Tn*5* transposase as a target identifies compounds that inhibit HIV integration in cells

Brandon Ason[1], Allison M. Balke[1], Daniel Knauss[2], George Merkel[3], Anna Marie Skalka[3], and William S. Reznikoff[1*]

[1] Department of Biochemistry, University of Wisconsin-Madison, 420 Henry Mall, Madison, WI 53706-1544, [2] McArdle Laboratory for Cancer Research, Department of Oncology, University of Wisconsin-Madison, Medical School, 1400 University Avenue, Madison, WI 53706-1599, [3]Fox Chase Cancer Center, Institute for Cancer Research, 333 Cottman Avenue, Philadelphia, PA 19111-2497

HIV-1 integrase is an underutilized drug target for treatment of human immunodeficiency virus infection. A limiting factor for drug development is the lack of co-structural information. The Tn*5* transposase is a structurally well-characterized, related protein that may serve as a useful surrogate for inhibitor discovery and development. Little data exist, however, on inhibitor cross reactivity between Tn*5* and HIV-1. To address this question, we screened 16,000 compounds and identified twenty compounds that inhibit Tn*5* transposase-DNA complex assembly. Six were found to also inhibit HIV-1 integrase activity. Most surprising is the discovery of several cinnamoyl derivatives that also inhibit HIV integration in cells. These compounds lack the pharmacophoric hydroxyl groups and are less toxic than several previously reported members of this inhibitor class. We further identified several coumarin dimers and benzoic acid inhibitors. Based on these results, we believe that the Tn5 system is well suited for the development of therapeutics targeting HIV-1 integrase.