

The Peptide Therapeutics Foundation: mapping the future of peptide therapeutics

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PEPTIDE THERAPEUTICS FOUNDATION

Promoting research and development of peptide therapeutics



Interest in the development of peptides as therapeutics has increased substantially in the past decade because of advances in peptide production, delivery and formulation technologies, and the increased acceptance by patients of injected or inhaled drugs. Sales for marketed peptide therapeutics have also grown to record levels, e.g., 2010 global sales of glatiramer acetate (Copaxone®; \$4.0 billion), leuprolide (Lupron®; \$3.0 billion), octreotide acetate (Sandostatin®; \$1.3 billion), goserelin acetate (Zoladex®; \$1.1 billion), teriparatide (Forteo®; \$830 million), and exenatide (Byetta®; \$710 million). In recognition of these advances and to help spur additional growth in the field, the non-profit Peptide Therapeutics Foundation (peptidetherapeutics.org/) was established in 2008. The mission of the Foundation is to promote research and development (R&D) of peptide therapeutics.

Fulfilling the Foundation's mission

The Foundation sponsors the Peptide Therapeutics Symposium, which is held in the San Diego area each year. The annual Peptide Therapeutics Symposium is an international forum that brings together leaders from academia, biopharmaceutical companies, contract manufacturing or research organizations, and investors interested in all aspects of developing peptides as therapeutics, including discovery, safety, toxicology, clinical studies, manufacturing, formulation, delivery and marketing approval. With its unique focus and format, the symposium provides participants with a yearly update on the most recent and exciting developments in the peptide field.

The 7th Annual Peptide Therapeutics Symposium will be held October 25-26, 2012 at the Salk Institute for Biological Studies in . This year's program will continue the special emphasis that the Foundation places upon peptide pharmacology, especially development candidates that have advanced to human application. As such, there will be lectures from companies such as Affymax Inc., Eli Lilly & Company, Kai Pharmaceuticals, Aileron Therapeutics, Naurex Inc., Amunix Inc., and Unigene Laboratories Inc., pertaining to their clinical studies with select, cutting-edge peptide therapeutics. As in the previous symposia, a sizable portion of lecture time will be devoted to technical advances directed at the inherent limitations associated with peptide therapeutics, such as parenteral administration and limited transport across cellular membranes. Keynote lectures at the 2012 symposium will be delivered by Professors Bill Degrado (*University of California, San Francisco*) and Matthias Tschoep (*Technische Universität München*). The scientific excellence in a setting of controlled size provides unparalleled opportunity for information sharing and networking, something that will remain a design feature of all future meetings.

The increasing interest in the development of peptide therapeutics prompted the Foundation, in collaboration with Tufts University's Center for the Study of Drug Development, to compile a comprehensive database of peptide new chemical entities (NCEs) that entered clinical development sponsored by commercial firms located worldwide. The database is currently composed of records for ~400 peptide NCEs, and includes information such as international non-proprietary or compound names; indications studied; current development status; number of amino acids; topology; manufacturing method, and molecular target. Data were collected from public sources such as company web sites, meeting reports, investor presentations, clinicaltrials.gov, biomedical literature, Drugs@fda and emea.europa.eu. The Foundation commissioned two reports, issued in 2008 and 2010, on development trends for peptide therapeutics that were based on analyses of the database.

Peptide therapeutics development trends

Examination of the Foundation's database reveals a notable trend toward clinical study of more peptide therapeutics over the past 15 years (Figure 1). On average, the number of peptides NCEs entering their first clinical study during the 1990s and 2000s was 9.9 and 19.5 per year, respectively. The current commercial pipeline of peptide therapeutics includes ~100 NCEs, with most in early phase studies and 15 in Phase 3 studies. The pipeline drugs are being studied in a wide variety of indications, including cancers (21%), metabolic (15%), cardiovascular (8%), allergy/immunological (8%), gastrointestinal (8%), antimicrobial (7%), pain (6%), dermatology (5%), central nervous system (5%), and urology (5%).

Analysis of the peptide therapeutics pipeline reveals trends toward clinical study of non-canonical peptides, e.g., peptides that have been modified to improve half-life, as well as those with the ability to selectively target cells or penetrate the blood-brain barrier. Four of these molecules, albiglutide (GlaxoSmithKline), dulaglutide (Eli Lilly & Company), NGR-hTNF (MolMed S.p.A), and davunetide (Allon Therapeutics), have progressed to Phase 3 studies and are highlighted in detail below.

