2007-2008 POCC Lecture Series

January 31st, 2008, 8:00 PM

Dr. Duane Burnett

Schering-Plough Research Institute

Discovery and Development of Zetia®

Serendipity and Design in the Discovery of Ezetimibe

Carolyn Hoff Lynch Lecture Hall
Chemistry Building, University of Pennsylvania

Biography: Duane Burnett attended Baylor University in Waco, Texas graduating with honors with a B.S. degree in chemistry in 1981. He obtained his Ph.D. in organic chemistry in 1986 at The Ohio State University with Professor David J. Hart. His Ph.D. research involved the synthesis of heterocyclics using free radical synthetic methodology and iminium ion chemistry as well as the stereoselective synthesis of β-lactams important to antibiotic research.

Dr. Burnett continued at The University of Utah with Professor Gary E. Keck. His postdoctoral research focused primarily on the use of free radical reactions for the synthesis of prostaglandins. To this end, the use of β-stannylenones as radical traps was developed for a formal total synthesis of $PGF_{2\alpha}$.

After leaving Salt Lake City, Dr. Burnett began his industrial research at the Schering-Plough Research Institute in Kenilworth, New Jersey as a medicinal chemist working in the field of atherosclerosis. There, he discovered a novel class of cholesterol absorption inhibitors that worked via an unknown mechanism of action. This work led to the identification of ezetimibe (Zetia®), the first marketed agent for the inhibition of cholesterol absorption. The unique mechanism of this novel cholesterol lowering agent was highlighted by its complementary LDL lowering action with statins. This complementary activity was key to the market entry of a fixed combination tablet of ezetimibe and simvastatin (Vytorin®) as the first marketed agent to treat both sources of high cholesterol. The fundamental understanding of the biology of cholesterol absorption and metabolism was advanced with the subsequent identification at SPRI of NPC1L1 as the crucial receptor mediating the intestinal uptake of cholesterol. At Schering-Plough, Dr. Burnett currently holds the title of research fellow and is involved in drug discovery efforts aimed at various GPCRs in the cardiovascular and CNS areas for treating a variety of human disorders including metabolic syndrome, chronic pain, and Alzheimer's disease.

Abstract: Lowering atherogenic LDL cholesterol in man has been shown to lower the incidence of heart disease and extend lives. While HMG-CoA reductase inhibitors have been particularly effective in this endeavor, they primarily treat endogenously synthesized cholesterol and have little impact on dietary or intestinally derived cholesterol. In our efforts to affect this second source of cholesterol, we discovered a novel class of β-lactam cholesterol absorption inhibitors that operated via an unknown mechanism. Optimization of the in vivo SAR led to the discovery of our first clinical candidate, SCH 48461. A close examination of the metabolism of this compound revealed an important oxidative metabolite with greatly improved potency. Incorporation of this "positive metabolism" and blocking additional sites led to the discovery of ezetimibe. Ezetimibe is the first molecular entity approved for use as a cholesterol absorption inhibitor alone or in combination with statins to treat hypercholesterolemia. In addition to our evolving medicinal chemistry program in the area, preclinical and clinical results will be presented showing the potency and efficacy of this agent alone and in combination with statins.