

# Chemistry Seminar

## “High Throughput Screening for Potential HIV-1 Reverse Transcriptase Ribonuclease H Inhibitors”

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Senior Thesis Presentation

Friday, November 13  
12 p.m.  
WSB-122

**Abstract.** A critical enzyme in the life cycle of HIV-1, reverse transcriptase (RT) catalyses both the synthesis of double-stranded DNA from viral single-stranded RNA (polymerase activity) and the necessary degradation of the RNA strand in the RNA-DNA intermediate created in the process (ribonuclease H (RNH) activity). These two mandatory steps of HIV-1 replication render RT a prime target for drug discovery. Although studies of the inhibition of the polymerase activity have led to the development of a subsequent number of therapeutic agents currently used clinically, RNH inhibitors remain fairly unexplored. In present study, I conducted the screening of a biased library of 150 compounds identified in a high-throughput screening of sixty seven thousand chemicals. Each compound was analyzed for *in vitro* inhibition of wild type (WT) RT RNH activity. Twenty six (26) compounds showed reduction of  $\geq 50\%$  activity of RT at the test concentration of  $10 \mu\text{M}$  and were further characterized. Inhibition coefficients ( $\text{IC}_{50}$ ) for RNH activity for best compounds were determined to be in range from 0.58 to  $9 \mu\text{M}$ . Current secondary assays for the biased library hits include screening for WT RT polymerase inhibition activity, strand transfer inhibition, *in vivo* antiviral activity, and the impact of drug resistance mutations on the compounds' inhibition of RT.