

PHILADELPHIA ORGANIC CHEMISTS' CLUB

DATE: Thursday, September 25th, 2003; 6:00 pm dinner, 8:00 pm seminar

PLACE: Room 102, New Chemistry Building, University of Pennsylvania, 34th and Spruce Streets, Philadelphia, PA

SPEAKER: **Steven D. Young, Ph.D.**, Senior Director,
Department of Medicinal Chemistry, Merck Research
Laboratories, West Point, PA

TITLE: **Discovery and Antiviral Activity of a New Class of HIV Integrase Inhibitors**

ABSTRACT: Current therapies available for treatment of HIV infection target only two of the three constitutive viral enzymes required for replication, namely the retroviral reverse transcriptase and protease. The third enzyme, HIV-1 integrase, is an attractive target for chemotherapeutic intervention in the treatment of AIDS in large part due to the absence of viruses harboring resistance to yet unknown integrase inhibitors. Unlike the reverse transcriptase and protease enzymes, successful drug candidates based on inhibition of integrase have yet to emerge despite a number of laboratories working on the problem. Previously, we disclosed a series of HIV-1 integrase inhibitors discovered through screening that have anti-replicative activity in cell culture. This antiviral activity is directly linked to the compound's integrase inhibitory activity. These screening leads come from a single class of molecules broadly described as 4-aryl-2,4-diketobutanoic acids (DKAs). Stepwise replacement of three critical elements of the pharmacophore led to a completely novel, metabolically stable series of condensed heterocyclic compounds. The antiviral activity of these compounds is undiminished against a variety of diverse clones and viral variants expressing significant resistance to all of the currently available licensed HIV-1 inhibitors, including PIs, NRTIs and NNRTIs. The leading compound from this new series has good pharmacokinetics in rats, dogs and rhesus macaques. Following preliminary safety assessment studies, this compound has moved into Phase I clinical trials for evaluation in healthy volunteers.

DINNER: The meeting will be preceded by cocktails (cash bar) at 5:30 pm followed by a dinner at 6:00 pm at Penne Restaurant & Bar, 3601 Walnut Street. Reservations should be made by calling Gregory Ott at (609) 252-3189 or by e-mail at gregory.ott@bms.com **before 5:00 pm, Monday, September 22nd, 2002. Please pay the \$40.00 for dinner when you attend.** Thank you.