing his Ph.D., he worked as Research Scientist at Wockhardt Research Centre, Aurangabad and then at Ranbaxy Research Laboratories at New Delhi before moving to USA as Post-doc Associate at University of Florida at Gainesville. After spending three years as a Post-doc in the area of Molecular Neuroendocrinology, he returned to India & joined NIPER as Assistant Professor of Pharmacology.

In the year 2000, Dr. Jain joined ZRC, when this Centre had just started its NCE Research Program and since then he has been associated with ZRC in various capacities. His group at ZRC has developed 11 IND molecules, including 3 peptidomimetic agents that are currently at different stages of clinical development. His group has also developed preclinical dossier for 8 recombinant therapeutic proteins and the H1N1 vaccine developed by Zydus Cadila. Currently about 15 different NCE discovery programs are ongoing at ZRC. Under his supervision, ZRC has received various accreditations including OECD-GLP, NABL & AAALAC. Dr. Jain has contributed to more than 30 patents as co-inventor and more than 130 research publications, including 68 full-length research papers in International Peer-reviewed Journals. Dr. Jain is connected with various academic institutes and has guided research work of several Masters & Ph.D students. He is a Fellow of Academy of Science & Animal Welfare, India and the Chairman of the Institutional Animal Ethics Committee at ZRC.

He is also a member of several International Scientific Communities including American Chemical Society, American Diabetes Association, European Association for Study of Diabetics, Indian Pharmacology Society, American Association for Advancement of Sciences, International Brain Research Organization and Who's Who of Professionals etc.

Rodney Lappe, Ph.D. | Director, Peptide Therapeutics Foundation; Group Sr. Vice President, Pfizer Worldwide Research & Development; Chief Scientific Officer, CovX Research
Panelist & Opening Remarks

Dr. Lappe is Group Sr. Vice President, Pfizer Worldwide Research and Development and Chief Scientific Officer for CovX in San Diego, California. Dr. Lappe joined Pfizer with the CovX acquisition in 2008, bringing 29 years of drug discovery experience in the pharmaceutical and biotech industries.

Dr. Lappe has been responsible for the advancement of protein bio-conjugates through the industry leading work at CovX. Three novel conjugates (CovX-bodies) addressing key medical needs in cancer and diabetes are now in clinical testing with two additional clinical candidates in late stage preclinical development. In addition to leading CovX, Dr. Lappe has recently taken on responsibility for the continued growth and productivity of Pfizer's other internal Biotech Units as well.

Prior to joining CovX as its first CSO in 2004, Dr. Lappe served as Vice President for cardiovascular and metabolic diseases at Pharmacia where he contributed to the registration of Inspra®, a novel aldosterone receptor antagonist. He was also site leader for Pharmacia in St. Louis. Prior to joining Pharmacia, he held positions of increasing responsibility with Wyeth, Rorer Central Research, CIBA Geigy and Searle Pharmaceuticals.

Dr. Lappe received his Ph.D. in Pharmacology from Indiana University and his BA from Blackburn College.

Lingjun Li, Ph.D. | Professor, School of Pharmacy and Department of Chemistry, University of Wisconsin
Comparative Peptidomic Analysis for Functional Discovery of Neuropeptides

Professor Lingjun Li received her B.E. degree in Environmental Analytical Chemistry from Beijing University of Technology and Ph.D. degree in Analytical Chemistry/Biomolecular Chemistry from University of Illinois at Urbana-Champaign in 2000. She then did a three-way postdoctoral research at the Pacific Northwest National Laboratory, Brandeis University, and University of Illinois before starting her tenure-track assistant professor position in December 2002. Dr. Li was recruited to UW-Madison campus through a campus-wide "Chemical Biology Cluster Hire" position and she currently holds joint faculty appointments in School of Pharmacy and Department of Chemistry. She was promoted to Associate Professor with tenure in 2008. Her research interests are in analytical neurochemistry, neuropeptidomics and biological mass spectrometry. Dr. Li's research program focuses on developing novel mass spectrometry tools in conjunction with microseparation techniques to study challenging neuroscience problems including the functional discovery of neuropeptides and biomarker discovery in neurodegenerative diseases. Dr. Li has established a highly productive research program and published over 100 peer-reviewed research papers, including 80 research papers since her independent position at UW-Madison. She has obtained more than $9 M research funding and served as reviewer on more than 60 scholarly journals and numerous federal grant review panels. She has received numerous awards including a highly prestigious National Science Foundation CAREER Award, Alfred P. Sloan Foundation Research Fellowship, Vilas Associate Award, the American Society for Mass Spectrometry Research Award, the Romnes Faculty Fellowship, and 2011 Pittsburgh Conference Achievement Award with a special Award Symposium recognizing and honoring her outstanding work in Bioanalytical Chemistry.

William M. Pardridge, Ph.D. | Distinguished Professor of Medicine, University of California, Los Angeles

Targeting Protein Therapeutics Across the Blood-Brain Barrier with Molecular Trojan Horses

William M. Pardridge, M.D., is Distinguished Professor of Medicine at UCLA. He has been studying blood-brain barrier (BBB) transport since 1970. Hs work includes the physiology and pharmacology of BBB transport of small molecules, via carrier-mediated transport, and large molecules, via receptor-mediated transcytosis. Dr. Pardridge invented the fields of molecular Trojan horses for BBB drug delivery of recombinant proteins, the Trojan horse liposome technology for intravenous non-viral gene therapy of the brain, and the field of BBB genomics. He has authored over 400 publications on the field of BBB drug and non-viral gene delivery. His most recent work focuses on the re-engineering of biopharmaceuticals for targeted drug delivery across the human BBB.

Michel Pettigrew, MBA | President of the Executive Board & Chief Operating Officer, Ferring Pharmaceuticals

Panel Introductions & Panelist

Mr. Pettigrew joined Ferring in May 2001. In addition to his role as President of the Executive Board, he is responsible for all Commercial, Global Marketing, Corporate Communications, Business Development, Medical Services, Technical Operations and Research activities of the Company. He is also President and CEO of Ferring Holding US, Ferring's largest subsidiary, and is responsible for all Clinical Development and Commercial activities in the United States. Prior to his arrival at Ferring, Mr. Pettigrew held several senior management positions throughout the world during a 21-year career with Bristol-Myers Squibb.

Michel Pettigrew has a Bachelor of Commerce degree from McGill University in Montreal and a MBA from York University in Toronto, Canada.

Pierre Rivière, Ph.D. | President & Director, Peptide Therapeutics Foundation; President, Ferring Research Institute & Senior Vice President, Research

Closing Remarks

Dr. Rivière is responsible for global research at Ferring Pharmaceuticals and for the Ferring Research Institute. Dr. Rivière joined Ferring in 1996 as Head of Biology before becoming Director of Research (2002), Vice President, Research (2006) and Senior Vice President, Research (2010). In recent years, Dr. Rivière has contributed to the discovery of several peptide new chemical entities, now at various stage of development, either in house or through licensees. He previously led the Gastroenterology drug discovery department of the Institut de Recherche Jouveinal in Fresnes, France. Dr. Rivière holds a Ph.D. in Biology and Physiology from the Institut National Polytechnique of Toulouse, France, and has completed a post-doctoral training in the Department of Pharmacology at the University of Arizona in Tucson, Arizona. Dr. Rivière is a co-founder of Cara Therapeutics, BioHeatMap, the Peptide Therapeutics Foundation and the Annual Peptide Therapeutics Symposium. Since 2008, he also serves as Director and President of the Peptide Therapeutics Foundation.

Peter Schultz, Ph.D. | Scripps Family Chair Professor, Department of Chemistry, The Scripps Research Institute
An Expanding Genetic Code

Peter G. Schultz graduated from Caltech in 1979 and continued there for his doctoral degree (in 1984) with Professor Peter Dervan. After a postdoctoral year at MIT, he moved to the University of California, Berkeley, where he was a Professor of Chemistry, a Principal Investigator at the Lawrence Berkeley National Laboratory and an Investigator in the Howard Hughes Medical Institute. He moved to The Scripps Research Institute in 1999 where he is currently the Scripps Professor of Chemistry. Schultz's scientific contributions include: (1) the discovery of catalytic antibodies, and their use to study fundamental mechanisms of biological catalysis and the evolution of binding and catalytic function; (2) the development and application of methods to add new building blocks to the genetic codes of prokaryotic and eukaryotic organisms; and (3) the development and application of molecular diversity technologies to problems in chemistry, medicine, and materials science. Schultz also established the Genomics Institute of the Novartis Research Foundation in 1999 in La Jolla (and served as its Director until 2010), which develops and applies state of the art high throughput chemical, proteomics, and genomics technologies to the development of new human therapeutics for cancer, immune, metabolic, cardiovascular and infectious disease.

Schultz is the author of ~450 scientific publications and has received numerous awards including the Alan T. Waterman Award, NSF (1988), the ACS Award in Pure Chemistry (1990), the U.C. Berkeley College of Chemistry Teaching Award (1992), the Wolf Prize in Chemistry (1994), the Paul Erhlich and Ludwig Darmstaedter Award (2002), and the ACS Arthur C. Cope Award (2006). Professor Schultz is a member of the National Academy of Sciences, USA (1993) and the Institute of Medicine of the National Academy of Sciences (1998). He is a founder of Affymax Research Institute, Symyx Technologies, Syrrx, Kalypsys, Phenomix, Ilypsa, Ambrx, Wildcat Discovery Technologies, and Ardelyx, which have pioneered the application of molecular diversity technologies to challenges in energy, materials and human health.

Jonathan Sweedler, Ph.D. | Professor of Chemistry, James R. Eiszner Family Chair, University of Illinois, Urbana-Champaign
Neuropeptidomics: From the Discovery of New Neuropeptides to the Elucidation of their Functions

Professor Jonathan V. Sweedler holds the James R. Eiszner Family Chair in Chemistry at the University of Illinois, is associated with the Beckman Institute, is the director of the UIUC Biotechnology Center, and has appointments in the Neuroscience Program, the Department of Physiology and the Bioengineering Program. His research interests focus on new metabolomic and peptidomic approaches for assaying small volume samples, and in applying these methods to study novel neurochemistry. He has received numerous awards including the Fields Award, the Merck Prize, the Instrumentation Award from the Analytical Division of the American Chemical Society, the Gill Prize and the Benedetti-Pichler Award for Microanalysis, and he is an associate editor for Analytical Chemistry.

Steven Taylor, Ph.D. | Director of Chemistry, Amylin Pharmaceuticals; Research Associate, Scripps Institution of Oceanography
High Resolution Mass Spectrometry-Based Profiling of Secreted Peptides for Drug Discovery

Steven Taylor received his Ph.D. in Chemistry from the University of Queensland, Australia and completed his post-doctoral training at the University of California, Davis, the University of Delaware and subsequently as an Alexander von Humboldt Research fellow at the University of Tübingen in Germany. Steve was an Assistant Professor in Philadelphia for one year then moved to San Diego to join the research faculty at the Scripps Institution of Oceanography (SIO). His research group focused on marine antimicrobial peptides and the elucidation of their post-translational modifications and mechanism of action. Steve joined the biotech industry in 2001, first leading a mitochondrial proteomics program at MitoKor in San Diego, and subsequently, a high-resolution mass spectrometry-based peptide discovery program at Amylin Pharmaceuticals Inc. where he is currently a Director in the Chemistry department. He also continues as a Research Associate to SIO.

