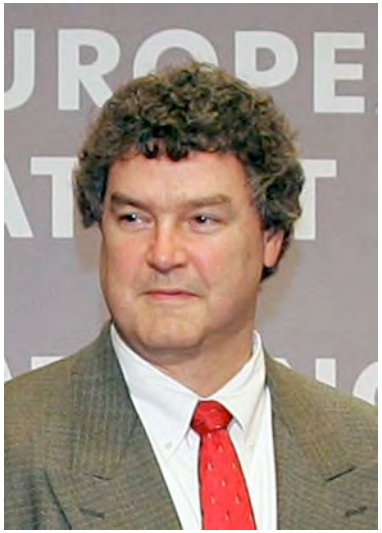

2012-2013 POCC Lecture Series

April 18, 2013, 8:00 PM

≈ POCC Industrial Award ≈

Dr. Bruce D. Dorsey

Cephalon, Inc., a subsidiary of Teva Pharmaceutical Industries Ltd.
West Chester, Pennsylvania

From HIV to Oncology:
A Journey of Structure Based Drug Design

Carolyn Hoff Lynch Lecture Hall, Chemistry Building, University of Pennsylvania

The Philadelphia Organic Chemists' Club

POCClub.org

To join us for dinner before the lecture please contact POCC's assistant secretary Simon Golec (SimonG1326@aol.com) at least one week ahead of time.

Bruce Dorsey, PhD is currently a Senior Director of Medicinal Chemistry at Teva Pharmaceuticals, where he is responsible for all medicinal chemistry small molecule programs to deliver drug candidates in the therapeutic areas of oncology, inflammation and CNS. He is a seasoned drug hunter with 23 years experience. Bruce began a career in medicinal chemistry at Merck and Co., Inc. contributing to medicinal chemistry teams in virology, anticoagulants, and neuroscience. Results from his laboratories within virology included the discovery of indinavir sulfate, Crixivan™, an HIV protease inhibitor launched by Merck and Inc. in the spring of 1996. This achievement was nationally and internationally recognized with several awards; American Chemical Society Award for Creative Invention (1999), PhRMA Discoverers Award (1999), and the European Inventor of the Year (2007). After twelve years at Merck he left to join an emerging biotech discovery company, Locus Pharmaceuticals. As a principle investigator at Locus Pharmaceuticals and head of the medicinal chemistry department, Bruce wrote for and received a Small Business Innovation Research Award for the design and synthesis of gp-41 inhibitors (HIV). In 2004, Bruce joined the Department of Medicinal Chemistry at Cephalon, Inc. During this time he has supervised a proteasome project (CEP-18770 currently in phase II clinical trials), kinase inhibitor programs including ALK (CEP-37440 IND ready), B-Raf (CEP-32496 IND open), FAK, JAK2, AXL and atypical PKC (all programs in lead optimization). He has been with Teva Pharmaceuticals since the acquisition of Cephalon in the fall of 2011. Bruce earned a Ph.D. degree from the University of Pennsylvania after which he joined the laboratory of Professor Stuart L. Schreiber and completed a National Institutes of Health postdoctoral fellowship spending time at Yale and Harvard University. He has co-authored 59 publications in chemistry and drug discovery, and is a co-inventor on 38 patents and patent applications.

Abstract: Introduction of novel antiretroviral therapy (ART) in 1996, particularly HIV protease inhibitors, ushered in a new era for HIV-infected individuals. Expanded treatment modalities and access to these medicines continues to impact the HIV worldwide-epidemic as seen with a continued decline in new infections and death from HIV/AIDS. Exploration of the hydroxylaminepentanamide (HAPA) transition-state isostere series of HIV protease inhibitors resulted in the identification of Crixivan (indinavir sulfate). This discovery will be presented through aspects of molecular recognition, i.e. conformational analysis and protein-ligand interaction utilizing the tools of x-ray crystallography and molecular modeling underpin potent ligand design. This, entwined with a balance of appropriate physiochemical properties like aqueous solubility, protein binding, and lipophilicity provides drug-like molecules. Application of these same principles applied to molecules that disrupt cell signaling will also be presented. Specifically, inhibitors of anaplastic lymphoma kinase (ALK) will be described. This is a cell membrane receptor tyrosine kinase associated with chromosomal translocations resulting in the identification of oncogenic proteins that drive a subset of specific cancers. Deregulated ALK acts through over expression in human glioblastoma or chromosome translocation in either anaplastic large cell lymphoma (NPM-ALK) or non-small cell lung cancer (EML4-ALK). Interest in ALK has increased significantly with the recent FDA approval of Crizotinib for the treatment of locally advanced or metastatic NSCLC that is ALK positive. Here we present the results of our efforts to design and synthesize clinically relevant ALK inhibitors.