2008-2009 POCC Lecture Series

April 23, 2009, 8:00 PM

Dr. Paige Mahaney

Wyeth Research

" The Evolution of a Medicinal Chemistry Program Targeting Norepinephrine Reuptake Inhibitors: Discovery and Optimization of Two Novel Series "

Carolyn Hoff Lynch Lecture Hall
Chemistry Building, University of Pennsylvania

The Philadelphia Organic Chemist's Club

POCClub.org

Dr. Paige E. Mahaney received her B.S. in chemistry, with dual minors in biology and physics, from Guilford College in Greensboro, NC (1991), and earned her Ph.D. in organic chemistry at MIT studying the total synthesis of taxane natural products. In 1995, Dr. Mahaney joined Discovery Research at Hoffmann-La Roche where she was involved in a number of projects in the areas of inflammation, oncology and metabolic disorders. Most notably, Dr. Mahaney made significant contributions toward Roche's pioneering efforts in the identification of allosteric activators of glucokinase, a glucose-phosphorylating enzyme that controls the threshold concentration for insulin release. These efforts culminated in the advancement of piragliatin into phase II clinical trials. In 2002, Dr. Mahaney joined Wyeth Research in Collegeville, PA where she has led multiple successful project teams that have resulted in the discovery and advancement of 5 clinical candidates in the areas of CNS disorders and metabolic diseases. She has authored publications in high impact journals including Science and J. Med. Chem. and is the inventor or co-inventor of 19 issued US patents with 14 additional applications pending.

Abstract: Norepinephrine (NE) deficiency has been implicated in a number of neurological disorders including depression, thermoregulatory dysfunction, stress urinary incontinence and certain pain disorders including fibromyalgia and diabetic neuropathy. The NE transporter (NET) is an integral membrane protein, located on the presynaptic neuron, responsible for controlling extracellular levels of NE in the synaptic cleft. Inhibition of NET blocks the reuptake of NE into the cell thereby increasing its availability to bind to postsynaptic adrenergic receptors resulting in increased neurotransmission. Thus the development of NE reuptake inhibitors (NRIs) for the treatment of a variety of neurological disorders is of considerable clinical interest. This seminar will detail our efforts toward the identification and optimization of two novel series of NRIs, the cyclohexanol ethylamines and the 1-(3-amino-2-hydroxy-1-phenylpropyl)indolin-2-ones. Series identification using database mining and virtual screening methods will be presented along with key optimization data (selectivity and PK properties) for selected compounds. These efforts resulted in the advancement of WAY-260022 into clinical trials, WAY-315193 as a clinical candidate and WAY-318068 as a preclinical candidate.