Willem van Werperen, MSc, MBA | CEO, to-BBB
Endogenous Peptides to Safely Enhance the Delivery of (peptide) Drugs to the Brain

Willem obtained a MSc degree in biomedical sciences from Utrecht University, and an Executive MBA degree from NIMBAS/Bradford University. He began his professional career in clinical research at Glaxo and joined Genzyme in 1994 in various European clinical, sales & marketing positions. From 2004 to 2006 he was globally responsible for marketing of the genetic disease business unit in Genzyme's worldwide headquarters in Cambridge, MA. In 2006 Willem moved back to lead the Genzyme Netherlands organization in Naarden.

In 2009 he joined the to-BBB team as their CEO to help develop their break-through brain delivery platform for patients with CNS diseases. to BBB is a clinical stage private company in Leiden focusing on enhanced drug delivery across the blood-brain barrier. The company is developing novel treatments for devastating brain disorders, such as brain cancer, neurodegenerative diseases and lysosomal storage diseases, by combining existing drugs with the G Technology®, to BBB's proprietary brain delivery platform. to BBB is applying the G Technology® for the delivery of doxorubicin for the treatment of brain cancer as its internal lead product 2B3 101. This product is currently investigated in a phase I/II clinical trial. A second product for neuroinflammation 2B3-201 is aimed to follow the same route. Together with several top tier pharma and biotech companies, to BBB is further investigating the versatility of the G Technology® for drugs that are unable to reach the brain within a tolerable therapeutic window.

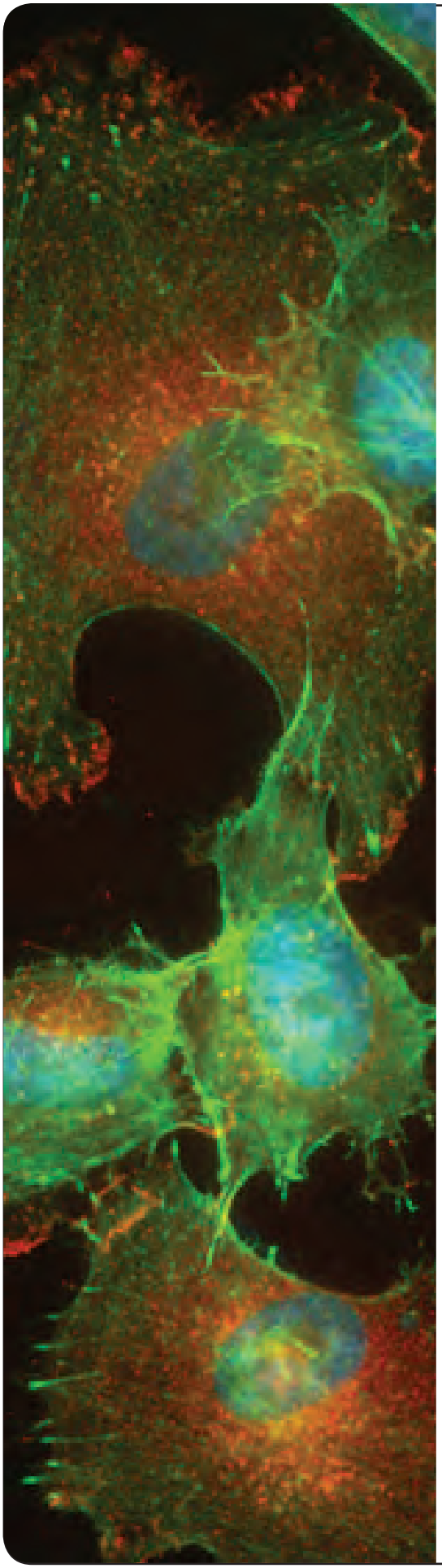
Ryan Watts, Ph.D. | Associate Director, Head of Neurodegeneration Labs, Department of Neuroscience, Genentech, Inc.

Enhancing CNS Uptake of Biologics through Molecular Engineering

Dr. Ryan J. Watts is the Associate Director and Head of the Neurodegeneration Labs in the Department of Neuroscience at Genentech. Dr. Watts joined Genentech in 2004 and initiated a program exploring molecules that coordinate the development of both the vascular and nervous systems and to define their role in cancer and axon regeneration. These early efforts in the Watts lab produced a clinical candidate for cancer. In 2006, Dr. Watts initiated and led research programs in two broad areas, neurodegeneration and the blood-brain barrier. Dr. Watts was the lead scientist and chair of a joint research partnership with AC Immune that produced a clinical candidate for Alzheimer's disease currently phase II clinical testing.

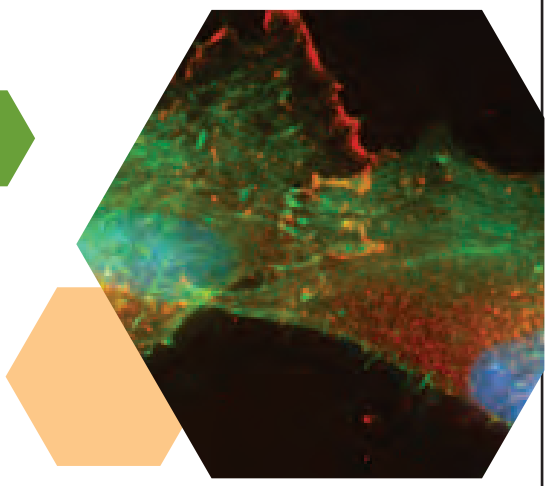
Dr. Watts is now leading a large group of scientists in the Neurodegeneration Labs, which focus on studying the basic biology of, and developing therapeutics for neurodegeneration, with an emphasis on Alzheimer's and Parkinson's disease. In addition to studying neurodegeneration, Dr. Watts' own lab is exploring the establishment and maintenance of the blood-brain barrier and the ability of molecules to transverse this physiological barrier.

Dr. Watts received his Ph.D. from the Department of Biological Sciences at Stanford University, where he focused on neuronal remodeling via degenerative mechanism during nervous system development. Dr. Watts received his undergraduate training form University of Utah with a B.S. in Biology.



Abstracts of Lecture Presentations

6th Annual Peptide Therapeutics Symposium



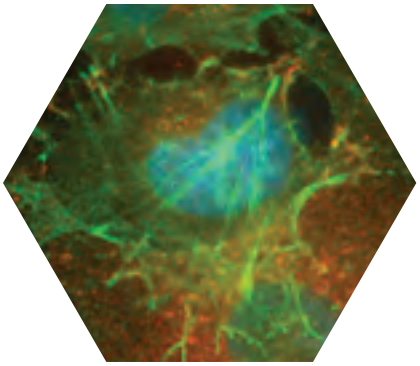


Photo courtesy of the laboratory of Sara Courtneidge, Ph.D., Professor, Sanford-Burnham Institute for Medical Research, La Jolla, CA

NPY2R Selective Peptide Agonists for the Treatment of Obesity: Balancing Efficacy, Time Action and Cardiovascular Profile

Jordi Alsina, Ph.D. | Senior Research Scientist
Eli Lilly & Company
Lilly Corporate Center, Indianapolis, IN 46285 | (317) 276-8817

PYY along with NPY and PP are homologous members of the pancreatic polypeptide fold family characterized by a 36 amino-acid primary sequence and a C-terminal tyrosine amide. The three also share a unique tertiary structural motif called the PP-fold, consisting of two anti-parallel helices that are operative in their interaction with NPY receptors. PYY is secreted by endocrine L-cells from the distal gastrointestinal tract in proportional response to nutrient intake. The action of DPP-IV converts the parent sequence into the truncated 3-36 form which exhibits enhanced selectivity for the pre-synaptic terminal of the NPY2R. Extensive preclinical evidence has established PYY3-36/NPY2R axis as an important mediator of appetite and energy balance. Recent studies have correlated PYY3-36/NPY2R signaling impairment with a genetic predisposition toward the development of obesity. While several clinical trials in normal weight and obese subjects have confirmed a potential therapeutic utility of PYY3-36 as a stand-alone anti-obesity agent, additional reports suggest that PYY3-36 may also enhance the anorectic effects of (when co-administered with) other peptide hormones.

Our structure-activity studies utilized both PYY and PP peptide backbones as starting points to develop highly selective Y2 agonists. Modification with polyethylene glycol (PEG) using a novel N-terminally directed ligation strategy produced a series of potent, chemically-stable, and long acting Y2 agonists. These analogs were tested in well-established rodent obesity models for efficacy and in a non-human primate model for cardiovascular safety.

Development of a Long-acting C-peptide (Ersatta™)

James Callaway, Ph.D. | President and CEO
Cebix Incorporated
1298 Prospect Street, Suite 2A, La Jolla CA 92037 | (858)729-6502

C-peptide represents the long-neglected second peptide that is produced in equimolar amounts with insulin in response to consumption of carbohydrate. In the past two decades, substantial data has been accumulated suggesting that C-peptide acts as a hormone to assure adequate supply of nutrients (primarily through vasodilation) to the cells throughout the body as they take up circulating glucose in response to co-expressed insulin. In this regard the C-peptide/insulin dual hormone story mirrors that of GLP-1/GLP-2/glucagon. It has been proposed that the absence of C-peptide in type 1 diabetes patients is an important factor in the early onset and precipitous advancement of associated long-term complications of the disease. To test this hypothesis, several preclinical studies in animal models of type 1 diabetes as well as clinical studies with C-peptide treatment up to 6 months have been completed. These studies demonstrated positive clinical signals in diabetic peripheral neuropathy through an improvement in nerve conduction velocity and global neuropathy score. Additionally, a reduction in microalbuminuria and improvement of glomerular structural abnormalities were observed in diabetic nephropathy after C-peptide administration. Efforts to develop an attractive product to replace circulating levels of C-peptide have been stymied by its short half-life (»1 hour) and the need for subcutaneous delivery. Cebix has successfully completed a development program to generate a long-acting product with subcutaneous delivery (Ersatta). The plan to confirm the extended half-life of Ersatta in a human pharmacokinetic study and subsequently demonstrate efficacy and safety in a study of type 1 diabetes patients with peripheral neuropathy will be presented.

EPiC Technology: Using Peptide to Physiologically Cross the BBB

Jean Paul Castaigne, M.D., MBA | President and CEO
AngioChem
201 President-Kennedy, Suite PK-R220, Montreal, PQ H2X3Y7, Canada | (514)788-7800

Angiochem is utilizing its proprietary EPiC platform to create and develop drugs that physiologically cross the blood-brain barrier (BBB). The platform has been validated in human in two US clinical trials with its lead compound GRN1005 for the treatment of brain metastasis and glioblastoma. This product was licensed to Geron Corporation and is now entering in Phase II pivotal clinical trials. Further validation were obtained from several pre-clinical studies which demonstrated the broad applicability of the technology from small molecules to biologics (peptides, proteins, MAbs, etc). The Epic technology

is based on a family of over 100 proprietary peptides called Angiopep that are all ligand to the LRP-1 receptor, one of the most expressed receptor on the BBB. Once attached to the receptor, the Angiopep are naturally transported to the brain via receptor-mediated transcytosis. The Epic compound combines an Angiopep to a drug candidate, creating a new chemical entity. This new drug crosses the blood-brain barrier thanks to the Angiopep and once in the brain, the drug moiety can act against brain diseases. The average increase in brain penetration of the EPiC compound compared to the native moiety range from 10 to 100 fold. Angiochem is developing its platform and its portfolio in wide varieties of indications including brain cancers, pain, obesity, Parkinson's and others. Angiochem forward strategy is to move some projects internally to POC and to license them and, in parallel, to establish collaboration with companies having drug candidates actives against some brain diseases but not crossing the BBB.

