

**PEPTIDE
THERAPEUTICS
SYMPOSIUM**

**Program and Proceedings
3rd Annual Peptide Therapeutics Symposium**

Friday, October 24th, 2008

The Grand Del Mar
San Diego, CA

www.peptidetherapeutics.org

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Dear Speakers and Delegates,

Welcome to the Third Annual Peptide Therapeutics Symposium. We are delighted that you were able to join us for this exciting gathering that brings together every year the world leaders in peptide research for a day of high-quality dialogue.

This year's program features exciting updates on emerging new drug discovery technologies, therapeutic approaches, state-of-the-art strategies to extend duration of action of peptides and for the first time in our field, a comprehensive and in-depth analysis of R&D success rates for peptide therapeutics.

Wishing you enjoyable and productive interactions with your peers, we hope that the meeting will contribute to accelerating innovation in the field of peptide therapeutics.

With kind regards,

The organizing committee:

Pierre Rivière, Ph.D.
*Managing Director & Vice President, Research
Ferring Research Institute Inc.*

David Maggs, M.D.
*Vice President, Medical Affairs
Amylin Pharmaceuticals*

Our Sponsors:

Amylin Pharmaceuticals
Ferring Research Institute
Novozymes Biopharma
PolyPeptide Laboratories
Bachem Americas



Amylin Pharmaceuticals

Amylin Pharmaceuticals is a biopharmaceutical company committed to improving lives through the discovery, development and commercialization of innovative medicines.

The company was founded in 1987 following the discovery of a hormone, amylin, produced by the same beta cells of the pancreas that make insulin. Since then, Amylin has built a strong foundation on research and development. Amylin's scientists are primarily focused on investigating the potential utility of new peptide hormone candidates. The company has amassed significant research and clinical expertise in metabolic medicine including the areas of diabetes, obesity and cardiovascular disease.

By "Challenging Science," Amylin challenges conventional thinking to create innovative approaches to the discovery, development and commercialization of novel therapies for metabolic diseases. Amylin's approach and dedication are rooted in the belief that they will be "Changing Lives" for millions of people – not only with the drugs currently in late-stage development, but also with their pipeline of future therapies.



Ferring Pharmaceuticals

Ferring Pharmaceuticals is a research-driven specialty biopharmaceutical company focused on peptides and proteins therapeutics in three core therapeutic areas: infertility, urology and gastroenterology. The company is headquartered in Saint-Prex (Switzerland), employs over 2,500 people worldwide and operates subsidiaries in over 50 countries. Ferring's key marketed products include MINIRIN/DDAVP, PENTASA and MENOPUR. The company R&D centers are located Saint-Prex (Switzerland), Copenhagen (Denmark), Mumbai (India), Be'er Tuvia (Israel) and San Diego (United States).

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 peptides/hormones to design peptide therapeutics with improved pharmacodynamics, pharmacokinetics and pharmaceutical properties. This has led 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 has today one of the largest portfolio and pipeline of peptide therapeutics.



Novozymes

Novozymes' natural solutions enhance and promote everything from removing trans-fats in food, to advancing biofuels to power the world tomorrow. Our never-ending exploration of nature's potential is evidenced by over 5,000 granted or pending patents, showing what is possible when nature and technology join forces. Our 4,900+ employees working in research, production and sales around the world are committed to shaping business today and our world tomorrow.

Novozymes is quoted on the Copenhagen Stock Exchange (NZYMB). Read more at www.biopharma.novozymes.com.

Novozymes Biopharma Limited (a subsidiary of Novozymes) delivers scientifically proven recombinant products for mammalian cell culture and protein drug formulation, and are the pioneers of yeast based protein expression and albumin fusion technology. We offer a range of customised bioprocess manufacturing services.



PolyPeptide Laboratories

PolyPeptide Laboratories 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 PolyPeptide Laboratories Group is available at www.PolyPeptide.com.

PolyPeptide Laboratories is a group of six companies, that are exclusively focused on the manufacture of active pharmaceutical ingredients (APIs) based on peptides and related substances. The PolyPeptide Laboratories Group is privately held and employs about 450+ staff worldwide.

The PolyPeptide Laboratories Group has been inspected by the FDA ten times as well by other Regulatory Authorities. Altogether, the Group has about 20 approved APIs.

Since the acquisition of NeoMPS, the service offerings of the PolyPeptide Laboratories 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.

Bachem

Bachem is an independent, technology-based, public biochemicals company providing full service to the pharma and biotech industry. Bachem specializes in the process development and the manufacturing of peptides and complex organic molecules as active pharmaceutical ingredients (APIs), as well as innovative biochemicals for research purposes. With headquarters in Bubendorf, Switzerland, with affiliates in Europe and the United States, Bachem works on a global scale and holds a leading position in the field of peptides.



Schedule of Events

Session Moderators ● ● ● Jane Salik, Ph.D., *CEO, PolyPeptide Laboratories*
 Les Miranda, Ph.D., *Director of Research, Peptide Research and Discovery, Chemistry Research and Discovery, Amgen*

1:00 – 1:45 p.m. **LAPSCOVERY Technology and its Application to Long Acting Peptide/Protein Drugs**
 Gwan Sun Lee, Ph.D., *Managing Research Director, Hanmi Research Center, Hanmi Pharm. Co., Ltd.*

1:45 – 2:30 p.m. **CovX-Body Biotherapeutics: From Concept to Applications**
 Joel Desharnais, Ph.D., *Senior Scientist, CovX*

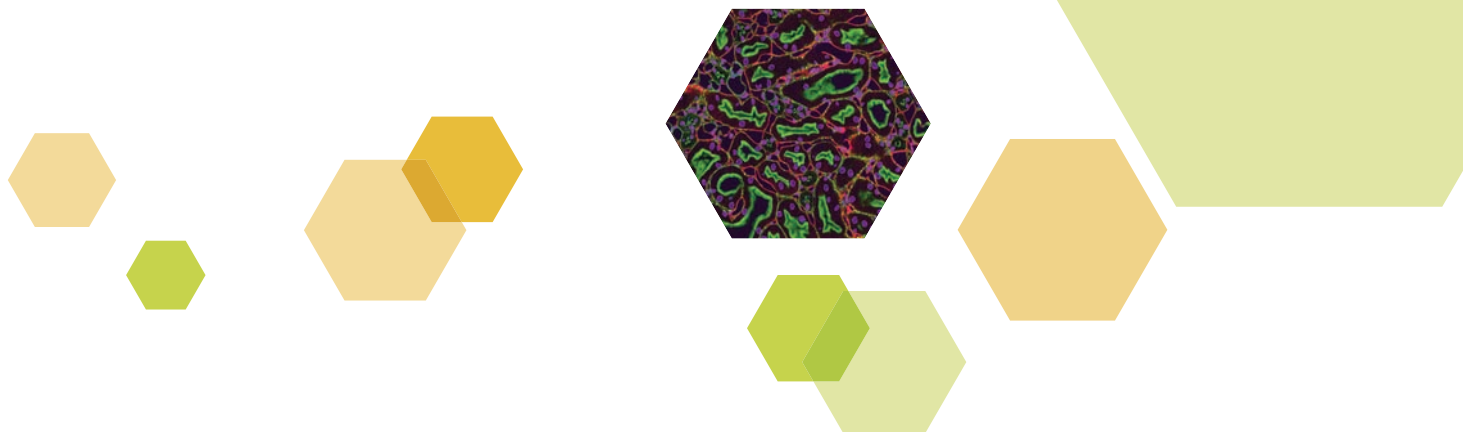
2:30 – 2:45 p.m. **Coffee Break**

Session Moderator ● ● ● Pierre Rivière, Ph.D., *Managing Director and Vice President Research, Ferring Research Institute Inc.*

2:45 – 3:30 p.m. **Trends in the Clinical Development and Approval of Synthetic Peptides**
 Janice Reichert, Ph.D., *Senior Research Fellow, Tufts Center for the Study of Drug Development, Tufts University*

3:30 – 3:45 p.m. **Closing Remarks**
 Pierre Rivière, Ph.D., *Managing Director and Vice President Research, Ferring Research Institute Inc.*

4:00 p.m. **Networking Reception**





Joel Desharnais, Ph.D. | Senior Scientist, CovX
CovX-Body Biotherapeutics: From Concept to Applications

Dr. Joel Desharnais received both a B.S. and Ph.D. in chemistry from the University of Montreal. He studied under Professor James D. Wuest in the field of supramolecular chemistry creating catalytic organic zeolites. Dr. Desharnais completed his postdoctoral fellow at The Scripps Research Institute in San Diego working with Professor Dale L. Boger in identifying small molecule agonists/antagonists of protein-protein interactions using solution-phase combinatorial chemistry and contributed to the synthesis of new folate enzyme inhibitors. In 2003, Joel joined a newly formed biotech company, Acidophil (San Diego), where he worked on the synthesis of chemotherapeutic conjugates with increase selectivity to tumor-specific kinases. In 2004 he moved to CovX, a biotechnology company creating long-acting biotherapeutics CovX-Bodies which combine the therapeutic potential of peptides with the beneficial clinical properties of antibodies. His efforts have been divided between optimizing the linker strategy, developing alternative conjugation chemistries for peptides and moving oncology and CVMED projects from concept to clinical candidates. More recently, Dr. Desharnais has been working closely with Pfizer's St. Louis research site to expand Pfizer's inflammation portfolio.



