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The Viral Fusion Protein Leucine-Zipper, Coiled-Coil Domain: A Target for the Discovery of Novel Antivirals. S. R. Petteway, C. Wild, D. Bolognesi, and T. Matthews. Trimeris, Inc., Durham, NC, U.S.A., Department of Surgery, Duke University Medical Center, Durham, NC, U.S.A.

Enveloped viruses must fuse with the membrane of susceptible cells in order to establish infection. This fusion event is most often mediated by a specialized transmembrane or fusion protein on the surface of enveloped virions. Wild et. al., PNAS, U.S.A., 89:10537, have recently demonstrated that a domain of the Human Immunodeficiency virus transmembrane protein, gp41, is a specialized helical domain called a leucine zipper, coiled coil. Importantly, this coiled-coil domain was reproduced as a synthetic peptide that assumed stable structure in solution. Circular dichroism studies demonstrate that the peptide, DP107, is a coiled coil. Unexpectedly, DP107 was an inhibitor of virus infection and virus-mediated cell fusion *in vitro,* at concentrations less than 1 μg/ml. Interrupting the structure of the coiled-coil peptide resulted in the total loss of all antiviral activity. This structure-function relationship provides the basis for a rational drug discovery program to identify agents that disrupt the structure of DP107 and, subsequently, the function of gp41. In addition, DP107 will be evaluated as a peptide agent for therapy of HIV infection. A recent report by Carr et. al., Cell, 73:823, has implicated a coiled-coil structure as essential for Influenza virus-mediated fusion. It is likely that coiled coils are important mediators of virus-associated membrane fusion and, as such, represent novel targets for the discovery of new classes of antiviral agents.

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A structural model for HIV-1 integrase. C. S. Ramanathan, E. W. Taylor, J. F. McDonald, and R. F. Schinazi. Department of Genetics (J.F.M.) and Computational Center for Molecular Structure and Design (E.W.T., C.S.R.), The University of Georgia, GA 30602, USA, and Dept. of Pediatrics, Emory University and Veterans Administration Medical Center, 1670 Clairmont Road, Decatur, GA, USA (R.F.S.).

As part of an extended pattern of evolution by the dual processes of duplication and transposition in polymerase and nuclease genes, we have observed that the retroid integrase (IN) gene has an overall topology remarkably similar to that of the RNA dependent polymerases, and reverse transcriptase (RT) in particular. There are various similarities between the HIV RT polymerase domain and HIV IN: they have almost the same number of residues, they both can be divided into 3 functional domains, the middle one being catalytic (RT palm, IN "core"), with the N- and C-terminal domains being involved in nucleic acid binding. The conserved regions of IN align with the analogous pol sequence motifs, e.g. the "TDNG" region of IN with pol motif A, both having an essential Asp (D116 for IN). We have modelled the core region of IN using the palm domain of polymerases. This places the known catalytic residues D116 and E152, as well as a region around a conserved Asn (N184) all near together in 3D space. The evolutionary implications will be discussed.