Development of CR845, a Novel, Peripherally-Acting Peptidic Kappa Opioid Agonist, for the Treatment of Postoperative Pain

Derek Chalmers, Ph.D., D.Sc. | President & CEO
Cara Therapeutics, Inc.
One Parrott Drive, Shelton, CT 06484 | (203) 567-1501

Each year, over 100 million people in the U.S. experience pain from surgery, arthritis, cancer, neuropathies, or other medical conditions. Despite this high prevalence, under-treatment of pain remains a critical clinical problem due to the limited effectiveness and substantial adverse effects of available analgesics, including centrally-acting opiates and NSAIDs. We have developed a novel opioid drug candidate, CR845, designed to produce potent analgesia in the absence of central nervous system adverse events. CR845 is a tetrapeptide kappa opioid receptor agonist exhibiting picomolar affinity and greater than 30,000-fold selectivity over mu and delta opioid receptors. The all-D-amino acid peptidic structure and accompanying physicochemical properties of CR845 distinguish this compound from the small molecule heterocycle kappa agonists developed to date, all of which exhibited significant adverse central nervous system effects that precluded their further development as analgesics.

In both single and multi-dose i.v. studies in healthy volunteers, CR845 exhibited linear and dose-proportional pharmacokinetics, with no evidence of metabolism or drug accumulation. CR845 was found to be safe and well tolerated, with no incidence of the dysphoric reactions reported previously with small molecule kappa opioid agonists. A double-blind, placebo-controlled Phase II study of CR845 in patients undergoing elective laparoscopic hysterectomy indicated that a single post-operative dose of CR845 significantly reduced pain intensity and need for morphine. In addition, patients treated with CR845 exhibited significantly less opioid-related side effects, including nausea and vomiting. A second controlled 200-patient Phase II trial is currently underway to assess the efficacy of CR845 administered both pre- and post-operatively in the same surgical population.

Long Acting Y2R Peptide Mimetic as a New Generation Therapeutic Agent for the Management of T2D

Waleed Danho, Ph.D. | Distinguished Research Leader
Hoffmann-La Roche Inc.
Roche Research Center, Nutley, NJ 07110 | (858) 461- 0983

PYY_{1-36} is a peptide secreted from the enteroendocrine L-cells in the gastrointestinal tract, which also secrete GLP-1. The first two amino acids of PYY_{1-36} are cleaved by the enzyme DPP-IV to give rise to the endogenous NPY2-receptor (Y2R) agonist, PYY_{3-36}. The latter peptide has been shown to reduce food intake in animal models of obesity, and lean as well as obese humans. However, PYY_{3-36} reportedly displays modest selectivity against other receptors in the NPY-receptor family. Moreover, PYY_{3-36} has a very short life time in circulation. Thus, PYY_{3-36} has major limitations for being developed into a therapeutic entity. The goal of this work is to develop long acting agonists of the Y2R to be used as a therapeutic agents for the management of T2D and other co-morbidities, with *clear advantages in regards to efficacy/tolerability* to known agents.

We identified and developed a novel Y2R peptide mimetic that demonstrates excellent anti-diabetic effects accompanied with significant weight loss. The Y2R mimetic exhibits the following key differentiation features as compared to PYY_{3-36}: a highly selective and long acting analog that exerts acute and sub-chronic anti-diabetic effects that are independent of body weight loss in diabetic *db/db* mice and ZDF rats. In addition, there is potential for pancreatic beta-cell preservation as observed in *db/db* mice. It also substantially reduced body weight gain, fat mass and lipids in DIO rodents, and improved insulin sensitization. The identification and development of this peptide mimetic will be presented.

Somatostatin-Dopamine Chimeric Molecules for Potential Treatment of Pituitary Adenomas and Neuroendocrine Tumors

Jesse Z. Dong, Ph.D. | Director, Peptide Therapeutics Foundation; Vice President, Compound Discovery
Ipsen
27 Maple Street, Milford, MA 01757 | (774) 396-6883

A novel class of chimeric compounds targeting growth hormone and prolactin secretions associated with pituitary tumors was developed. These conjugates contain key structural elements of somatostatin and dopamine. The conjugates interact simultaneously with somatostatin and dopamine receptor subtypes located on the same cell surface. Due to the simultaneous engagement of both receptors, the compounds produce significant synergistic effects in the inhibition of both growth hormone and prolactin secretions, not observed by somatostatin or dopamine alone or in combination. This class of compounds may potentially represent a new treatment for pituitary adenomas and neuroendocrine tumors.

ZYPH0907: A Novel Orally Active PTH1R Agonist for Treatment of Osteoporosis

Mukul Jain, Ph.D. | Senior Vice President
Zydus Research Center
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Osteoporosis is characterised by diminished bone mineral density (BMD), reduced bone strength and increased risk of fracture. Parenteral administration of parathyroid hormone (PTH) increases BMD, bone strength and reduces incidences of fractures. PTH exerts its pharmacological effects due to interaction with PTH1R. Unfortunately, because of large molecular weight and metabolic instability, therapeutic application of this peptide via oral route is not possible. We have developed a novel orally bioavailable peptidomimetic-based PTH-1R agonist named as ZYPH0907 for the safe and effective treatment of osteoporosis.

ZYPH0907 is a potent and specific agonist of PTH1R. In vitro assay using UMR106 cells revealed potent PTH1R agonistic activity of ZYPH0907 (EC_{50}: 35 nM). A single p.o. dose of ZYPH0907 in thyroid-parathyroidectomized (TPTX) mice showed dose-dependent increase in the serum calcium levels (ED_{50}: 4.39mg/kg). Repeated daily dosing of ZYPH0907 for 14 days in ovariectomized SD rats caused dose-dependent increase in levels of bone formation biomarkers, osteocalcin and PINP, whereas the levels of TRAP5b, a bone resorption biomarker were reduced. ZYPH0907 was found to be quite stable in gastrointestinal fluids and liver microsomes. In pharmacokinetic (PK) studies, ZYPH0907 showed dose-dependent oral absorption in mice, rats and dogs with short half-life. In a battery of safety pharmacology studies, ZYPH0907 did not show any adverse effect related to CNS, CVS respiratory and GI parameters when tested at doses that are several fold higher than the ED_{50} dose. No off-target interaction was noticed, when ZYPH0907 was screened against a panel of more than 75 molecular targets at 10 mM concentrations. ZYPH0907 was found to be non-mutagenic and non-clastogenic in genotoxicity studies. In acute and repeated dose toxicity studies in Wistar rats and beagle dogs, ZYPH0907 was well tolerated and the NOAEL was found to be several folds higher than efficacy dose. In these studies, the effects observed were either directly or indirectly related to the known pharmacological actions of PTH and were found to be reversible upon cessation of the treatment over a period of two weeks.

In conclusion, ZYPH0907 represents a novel and orally active PTH-1R agonist for the safe and effective treatment of osteoporosis.

Comparative Peptidomic Analysis for Functional Discovery of Neuropeptides

Lingjun Li, Ph.D. | Professor, School of Pharmacy and Department of Chemistry
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All nervous systems employ a large number of amines, amino acids and neuropeptides as neurotransmitters and neuromodulators. Using a highly sensitive mass spectrometry (MS)-based peptide profiling and de novo sequencing strategy, more than 200 neuropeptides have been discovered in a well-defined crustacean nervous system, revealing that even a relatively simple neural network contains an unexpectedly-rich diversity of neuropeptides. To further explore the function of these neuropeptides, an affinity enhanced in vivo microdialysis sampling technique that utilize antibody-linked magnetic nanoparticles is explored to improve peptide recovery from extracellular fluids, thus enabling LC-MS monitoring of neuropeptide secretion during behavior. Furthermore, binary isotopic labeling technique based on formaldehyde labeling and a multiplexed set of isobaric labeling reagents based on dimethylated amino acids have been developed and employed to produce differential display of neuropeptidomes under different physiological conditions. Examples of neuropeptide regulation of feeding behavior and neural network development will be highlighted in this presentation. Collectively, these combined peptidomic and physiological studies will help to elucidate the functional roles that neuropeptides play in regulating neural network plasticity.

Targeting Protein Therapeutics Across the Blood-Brain Barrier with Molecular Trojan Horses

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Biopharmaceuticals, including recombinant proteins and monoclonal antibody therapeutics, cannot be developed as drugs for the brain, because these large molecules do not cross the blood-brain barrier (BBB). Biopharmaceuticals can be re-engineered to cross the BBB, and this is possible with the engineering of IgG fusion proteins. The IgG is a peptidomimetic monoclonal antibody (MAb), which acts as a molecular Trojan horse (MTH) that ferries the fusion protein across the BBB via receptor-mediated transport on endogenous BBB receptors. The most potent BBB molecular Trojan horse is a MAb against the human insulin receptor. MTH fusion proteins have been engineered and validated for neurotrophins (erythropoietin, GDNF), decoy receptors (TNFR), single chain Fv antibodies (against the Abeta peptide), and lysosomal enzymes (iduronidase, iduronate 2-sulfatase). Peptides, that are not candidates for MTH fusion proteins, may be re-engineered for BBB transport with the combination of MTH fusion protein and avidin-biotin technology. The co-injection of the mono-biotinylated peptide and an MTH-avidin fusion protein enables brain penetration of peptide therapeutics.

An Expanding Genetic Code

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The development of new orthogonal aminoacyl-tRNA synthetase/tRNA pairs has led to the addition of approximately 70 unnatural amino acids (UAAs) to the genetic codes of Escherichia coli, yeast, and mammalian cells. These UAAs represent a wide range of structures and functions not found in the canonical 20 amino acids and thus provide new opportunities to generate proteins with enhanced or novel properties and probes of protein structure and function.

Neuropeptidomics: From the Discovery of New Neuropeptides to the Elucidation of their Functions

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Neuropeptides are critical molecules that modulate the physiological activity of almost every neuronal circuit in the brain. Surprisingly, though, more and more brain peptides are being discovered. Even the rate of brain peptide discovery is accelerating. What do these novel peptides do? Two major areas are addressed here, one technical and one biological. The first area highlights mass spectrometry-based technologies to characterize the brain peptides from samples ranging from brain regions to single cells. Using these cutting-edge mass spectrometry-based approaches, we generate lists of known and unique peptides from specific brain regions, with these lists reaching to hundreds of peptides. Even for small brain areas, we still detect hundreds of peptides, making follow-up studies daunting. The second area addresses the question of which peptides are worth extensive follow-up studies. Using the suprachiasmatic nucleus (SCN) as an example, we describe functional studies such as measuring the peptides released from the SCN in an activity dependent manner and at specific times of the day. Knowing that a novel peptide is only detectable at a specific time of the day or under specific electrical stimulation protocols yields critical information on potential peptide function. For example, the SCN peptide “little SAAS” exhibits robust retinohypothalamic tract–stimulated release from the SCN, and exogenous application of little SAAS induces a phase delay consistent with light-mediated cues regulating circadian timing. In other cases, well-known brain peptides are shown to have unique functions. Several additional examples of neuropeptide discovery are described across a range of metazoan life.

