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New Classes of Reagents that Attack Conserved and Chemically Reactive Zinc Fingers in Retroviral Nucleocapsid Proteins: A strategy for Rational Drug Design W. G. Rice*, C. A. Schaeffer*, J. A. Turpin*, L. Coren†, R. C. Sowder II†, B. Kane†, J. Bader$^{\Phi}$, L. O. Arthur†, and L. E. Henderson†: *Laboratory of Antiviral Drug Mechanisms and †AIDS Vaccine Program PRI/DynCorp, NCI-FCRDC, Frederick, MD, USA and $^{\Phi}$Developmental Therapeutics Program, National Cancer Institute, Bethesda, MD USA

The p7 nucleocapsid (NC) protein of HIV-1 contains two retroviral zinc fingers having a 14 amino acid peptide segment of $Cys(X_2)Cys(X_4)His(X_4)Cys$ that chelates zinc through cysteine thiolate and histidine imidazole coordination. The CCHC residues and their spacing are absolutely conserved in all strains of HIV-1 and among the NC proteins of all members of the Oncovirinae and Lentivirinae subfamilies of Retroviridae. The zinc finger motif is essential for selection of viral genomic RNA and assembly of new progeny virions and for early events in the viral replication cycle. Because of the absolute conservation and roles in two separate stages of the replication cycle, these mutationally intolerant motifs are ideal targets for anti-retroviral therapy. Utilizing recently developed assays, numerous compounds have been identified that contain defined functional groups which react with the CCHC motif, including C-nitrosos, disulfides, disulfoxides and thiurams. Depending on the functional group, the compounds modify the thiolates of the CCHC motif through acetylation, mixed disulfides between the compound and the thiolates or disulfide bond formation between the thiolates of the fingers. Compounds exhibited selective capacities to attack the zinc fingers of purified p7NC protein, to modify the p7NC within intact virions and to directly inactivate HIV-1 infectivity. Thiurams, which induced disulfide bonds among the zinc finger thiolates and inactivated intact virions of distantly-related retroviruses, are generally known to have very low *in vivo* toxicity, and tetraethylthiuram disulfide (Antabuse) is an FDA-approved drug. In addition, the NCI Drug Discovery Program has identified and developed a number of proprietary compounds that belong to a new class of zinc finger-reactive compounds, which are effective against laboratory and field isolates of HIV-1 (including monocytotropic and drug-resistant strains), HIV-2 and SIV. These compounds blocked production of new virus from previously infected cells, inactivated cell free virus, modified p7NC in the virus and showed high synergy in combination with currently utilized antiviral compounds. Antabuse and other of the compounds are being evaluated for *in vivo* efficacy in both murine and non-human primate models of retroviral infection. HIV-1 p7NC protein zinc fingers exhibit a previously unrecognized nucleophilic nature that may prove fundamental for development of novel classes of rationally designed antiviral drugs.