Albiglutide and dulaglutide are both glucagon-like peptide-1 (GLP-1) receptor agonists with half-lives in the range of 4-7 days, which allows for once weekly dosing. The extended half-life is due to the fusion of GLP-1 moieties to either human albumin, in the case of albiglutide, or, in the case of dulaglutide, a human IgG4 Fc heavy chain that was engineered for stability and for reduced immunogenicity and effector functions. Albumin and Fc-containing molecules are protected from degradation in cells via binding to the receptor FcRn.

Albiglutide is being studied in a total of eight Phase 3 studies of patients with Type 2 diabetes, with two completed and six on-going. The two completed studies evaluated the safety and efficacy of weekly, subcutaneously injected doses of albiglutide compared to other treatments such as liraglutide or insulin glargine. The primary outcome measures were the change from baseline of glycosylated hemoglobin (HbA1c) levels within a timeframe of either 16 or 32 weeks. In the on-going studies, changes in HbA1c levels are being assessed in timeframes of up to two years. GlaxoSmithKline announced in April 2012 that the combined top-line data from seven of the eight Phase 3 clinical studies support advancing albiglutide into regulatory review.

Dulaglutide is undergoing evaluation in one Phase 2/3 study and eight Phase 3 studies of patients with Type 2 diabetes. The Phase 2/3 study is an adaptive dose finding and efficacy study to evaluate the effects of once weekly injection of dulaglutide compared to sitagliptin in patients with Type 2 diabetes. Dulaglutide is administered by subcutaneous injection once-weekly for up to 24 months at seven doses. Two Phase 3 studies (AWARD-1, and -2) are evaluating two doses of once weekly subcutaneously administered dulaglutide; the primary outcome measure is change in baseline HbA1c at either a 26 week or 52 week endpoint. Additional Phase 3 studies are evaluating the drug in Japanese patients and assessing the effect of dulaglutide on major cardiovascular events in patients.

NGR-hTNF comprises a selective cell-targeting peptide fused to tumor necrosis factor (TNF). The ligand (NGR) of aminopeptidase N/CD13 is thus used to target TNF to endothelial cells of angiogenic vasculature such as that found in tumors. The drug is undergoing evaluation in 10 Phase 2 studies as a treatment for a variety of solid tumor types, and a Phase 3 study of patients with advanced malignant pleural mesothelioma. The estimated study completion date for the Phase 3 study is February 2013. NGR-hTNF has orphan drug designation in the European Union (EU) and United States (US) for malignant mesothelioma.

Davunetide is an eight amino acid fragment of activity-dependent neuroprotective protein that penetrates the blood-brain barrier and has been shown to affect multiple pathways relevant to neurodegenerative diseases. A Phase 2/3 study to evaluate the safety and efficacy of davunetide for the treatment of progressive supranuclear palsy is on-going. In this study, the drug is administered as a nasal spray at doses of 30 mg twice daily for 1 year; the estimated study completion date is December 2012.

Outlook on approvals of peptide NCEs in 2012

The pipeline of peptide NCEs delivered three products (lucinactant, peginesatide, pasireotide) to the market during January-May 2012; an additional five peptide NCEs (carfilzomib, linaclotide, teduglutide, lixisenatide, afamelanotide) are undergoing regulatory review in the EU or US (Table 1). Like the pipeline drugs, the recently approved peptides and those in regulatory review are intended as treatments for a wide variety of indications, e.g., respiratory distress syndrome, anemia, Cushing's disease, hematological cancer, gastrointestinal disorders, diabetes, genetic blood disease.

Lucinactant (Surfaxin; Discovery Labs) was approved in the US on March 6, 2012 for the prevention of respiratory distress syndrome in premature infants, and peginesatide (Omontys; Affymax Inc.) was approved in the US on March 27, 2012 for the treatment of anemia due to chronic kidney disease in adult patients on dialysis. Novartis announced on April 25, 2012 that pasireotide had been approved by the European Commission for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.

As of May 2012, linaclotide (Ironwood Pharmaceuticals) and teduglutide (NPS Pharmaceuticals) are in regulatory review in both the EU and US, while lixisenatide (Sanofi) and afamelanotide (Clinuvel Pharmaceuticals) are in review only in the EU and carfilzomib (Onyx Pharmaceuticals) is in review only in the US. The Food and Drug Administration's action dates for applications occur in the second half of 2012 for teduglutide, in July 2012 for carfilzomib, and in September 2012 for linaclotide.