High Resolution Mass Spectrometry-Based Profiling of Secreted Peptides for Drug Discovery

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Peptide hormones derived from the neuroendocrine system have great therapeutic value because of their high activity, specificity and low toxicity. Traditionally, characterization of natural peptides has involved collection of a large amount of source material followed by laborious subfractionation following specific activity assays. Mass spectrometric-based techniques, coupled with genomic information and new informatic algorithms, have accelerated the process of peptide characterization from minute quantities. We adopted a strategy called the PHASST-MS approach (Peptide Hormone Acquisition by Smart Sampling Techniques-Mass Spectrometry) involving analysis of secreted peptides from tissue enriched in endocrine cells e.g. from pancreatic islets and gut tissue. In contrast to analysis of cellular lysates, the study of living cells is advantageous because (a) they are responsive to physiological and pharmacological stimuli and (b) less intracellular protein background is produced which can mask the detection of secreted peptides. Minimal sample manipulation minimized adsorptive loss of low abundance peptides which were simply desalted, concentrated and directly analyzed by high resolution LC/MS. Peptide identity was established through a variety of gas phase fragmentation techniques from which amino acid sequence was derived by MS informatics. The use of mass maps for relative quantification, allowed us to see differences in peptide profiles reflective of cellular state (e.g. stimulated or unstimulated, diseased or healthy). By adopting peptidomic rather than proteomic approaches where trypsin digestion is employed, we captured full length posttranslationally-processed peptides <1 to 16 kDa rather than proteolytic fragments for identification (i.e. a “top down” approach). The PHASST-MS collection represents a subset of Amylin’s proprietary PHORMOL library and has been synthesized by low and high throughput techniques for assessment of bioactivity through in vitro and in vivo screening.

Endogenous Peptides to Safely Enhance the Delivery of (peptide) Drugs to the Brain

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Peptides are promising candidates for the treatment of some central nervous system (CNS) disorders. In order to achieve CNS-effects, they must be able to effectively cross the blood-brain barrier (BBB). The distribution of peptides across the BBB is however often limited due to their hydrophilic properties, and short half-life in plasma.

The endogenous tripeptide glutathione (GSH) is found at high levels in the brain and is actively transported across the blood-brain barrier. Glutathione-conjugated pegylated liposomes were found to mediate safe targeting and enhanced delivery of encapsulated drugs to the brain.

to-BBB is developing glutathione pegylated liposomal doxorubicin for patients with brain cancer. The product is based on the marketed pegylated liposomal doxorubicin (Doxil), and was shown to be superior in increasing brain uptake and reducing brain tumor growth in experimental models. The first clinical trial in patients with brain metastases was initiated mid 2011.

A second product in development is glutathione pegylated liposomal methylprednisolone (2B3-201) for the treatment of neuroinflammation. 2B3-201 was shown to have superior efficacy over free methylprednisolone at a much lower dose, and also over (non-targeted) pegylated liposomal methylprednisolone.

Another project aims to study the distribution of a peptide across the BBB on its own and encapsulated into the glutathione pegylated liposomes by using simultaneous blood and brain microdialysis. The steady-state unbound plasma concentrations were kept identical, while the liposomes significantly increased brain peptide delivery.

Finally, in vitro experiments were performed with dextran-FITC (4kDa) encapsulated in glutathione pegylated liposomes and (non-targeted) pegylated liposomes. A significant 5-fold higher uptake of GSH-coated liposomes was observed using microscopy and cell lysates. This specific uptake was liposome size and temperature dependent, indicative of an active endocytotic uptake process.

In conclusion, glutathione pegylated liposomes offer a promising platform for safely enhancing the delivery of (peptide) drugs to the brain.

Enhancing CNS Uptake of Biologics through Molecular Engineering

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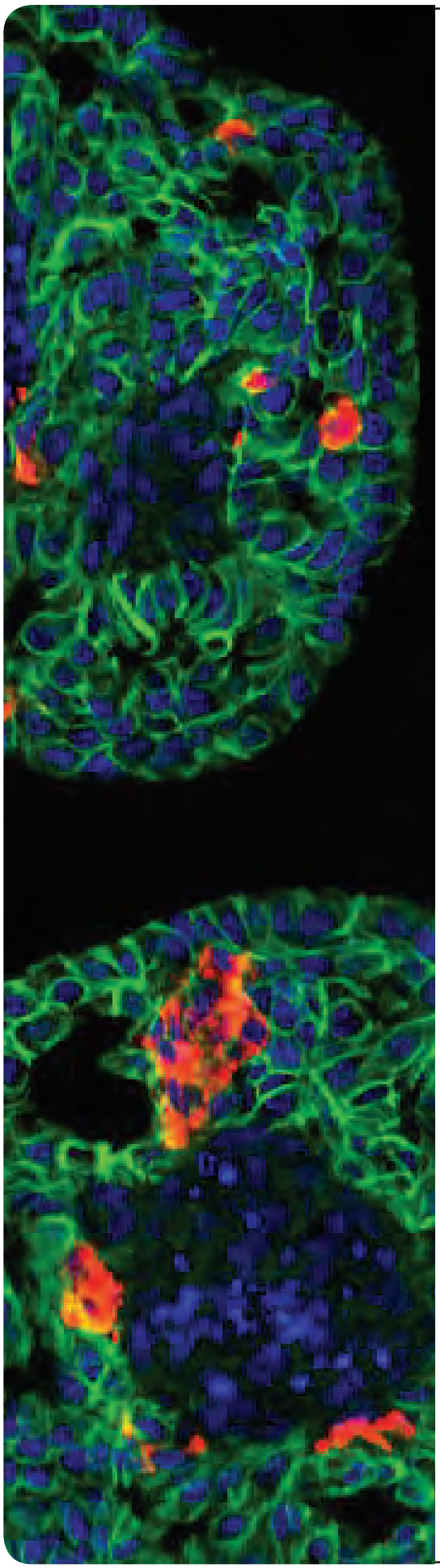
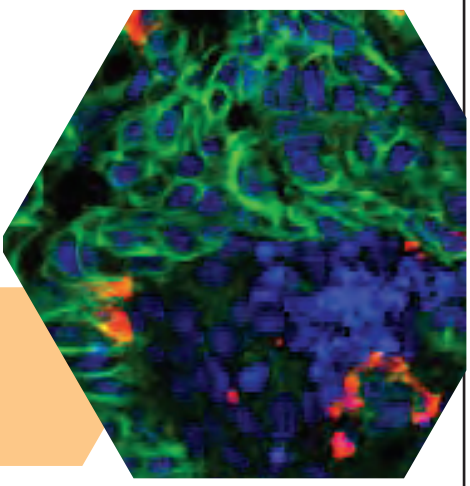
Utilizing receptor-mediated transcytosis (RMT) pathways to cross the blood-brain barrier (BBB) has been explored for several decades as a mechanism to increase protein delivery to the brain. Nevertheless, many have discovered that antibodies targeting RMT pathways, particularly transferrin receptor (TfR), accumulate in CNS vasculature and fail to cross the BBB in appreciable concentrations. We have discovered that reducing the affinity of an antibody for the TfR enhances RMT of the anti-TfR antibody across the BBB into the mouse brain where it reaches therapeutically relevant concentrations. Anti-TfR antibodies that bind with high affinity to TfR remain associated with the BBB, whereas lower-affinity anti-TfR antibody variants are released from the BBB into the brain and show a broad distribution 24 hours after dosing. We designed a bispecific antibody that binds with low affinity to TfR and with high affinity to the enzyme b-secretase (BACE1), which processes amyloid precursor protein into amyloid-beta (Abeta) peptides including those associated with Alzheimer's disease. Compared to monospecific anti-BACE1 antibody, the bispecific antibody accumulated in the mouse brain and led to a greater reduction in brain Abeta after a single systemic dose. TfR-facilitated transcytosis of this bispecific antibody across the BBB may enhance its potency as an anti-BACE1 therapy for treating Alzheimer's disease.



Abstracts of Posters

6th Annual Peptide Therapeutics Symposium



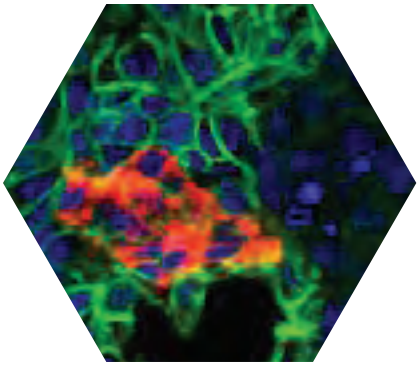


Photo courtesy of the laboratory of Pamela Itkin-Ansari, Ph.D., Adjunct Assistant Professor, Sanford-Burnham Medical Research Institute/UCSD, La Jolla, CA

P 01 Site-specific Antibody-Drug Conjugates by Genetically Incorporated Unnatural Amino Acids

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Antibody-drug conjugates can selectively deliver drugs to cells presenting tumor associated surface markers thereby reducing systemic toxicity. Traditionally, protein conjugations are done through cysteine or lysine residues, but these chemistries often lead to heterogeneous products and process challenges in scale-up. We demonstrate the use of genetically encoded unnatural amino acids with unique chemical reactivity to facilitate the construction of antibody-drug conjugates and provide site, stoichiometry, and homogeneity control. An orthogonal tRNA/aminoacyl-tRNA synthetase pair is used to site-specifically incorporate p-acetylphenylalanine in response to an amber codon in Fab fragments, made in E. coli, and full-length IgG, in mammalian cells. We conjugate monomethyl auristatin E to trastuzumab (anti-Her2) and demonstrate effective in vitro and in vivo cytotoxicity. Our technology can be expanded to any site-specific conjugation of protein to peptides, DNA, or small molecules.

P 02 Challenges in Insulin Purification

Anders Torncrona, Britt Kofoed-Hansen, Jared W. Benedict and P.K. Dutta

AkzoNobel N.V.

Reversed phase liquid chromatography (RPLC) has proven to be a very efficient tool to polish crude solutions of polypeptides. Silica-based reversed phase materials for polypeptide polishing have been on the market for many years now. The single largest application for polypeptide polishing by RPLC is insulin purification. Over the years, there have been many attempts to "optimize" RPLC insulin purification by tailoring the silica backbone and/or bonded phases.

This poster illustrates the effects of silica pore size and bonded phase on the purity and recovery of human insulin. The adsorption capacity has been measured by insulin breakthrough curves for various materials. In addition to the standard silica on the market some prototypes, including a pH stable phase, was included in the study. The exploration of existing and new materials shows the best phase for insulin purity and recovery in this study.

P 03 Bioanalysis of Therapeutic and Endogenous Peptides in Human Plasma

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The purpose of this study is to develop a platform-based approach for bioanalysis of therapeutic and endogenous peptides (including biomarkers) in human plasma. A solid phase extraction (SPE) screening strategy consisting of 1 protocol and 2 mixed-mode sorbents was employed to simplify SPE method development. An LC screening method was developed on a low dispersion system. MRM detection of multiply charged parents and singly or multiply charged fragments was performed using Xevo TQ-S tandem quadrupole MS operating in ESI + mode.