Paul Herbert | Vice President, Process Development, Alkermes, Inc.
Sustained Release of Peptides using Microencapsulation and the Development of Long Acting Exenatide

Mr. Paul Herbert has 29 years experience as a chemical engineer including 15 years in pharmaceutical process development for Alkermes. He is currently Vice President of Process Development for Alkermes overseeing a group focused on a broad range of technologies currently under development. Prior to Alkermes, Mr. Herbert worked 14 years for DuPont as a chemical engineer involved in process modeling, extrusion, film coating, polymerization, and microencapsulation. He graduated from Rensselaer Polytechnic Institute with a B.S. and Master of Engineering degree in Chemical Engineering.



Donald W. Landry, M.D., Ph.D. | Chair, Department of Medicine, Columbia University
Via Agonists in Vasodilatory Shock: From Bedside to Bench, and Back

Dr. Donald W. Landry is Professor of Medicine and Director of the Division of Experimental Therapeutics at the Columbia University College of Physicians and Surgeons. He is also the Director of the Division of Nephrology. His laboratory in experimental therapeutics focuses on innovative organic chemical solutions to intractable and unmet medical problems. Dr. Landry obtained a Ph.D. degree in organic chemistry from Harvard University with Nobel Laureate Robert Burns Woodward, his M.D. from the Columbia University College of Physicians and Surgeons and completed residency training at the Massachusetts General Hospital and Harvard Medical School.



**Gwan Sun Lee, Ph.D. | Managing Research Director, Hanmi Research Center,
Hanmi Pharmaceutical Company, Ltd**
LAPSCOVERY Technology and Its Application to Long Acting Peptide/Protein Drugs

Dr. Gwan Sun Lee has served as Head of Hanmi Research Center since January 1995. He joined the Hanmi Research Center in 1984 as Principal Scientist. Prior to that, he was an invited researcher at the Department of Chemistry and Pharmacy at Regensburg University in Germany. He holds a B.S. from Seoul National University and earned his

M.S. and Ph.D. from Korea Advanced Institute of Science and Technology where he studied the “Synthesis of Thienamycin Intermediate from 6-Aminopenicillanic Acid” and “Total Synthesis of Naphthoindolizidine Alkaloid Derivatives”, respectively. Dr. Lee previously held the position of Vice Chairman of the Korean Chemical Society and is the current Vice Chairman of the Korean Society of Applied Pharmacology and Vice Chairman of the division of life-science chemistry within the Korean Chemical Society. He is an Adjunct Professor, College of Biotechnology and Life Science, Korea University.



David Maggs, M.D. | Vice President, Medical Affairs, Amylin Pharmaceuticals

Welcome Remarks

Dr. David Maggs has served as Vice President, Medical Affairs since March 2005. He previously served as Executive Director, Medical Affairs, and joined Amylin in October 2000 as Senior Director, Medical Affairs. Previously, Dr. Maggs served as Director, Medical Research, Diabetes and Metabolism for Parke-Davis Co. Prior to that he was an Assistant Clinical Professor at Yale School of Medicine from 1997 to 1999 and completed fellowships at the University of Nottingham and at Yale School of Medicine. Dr. Maggs completed his original medical training and received his M.B.B.S. and M.R.C.P. degrees from Guys Hospital, University of London and the Royal College of Physicians in London.

Andrew E. Nixon, Ph.D. | Vice President, Lead Discovery and Biochemistry, Dyax Corporation

Engineering Kunitz Domains Using Phage Display

Dr. Andrew Nixon is Vice President of Research at Dyax, responsible for Lead Discovery & Biochemistry activities within the discovery research group. In this role he oversees all aspects of Dyax’s phage display technology, including library selections, isolate screening, and the production and characterization of selected leads. Additionally he is responsible for production of target antigens to support selection and screening of the Dyax phage display libraries. Prior to joining Dyax in 1999, Dr. Nixon completed a post-doctoral fellowship in the laboratory of Prof. S.J. Benkovic in the Department of Chemistry at Pennsylvania State University, where he was involved in the development of techniques to facilitate enzyme engineering. Dr. Nixon earned his Ph.D. from the University of London for studies completed at the MRC’s National Institute for Medical Research.



Janice Reichert, Ph.D. | Senior Research Fellow,

Tufts Center for the Study of Drug Development, Tufts University

Trends in the Clinical Development and Approval of Synthetic Peptides

Dr. Janice Reichert is a Senior Research Fellow at Tufts Center for the Study of Drug Development (CSDD) and Editor-in-Chief of mAbs, a new Landes Bioscience journal. She has studied innovation in the pharmaceutical and biotechnology industries at the Tufts CSDD since 1999. Her work includes strategic analyses of candidate and approved products, including clinical development and approval times and probabilities of success for new therapeutics and vaccines. These analyses have been featured in over 25 publications by Dr. Reichert.

As Editor-in-Chief of mAbs, Dr. Reichert has recruited a 63-member editorial board and is actively preparing for the journal’s launch in January 2009.

Dr. Reichert has presented her research results as an invited speaker at conferences in

the United States, Canada, Europe and China. She was co-chair of the Massachusetts Biotechnology Council's Clinical Trials Committee for five years and has served on the editorial boards of three journals. In addition, Dr. Reichert regularly provides input to various government, non-profit, and industry organizations such as the National Institutes of Health, the European Commission, the Organization for Economic Cooperation and Development, the International AIDS Vaccine Initiative, and the Biotechnology Industry Organization.

Dr. Reichert received her Ph.D. in organic chemistry from the University of Pennsylvania and her postdoctoral training as a National Institutes of Health Research Fellow at Harvard Medical School. Before joining the Tufts Center for the Study of Drug Development, Dr. Reichert performed drug discovery research and preclinical development at several companies in the Boston area.



Pierre Rivière, Ph.D. | Managing Director & Vice President Research, Ferring Research Institute Inc.
Closing Remarks

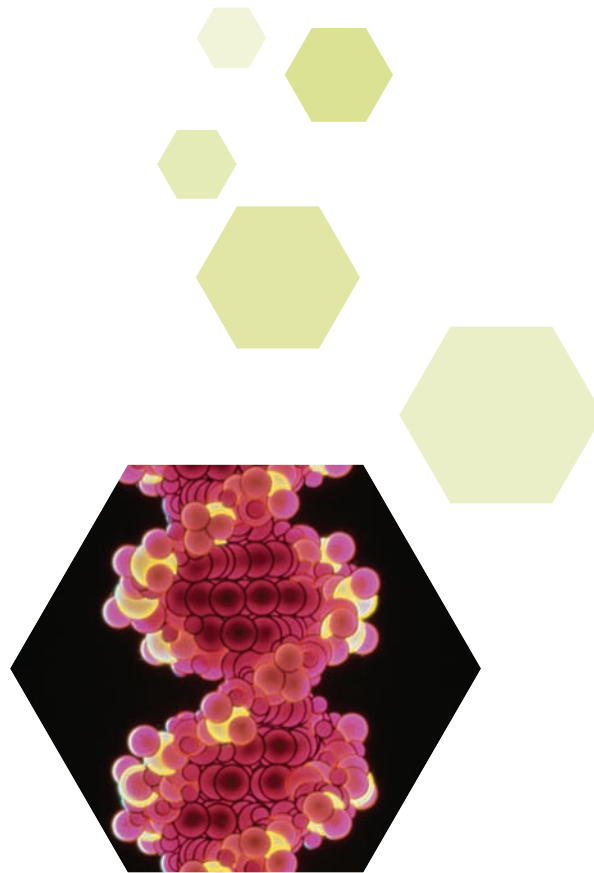
Dr. Pierre Rivière has served as Managing Director & Vice President, Research, of Ferring Research Institute Inc., in San Diego since January 2006. He joined Ferring in 1996 as Head of Biology and became Director of Research in 2002. In recent years, he contributed to the discovery of a number of peptidic new chemical entities now at various stages of development. Previously, Dr. Rivière occupied various research and managerial positions in drug discovery at the Institut de Recherche Jouveinal in Fresnes, France. He holds a Ph.D. in biology and physiology from the Institut National Polytechnique of Toulouse, followed by post-doctoral training in the Department of Pharmacology of the University of Arizona in Tucson. Dr. Rivière is scientific co-founder and advisor of Cara Therapeutics.

