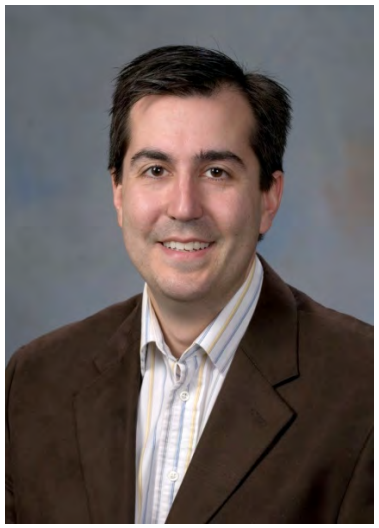

2009-2010 POCC Lecture Series

May 13, 2010, 8:00 PM

Mr. Robert Kester

Roche Pharmaceuticals

"Discovery of Piragliatin, a small molecule activator of GK"

Carolyn Hoff Lynch Lecture Hall
Chemistry Building, University of Pennsylvania

The Philadelphia Organic Chemist's Club

POCClub.org

Robert Kester attended Ursinus College and graduated in 1993 with a B.S. degree in Chemistry. After completing a master's degree with David A. Evans at Harvard University, he joined Roche-Nutley as a Senior Scientist in 1997 working in the lab of Dr. Ramakanth Sarabu. Over the past 13 years he has been working primarily on Metabolic Disease programs, most notably Glucokinase Activators (GKAs) for Type 2 Diabetes and MCHR antagonists for obesity. Rob has been an adjunct professor at Kean University in Union, NJ and has risen to the rank of Senior Principal Scientist at Roche. Rob is a co-inventor on more than 10 patent applications and has had the opportunity to present aspects of Roche's GKA program at a number of national conferences. In recognition of these accomplishments, he is one of the 2010 recipients of The Technical Achievement in Organic Chemistry award sponsored by the Organic Division of the ACS.

Abstract: Glucokinase (GK) plays a key role in whole-body glucose homeostasis by catalyzing the phosphorylation of glucose in cells that express this enzyme, such as pancreatic β cells and hepatocytes. A class of antidiabetic agents that act as nonessential mixed-type GK activators (GKAs) by increasing the glucose affinity and maximum velocity (V_{max}) of GK has been identified. This presentation will provide detailed structure activity relationships (SAR) surrounding the phenylacetamide class of GKAs focusing on the progression from a single high throughput screening hit to a phenylacetamide incorporating an aminothiazole ring, RO0281675, the first clinical candidate. During the course of preclinical development, this molecule was found to produce a potentially troublesome thiourea metabolite, which posed a safety risk and prevented its further development. Subsequent *in vitro* and *in vivo* work led to an understanding of the mechanism of formation of the thiourea. The information gained from this exercise provided insight into the structure activity and property relationships (SPR) around the heteroaromatic amine portion of the molecule and led to the identification of a second lead compound, which did not contain a thiazole. Further profiling of this compound *in vivo* led to the identification of an active, novel ketone metabolite that was found to have superior *in vitro* safety characteristics (e.g. hERG, covalent binding) and progressed into the clinic. Early clinical data on Piragliatin in type 2 diabetic patients will be shown.