The chromatographic system produced peaks 2-4 seconds wide at base for 12 diverse peptides using the basic LC screening protocol. With minor modifications to the SPE methods for 3 peptides, extraction recovery became > 82% for all peptides. Absolute matrix effects for 8 out of 12 peptides were determined, and found to be <11%. SPE was performed using the µElution format to minimize sample volume used and to concentrate analytes without evaporation and reconstitution. This improved detection limits and eliminated potential adsorptive losses during evaporation and reconstitution. Linearity over 3.5 orders of magnitude and LOD/LLOQ's in the pg/mL range is demonstrated for representative peptides. This study describes initial sample preparation methods and chromatographic conditions for 12 diverse peptide therapeutics/biomarkers using the LC, MS, and SPE screening methods described.

P 04 Optimization of the Native Glucagon Sequence for Medicinal Purposes

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Glucagon is a life-saving medication used in the treatment of hypoglycemia. It presents unique structural challenges to the identification of an analog of high biological activity and selectivity that also possesses sufficient aqueous solubility and stability such that it might be developed as an emergency use medicine. At low and high pH the peptide can be formulated at a milligram per milliliter but the chemical stability of the hormone is limited, as evidenced by the formation of multiple degradation peptides. Consequently, the commercial preparation is provided as a lyophilized solid with an acidic diluent and directions for rendering it soluble at the time of use. A set of glucagon analogs was prepared to explore the identification of a glucagon analog with enhanced solubility and chemical stability at physiological pH. We observed the previously characterized formation of glucagon degradation products upon incubation of the peptide in dilute acid for extended periods, or elevated temperature. Lowering the isoelectric point of the hormone through the substitution of asparagine 28 with aspartic acid significantly increased the solubility at physiological pH. Similarly, the C-terminal extension of the hormone with an exendin-based, ten-residue C-terminal sequence yielded a peptide of dramatically enhanced solubility. These two glucagon analogs D28 and CEX maintained high potency and selectivity for the glucagon receptor relative to GLP-1 receptor. The glucagon analogs D28 and CEX demonstrated all of the chemical, physical, and biochemical properties supportive of further study as potential clinical candidates for treatment of hypoglycemia.

P 05 An Expanded Self-Antigen Peptidome Is Carried by the Human Lymph As Compared to the Plasma

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The pre-nodal afferent lymph is the fluid which directly derives from the extracellular milieu from every parenchymal organ and, as it continues to circulate between the cells, it collects products deriving from the organ metabolism/catabolism. A comprehensive qualitative and quantitative investigation of the self-antigenic repertoire transported by the human lymph is still missing. Our results showed a major difference between lymph and plasma that could be visualized by FPLC and 2D gel in the amount of low molecular weight products corresponding to peptide fragments. with MW<5000 Da. Naturally processed peptides in normal pre-nodal human lymph were then fractionated by HPLC and characterized by multidimensional nano-LC-MS/MS mass spectrometry. Analysis of more then 300 sequences identified self-peptides derived from both intracellular and extracellular proteins revealing the variety of catabolic products transported by human lymph. Quantitative analysis established that at least some of these peptides are present in the circulating lymph in nanomolar concentration. The peptidome, generated by physiological tissue catabolism and transported by the pre-nodal lymph, is in addition to the self-peptidome generated in endosomal compartment. Unlike self antigen processed by local or nodal APC, which mostly produce epitopes constrained by the endosomal processing activity, self antigens present in the lymph could derived from a wider variety of processing pathways; including caspases, involved in cellular apoptosis, and ADAM and other metalloproteinases involved in surface receptor editing, cytokines processing and matrix remodeling. Altogether, expanding the tissue-specific self-repertoire available for the maintenance of immunological tolerance.

P 06 Rational Design, Synthesis and Structural Characterization of D-Phe-Pro-D-Arg-Derived Thrombin Inhibitors

Ana Carvalho Figueiredo#[a], Cristina C. Clement#*[b], Sheuli Zakia[b], Julian Gingold[c], Manfred Philipp[b] and Pedro José Barbosa Pereira[a*] #These authors contributed equally to this work
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Novel hexapeptides, pentapeptides and tetrapeptides were designed using *in silico* structure-based design approaches and further tested for their ability to inhibit α-thrombin *in vitro*. Initial molecular docking experiments generated a candidate group of compounds with both L- and D- amino acids, containing the D-Phe(P3)-Pro(P2)-D-Arg(P1)-P1'-P2'-P3'-$CONH_2$ sequence. The use of D-Arg in the P1 position made the designed peptides inhibitors stable to proteolysis. The structure-activity relationship revealed the lead compounds as being tetrapeptides from the series D-Phe-Pro-D-Arg-P1'-$CONH_2$. The P1' position was scanned with L and D-isomers covering the major chemical classes of natural or unnatural amino acids, such as L-2-thienylalanine (L-Thi). The lead tetrapeptide, D-Phe-Pro-D-Arg-D-Thr-$CONH_2$, has a K_i of 0.85 mM. The three-dimensional structures of three complexes of human α-thrombin with three lead peptidic inhibitors (with L-isoleucine (p3), L-cysteine (p4) or D-threonine (p6) at the P1' position of the lead D-Phe-Pro-D-Arg-P1'-$CONH_2$ sequence) were determined by X-ray

crystallography. All the inhibitors bind in a substrate-like orientation to the active site of thrombin. The X-ray analyses of all three complexes show the upstream residues sitting deeper in the S2 and S3 pockets while the cleavable bond adopts an unfavorable geometry for nucleophilic attack by the serine side chain (3.69Å, 2.85Å and 2.96Å distance between the Ser195 Oy and the arginine carbonyl carbon for p3, p4 and p6, respectively). Thus, our crystal structures of human α-thrombin complexes with peptidic inhibitors with D-Arg in the P1 position provide insights into the main structural features that enabled them to be totally stable to proteolysis.

P 07 Design and Synthesis of Novel Bifunctional ligands (Bradykinin Antagonists and Opioid Agonist) for Treatment of Chronic and Neuropathic Pain

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Kinins are naturally occurring vasoactive peptides which are known to be important mediators of a variety of biological effects, including cardiovascular homeostasis, inflammation, and nociception. The kinin family includes Bradykinin, Kallidin and their active metabolites des-Arg-bradykinin and des-Arg-kallidin. The biological actions of these kinins are mediated by two major G-protein-coupled Bradykinin receptors: B1 and B2. Opioid receptors belong to the big family of G-protein-coupled receptors which mediates antinociceptive effects in humans. Here we designed and synthesized novel bifunctional ligands containing Bradykinin antagonist and Opioid agonist pharmacophore, these novel ligands have novel biological activity profile in pain pathways, wherein the Opioid pharmacophore is maintained towards the N-terminal.

Opioid μ/dAgonists_____ B2 Receptor Antagonist
Tyr-Pro-Phe-DArg -Arg-Pro -Hyp -Gly -Thi –Ser-DTic –Oic-Arg
Tyr-DAla-Gly-Phe-DArg-Arg-Pro-Hyp-Gly-Thi-Ser-DTic-Oic-Arg

1. Supported by a grant from the U.S.Public Health Service NIDA
2. Leeb-Lundberg,L.M.F.; Marceau, F.;Muller-Esterl,W.; Pettibone, D. J.; Zuraw, B. L. Pharmacol. Rev. 2005, 57
3. Dziadulewicz, E. Ann. Reports in Med. Chem. 39,113-121, 2004

P 08 Enhanced Albumins and Albumin Fusion Technology, Albufuse®Flex – Tailored Circulatory Half-life to Meet Medical Needs

Randall Engler
Novozymes Biophama UK Ltd.

A major challenge for the therapeutic use of many peptides and proteins is their short circulatory half-life. Albumin is the most abundant plasma protein and has an extended circulatory half-life due to its size and FcRn recycling, a property shared with IgG. Recombinant fusions to albumin have been shown in the clinic to have significantly enhanced pharmacokinetics whilst retaining the bioactivity of the therapeutic peptide or protein. While the IgG:FcRn interaction is extensively mapped and modifications to this interaction have been shown to improve the pharmacokinetics of these modified antibodies, the characterisation of the albumin:FcRn interaction is in its infancy. Amino acid positions have been identified within the albumin sequence that allow the modulation of the albumin:FcRn interaction — this data set starts the process of mapping the entire albumin:FcRn interaction surface leading to the definition of a smaller FcRn binding site within the albumin structure. Through subtle modification of the albumin molecule this innovative technology aims to prolong the circulatory half-life of the albumin molecule itself, thereby conferring these advantageous properties to any associated therapeutic. As a consequence this may allow scientists the opportunity to tailor their drug design to fit the patient's specific medical needs, reducing drug side effects, improving patient compliance and quality of life. The presentation will describe key advances in the developing the next generation albumin fusion/conjugation half-life enhancing technologies.

P 09 In Vivo Targeting of Human Cancers with Radiolabeled Somatostatin Antagonists

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The use of radiolabeled somatostatin agonists targeting neuroendocrine tumors over-expressing somatostatin receptor subtypes (sst_{1-5}) is an established diagnostic and therapeutic procedure in oncology. We show that similarly radiolabeled somatostatin antagonists, even though they do not internalize, can be better radioligands to target tumors than somatostatin agonists with comparable binding characteristics. For example, the somatostatin agonist, ^{111}In-DOTA–[1-Nal^3]-octreotide with strong sst_3-binding and internalization properties showed a much lower and shorter-lasting uptake in mice bearing sst_3 tumors than our sst_3-selective antagonist ^{111}In-DOTA-sst_3-ODN-8. Similarly, the tumor uptake of the sst_2-selective antagonist (^{111}In-DOTA-BASS) was considerably higher than that of a highly potent sst_2-selective agonist ^{111}In-DTPA-TATE in mice bearing sst_2 tumors. Additionally, the sst_2-selective antagonists showed more lesions (^{111}In-DOTA-BASS, 16 lesions, 2.4 injected activity (%IA), ^{111}In-DOTA-JR11, 36 lesions, 7.2% IA) than the agonist ^{111}In-DTPA-octreotide (11 lesions, 1.3% IA). We have also evaluated whether DOTA or NODAGA chelator-coupled somatostatin antagonists are affected by the nature of the radiometal. Indeed, we show that complexation with In(III), Y(III), Lu(III), Cu(II) and Ga(III) impacts binding affinity in an unpredictable way. Overall, these results emphasize the fact that the use of biologically active peptide antagonists versus agonists will significantly affect peptide receptor–mediated imaging and therapy.