Martin Robitaille, Ph.D. | Director, Peptide Chemistry, ConjuChem Biotechnologies, Inc.
Preformed Conjugate-Drug Affinity Complex (PC-DAC™) Technology

Dr. Martin Robitaille has served as Director of Peptide Chemistry at ConjuChem Biotechnologies Inc. since January 2006. He joined ConjuChem Inc. as a Research Scientist in the fall of 1999 and established the peptide solid phase program that investigates the versatility of the DAC™ technology. With more than a dozen DAC™ projects exploring peptides such as Dynorphin, GLP-1, Exendin-4, GRE, GLP-2 and PYY, the platform now exceeds 900 peptide variations. His responsibilities include; design and production of DAC™ peptides, analytical method development and technology transfer. He attended Bishop's University for his undergraduate studies, earned his graduate degree from University of Sherbrooke and is co-author on more than 60 papers in the combined fields of patent, patent application and science.

Abstracts

3rd Annual Peptide Therapeutics Symposium



V1a-Agonists in Vasodilatory Shock: From Bedside to Bench and Back

Donald W. Landry, M.D., Ph.D. | Interim Chair, Department of Medicine, Columbia University

PH 8 East Room 105, 630 West 168th Street, New York, NY 10032-3784212-305-5839 | dwl1@columbia.edu

The peptide hormone vasopressin is best known for its anti-diuretic action mediated by V_2 -receptors present on the collecting duct on the kidney. But as the name suggests vasopressin, at very low concentrations (0-5 pg/mL), is also a vasopressor hormone and in this capacity it acts through V_{1a} -receptors present on vascular smooth muscle. *In vitro*, vasopressin is 100-fold more potent as a vasopressor than the catecholamine norepinephrine but *in vivo* vasopressin has little effect on blood pressure at concentrations of hundreds of pg/mL. However, we (DWL) discovered that in vasodilatory shock, vasopressin is transformed into an exquisitely potent vasopressor that decreases the requirement for catecholamine pressors.

Low blood pressure and endotoxemia raise plasma vasopressin levels in experimental animals to > 300 pg/mL but we (DWL) discovered that patients in septic shock are vasopressin deficient with circulating levels of 0-5 pg/mL. Numerous investigators have confirmed vasopressin deficiency and pressor hypersensitivity to be hallmarks of septic shock. The recently reported VASST trial further suggests that vasopressin replacement could be beneficial for patients with moderately severe septic shock.

However questions remain as to whether the natural hormone, a non-specific V_{1a}/V_2 -receptor agonist, is the ideal agent for the treatment of septic shock. Normal subjects, but not patients with congenital nephrogenic diabetes insipidus also lack functioning V_2 -receptors, experience a decrease in blood pressure in response to administration of a V_2 -selective agonist, consistent with findings that the V_2 -receptor mediates vasodilatation. Further, infusion of vasopressin itself into the brachial artery results in forearm vasodilatation indicating that V_2 activity can dominate V_{1a} in selected vascular beds. Thus, we (Ferring) sought to develop V_{1a} selective agonists and FE 202158 was identified from a focused peptide library.

FE 202158 demonstrated excellent selectivity for human V_{1a} -R over V_{1b} -R hOTR and hV₂R: 1/142, 1/440 and 1/1107, respectively; and in contrast to that of vasopressin: 1, 1/18, 1/92, 5. (Figure 1) FE 202158 was also potent and selective across multiple species of interest for preclinical trials including rat, dog, sheep and pig. (Figure 2)

In studies of pseudomonas sepsis in pig, and platelet activating factor administration as a model of septic shock/anaphylactic shock in rat, FE 202158 was a potent vasopressor agent at concentrations that mimicked low dose hormone replacement with vasopressin. Various clinically significant benefits with respect to fluid balance were identified.

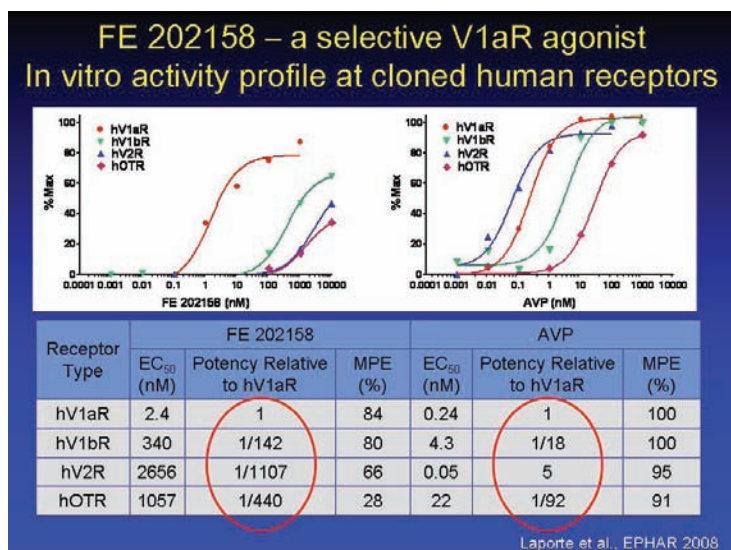


Figure 1.

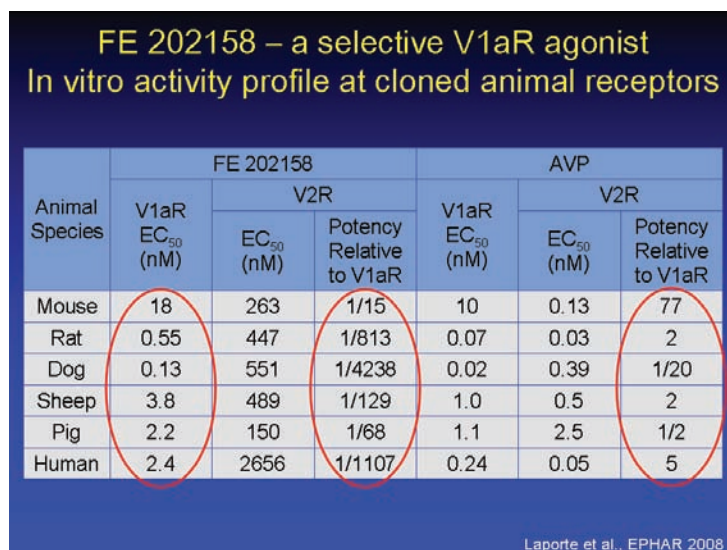


Figure 2.

Collaborators: Ferring : Pierre Rivière, Claudio Scheingart, Régent Laporte, Kazimierz Wisniewski, Glenn Croston, Sudarkodi Alagarsamy, Per Cantor, Peter McNulty, Ayman AL-Shurbaji
Columbia University: Juan A. Oliver, Joanne MacDonald. University of British Columbia: James Russell, Keith R. Walley. University of California at Davis: Fitz-Roy Curry, Joyce Lenz.
University of Texas Medical Branch: Daniel L. Traber, Perenlei Enkhbaatar.

University of Ulm: Peter Radermacher, Enrico Calzia

CovX-Body Therapeutics: From Concept to Applications

Joel Desharnais, Ph.D. | Senior Scientist, CovX

9381 Judicial Drive, Suite 200, San Diego, CA 92121, 858-964-2041 | jdesharnais@covx.com

Peptides hold therapeutic and commercial promise (e.g., Byetta™, Humalog™, Lupron™, Fuzeon™) because they possess enormous structural diversity, are highly specific and potent, and generally have fewer safety issues relative to small molecules. Despite the specificity and potency advantages, peptides have been handicapped by their poor half-life. CovX technology provides a means to markedly extend the half-life of peptide-based drugs without diminishing specificity and potency (Figure 1).

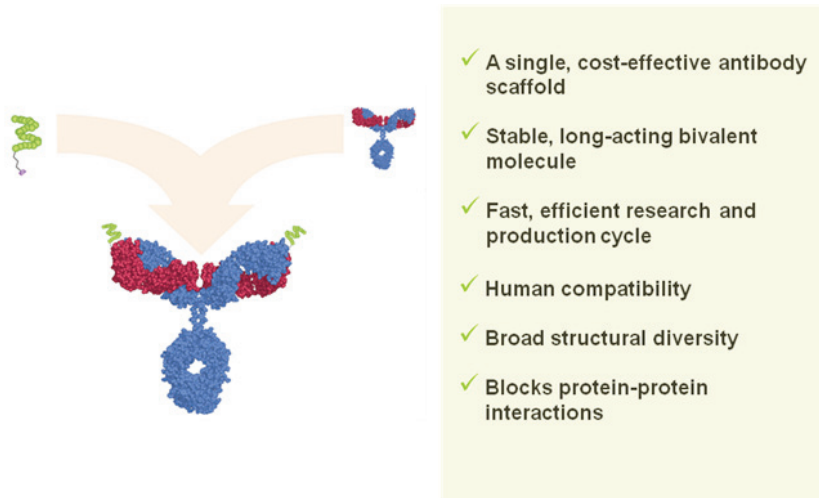


Figure 1: The CovX-Body advantage.

