Tn*5* transposase as a surrogate for HIV-1 integrase in drug screens

B. Ason[1], A.M. Balke[1], D. Knauss[2], G. Merkel[3], A.M. Skalka[3], and W.S. Reznikoff[1*]. 1) Dept. of Biochemistry, Univ. of Wisconsin, Madison, WI; 2) McArdle Laboratory, Univ. of Wisconsin, Madison, WI; 3) Fox Chase Cancer Center, Philadelphia, PA.

The identification of small molecule inhibitors of a biochemical process can lead to useful compounds for studying intermediate steps in the overall process and, if the process in question is medically important, can lead to the development of pharmacologically useful compounds. High-throughput assays have been developed for Tn*5* transposase with the goal of isolating compounds that can block (or enhance) various steps in the transposition pathway. In addition, since Tn*5* transposase shares structural and mechanistic features with HIV-1 integrase, some of the identified compounds may also act on this important protein. 16,000 compounds were screened against Tn*5* transposase and twenty compounds were found to inhibit transposase-DNA complex assembly. Six of these twenty were found to also inhibit HIV-1 integrase activity. One of the six was found to block HIV-1 integration within cells at concentrations significantly below the cytotoxic dose. This last compound was used as a lead to find two more inhibitors of HIV-1 integration. The structures of these compounds will be discussed.