

POSTER 39**COMPARISON OF THIOCARBAMATES AND FORMIMIDOESTER DISULFIDES AS INHIBITORS OF HIV-1 RT**

Barry C. Johnson¹, Sara Cesarini², Angelo Ranise², and Stephen H. Hughes¹

¹HIV Drug Resistance Program, National Cancer Institute-Frederick, Frederick, MD 21702, USA;

²Department of Pharmaceutical Science, University of Genova, Viale Benedetto XV 3, I-16132 Genova, Italy

O-(2-phthalimidoethyl)-*N*-arylthiocarbamates (C-TCs) have been shown to be effective inhibitors of HIV-1 replication. C-TCs function as non-nucleoside reverse transcriptase inhibitors (NNRTIs) and have shown nanomolar EC₅₀ values against wild-type RT in MTT assays. Disulfide-linked molecular duplicates (DSs) of these compounds have been synthesized and tested for activity against wild-type HIV-1 and a panel of HIV-1 vectors carrying common NNRTI resistance mutations. The five C-TC/DS pairs differed in the substituents on the *N*-phenyl ring. The activities of relatively weak C-TCs were improved in their DS counterparts; however, duplication of more active C-TCs showed either no improvement or slight decreases in activity. Docking studies were performed to gain insight into the binding mode of several of the C-TC and DS compounds. Half of the disulfide-linked duplicate is predicted to bind similarly to published crystal structures of C-TC/RT complexes, while the other half of the DS is exposed to solvent and makes only minor surface contacts. Mutations of both Y181 and Y188 dramatically decrease the activity of both C-TCs and DSs. This is likely caused by the interaction of the phthalimide moiety present on all these compounds with these tyrosine residues. Several compounds with modifications to the phthalimidoethyl portion showed mixed results. However, all of the compounds tested showed a marked decrease in activity against at least one of the four mutants in this study. Future plans include testing other modifications to the phthalimide moiety and the ethyl linker, or substituting the phthalimide moiety altogether. The possibility of generating asymmetric disulfide-linked compounds in which the two thiocarbamates have different activity profiles is also under investigation.