CovX's scaffold is a humanized IgG1 antibody with an inherent ability to form a covalent bond with the CovX linker in the Fab-binding domain. The distinctive and unique feature of this antibody is the presence of two lysine residues that are each deeply buried, yet accessible at the base of a hydrophobic cleft in the distal Fab regions of the antibody (Figure 2). CovX has created a library of electrophilic linkers to react with the antibody in a site-specific, stoichiometric manner. The reaction occurs spontaneously in aqueous solution at room temperature and has been proven from research grade material to clinical drug product manufacturing.

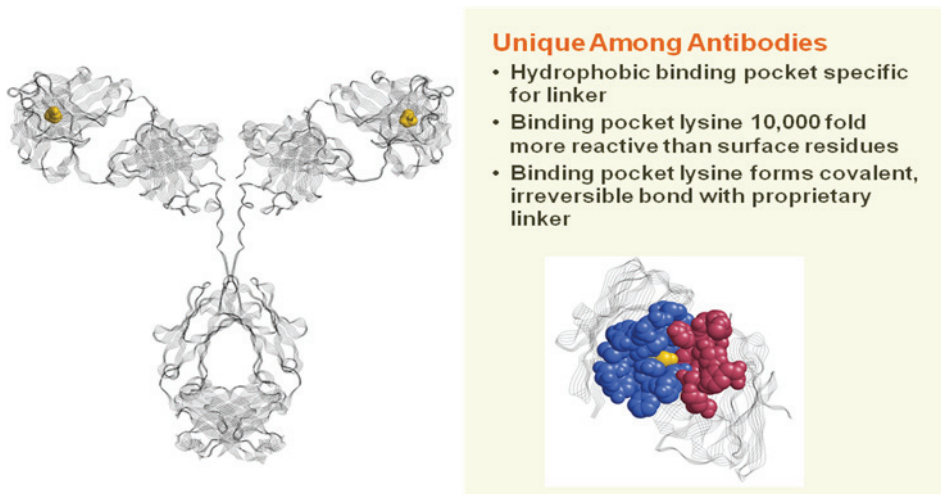


Figure 2: Reactive lysine residues inside this unique antibody scaffold.

CovX-Body properties are governed by both the antibody and the peptide. While the antibody prevents renal clearance and protects against proteolytic degradation, the peptide provides efficacy to the drug conjugate by binding to its respective target. It is essential to carefully refine the presentation of the peptide on the surface of the antibody not only to ensure optimum interaction with the biological target, but also to maximize the pharmacokinetic benefits of the antibody scaffold. The peptide optimization phase involves: 1) modifications of the peptide sequence by the introduction of natural and non-natural amino acids to optimize the peptide activity and selectivity, 2) defining the preferred location and composition of the linker. The unique strength of CovX technology is the ability to functionalize any position across the length of the peptide sequence with the linker.

Insulinotropic peptide hormone glucagon-like peptide (GLP-1) analogs are used for the management of type 2 non-insulin-dependent diabetes mellitus as well as related metabolic disorders, such as obesity. While useful, GLP-1 and analogues suffer from limited duration of action associated with short plasma half-life *in vivo*, mainly due to rapid serum clearance and proteolytic degradation. We, and others, have sought to make long-lasting GLP-1 analogues that would maintain the peptide activity while improving *in vivo* half-life.

Programs to optimize the GLP-mimetic CovX-Body confirmed substantial differences in desirable drug product characteristics including half-life, subcutaneous bioavailability and efficacy based upon peptide structure. CVX-096 demonstrated an outstanding pharmacokinetic profile with subcutaneous half-life of 90 and 80 hours in mouse and rat respectively. CVX-096 also sustained glucose tolerance 72 hours after a single dose. In addition, a prolonged dose-dependent reduction in food intake was observed along with dose dependent reduction in body weight gain. CVX-096 compares favorably against other long-acting GLP-mimetic both in terms of half-life and potency (Figure 3). This product is currently in Phase I studies.

Product	Half-life (Rodent - IV)	Potency (nM)
CVX-096	66	2.5
PC-DAC:Exendin-4 (Conjuchem)	17	29
Albugon (HGS/GSK)	11	20
GLP-1 Transferrin Fusion (BioRexis/Pfizer)	14	5

Figure 3: Comparison of long-acting GLP-1 mimetics.

A powerful concept currently under evaluation is the effect of multivalency on the efficacy of drug conjugates. For a specific anti-angiogenic project, we observed 10-fold increase in the potency of a multivalent CovX-Body (with 4 peptides attached) versus the traditional CovX-Body (with two peptides). As a next step in this approach we are developing CovX-Bodies functionalized with two different peptides, each binding a distinct molecular target.

Clearly, the CovX technology is a powerful method to create peptide-based therapeutics. CovX has now three compounds in clinical trials with rapidly developing pre-clinical programs.

LAPSCOVERY Technology and Its Application to Peptide/Protein Drugs

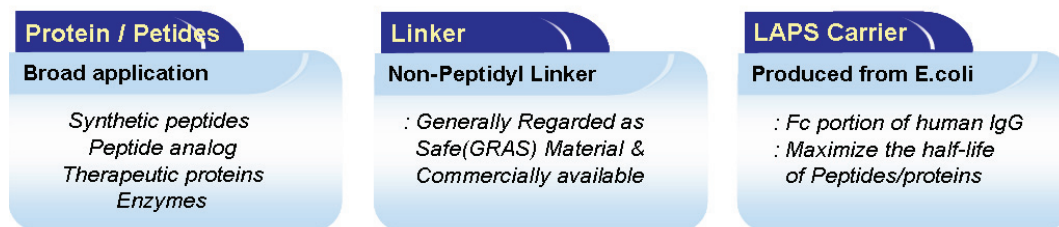
Gwan Sun Lee, Ph.D. | Managing Research Director, Hanmi Research Center, Hanmi Pharmaceutical Company, Ltd
45 Bangi-dong, Songpa-gu, Seoul, 138-724, Korea | gwansun@hanmi.co.kr

The development of peptide therapeutics has become one of the hottest area in the pharmaceutical and biotechnology industries because peptides offer molecular diversity and the potential to treat a variety of unmet medical needs. But, the short half-life of peptides in human requires frequent dosing regimen, leading to patient non-compliance. Hanmi has developed a long-acting peptide/protein delivery technology named “LAPSCOVERY Technology” that is described in the following figure.

LAPSCOVERY Technology: Overview



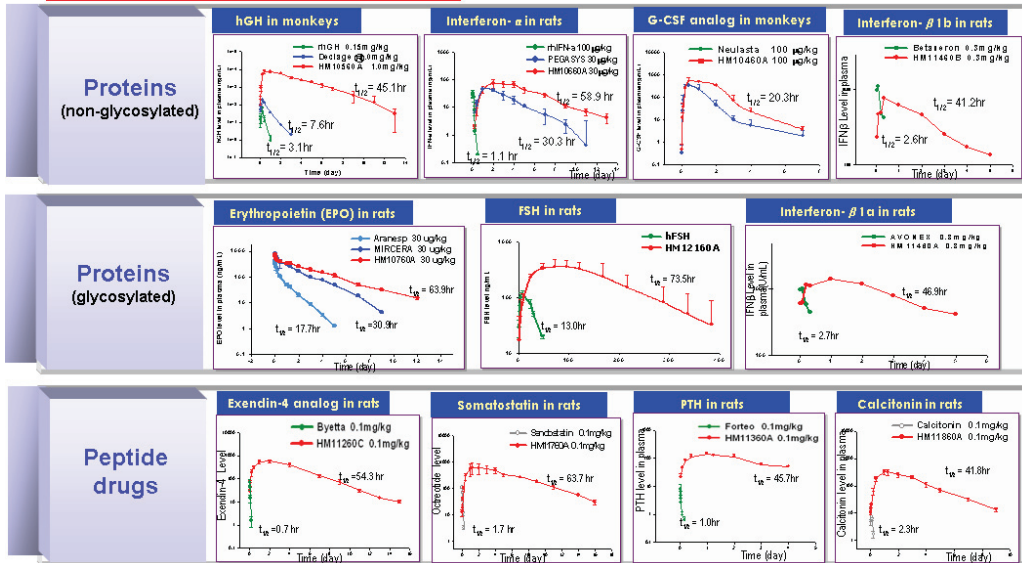
LAPSCOVERY Technology: Long Acting Protein(Peptide) Discovery Technology