The Foundation's sponsors

The work of the Peptide Therapeutics Foundation, including reporting trends in the development peptide therapeutics and providing a forum for scientific discourse on peptide therapeutics R&D at its annual symposium, is made possible through the generous support of corporate sponsors Amylin Pharmaceuticals, Roche, Ipsen, the PolyPeptide Group, Zydus Cadilla, Pfizer/CovX, and Ferring Research Institute. A brief profile of each sponsoring company is provided below.

Amylin Pharmaceuticals, Inc. is a biopharmaceutical company dedicated to improving lives of patients through the discovery, development and commercialization of innovative medicines. Amylin has ~1400 employees and maintains its corporate headquarters in San Diego. The company is focused on the therapeutic potential of new peptide hormone drug candidates and the creation of novel and groundbreaking therapies for the treatment of diabetes, obesity, and other metabolic diseases. A key element of the company's R&D strategy is leveraging its understanding of the physiology of peptide hormones and their interplay to develop the next generation of drugs and combination therapies. The company markets two first-in-class diabetes drugs and recently introduced the first once-weekly therapy for the treatment of diabetes. Amylin has been a sponsor of the Peptide Therapeutics Foundation since 2008 and actively supports the mission of this organization to serve as a forum for scientific exchanges around peptide science and peptide drug development.

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 has sponsored the PTF since 2011. Roche sees peptides as an important therapeutic modality with significant future potential that complements small molecules and biologics. Roche is pursuing peptide projects in research both for intracellular and extracellular targets.

Ipsen (Euronext: IPN; ADR: IPSEY) is a global specialty-driven pharmaceutical company with total sales exceeding €1.1 billion in 2011. Ipsen's ambition is to become a leader in specialty healthcare solutions for targeted debilitating diseases. Its development strategy is supported by four franchises: neurology / Dysport[®],

endocrinology / Somatuline[®], uro-oncology / Decapeptyl[®] and hemophilia. Moreover, the Group has an active policy of partnerships. Research and development is focused on innovative and differentiated technology-driven platforms, peptides and toxins. In 2011, R&D expenditure totaled more than €250 million, above 21% of Group sales. The Group has total worldwide staff of close to 4,500 employees. With its flagship peptide drugs Decapeptyl[®] and Somatuline[®], Ipsen is committed to R&D of peptide therapeutics in its targeted diseases areas. Ipsen supports the Peptide Therapeutics Foundation to promote the peptide research community, enhance peptide scientific network and innovation and be fully engaged in therapeutic peptide R&D.

The PolyPeptide Group is historically one of the most experienced therapeutic peptide manufacturers in the world. Although the Group itself was formally launched in 1996, its involvement in peptide therapeutics dates back through its corporate roots to the early 1950s. Today the privately-held PolyPeptide Group comprises 6 manufacturing facilities on 3 continents and employs ~450 staff worldwide. While its focus remains heavily on the GMP manufacture of proprietary and generic peptides at scales from multi-grams to over 100 kilograms, the Group offers a comprehensive range of non-GMP services, including small-scale custom synthesis, radiolabelling and research-grade catalog items. It also offers large-scale manufacturing of cosmetic peptides and some organic molecules. The PolyPeptide Group has been inspected by the FDA and other regulatory authorities many times and has over 20 approved APIs. The PolyPeptide Group has been a sponsor of the Peptide Therapeutics Foundation since 2008. Its support for the Foundation is rooted in the belief that companies involved in the manufacture of both peptide-based drug substances and drug products benefits from a non-profit organization that promotes their common interests.

Zyodus 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 Ahmedabad, India, the group has global operations spread across USA, Europe, Japan, Brazil, South Africa and 25 other emerging markets. Zyodus has a team of over 1000 scientists engaged in R&D focused on finding innovative therapies for diseases affecting mankind. The major areas of research include diabetes, obesity, cardiovascular diseases, inflammation, pain, and oncology.

CovX, a biotechnology unit within Pfizer Worldwide Research & Development designs innovative bioconjugate products that are engineered to optimize efficacy, safety and compliance. Collaborating with other Pfizer sites, CovX scientists combine skills in peptide innovation and optimization with state-of-the-art bioconjugation capabilities to provide therapies for oncology and metabolic disease. Continuing innovation on the part of the 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 entered several molecules into clinical studies, including CVX-060, an anti-angiogenesis agent for cancer and CVX-096, a drug for the treatment of diabetes.