P 10 Towards Orally Available Peptide Therapeutics

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EvoRx Technologies, South Pasadena, CA 91030

Peptides are promising next-generation therapeutics exhibiting high binding specificities and affinities. However, they are unstable in vivo and it is difficult to rationally stabilize peptides without loss or change of function. Here, we describe a novel mRNA display platform to evolve highly stabilized unnatural cyclic peptides with potent anti-tumor properties. We designed a 20 million member library that included a non-natural N-methyl amino acid and pre-selected for stabilized peptides by exposure to proteases. The resulting peptides exhibited a ~500-fold improvement in human serum stability ($t_{1/2}$ = 160 hours). Simple conjugation to a non-toxic, small molecule, natural product allowed for efficient oral uptake in vivo. We used this library to evolve ligands targeting the oncogenic protein Her-2 by targeting human breast cancer cells overexpressing Her-2. Two ligands were tested in a breast cancer cell model, showing 25% and 44% inhibition of growth when administered separately, and 61% inhibition when administered together. This is in comparison to 25% inhibition by Herceptin. Our peptides demonstrate comparable efficacy to Herceptin in mouse xenografts as co-administration of these ligands results in an average tumor size reduction of >35% in mouse xenografts over 4 weeks of treatment, while untreated mouse tumors grew to 2.5 times their original size. This work provides a roadmap for the development of orally bioavailable peptidic ligands with excellent stability and therapeutic efficacy for multiple disease states.

P 11 Enhanced Efficacy in Treating the Metabolic Syndrome by Peptide-Directed Estrogen

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Rodent and human clinical studies established that estrogen possesses robust anti-diabetic and weight-lowering actions, however, the clinical application of estrogen is limited due to the fear of its oncogenic potential and gynecological action. To enhance the therapeutic index of estrogen, we explored the preferential targeting of estrogen to desired tissues while minimizing action at breast and endometrial tissues through the use of incretin-based peptide conjugates. By marrying the pharmacologies of GLP-1 and estrogen, we envision a constructive beneficial effect on glycemic and energy homeostasis by the combined insulinotropic and anabolic activities on pancreatic beta cells with an anorectic effect at the hypothalamus. A set of peptide-estrogen conjugates were synthesized to possess full GLP-1 agonism with a broad range of activities and with linker chemistries that enable differential estrogen release from chemical forms that are stable to other forms that fully release estrogen in a few hours. In metabolically-challenged non-diabetic mice, a fully active GLP-1 agonist with a stably-linked estrogen consistently proved to be more efficacious in improving blood glucose and body weight than the comparative GLP-1 and estrogen controls which likely results from synergistic hormone action rather than enhanced pharmacokinetics; however, the mechanism by which these beneficial effects are achieved, particularly the tissues of action and estrogen receptors responsible, remains a focus of ongoing investigation. Furthermore, this highly potent GLP-estrogen conjugate is devoid of classical estrogenic activity in endometrial tissues as assessed by the lack of uterine hypertrophy, however, the oncogenic potential in breast tissue is currently being evaluated through xenograft studies.

P 12 Anesthesiologists: The Primary Profession Which Delivers Peptide Therapeutics In The Clinic?

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Department of [1]Anesthesiology and [2]Chemical and Systems Biology, Stanford University

Anesthesiologists are physicians that have integral roles across hospital infrastructure, including providing services in the operating room, obstetric suite, intensive care unit, pain clinics and during code situations. With peptide therapeutics having quick onset, specific target of action, rapid metabolism, minimal drug-drug interactions and efficient elimination, peptides are ideal agents to be used by an anesthesiologist. However, the number of peptides in the clinic given by anesthesiologists is unknown. Therefore, in addition to personal experience, we undertook a literature search to identify what peptides are approved by the US FDA and what peptides currently in clinical trials have indications related to anesthesiology practice.
We conducted a Pubmed literature search using a specific peptide name and the word anesthesia. From literature review and personal experience, it is estimated an anesthesiologist uses 14 of the approximately 26 clinically approved peptides in the US, or 54%. These include agents such as octreotide, bilvirudin, ziconotide, pitocin, vasopressin, nesiritide and eptifibatide. Peptides in clinical trials, such as depelestat and linaclotide, will also be frequently used by anesthesiologists if approved. These findings suggest anesthesiologists are likely the principle administrators of peptides in the clinic and perhaps for peptides approved for future use. Potential reasons why peptides are commonly used among anesthesiologists and the benefits and problems of clinical trials carried out by anesthesiologists will also be discussed.

P 13 Pharmacological Characterization of FE 203799, a Novel Long Acting Peptide Analog of Glucagon-like peptide-2 (GLP-2)

Diane Hargrove, Sudar Alagarsamy, Steve Qi, Karthik Srinivasan, Glenn Croston, Regent Laporte, Javier Sueiras-Diaz, Kazimierz Wisniewski, Jennifer Hartwig, Halina Wisniewski, Mark Lu, Alexander Posch, Claudio Schteingart, Pierre Rivière
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GLP-2 is a 33 amino acid peptide that is released from intestinal L-cells following nutrient ingestion and acts at distinct G protein coupled GLP-2 receptors in the small intestine and colon to potently stimulate intestinal growth. GLP-2 also increases nutrient absorption, stimulates mesenteric blood flow and modulates gastrointestinal motility. GLP-2 agonists are efficacious in animal models of disease including models of large and small bowel inflammation, short bowel syndrome and chemotherapy- and radiation-induced mucositis suggesting they may have therapeutic potential for the treatment of gastrointestinal diseases and disorders. Clinical development of GLP-2 agonists is testing this hypothesis.

Peptides are widely believed to have rapid clearance and a short half-life, limiting their clinical utility. Indeed, native GLP-2 has a short circulating half-life due to cleavage by dipeptidyl peptidase IV (DPP4) limiting its development as a therapeutic agent. A DPP4 resistant analog of GLP-2 (teduglutide, h[Gly2]GLP-2 (1-33)) with somewhat lower clearance than GLP-2 is in clinical trials in patients with short bowel syndrome.

Herein we report on the characterization of FE 203799, a novel GLP-2 analog that retains potency and selectivity at the hGLP-2 receptor and has a greatly improved pharmacokinetic (PK) and pharmacodynamic profile. In vitro potency (EC_{50}) at the hGLP-2 receptor was determined using HEK-293 cells transiently co-transfected with hGLP-2 receptor and a cAMP responsive luciferase reporter plasmid. The EC_{50} values for FE 203799, hGLP-2 and teduglutide were 0.03, 0.07 and 0.09 nM respectively. In rat PK studies, FE 203799 was shown to have dramatically lower clearance than GLP-2 or teduglutide, resulting in a long half-life. Following intravenous (IV) bolus administration, the elimination half-life of FE 203799 was 8- and 25-fold longer than teduglutide and hGLP-2 respectively. The half-life of FE 203799 was even longer following subcutaneous (SC) administration. Treatment with FE 203799 resulted in greater in vivo potency and less frequent dosing to achieve pharmacodynamic efficacy for stimulation of intestinal growth in rats, likely stemming from the observed increase in half-life.

These unique properties of FE 203799 relative to analogs currently in clinical trials may confer a superior therapeutic profile for the treatment of gastrointestinal diseases.

P 14 Novel T Cell Driven Approach Leads to the Identification of Immunoprevalent Antigens

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The prevention and treatment of infectious diseases is highly dependent on the availability of reliable diagnostic tests and protective or therapeutic vaccines. There also exists an urgent need to develop reliable biomarkers to monitor treatment success and to predict disease progression from asymptomatic to symptomatic disease in several disease scenarios. The elucidation of the disease-relevant antigens that elicit the protective immune responses is critical and required for the development of diagnostics and treatments. Here we present a novel "T cell driven approach" that permits the direct identification of pathogen epitopes and protein antigens capable of triggering specific T cell responses upon immunization in humans. This approach includes a single pathogen in vitro stimulation, the generation of pathogen specific T cell clones, the evaluation of their specificity by multiple cytokine production, and the screening of the clones with positional scanning peptide libraries. PBMC from smallpox vaccinated donors were used to generate vaccinia specific CD4+ T cell clones. The peptide specificity of these T cells was elucidated in a completely unbiased fashion by screening each of the clones with positional scanning libraries composed in total of trillions of peptides. Ten novel epitopes and their corresponding protein antigens from vaccinia virus that trigger CD4+ responses upon smallpox vaccination in humans were identified. GM-CSF, while not a standard cytokine used for monitoring T cell responses against vaccines or infections, was found to require lower antigen concentration for its production than other cytokines, such as IFN-g, IL-2, and TNF-a. Furthermore, a comprehensive analysis of the reported immunogenicity of the vaccinia proteins from which the identified epitopes are derived revealed that the "T cell driven" approach presented here results in the identification of peptides derived from highly immunoprevalent vaccinia proteins. This "T cell driven" approach can be readily implemented to determine the specificity of the response following vaccination or infection with large size pathogens for which other methodologies could be more cumbersome.

P 15 Development of Therapeutic Antibody Conjugates via Unnatural Amino Acid Chemistry

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Immunoconjugates and bispecific antibodies are of considerable interest in oncology because of their ability to target tumor cells with high specificity while leaving healthy tissue unharmed. Recombinant antibodies and antibody conjugates are now a major class of therapeutics. The FDA has approved over twenty therapeutic antibodies; however, there are still significant discovery and manufacturing issues due to conjugation methods. The primary goal of my research hopes to overcome these obstacles by incorporating site-specific unnatural amino acids (UAAs) into the constant region of antibodies. These UAAs have reactivity orthogonal to the twenty canonical amino acids and can be conjugated effectively to different moieties (e.g. hydroxlamines) to create geometrically controlled bispecific antibodies and immunoconjugates. We have site-specifically labeled various antibodies (anti-Her2, anti-CD20, anti-CD3, etc.) with single-stranded DNA and PNA (peptide nucleic acids). This technique allows for control over both the valency and orientation of multivalent proteins by exploiting the sequence specific base pairing of oligonucleotides. Libraries of "binder" (e.g. antibodies) and "effector" (e.g. toxins) molecules can be easily generated, creating a combinatorial library of all possible multivalent conjugates that can then be rapidly screened for therapeutic agents.

P 16 A Novel Linker Technology to Improve Therapeutic Function of Lead Peptides

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While PEGylation is well established method to enhance its life in body, it is achingly challenging to apply to peptide drug candidates directly because it often loss primary therapeutic effect. This phenomenon is derived from the position where the functional moiety is appended on the peptides. Jitsubo established a novel linker technology avoiding such concerns as to connect functional moiety into therapeutic sequences with conventional methods. This poster will show a new design peptides to inhibit osteoclast formation with PEG modification and optimized processes from original cyclic peptide containing a disulfide bond.

P 17 HT Screening for Bioactive Peptides that Increase Radiation Tolerance Using a Pooled Lentiviral Peptide Scanning Library

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There is much interest in developing therapeutics that increase tolerance to radiation exposure. However, despite significant effort, few compounds have yet been identified. To address this need, we have adopted a novel approach that uses a pooled lentiviral scanning peptide expression library to screen for peptide sequences that stimulate the NF-kB pathway, which is thought to increase resistance to ionizing radiation. The peptide expression library, designed from all known extracellular proteins, was used to transduce an NF-kB reporter cell line. Cells expressing peptide agonists that demonstrate modulation of the NF-kB pathway were isolated by FACS and the peptide sequences then identified by high throughput sequencing. Subsequent validation of both individual lentiviral peptide constructs and chemically-synthesized peptides confirmed activation of NF-kB, proving that the approach identifies activity, not just binding. In vivo testing is underway to evaluate the extent that the individual peptides confer actual protection from radiation.