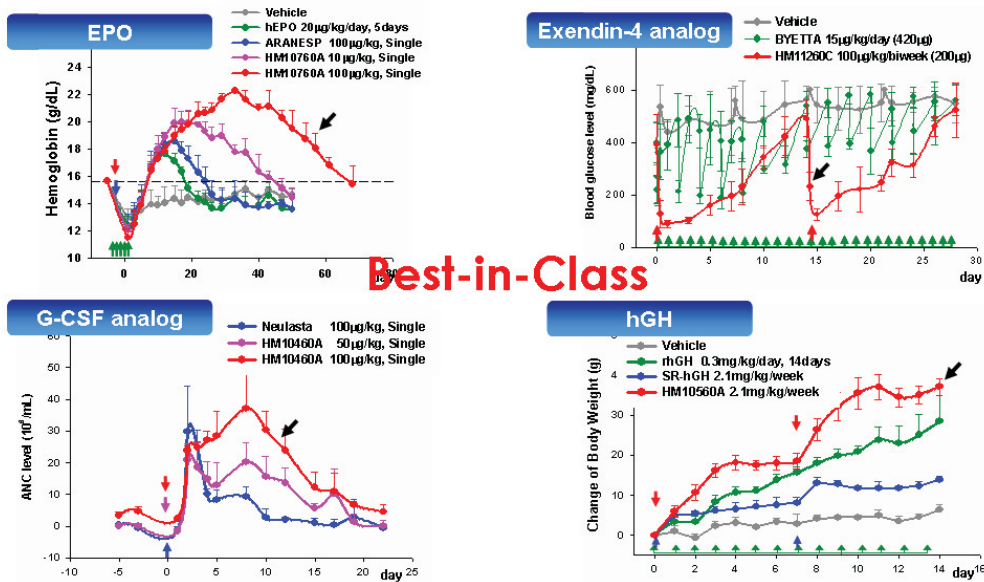
LAPSCOVERY technology has been applied to various kinds of proteins and peptides, and their pharmacokinetic profiles were then measured in animals. They showed extended half-life relative to the second generation protein products. The half-life extension effect was most remarkable with peptide drugs as shown in the PK profiles.

LAPSCOVERY products also showed better and extended in vivo efficacies compared to first and 2nd generation products, even with lower doses and longer dosing intervals, indicating the potential to be developed as best in class drugs.

LAPSCOVERY Technology : Complete solution for extending half-life



LAPSCOVERY Technology : Excellent in vivo efficacy



We generated more potent exendin-4 analog by modifying the N-terminal part, i.e., amino acid modifications, truncations and deletions, and substitutions. To select the best exendin-4 analog, we made LAPS-Carrier conjugates and compared glucose lowering effect in db/db mouse. Among the Exendin-4 analogs tested, the CA Exendin-4 conjugate was most potent and showed prolonged efficacy. It was therefore selected as developmental candidate. The maximal insulinotropic activity of CA Exendin-4 was 2-fold greater than Exendin-4 and its in vivo glucose lowering effect was 4-fold greater than Exendin-4.

Receptor affinity of CA exendin-4 was measured in comparison with Exendin-4 by SPR analysis. CA Exendin-4 showed very rapid dissociation characteristics compared to Exendin-4 and the relative affinity was 1/14. This indicates that CA Exendin-4 will have better efficacy compared to Exendin-4 by acting to more GLP-1 receptor with limited number of molecules. In addition, CA Exendin-4 showed slower receptor mediated clearance than Exendin-4 in hGLP-1 receptor bearing cells probably due to its high dissociation rate. The PK profiles of HM11260C which is a LAPS Carrier conjugate of CA Exendin-4 and its half-life was calculated as 54 hours, which is 70 fold longer than exendin-4. Glucose lowering effects of HM11260C was measured in comparison with Exendin-4 conjugate, HM11260A, in db/db mouse for 1 month, and was found to have better and prolonged efficacy. Beta cell mass in db/db mouse after 2 months treatment with HM11260C was remarkably and dose dependently increased, whereas excess dosing of Exendin-4 didn't show any increase in beta cell mass.

Oral glucose tolerance test was conducted in ZDF rat. Insulin secretion increased and glucose level decreased in a dose dependent fashion and was saturated at 50µg/kg of HM11260C. Gastrointestinal motility of HM11260C and Exendin-4 has been assessed in rat. When the same dose of each compound was injected by sc route, HM11260C showed higher transit index, indicating less inhibition of GI motility. The anti-obesity effects were measured using ob/ob mouse and confirmed better weight reduction than excess dosing Exendin-4. Our candidate showed dose dependent weight reduction. Similar trend has also been confirmed in total cholesterol and adipocyte index. Immunogenic potential of HM11260C and Exendin-4 conjugate has been measured by IL-2 and IFN-gamma Elispot assay using human PBMNC and we confirmed that neither of the products has immunogenic potential. As a result, HM11260C has the potential to be developed to treat diabetes and obesity by once weekly/or bi-weekly administration.

In summary, we have secured strong IP protection for our platform technologies and have shown animal PoC. Five candidates are now in pre-clinical development and three of them will enter the phase I clinical study in the 1st quarter next year. Our partnering strategy is pursued in two ways. One is the licensing or co-development of our candidates, and the other is research collaboration with new peptide holder to make next generation products. Our research collaboration model is very simple, for example, after non-binding MTA has been agreed and then free of charge feasibility test is conducted for maximum 3 month per peptide including essential evaluation. If the result of feasibility test is acceptable, we can discuss the next steps for further development.

LAPSCOVERY Technology : Summary & Partnering Strategies

◆ Our Performance

- Strong IP position and proved animal POC
- Five products in pre-clinical stage / a project licensed out
- Plan 3 phase1 studies at 1Q, 2009

◆ Partnering Strategies

- Licensing or co-development of preclinical candidates
- Research collaboration

New Peptides + LAPSCOVERY → Next Generation Products

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Engineering Kunitz Domains Using Phage Display

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Phage display is a well established technology for identifying molecules that bind to targets from a variety of library types. Libraries of molecules displayed on phage can range greatly in size and function, from short linear peptides, to more complex proteins such as Kunitz domains and to larger heterodimeric proteins such as the Fab fragment of antibodies (Buckler et al., 2008, Nixon & Wood, 2006, Sato et al 2006). The diversity of molecular structures that can be identified from phage display libraries represent a rich source of potential therapeutic candidates.

Proteases represent 2 – 3 % of all human genes (Rawlings et al., 2008) and as such are an important family of proteins. It has become clear that proteases play key roles in regulating signaling pathways. They are able to both switch on pathways, through mechanisms such as liberation of soluble receptor ligands from membrane bound precursors, as is the case for the EGFR family of ligands, and turn pathways off by cleaving and shedding extracellular receptors. Of note is that unlike other methods of post-translational control such as phosphorylation, proteolysis is an irreversible commitment.

The ability to identify potent and specific small molecule inhibitors of proteases has proven to be extremely challenging. This is likely to be due to the fact that the protease families often have remarkably similar structures, providing few differentiating features for small molecules. Generally, small molecules are either potent but with limited specificity or specific but with limited potency. There have been relatively few successful small molecule protease inhibitors with the HIV protease and ACE inhibitors being clear exceptions (Turk, 2006). Additionally there have been some well documented failures such as the MMP inhibitors that were identified and tested clinically in the early 1990's.

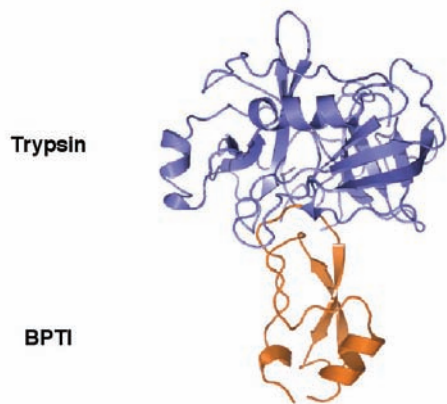
The short comings of the small molecule protease inhibitors, the lack of both potency and specificity, may be addressed by developing protein based inhibitors. Endogenous protein inhibitors of proteases generally have a larger region of interaction with the target protease than a small molecule would and as such have the potential to be both potent and specific. Engineered protein inhibitors of proteases therefore represent potential new therapeutic candidates.

