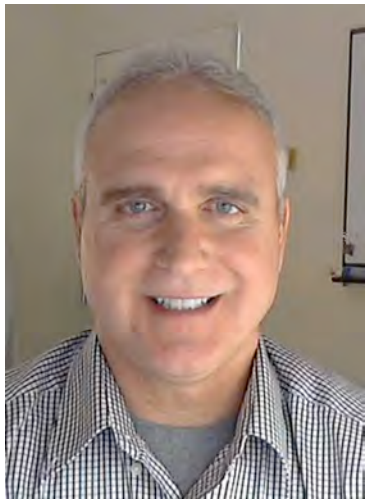

2013-2014 POCC Lecture Series

January 30, 2014, 8:00 PM

Ralph A. Rivero, Ph.D.
GlaxoSmithKline

Identification of GSK2636771, a Potent and Selective, Orally Bioavailable Inhibitor of Phosphoinositide 3-Kinase-beta (PI3Kβ) for the treatment of PTEN Deficient Tumors

Carolyn Hoff Lynch Lecture Hall
Chemistry Building, University of Pennsylvania

The Philadelphia Organic Chemists' Club

POCClub.org

BS in Biochemistry 1982 – Lehigh University

PhD in Organic Chemistry 1987 – University of Pennsylvania, working in the labs of Professor Amos B. Smith III – Natural Product Synthesis

26 + years in the Pharmaceutical Industry;

Medicinal Chemist, Merck, Rahway NJ 1987 – 1995 – worked on developing protease and kinase inhibitors, 7TM receptor antagonist / agonists; worked on angiotensin receptor antagonist Losartan; early adopter of high throughput organic chemistry technology

Team Leader, Site Director JNJ, Spring House, PA 1995 – 1998 – Implemented high throughput organic synthesis, worked on kinase inhibitors, 7TM receptor agonists / antagonists, lead identification

Medicinal Chemistry Director, GlaxoSmithKline 1998 – present – Current Leader of the Philadelphia Flexible Discovery Unit, previously led the High Throughput Chemistry Unit, the UM/UP Discovery Chemistry Unit, and led the PI3K-beta program team as a Director in Oncology Medicinal Chemistry

Author / Co-author of 59 publications in peer-review journals

Inventor / Co-inventor on 42 patents

Abstract: Dysregulation of the PI3K pathway is one of the most common causes of tumorigenesis and aberrant pathway activation occurs frequently through loss of the tumor suppressor protein, PTEN. Loss of PTEN protein has been observed in approximately 40% of glioblastoma, 50% of prostate, 57% of endometrial cancers, as well as in a number of other tumor types, including melanoma and breast cancers. Preclinical studies have shown that selective depletion of the PI3Kβ isoform inhibits tumorigenesis and reduces downstream PI3K signaling in PTEN deficient tumors. This data presents an opportunity for a clear patient selection strategy based on the presence or absence of PTEN. During an extensive knowledge-based lead identification and optimization effort starting from the reported PI3K beta-selective compound TGX-221, we identified several unique series of potent and selective inhibitors with less than desirable pharmacokinetic properties. Through a combination of structure-based and knowledge-based design, we ultimately identified substituted benzimidazole GSK2636771 as a potent, orally bioavailable, PI3K beta-selective inhibitor. The evolution of our selective inhibitors, leading to the discovery, design, and optimization of GSK2636771 and related analogs, will be described.