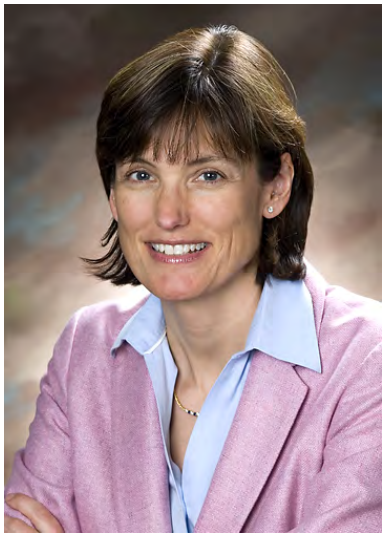

2010-2011 POCC Lecture Series

April 28, 2011, 8:00 PM

≈ POCC Industrial Award ≈

Dr. Ann E. Weber

Merck Research Laboratories – Rahway, NJ

JANUVIA® and Beyond: Selective Dipeptidyl Peptidase IV Inhibitors for the Treatment of Type 2 Diabetes

Carolyn Hoff Lynch Hall, Chemistry Bldg, U of Pennsylvania

The Philadelphia Organic Chemist's Club

POCClub.org

Dr. Ann E. Weber is Vice President – Discovery & Preclinical Sciences and Discovery Chemistry Site Head at the Rahway, NJ site of Merck Research Laboratories. In this role, she is responsible for the discovery of innovative therapeutic agents to treat patients with cardiovascular disease and metabolic disorders. Dr. Weber obtained her B.S. degree in chemistry summa cum laude from the University of Notre Dame and her Ph.D. degree from Harvard University with Professor David A. Evans. Following completion of her degree in 1987, Dr. Weber joined Merck Research Laboratories as a Senior Research Chemist and has assumed roles of increasing responsibility. Dr. Weber's research interests include the design and synthesis of ligands for G-protein coupled receptors, ion channels and enzymes. Her work has led to 17 development candidates, including JANUVIA® (sitagliptin phosphate), a new treatment for patients with Type 2 diabetes. Dr. Weber is the author of over 70 publications and co-inventor on 28 issued US patents with 11 additional applications pending. She has received a number of awards including the Thomas Alva Edison Patent Award, a Directors' Award from Merck, the Robert M. Scarborough Award for Excellence in Medicinal Chemistry and the ACS Heroes of Chemistry Award.

Abstract: Dipeptidyl peptidase IV (DPP-4), a proline selective serine dipeptidase, is responsible for the N-terminal inactivation of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), incretin hormones that evoke glucose dependent secretion of insulin and inhibition of glucagon release. Inhibitors of DPP-4 have been shown to increase circulating levels of GLP-1 and GIP, both in animal models and in the clinic, resulting in improved glucose tolerance. Thus, DPP-4 inhibitors represent a new therapy for type 2 diabetes. Early α-amino acid-derived inhibitors that were not selective over related family members, in particular DPP-8 and DPP-9, induced profound toxicities in preclinical species. SAR studies in a β-amino amide series led to the discovery of JANUVIA® (sitagliptin phosphate), a highly selective DPP-4 inhibitor that was very well tolerated in pre-clinical toxicity studies and in human clinical trials. In addition, using different approaches, three preclinical candidates were identified as potential back-up compounds to sitagliptin. With the approval of JANUVIA® in more than 80 countries including the US, Europe and Japan, a new treatment is now available for patients with type 2 diabetes.