One approach to developing such protein inhibitors has been to engineer endogenous protease inhibitors. One such inhibitor that has been engineered has been the first Kunitz domain of tissue factor pathway inhibitor (TFPI-D1). Kunitz domains are small proteins

~ 58 amino acids in length that are stabilized by the presence of three disulphide bonds and are specific for serine proteases. The canonical interaction of a Kunitz domain with its cognate protease has been determined from crystal structures of bovine pancreatic trypsin inhibitor bound to trypsin (Figure 1.).

Analyses of such structures have allowed the identification of a region of the Kunitz domain that binds to the serine protease in a substrate like manner, the 'primary loop' and then secondary regions that provide lesser contacts with the protease and with the primary loop (Figure 2). Using this structural information it has been possible to generate phage display libraries of mutations in both the primary loop and the secondary contact regions and to use these libraries to identify therapeutic candidates.

Canonical Interaction of Kunitz Domains with Serine Proteases



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Figure 1

Potency and Specificity: DX-88 vs other pKal inhibitors



DX-88 vs plasma kallikrein	~0.025 nM
DX-88 vs F.XIa	2 nM
DX-88 vs others	>137 nM
C1 INH vs pKal	13 nM
C1 INH vs plasmin	10 nM
C1 INH vs C1s,a	10 nM
C1 INH vs F.XIIa, F.XIa	23 & 40 nM
Aprotinin vs pKal	30 nM
Aprotinin vs tissue kallikrein	4 nM
Aprotinin vs plasmin	0.9 nM



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Adapted from Williams and Baird, 2003 www.dyax.com

Figure 3

Additional Kunitz domain inhibitors of plasmin, DX-1000, and neutrophil elastase, DX-890, have been identified using a similar approach. The K_i for plasmin inhibition is ~ 180 pM and for neutrophil elastase inhibition is ~ 2 pM. This is achieved with relatively few changes in the primary binding loop. Three amino acid differences separate both DX-890 and DX-1000 from DX-88 (Ley et al., 1996).

The small size of the Kunitz domains means that they are rapidly cleared from systemic circulation by renal filtration. In rodents this happens relatively quickly making it a challenge to ensure sufficient exposure for chronic treatments. A number of approaches have been considered to reduce plasma clearance, including genetic fusions to albumin and labeling with polyethylene glycol (PEG).

Albumin is the most abundant plasma protein, typically found at a concentration of 45 g/L. It is very stable and has a long plasma residence time ~ 19 days. Albumin is not glycosylated and can be produced at high levels in yeast. That it is a single polypeptide means that it is relatively straightforward to fuse albumin to other proteins such as a Kunitz domain.

Albumin fusions have previously been generated and are currently being evaluated in the clinic. Interferon alpha was fused to albumin to generate albuferon (Osborn et al., 2002). The plasma clearance time for interferon alpha is ~ 5 hours following subcutaneous injection in to a monkey. When fused to albumin this is increased 18 fold to 96 hours.

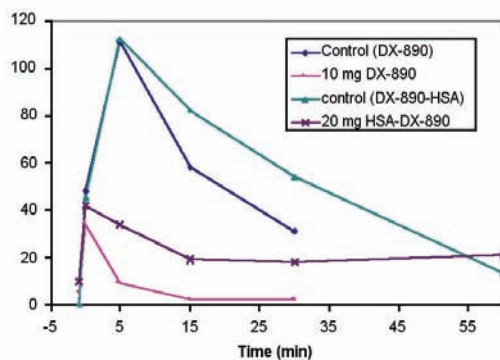
An imbalance in the protease/protease inhibitor balance in the airway has long been thought to play a role in the development of COPD. In experimental models of disease, instillation of neutrophil elastase can result in symptoms similar to those of emphysema and additionally is able to cause bronchoconstriction through increased tissue kallikrein activity (Scuri et al., 2001). Development of neutrophil elastase inhibitors may therefore be of interest as a potential treatment for airway inflammatory diseases. As highlighted above, one such inhibitor is DX-890, a potent and specific inhibitor of neutrophil elastase that was identified from a phage display library.

A number of approaches have been used to increase the molecular size of DX-890 with the aim of reducing its clearance time.

DX-890 was fused to the carboxy-terminus of serum albumin and expressed in *Saccharomyces cerevisiae*. The resulting protein was purified to homogeneity and evaluated in a potency assay. The K_i of the albumin fused DX-890 (HSA-DX-890) was found to be approximately equivalent to that of native DX-890. Clearance of the fusion protein was compared to non fused DX-890 and PEGylated versions in mice. DX-890 was cleared with a terminal half-life of 78 mins, DX-890 labeled with 20 K PEG was cleared in 300 mins, while the HSA-DX-890 fusion and DX-890 labeled with 30 K PEG were cleared with terminal half-lives of 378 mins and 504 mins respectively.

To evaluate the effect of albumin fusion of DX-890 in a pre-clinical setting DX-890 and HSA-DX-890 were compared using neutrophil elastase induced bronchoconstriction. Here instillation of DX-890 and HSA-890 following instillation of neutrophil elastase resulted in a 35-40 % increase in lung resistance compared to 110 % increase when either buffer alone or HSA alone was used

Effect of DX-890 on Elastase-induced Bronchoconstriction in Sheep Lung



DX-890 or DX-890 HSA inhaled 30 minutes prior to elastase



Dr. William Abraham, Mount Sinai Medical Center, Miami Beach
October 2008 www.dysid.com

Figure 4

These in vitro and in vivo data demonstrate that the use of albumin as a fusion partner has the potential to reduce plasma clearance of Kunitz domains without affecting potency. This opens up the opportunity to use Kunitz domain based protease inhibitors in the treatment of chronic disease.

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Trends in the Clinical Development and Approval of Peptides

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Although peptides have long been staples of research and development (R&D), the study of therapeutic peptides has recently attracted a great deal of attention from the pharmaceutical industry. Interest has been piqued in part because of advances in synthetic, delivery and formulation technologies, and acceptance of injectable therapeutics (e.g., monoclonal antibodies) in markets world-wide. Due to these factors, the pharmaceutical industry is aggressively investing in therapeutic peptide R&D by initiating internal programs and by acquiring companies that focus on this area.

Tufts Center for the Study of Drug Development continuously collects data for both new candidates entering clinical study and those recently acquired by companies from non-commercial sources. In cooperation with Ferring Research Institute, we have established a data set of over 400 peptide therapeutics, vaccines and diagnostics based on information available in the public domain. As of October 2008, the data set included a total of 419 peptides that were either developed in-house or in-licensed by commercial firms, and had been studied in a clinical setting. The majority (76%) of the candidates were therapeutics, with the remainder studied as vaccines (21%) or diagnostics (3%). This data set was used to determine trends in the development and approval of peptide therapeutics reported here.

The combined efforts of biotechnology and pharmaceutical firms have led to a notable increase in the average number of molecules entering clinical study each year (Figure 1). This number nearly doubled between the 1990s and the 2000-2007 periods. Final fates (approval in any country or discontinuation of all clinical development) are known for most (87%) of the therapeutic peptide candidates that first entered clinical study in the 1980s and 1990s, but the majority of candidates that entered the clinic recently are still being evaluated in early-stage studies.

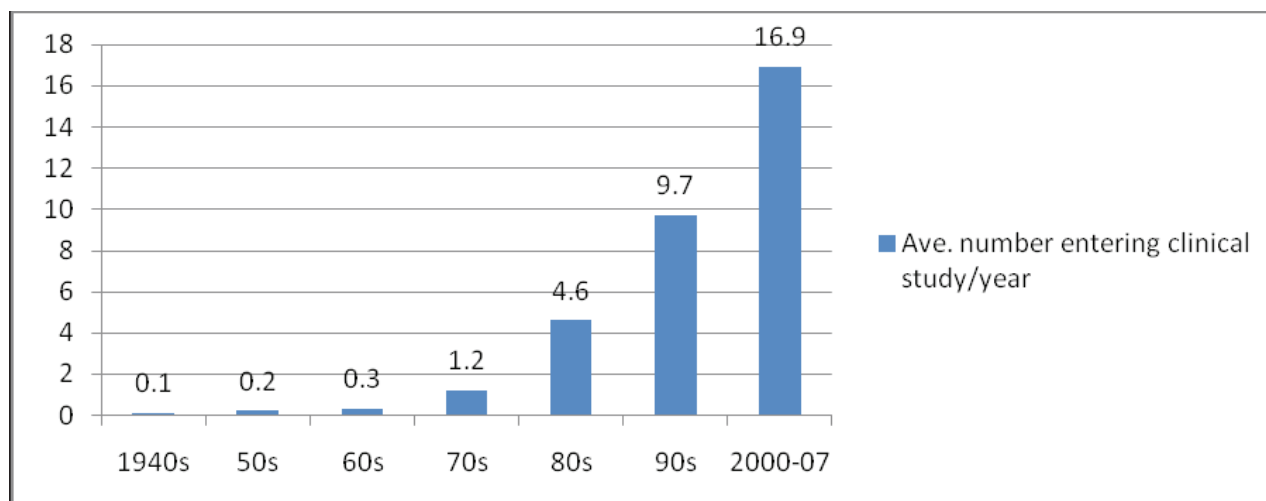


Figure 1: Average annual number of peptide therapeutics entering study during seven time periods

Therapeutic peptides were studied in a total of 15 therapeutic categories during the 1990s and 2000-2007 periods, which was an increase from the 11 categories investigated in the 1980s (Figure 2). During 2000-2007, new therapeutic peptides entering study were most frequently treatments for metabolic indications (26%), whereas only 4% and 8% of peptides entering study in the 1980s and 1990, respectively, were studied for these disorders. Decreases were observed in the study of peptides as treatments for cardiovascular (20%, 10% and 9% for the 1980s, 1990s and 2000-07 periods, respectively) and allergy & immunological diseases (17%, 18% and 10% for the 1980s, 1990s and 2000-07 periods, respectively).