P 18 Demonstration of Anti-tumor Efficacy in Multiple Preclinical Cancer Models Using a Novel Peptide Inhibitor (Aurigene-012) of the PD1 Signaling Pathway

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Programmed cell death-1, an immunoreceptor belonging to the CD28 family, plays an important role in negatively regulating immune responses. Blocking of PD-1 signalling pathway has been shown to result in restoration of defective immune cell functions in cancer and chronic infections. PD-1 targeted therapies in the ongoing clinical trials are based on either antibodies or fusion proteins. To exploit unique advantages of peptides over antibodies or fusion proteins, herein we report a peptide based strategy to block the PD1 signaling pathway. Sequences critical for ligand-receptor interaction were identified and combined in a non-linear fashion. The strategy resulted in a novel peptide, AUR-012 (29 mer), which displayed sub-nanomolar potency in disruption of PD1-PDL1/2 interaction, and highly effective restoration of proliferation and effector functions of splenocytes and PBMCs. In vivo studies demonstrated an excellent PK-PD correlation with sustained PD for >24 h. In preclinical models of melanoma, breast and kidney cancers, AUR-012 showed superior efficacy compared to therapeutic agents currently used in the clinic in inhibition of both primary tumor growth and metastasis. Interestingly, dosing once in three days was equally efficacious as once a day dosing with no signs of overt toxicity and generation of neutralizing activity. These findings support further development of AUR-012 for potential clinical use.

P 19 Development of Non-opioid Dynorphin A Analogs Interacting with Bradykinin Receptors as an Antagonist

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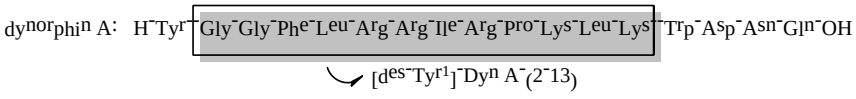
It has been shown that after nerve injury, up-regulated dynorphin directly interacts with bradykinin receptors (B1R and B2R) resulting in hyperalgesia, and HOE140, a bradykinin 2 receptor antagonist, affords antihyperalgesic effect by blocking the interaction between B2R and dynorphin.[1, 2] This is a non-opioid effect that cannot be blocked by opioid antagonists. Since [des-Tyr[1]] dynorphin (2-13) is known to bind allosterically with the B2R in the micromolar range, systematic structure-activity relationships study on the ligand was performed to identify the structural features for the receptor. The SAR results will be discussed in detail. Supported by grants from the U.S.Public Health Services, NIH, and NIDA.



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P 20 BioHeatMap: Search, Visualize and Discover New Opportunities from the Scientific Literature

Robert Meadows
Bioheatmap Inc.

At the center of the pharmaceutical researchers' literature interest is the worldwide biomedical scientific knowledge covered by NIH's PubMed™. It amounts to more than 19 million articles and grows exponentially: From one million articles produced in the 50s, to seven million new articles in the 00s. Over one million articles will be published in 2010 in the over 5,000 covered scientific journals. Using this information effectively is time consuming. Many scientists have to split their time between laboratory endeavours and literature analysis to find experts and to support existing and new efforts An individual scientist may spend as much as 50% of his/her time at the computer, data mining, filtering and reading PubMed™ information one abstract at a time. This is an opportunity cost that slows down the research process, drives up research costs and will continue to burden the pharmaceutical industry as data sources become larger and more topic-focused.

We present a web-based software suite designed to give scientists both panoramic and narrow views of the scientific literature. With a few mouse clicks researchers can see disease-substance relationships, authors and centers of interest, timelines and activity/intensity metrics and much more. Our poster describes the software and illustrates its utility by answering the question:

According to Pubmed™ who are the prolific authors, what are the indications, what are the related substances, when was it popular and where are the centers of excellence for Desmopressin?

P 21 Reduction in Food Intake and Weight Loss in Dogs with UGP281, an Oral Anorexigenic Peptide

Nozer Mehta, William Stern, Amy Sturmer, Steven Carl, Vicki Ray, Angelo Consalvo, Christopher Meenan, Christina Sisk, Frank Ritacco, Nancie Souders, Seth Pennington, Jenna Giacchi, Karen Veintimilla, Austin Vryhof and Ali Bolat.
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Unigene's lead peptide drug, UGP281, is produced by recombinant expression in E. coli with yields of approximately 500 mg/L of intact, extracellular secreted peptide. An enteric-coated capsule formulation for oral delivery of this peptide has been developed that includes excipients for the inhibition of intestinal proteases and enhancement of paracellular transport through the lumen of the intestine. The physiological effect of UGP281 on food intake and body mass in Beagle dogs, has been investigated in placebo-controlled studies using injectable or enteric-coated capsule formulations. In a crossover design placebo controlled study over two weeks, daily intra muscular injections of UGP281 at a concentration of 5 µg/kg resulted in a reduction in food intake of 60 to 80% and a weight loss of 6 to 8%. In a chronic oral dosing study, 2 groups of 4 dogs each were fasted overnight and given a single oral capsule containing either UGP281 or placebo in the morning and fed for 6 hours per day. An acute reduction in food intake and sustained weight reduction of >8% compared to placebo was observed for a period of 5 weeks. In comparative studies by intra muscular injections in a rat model, UGP281 demonstrates greater reductions in food intake and body weight than other peptide drugs in clinical development. Based on the results to date, UGP281 offers the potential of a potent, patient friendly orally dosed peptide therapy for the management of obesity.

P 22 Branched Peptide Inhibitors of Akt1

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The Akt kinase is a critical intracellular signaling node which governs many pro-growth, anti-apoptotic pathways. The therapeutic efficacy of small molecule Akt inhibitors is often compromised by poor specificity, a feature common to most kinase inhibitors that target the highly conserved binding pockets that define the active site. Here we present the use of iterative in situ click chemistry to assemble a branched peptide triligand that displays low-micromolar inhibitory potency against Akt1 while binding outside the active site. Iterative in situ click chemistry utilizes the target protein to catalyze the azide-alkyne cycloaddition reaction between a soluble anchor peptide and a resin-bound OBOC peptide library. To characterize the efficiency of the on-bead in situ click reaction, we developed a novel QPCR-based strategy that enabled the first quantitative evaluation of its

yield relative to the copper-catalyzed process. These experiments also demonstrated the effect of the protein target, ligand orientation, and linker geometry on reaction efficiency. The resulting triligand shows mid-nanomolar affinity and excellent selectivity for Akt1 and efficiently immunoprecipitates full-length Akt from OVCAR3 ovarian cancer cell lysates. A fluorescent version of the triligand was used to localize Akt in cells stimulated with EGF and Insulin demonstrating its utility as a tool for cell biology and immunocytochemistry. Kinetics experiments were used to rule out competitive inhibition with respect to the ATP and peptide substrates, suggesting a novel allosteric mechanism of inhibition We are currently optimizing the inhibitory potency of the triligand and exploring its in vivo efficacy in multiple cancer cell lines.

P 23 Inhibition of Myelin-reactive T Cell Responses by a Small Molecule Peptide Mimetic HLA-DR2 Inhibitor for the Treatment of MS

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PV-267 is a novel, highly specific small molecule inhibitor of antigen binding to the MS-associated MHC class II molecule HLA-DR2. The peptide mimetic compound is stabilized toward cathepsin degradative enzymes found in antigen presenting cells and is also fully stable in plasma. PV-267 is highly efficacious in the prevention and treatment of EAE in HLA-DR2 transgenic mice. Importantly, the compound is highly effective in inhibiting the production of proinflammatory cytokines by myelin-specific T cells from HLA-DR2+ MS patients. Exploratory pharmacokinetics, toxicology, formulation, and synthesis studies support the selection of PV-267 for development as a therapeutic for MS

The work has been partially supported by an NIH SBIR grant (1R43 NS048731-01), by the NJ Economic Development Authority, and by Fast Forward LLC, the investment arm of the National Multiple Sclerosis Society.

P24 Discovery of Bi-Functional Peptides Balanced in Glucagon Antagonism & GLP-1 Agonism

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GLP-1 provides unique efficacy in the control of blood glucose in the treatment of adult-onset diabetes by enhancing insulin and partially suppressing glucagon secretion. It seems plausible that addition of glucagon-receptor antagonism to selective GLP-1 agonists would enhance glucose lowering. The identification of a dual-acting peptide functioning as an antagonist at the glucagon receptor and an agonist at the GLP-1 receptor constitutes a molecular challenge due to their structural homology. Our observations into the structure-activity, starting with glucagon/GLP-1 co-agonists demonstrate that N-terminal truncation to yield a specifically shortened analog fully antagonizes glucagon action while maintaining full GLP-1 receptor agonism. The chemical refinement of the position 6 amino acid in addition to backbone secondary structure stabilization by covalent lactam bond yielded a balanced dual-acting peptide individually characterized in vitro to possess an IC50 at the glucagon-receptor and an EC50 at the GLP-1 receptor of 20nM. The mixed-action peptide, when administered in mice, exhibited both activities and lowered blood glucose. The molecular basis for differential activity at two homologous receptors constitutes a conundrum and something worthy of structural definition. Homology analysis revealed a set of putative GLP-1 receptor sites where mutations were introduced to identify the source of differential activity. The initial results indicate that the core domain in each receptor determines the pharmacology.

P 25 BMP-2 Derived Peptide Loaded Collagen Matrix For Bone Regeneration Therapy

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Recombinant human bone morphogenetic protein stimulates regeneration of alveolar bone and cementum in periodontal defects. We hypothesize that synthetic peptide derived from BMP receptor I and receptor II binding domains of BMP-2 would have bone regeneration activity. We chose collagen matrix as a supportive biomaterial for bone regeneration. Collagen is a biocompatible protein and maintains structure of bone. Herein, collagen matrix was fabricated and modified with synthetic peptide derived from BMP-2 in order to increase bone regeneration.

Synthetic peptide was synthesized and loaded into the collagen matrix. Cell attachment and proliferation on the modified collagen matrix was examined by MTT assay, scanning electron microscopy, and confocal microscopy. Osteoblastic differentiation was assessed by ALPase activity, Alizarin Red S, Calcein staining. Expression of functional genes and activation of cell signaling were assessed by reverse transcription-polymerase chain reaction and Western blot.
In this study, BMP-2 derived peptide modified collagen matrix promoted osteogenic differentiation in a manner similar to BMP-2. These results demonstrated that the peptide derived from BMP-2 loaded collagen matrix can be applied as a bioactive material for bone regeneration therapy.

P 26 Peptide-Fibrin Matrix as a Tissue Engineering Scaffold

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Fibrin matrix exploits the final stage of the coagulation cascade in which fibrinogen molecules are cleaved by thrombin, convert into fibrin monomers and assembled into fibrils, eventually forming fibers in a three-dimensional network. In the present study, we determined the in vitro optimal fibrin binding peptide for HaCaT cells proliferation in fibrin matrix. All fibronectin derived (FND) peptides were manually synthesized by the F-moc chemistry. The present study has assessed a simplified version of a fibrin clot prepared by using solutions containing fibrinogen, fibronectin derived peptides, thrombin, calcium and aprotinin. The direct binding kinetics of FND peptides to fibronectin was examined using SPR. Fibrin structure can be determined microscopically, using atomic force microscope, scanning electron microscopy or thermogravimetry. In this study, we report that FND peptides incorporated into a fibrin clot promotes cell spreading and cytoskeletal organization that is very different from that seen on fibrin alone. The novelty of the manuscript is based on the functionalized system by mixing FND peptides specifically to the fibrin scaffold matrix to provide signal and scaffold functions for tissue regeneration.

