

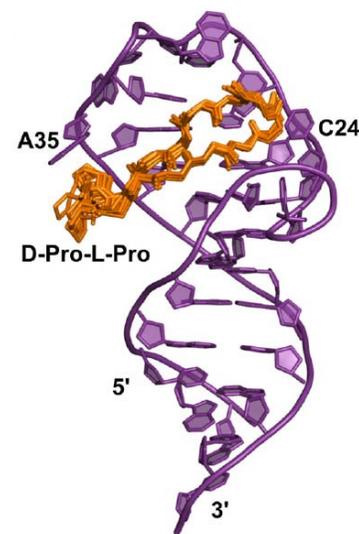
Science Made Possible

A Hairpin Turn

EMSL resources aid development of method for design, optimization of antivirals

Researchers have developed a promising new strategy for antiviral development with the help of nuclear magnetic resonance capabilities at the Department of Energy's EMSL. Using HIV-1 as a system of study, EMSL users from the University of Washington, University of Zurich, and Case Western Reserve University demonstrated a rational, structure-based method for designing and optimizing antiviral peptides. The team's successful results with HIV-1, reported in a recent *Proceedings of the National Academy of Sciences* article, give reason to be optimistic that the approach will be adaptable for a range of viral strains.

The team's work centers on the HIV-1 Tat-TAR binding site. A protein-RNA interaction essential to HIV-1 replication and unique to the virus, Tat-TAR is an intriguing target for HIV therapeutic development. Traditional methods to interrupt Tat-TAR binding with pharmacologicals have been met with limited success for a number of reasons, including the lack of an existing structure for the Tat-TAR complex. Overcoming the absence of this information, the research team used a different, but known and highly homologous structure to HIV, BIV (bovine immunodeficiency virus), to design peptides, or Tat mimics, against the TAR site. The team created a family of approximately 100 Tat mimics, each built as a closed circle with a β -hairpin loop on one end such that it would nestle snugly into the TAR binding site for Tat, disrupting the Tat-TAR interaction. Each member of the family differed slightly in the amino acid sequence on the surface of the peptide predicted to face TAR. Upon testing for their binding activity to HIV, three peptides stood out from the crowd for their notable potency, displaying HIV-binding activity in the low nM range. With the help of NMR, the team determined the structure of one promising peptide, designated L-22, bound to HIV-1 TAR. The structural data garnered from such studies yield molecular-level insight into the basis for peptide activity and selectivity, which is critical information for peptide optimization.



Structure of the HIV-1 Tat-TAR complex.

Scientific impact: The team's approach offers the research community a new, rational structure-based method for antiviral development and optimization and demonstrates new, structural principles for RNA recognition. In addition, this work supports EMSL's goal to predict biological functions from molecular and chemical data.

Societal impact: This new method yielded effective HIV inhibitors that demonstrate high activity at doses low enough to not yield cytotoxic side effects. The method may be adapted to the development and optimization of a wide range of antiviral drugs.

Reference: Davidson A, TC Leeper, Z Athanassiou, K Patora-Komisarska, J Karn, JA Robinson, and G Varani. 2009. "Simultaneous Recognition of HIV-1 TAR RNA Bulge and Loop Sequences by Cyclic Peptide Mimics of Tat Protein." *PNAS* 106(29):11931-11936.

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