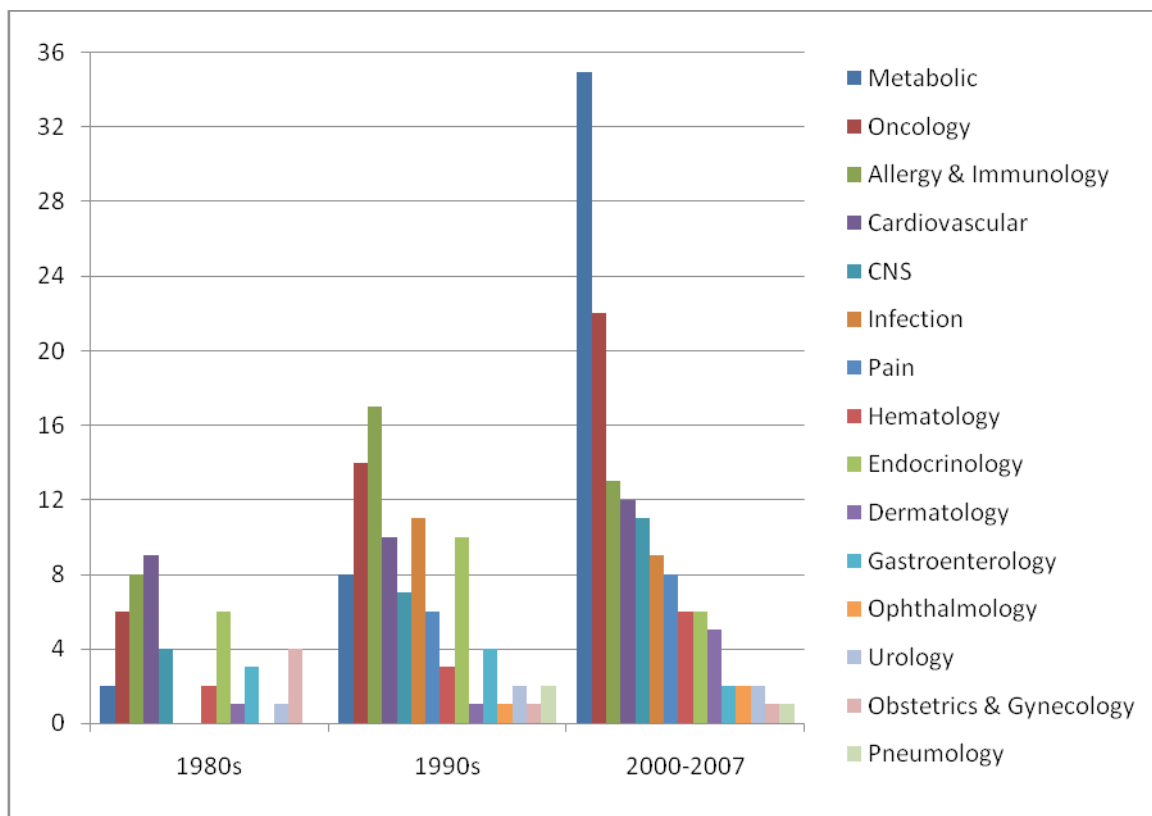


Figure 2: Therapeutic categories for peptide candidates entering study in three time periods

The majority of therapeutic peptide candidates were directed toward extracellular targets, with less than 10% known to bind intracellular molecules. The most common extracellular targets were G-protein coupled receptors (GPCRs). Other targets included the cytokine receptor superfamily, the natriuretic peptide receptor family, channel molecules, enzymes, cell adhesion molecules, viral proteins, cholesterol metabolism and transport, the insulin receptor family, glycoprotein IIb/IIIa, and gap junction molecules. Of the candidates targeting GPCRs, nearly all therapeutic peptides studied in the 1980s were directed toward GPCR A. During the 1990s, about two-thirds targeted GPCR A and one-third targeted GPCR B. The focus on GPCR B has increased in the 2000s - nearly half of peptides known to target GPCRs that entered studies during 2000-2007 were directed toward GPCR B.

Phase transition probabilities for therapeutic peptides have remained relatively steady over three overlapping periods encompassing 1984-2005. The results suggest that demonstration of efficacy is the primary bottleneck in the clinical development process (45% Phase 2 to 3 transition value). The cumulative success rates for peptides (20-30% overall) compare favorably to the values for antibody therapeutics while being approximately twice that for small molecules. Probabilities of success are important for strategic planning, but it is important to note that success rates will vary at least somewhat until fates of all candidates in the cohorts are known.

A total of 48 peptide therapeutics are now approved for marketing either in the US and other countries (24 products), or only outside the US (an additional 24 products). The near-term prospects for additional approvals are promising – four peptide candidates were undergoing US regulatory review as of October 2008. These are mifamurtide, sinapultide, liraglutide, and degarelix.

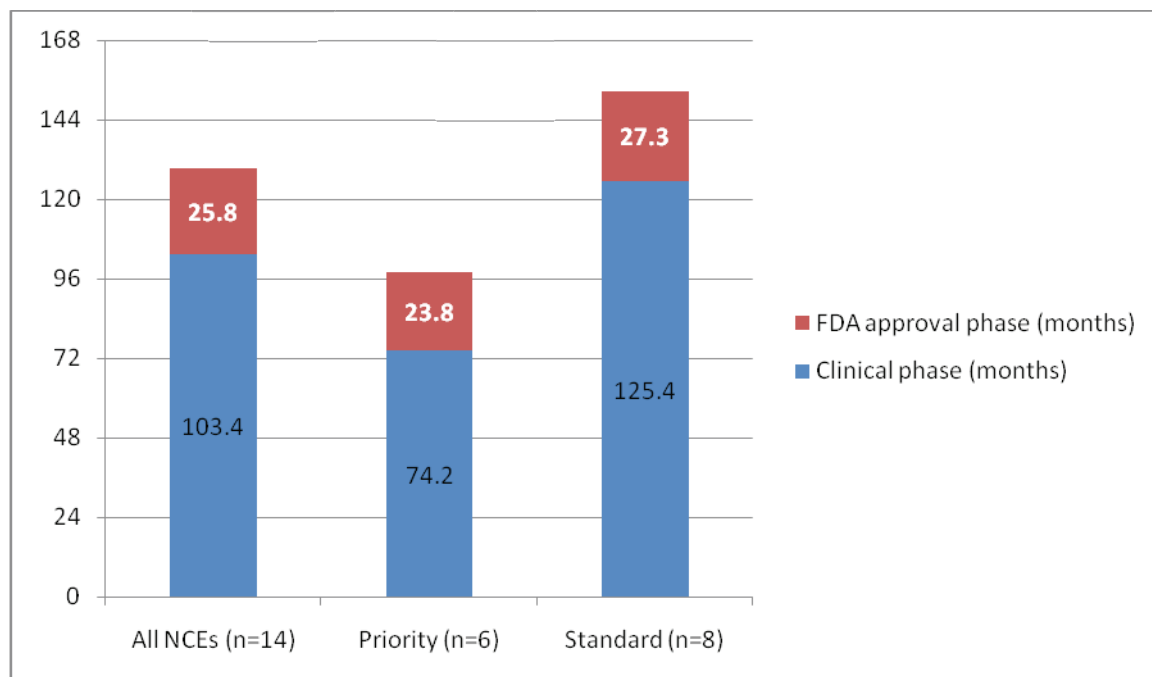


Figure 3: Mean clinical and US approval phases for peptide new chemical entities approved after 1992

Average clinical and approval phase lengths were calculated for 14 peptide new chemical entities approved by FDA after enactment of the Prescription Drug User Fee Act of 1992. This legislation and subsequent reauthorization acts defined timeline goals for the review of candidates based on a two-tier ranking system. Under the current guidelines, candidates are given a priority or standard review, with goals of six and ten month time to first action. Priority reviews are given to candidates that are intended as treatments for serious or life-threatening diseases or that might represent a significant improvement in the treatment of a disease. The average clinical phase for candidates ultimately given a priority review by FDA was notably shorter (41%) compared those given a standard review. The average FDA approval phase was also shorter for priority-reviewed products, but by 3.5 months (13%) only. On average, clinical evaluation and FDA review of new therapeutic peptides required 10.8 years, although the length of this period was notably different for candidates granted priority review (8.2 years) compared to those granted standard review (12.7 years).