P 27 Use of a Positional Scanning Tetrapeptide Library to Discover Ligands that Restore Function at a Human Melancortin-4 Receptor Polymorphism

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The L106P melanocortin-4 receptor SNP has been reported as a heterozygous polymorphism in an obese patient.[1] Endogenous melanocortin agonists have decreased affinity at L106P, while tetrapeptides were shown to exhibit potent activity[2]. This mutation is located in the putative binding region for ligands and may be distorted due to the amino acid change. The screening and deconvolution of a positional scanning tetrapeptide library[3] composed of L, D and unnatural amino acids that in total represents more than 14 million tetrapeptides resulted in the identification of tetrapeptides that restore functional activity. We found that the incorporation of (pI)-D-Phe at position 2 and (pNO2)-D-Phe at position 4 exhibited nM potency at the L106P hMC4R. This study demonstrates the utility of positional scanning libraries for the identification of compounds that can restore function at natural human polymorphisms in obese patients.

This work is supported by NIH grant RO1 DK64250 (U. Florida) and the State of Florida, Executive Officer of the Governor's Office of Tourism, Trade and Economic Development (TPIMS).
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P 28 Bioanalysis and Pharmacokinetics Profile of FE 203799: A Novel Glucagon-Like Peptide-2 (GLP-2) Long Acting Peptide Agonist

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GLP-2 is a 33-amino acid peptide that is released from intestinal L-cells following nutrient-ingestion. It is known to stimulate intestinal growth, nutrient absorption and mesenteric blood-flow and to modulate gastrointestinal motility. Native GLP-2 has a short elimination half-life (6.4 and 7.2 min in rats and humans, respectively) and high clearance (24.6 and 6.8 ml/min/kg in rats and humans, respectively) due in part to its susceptibility for the dipeptidyl peptidase-IV (DPP4) enzyme. A DPP4 resistant analog of GLP-2, teduglutide, has a lower, but still relatively high, clearance (9.9 and 2 ml/min/kg in rats and humans, respectively) than GLP-2. Herein, we describe a novel GLP-2 analog, FE 203799, which retains potency and selectivity at the hGLP-2 receptor but has a superior ADME/pharmacological profile.

The novel GLP-2 analogue FE 203799 was found to be equipotent to hGLP-2 and teduglutide in an in vitro functional assay. In rats, FE 203799 was shown to have dramatically lower clearance (0.27 ml/kg/min) than GLP-2 or teduglutide. The PPB of FE 203799 was found to be 99.7%, which may be the main reason for its low systemic clearance. Following IV-bolus administration, the elimination half-life of FE 203799 (159 min) was 8- and 25-fold longer than teduglutide and hGLP-2, respectively. The SC half-life of FE 203799 was even longer (701 min, bioavailability of 74%), suggesting rate limiting SC absorption. The PK parameters of FE 203799 obtained in the various species gives insights to attempt to predict its PK in humans. Treatment with FE 203799 in rats resulted in greater in vivo potency and less frequent dosing when compared to teduglutide, likely due to its longer half-life. These unique properties of FE 203799 may, in-turn, confer a superior therapeutic profile in the treatment of gastrointestinal disease.

P 29 Novel Selective Peptide Regulator of Protein Kinase C Based on Rational Approach Design

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Stanford University, Palo Alto, CA

Protein kinase C (PKC) plays a critical role in various diseases such as cancer and stroke, and is a key player in a variety of signal transduction pathways such as apoptosis and cell proliferation. PKC is a large family of serine/threonine kinases that translocate from one cell compartment to another following activation. Based on a number of rational approaches, short peptides were developed to regulate PKC isozyme interaction. ψPDK, a peptide that derived from the PKC C2 domain, was designed to affect protein-protein interactions that are unique for pathological conditions and not other functions. An ex-vivo model of ischemia and reperfusion (I/R) injury showed that ψPDK is delta PKC-specific regulator that selectively induces delta PKC interaction with distinct substrates in the mitochondria. After I/R (event that occur during heart attack) delta-PKC translocates to the mitochondria in the heart. We have previously shown that delta-PKC activation increases cardiac damage through the phosphorylation of pyruvate dehydrogenase kinase (PDK) and consequent phosphorylation of mitochondrial enzyme pyruvate dehydrogenase (PDH), results in a decrease in ATP regeneration. We found that the ψPDK peptide inhibit specifically the interaction of delta-PKC with PDK, which lead to cardiac protection following I/R. Since there are known more than 60 different proteins that contain a C2 domain, many of which are signaling proteins, we suggest that our approach can be used to generate unique pharmacological tools to study these proteins and perhaps also, for identifying new drug for important human diseases.

P 30 Predictable and Tunable Drug Release From Macro-molecular Conjugates

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ProLynx has developed a new format for releasable macromolecule-drug conjugates that does not require enzyme hydrolysis, is highly tunable, and gives predictable cleavage rates both *in vitro* and *in vivo*. The technology uses novel linkers that undergo ß-elimination reactions at pre-programmed rates to release native peptides, proteins and small molecule drugs from conjugates, e.g. those using polyethylene glycol as carrier. A set of modular linkers is described having a succinimidyl carbonate group for attachment to an amine-containing drug or prodrug, an azido group for conjugation to a macromolecular carrier, and a tunable modulator group that controls the rate ofß-eliminative cleavage by controlling the acidity of an adjacent ionizable hydrogen. Variation in the structure of the modulator translates into variation in the rate of drug elimination as described by a linear free energy relationship. These linkers are shown to provide predictable, tunable release rates of drugs from macromolecular conjugates over a range spanning hours to months at physiological pH.? The *in vitro* cleavage rates show excellent correlation with *in vivo* rates. These linkers are expected to find use with both circulating and non-circulating conjugates.

P 31 Native Chemical Ligation Derived Method for Peptide/Protein C-terminal Amidation

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Many peptide or protein therapeutics exist as C-terminal amides for their biological activity and for stability. While short peptides can be made by solid phase synthesis, the need remains for processes that can produce long peptide/protein amides using cost-effective recombinant procedures coupled with post-translational amidation.

Enzymatic as well as chemical methods have been developed for C-terminal amidation, most of which have limitations such as low conversion rate, specific sequence requirements, special purification requirements or enzyme accessibility. We have developed a chemical amidation method that converts peptide/protein thioester into corresponding c-terminal amides. With this method, peptide/protein thioester is treated with a 2-amino mercaptoethanol auxiliary in a native chemical ligation (NCL) reaction to form an intermediate, which upon removal of the auxiliary with TFA yields the peptide/protein amide. We successfully converted two synthetic peptide thioesters (Davalintide and PYY[3-36]) to peptide amides with high conversion rates for validation of the methodology. Preliminary results of converting a recombinant peptide thioester to its amide form will also be reported.

We believe this method can be applicable to most peptides/proteins as it involves mild native chemical ligation condition and a TFA treatment step widely used in solid phase synthesis of peptides.

P 32 In-silico Tools for Drug Discovery: Protein Building Blocks, Peptide Design and the FoldX Energy Force Field

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We will present BriX (http://brix.crg.es), a vast collection of structural protein fragments (4-14 residues long), gathered from over 7000 non-homologous proteins and classified according to structural similarity. These fragments accurately describe “protein space” with sub-angstrom resolution and can be used for protein modeling and design. We will show how they can be used for the modeling of protein loops, variable parts of the protein structure that are notoriously hard to predict. When combined with the FoldX force field, we show how these fragments and their local interactions can be used to predict the structure of protein-targeting peptides, and how this can be applied for the novel discovery of peptides.

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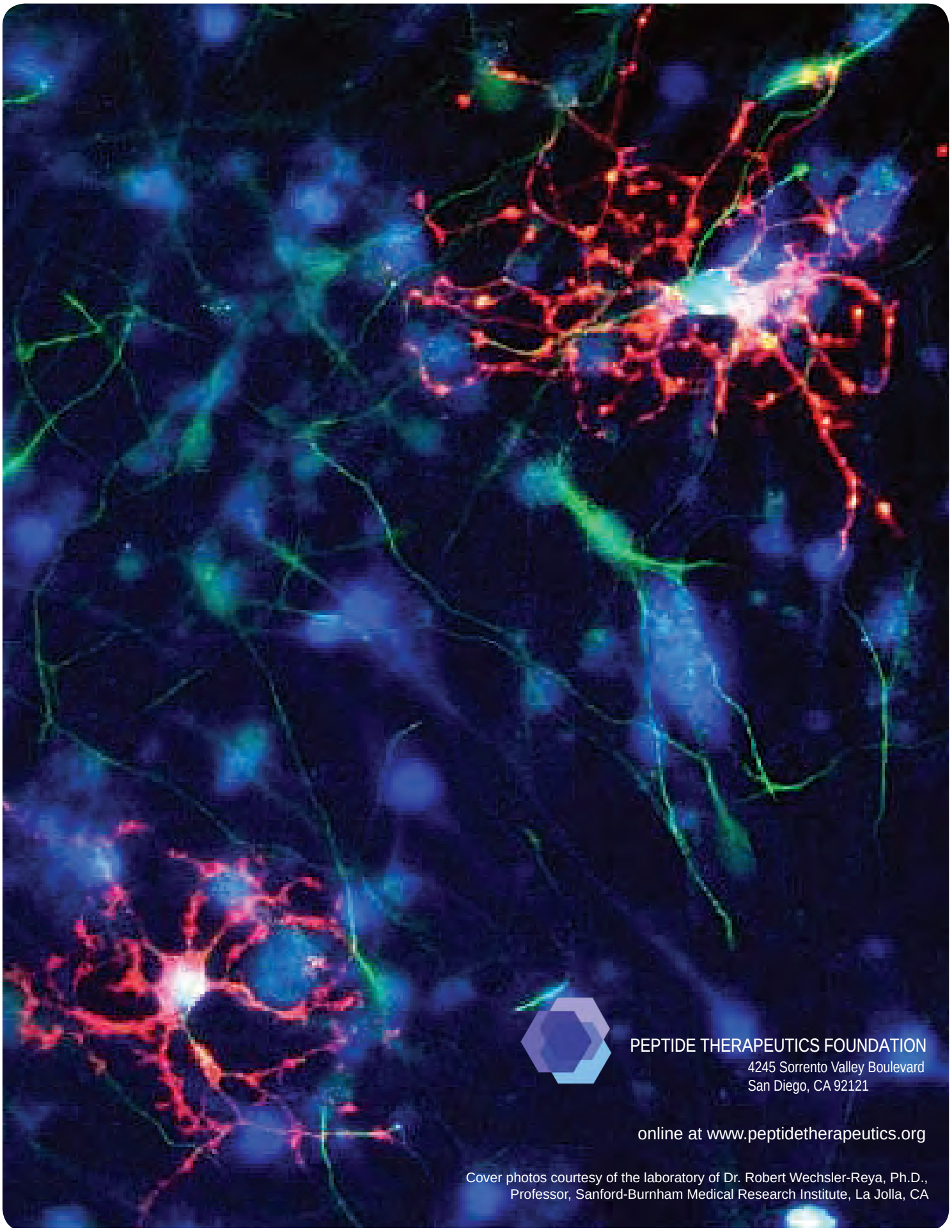

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