Ferring Pharmaceuticals (Ferring) is a private, research-driven specialty biopharmaceutical company active in global markets. The company identifies, develops and markets innovative products in the fields of endocrinology, gastroenterology, infertility, obstetrics, urology and osteoarthritis. Ferring has over 4,500 employees world-wide, it operates subsidiaries in over 50 countries and makes its products available in more than 90 countries. As part of its commitment to developing innovative products Ferring invests heavily in its research infrastructure both in terms of people and technology.

Ferring Research Institute (FRI), headquartered in San Diego, California FRI was established in 1996 as a core component of Ferring's research and innovation efforts. Scientists at FRI are committed to the development of a portfolio of novel, innovative peptide pharmaceuticals. In addition to its own drug discovery and development efforts, FRI works in close collaboration with the world's leading academic laboratories to translate new ideas emerging from basic research into innovative medicines. Ferring's support of the Peptide Therapeutics Foundation enables them to actively support the peptide research community, engage with the global network of peptide scientists, and promote peptide R&D in academia and industry.

Future plans

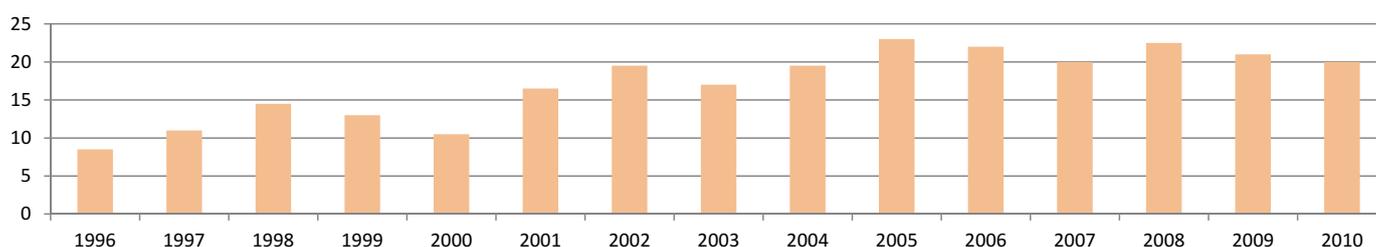
As is made clear at the Peptide Therapeutics Symposium each year, peptide therapeutics R&D is highly dynamic. Increasing numbers of innovative molecules are entering clinical study in a wide array of therapeutic categories, and a record annual number of peptide NCEs are likely to receive marketing approvals in 2012. The Peptide Therapeutics Foundation anticipates that the biopharmaceutical industry will continue to focus on these versatile molecules because of new technologies aimed at improving their biological properties, manufacturing, delivery and formulation, and looks forward to serving in its role as a forum for the exchange of ideas within this exciting field. For additional information on how to become involved in The Foundation's activities, please visit their web site at www.peptidetherapeutics.org.

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Supporting Material

Figure 1. Average number of new peptide therapeutics entering clinical study during 1996-2010.



Note: Data presented as two-year moving averages

Table 1. Peptide therapeutics recently approved* or in review in the EU or US.

INN	Trade name	Status	Indication	Target
Lucinactant	Surfaxin	Approved in US (2012)	Prevention of RDS in premature infants	DPPC
Peginesatide	Omontys	Approved in US (2012), regulatory review in EU	Anemia	EPO receptor
Pasireotide	Signifor	Approved in EU (2012)	Cushing's disease	Somatostatin receptors
Carfilzomib	(Pending)	Regulatory review in US	Multiple myeloma	Chymotrypsin-like protease
Linaclotide	(Pending)	Regulatory review in EU and US	Constipation-predominant IBS, chronic idiopathic constipation	GC-C receptor
Teduglutide	(Pending)	Regulatory review in EU and US	Short bowel syndrome	GLP-2 receptor
Lixisenatide	(Pending)	Regulatory review in EU	Diabetes	GLP-1 receptor
Afamelanotide	(Pending)	Regulatory review in EU	Erythropoietic protoporphyria	MC1 receptor

* Data available as of May 30, 2012.

Abbreviations: DPPC, dipalmitoylphosphatidyl choline; EPO, erythropoietin; EU, European Union; GC-C, guanylate cyclase C; GLP, glucagon-like peptide; IBS, irritable bowel syndrome; INN, international non-proprietary name; MC, melanocortin; RDS, respiratory distress syndrome; US, United States.