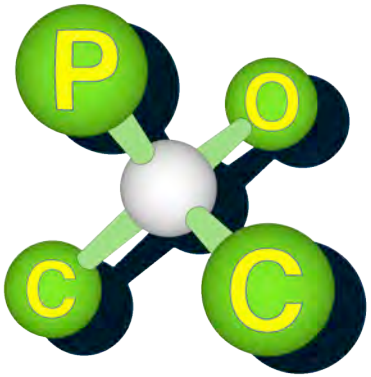
2008-2009 POCC Lecture Series

September 25, 2008, 8:00 PM

Dr. Ann E. Weber
Merck Research Laboratories

Discovery of JANUVIA™ (Sitagliptin), a Selective Dipeptidyl Peptidase-4 Inhibitor for the Treatment of Type 2 Diabetes

Carolyn Hoff Lynch Lecture Hall
Chemistry Building, University of Pennsylvania



Dr. Ann E. Weber obtained her B.S. degree in chemistry *summa cum laude* from the University of Notre Dame. She earned her Ph.D. degree from Harvard University, studying synthetic organic chemistry is the laboratories of Professor David A. Evans. Following completion of her degree in 1987, Dr. Weber joined Merck Research Laboratories in Rahway, NJ as a Senior Research Chemist. She is currently Executive Director of medicinal chemistry. Dr. Weber is the author or co-author of over 65 publications. She is co-inventor on 24 issued US patents with 11 additional applications pending. In 2002 she was named Women at the Forefront of Chemistry by the American Chemical Society Women Chemists Committee. She received the 2007 Thomas Alva Edison Patent Award from the Research and Development Council of New Jersey and a Directors' Award from Merck for her contributions to the discovery of JANUVIA™. She was part of a team that received the 2007 Prix Galien USA for JANUVIA™, and was named among the 2008 Outstanding Women in Science by the New Jersey Association for Biomedical Research.

Abstract: Dipeptidyl peptidase-4 (DPP-4), a member of a family of proline selective serine dipeptidases, is responsible for the *N*-terminal inactivation of GLP-1 and 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 potential new therapy for type 2 diabetes. Early α-amino acid-derived DPP-4 inhibitors that were not selective over related family members, in particular DPP-8 and DPP-9, induced profound toxicities in preclinical species. SAR studies on two novel screening hits provided a series of β-amino acid-derived inhibitors that were highly selective over these enzymes. Optimization of this series led to the discovery of JANUVIA™ (sitagliptin), a selective DPP-4 inhibitor that was recently approved by the FDA for the treatment of type 2 diabetes.