

December Meeting

The 865th Meeting
of the
Northeastern Section
of the
American Chemical Society



Northeastern Section
American Chemical Society

Symposium NEW TARGETS FOR TYPE II DIABETES (Part II) Organized by the Medicinal Chemistry Section of the Northeastern Section, American Chemical Society

Thursday - December 8th, 2005

Holiday Inn Select Hotel, 15 Middlesex Canal Park Road, Woburn, MA

- 3.00 pm Refreshments
3.15 pm Welcome
Raj (SB) Rajur, Program Chair
3.20 pm Introductory Remarks
Norton Peet, North Andover, MA
3.30 pm **RNAi Technology Drives the Development of Molecular Medicines to Treat Obesity & Type II Diabetes**
Mark Tepper, CytRx Corporation, Worcester, MA
4:30 pm **Development of DPPIV Inhibitors Using High Throughput Crystallography**
G. Sridhar Prasad, Merck & Co., Inc., West Point, PA
5:30 pm **Design of DPPIV Inhibitors for the Treatment of Type 2 Diabetes**
Subramanyah Hosahalli, Aurigene Discovery Technologies, Bangalore, India
6.30 pm Social Hour
6.45 pm Dinner
7.45 pm **The story of Vildagliptin (LAF237): A DPP4 inhibitor for the treatment of type 2 diabetes.**
Edwin B. Villhauer, Novartis Pharmaceuticals, East Hanover, NJ

Dinner reservations should be made **no later than 12:00 noon on Thursday, December 1, 2005** by contacting Marilou Cashman at (800) 872-2054 or (508) 653-6329 or mcash0953@aol.com. Reservations not canceled at least 24 hours in advance must be paid. Members, \$28.00; Non-members, \$30.00; Retirees, \$15.00; Students, \$10.00. Payment is made at the door by cash or check (no credit cards or purchase orders.) Anyone who needs handicapped services/transportation, please call a few days in advance so that suitable arrangements can be made.

Directions to Holiday Inn Select Hotel (Previously Radisson)

<http://www.radisson.com/woburnma>

A. **From Boston - Cambridge - Points North:** Take Route I-93 to Route 95/128 West. After 1 mile, take Exit 35 South to Route 38 (Main Street).

*After about 500 feet at the traffic light, turn right into Middlesex Canal Street to the hotel entrance.

B. **From the West:** Take Route 95/128 North to Exit 35 South (Route 38 - Main Street). Follow directions from * above.

THE PUBLIC IS INVITED

Mark Tepper

RNAi Technology Drives the Development of Molecular Medicines to Treat Obesity & Type II Diabetes

CytRx Laboratories have developed powerful new RNAi gene silencing technology to drive the discovery and development of both traditional small molecule and new RNAi-based therapeutics. This talk will focus on our strategy of applying high throughput RNAi based screens and target validation technology in metabolic tissues to decode the function of key targets for treating obesity and diabetes. Using this technology we have identified a number of novel drug target which we have begun to develop small molecule and RNAi based therapeutics for the treatment of obesity, diabetes and diabetic complications.

Mark Tepper is President and co-founder of CytRx Laboratories, Worcester, MA (formerly Arais, Inc.) and Senior Vice President of CytRx Corp. Los Angeles, CA. He previously served as President and CEO of Arradial, Inc., an Oxford Biosciences Venture backed company developing a novel microfluidics based drug discovery platform. From April 1995 to March 2002, Dr. Tepper served in a number of senior management roles at the US based Serono Pharmaceutical Research Institute most recently as Vice President, Research and Operations and Executive Director of Lead Discovery. His responsibilities included the discovery and development of new medicines in the area of endocrinology, metabolism, oncology, and immunology. While at Serono, Dr. Tepper invented a 2nd generation Interferon drug for MS called Infercept™, advancing the drug from discovery to clinical phase II. From 1988 to 1995, Dr. Tepper held a variety of functional and project based roles at the Bristol Myers Squibb Pharmaceutical Research Institute working on the discovery and development of small molecule and biologic therapeutics in the area of Oncology and Immunology. Prior to BMS, Dr. Tepper was a post-doctoral fellow at the University of Massachusetts Medical School in the laboratory of Dr. Michael Czech. Dr. Tepper received his Ph.D. in Biochemistry and Biophysics from Columbia University in 1985, and his B.A. in Chemistry from Clark University with highest honors in 1979.