Peptide therapeutic R&D is highly dynamic with increasing numbers of candidates entering clinical study in a wide array of therapeutic categories. We anticipate that the pharmaceutical and biotechnology industries will continue to focus on these versatile molecules because of the availability of new technologies aimed at improving synthesis, delivery and formulation and because of the relatively high approval success rates. In order to report on future trends, we will continue to collect data for these important therapeutic products.

The full study report "Development Trends for Peptide Therapeutics" will be available for purchase from the Peptide Therapeutics Foundation (www.peptidetherapeutics.org) in February 2009.

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Unexploited potential of peptides

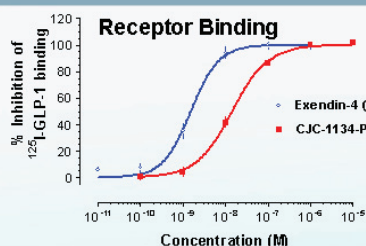
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- Short Plasma half-life

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- Improved distribution and pharmacodynamic profile of peptides

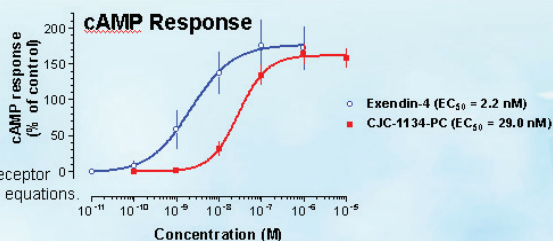
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Comparative study CJC-1134 PC vs Exendin-4



- Membranes of CHO-K1 cells stably transfected with human GLP-1 receptor
- IC₅₀ values were calculated with 4-parameter logistic equations.
- N = 3 for each compound.



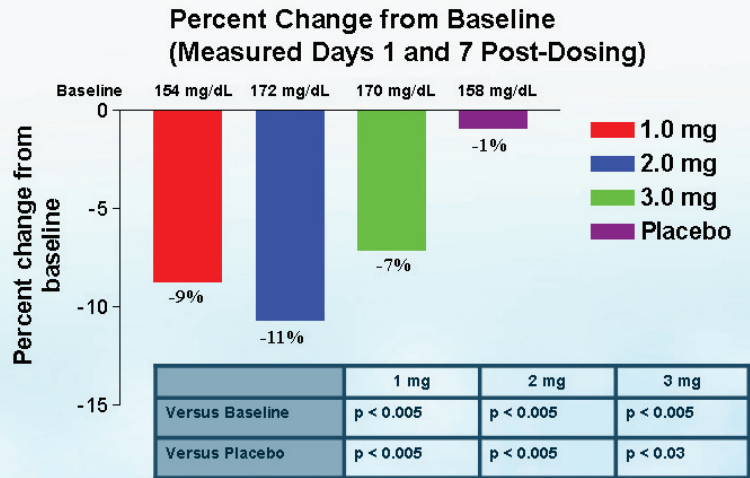
- CHO-K1 cells stably transfected with human GLP-1 receptor
- EC₅₀ values were calculated with 4-parameter logistic equations.
- N = 3 for exendin-4 and 6 for CJC-1134-PC.

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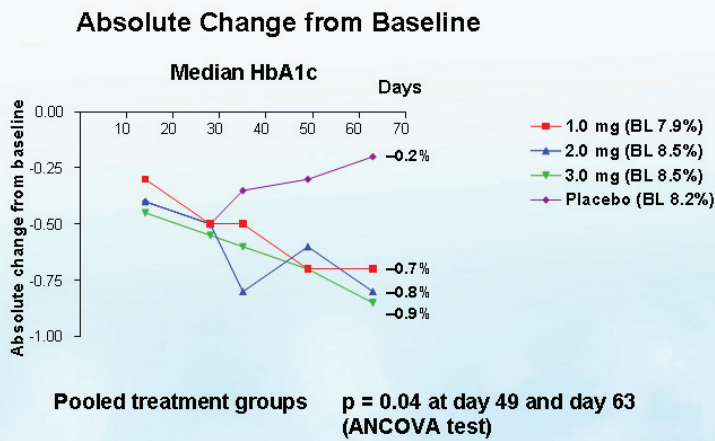
All Dosing Groups Effective In Lowering Fasting Plasma Glucose



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A forum for discussion and knowledge dissemination. Previous topics have included: peptide research, development of peptide-based technologies, peptide manufacturing technologies, and drug delivery methods.

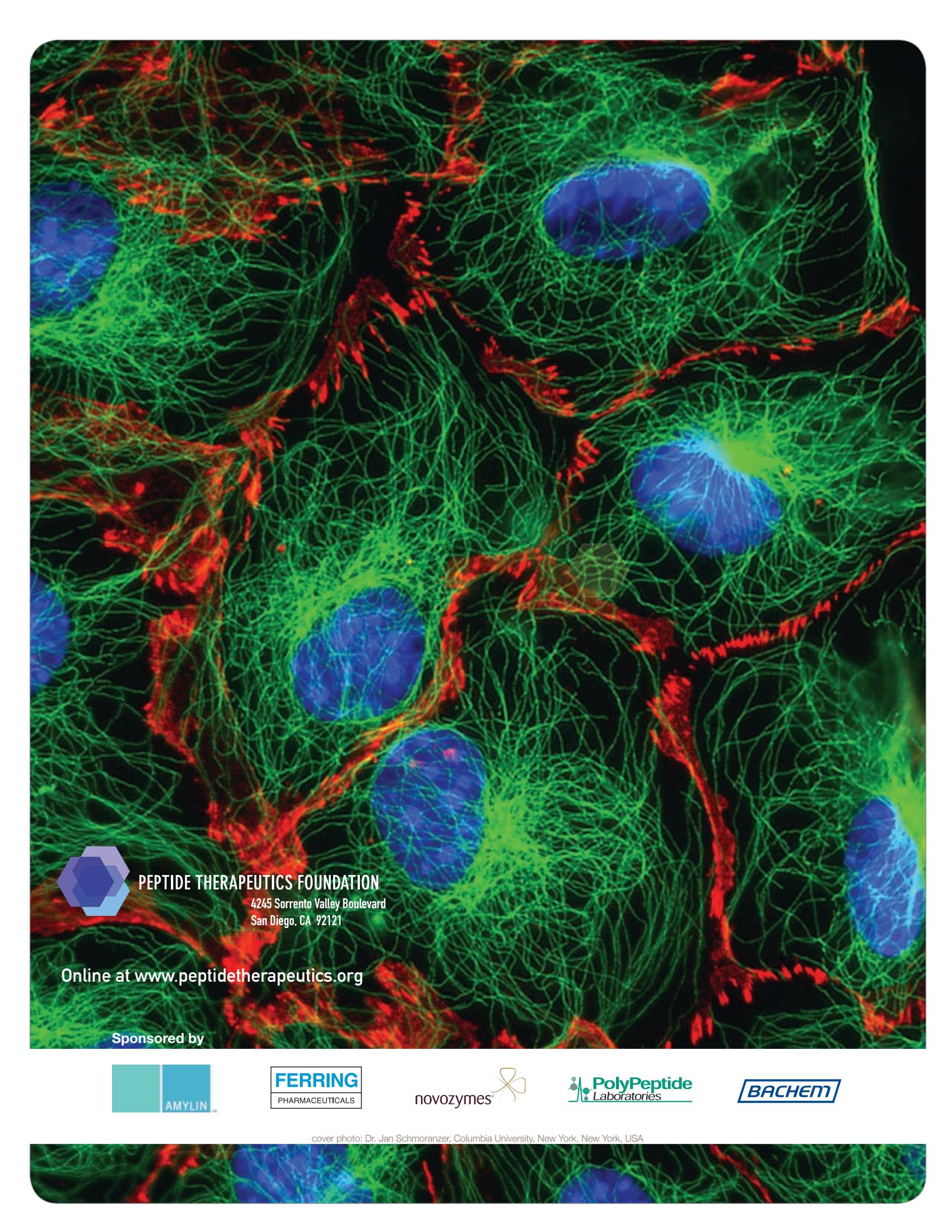
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