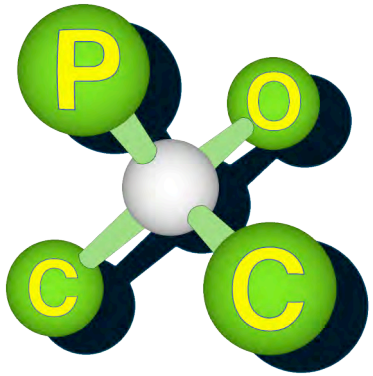
# 2007-2008 POCC Lecture Series

February 21st, 2008, 8:00 PM

**Dr. Juan I. Luengo, GlaxoSmithKline**

***Discovery of Eltrombopag, a Small-Molecule Oral Thrombopoietin Receptor Agonist: From Screening to the Clinic***

Carolyn Hoff Lynch Lecture Hall
Chemistry Building, University of Pennsylvania




Dr. Luengo received his Chemical Sciences B.S., majoring in organic chemistry, from Universidad Complutense (Madrid) in 1980, and a Ph.D. from the University of Michigan under the guidance of M. Koreeda in 1985. Following a postdoctoral appointment at Stanford University with Barry Trost, he joined SmithKline Beecham in 1988. Working in cardiovascular, immunosuppressive, hematology, antiviral, musculoskeletal and oncology areas, Dr. Luengo became Director of Chemistry in the Medicinal Chemistry Department of GlaxoSmithKline in 2001.

**Abstract:** Thrombopoietin (TPO) is a 332 amino acid cytokine that regulates the production of platelets through interaction with its own receptor (TPO-R) on the surface of megakaryocytes and platelets. To investigate the possibility of discovering small-molecule TPO receptor agonists, a high-throughput screen was carried out, using a cell-based reporter gene assay. Several hits able to activate the TPO-R were obtained in the screen, and from these, one chemical series was selected for lead optimization. SAR studies to improve stability and oral bioavailability properties of this series resulted in the identification of Eltrombopag (SB-497115).

Eltrombopag is a potent TPO-R agonist in cell proliferation and human bone marrow megakaryocyte differentiation studies. TPO agonist activity was confirmed in Phase I-III clinical studies, by its dose-dependent elevation of platelet counts in human volunteers.

The identification of Eltrombopag as a TPO-R agonist provides the first example of a small non-peptidyl molecule which can induce the selective activation of a receptor of the cytokine superfamily.