Sridhar Prasad

Development of DPPIV Inhibitors Using High Throughput Crystallography

Dipeptidyl peptidase IV (DPPIV) is a member of the prolyl oligopeptidase family of serine proteases. DPPIV removes dipeptides from the N terminus of substrates including chemokines, neuropeptides and peptide hormones. Studies to date indicate that DP4 plays an important role in regulating insulin levels in the body. In early-stage clinical trials conducted primarily by large pharmaceutical companies, orally delivered DP4 inhibitors reduced blood glucose and increased insulin response in patients. These data indicate that small-molecule inhibitors that target DP4 could be potential treatments for major human diseases including type II diabetes, obesity, high cholesterol and other metabolic syndromes. Structure-Based Drug Design (SBDD, also known as rational drug design) is a technique that accelerates the drug discovery process by utilizing structural information to improve the lead optimization process. This technique applied on a high throughput mode for the determination of the three dimensional structure of DPPIV followed by rapid generation of co-crystal structures led to the development of three preclinical candidates in a period of 18 months. The strategy and results of these preclinical development will be presented.

Sridhar Prasad is currently a research fellow in the structural Biology Department, at Merck & Co., Inc., West Point, PA. Prior to this position, Sridhar served as an associate director of crystallography at Syrrx Inc. San Diego CA, where he was leading the DPPIV drug discovery program. Sridhar, received his PhD in biomolecular crystallography from Indian Institute of Science Bangalore, India and did his Postdoctoral work at the University of Minnesota and Scripps Research Institutes. Sridhar holds four US patents and published more than 50 papers in peer reviewed journals.

Hosahalli Subramanyah

Design of DPPIV Inhibitors for the Treatment of Type 2 Diabetes

Design of novel DPPIV inhibitors will be discussed during the presentation

Hosahalli Subramanyah received his PhD degree from the Indian Institute of Science in Bangalore, India, and was a Postdoctoral Fellow in the Department of Molecular Biophysics and the Dunn School of Pathology at Oxford University, in the United Kingdom. Subsequently, Dr. Subramanyah became an Assistant Director at the Central Drug Research Institute in Lucknow, India, prior to joining Aurigene Discovery Technologies in Bangalore. Presently, Dr. Subramanyah is the Head of Structure-Guided Drug Design at Aurigene.

Edwin B. Villhauer

The Story of Vildagliptin (LAF237): A DPP4 inhibitor for the treatment of type 2 diabetes

Dipeptidyl peptidase IV (DPP4) inhibition has the potential to become a valuable therapy for type 2 diabetes. The synthesis and structure activity relationship of a new DPP4 inhibitor class, N-substituted-glycyl-2-cyanopyrrolidines, are described as well as the path that led from clinical development compound 1-[2-[5-cyanopyridin-2-yl)amino]-ethylamino]acetyl-2-cyano-(S)-pyrrolidine (DPP728) to its follow-up, 1-[[3-hydroxy-1-adamantyl) amino]acetyl]-2-cyano-(S)-pyrrolidine (Vildagliptin, LAF237). The pharmacological profile of Vildagliptin in obese Zucker fa/fa rats along with pharmacokinetic profile comparison of DPP728 and Vildigliptin in normal cynomolgus monkeys and humans is discussed. The results suggest that Vildagliptin is a potent, stable, selective DPP4 inhibitor possessing excellent oral bioavailability and potent antihyperglycemic activity with potential for once-a-day administration. The results from recent clinical studies will be discussed during the congress.

Edwin Villhauer is currently a Principal Fellow Research Scientist in Process Research at Novartis Pharmaceuticals in East Hanover, New Jersey. Until the move of Novartis Research to Boston in 2003, he worked for over 17 years as a medicinal chemist in preclinical asthma, cardiovascular, obesity and diabetes programs at Sandoz and then Novartis in New Jersey as well as Basel, Switzerland. He has led, and championed numerous diabetes and obesity programs while specializing in protease inhibition and combinatorial chemistry. Due to his inventions of Novartis's two diabetes development compounds in the DPP4 inhibitor field (DPP728 and its successor, LAF237), he was recently awarded the title of Novartis Leading Scientist. He is the author of over two dozen publications and inventor of 9 issued US patents. Dr. Villhauer received his B.S., M.S., and Ph. D. from the University of Rochester.