

 ANTIVIRALS

Mirror image inhibition

DOI:

10.1038/nrd2474

Preventing the entry of HIV to host cells is an attractive antiviral strategy, which was first validated by the approval of the peptide drug enfuvirtide (Fuzeon; Roche) for treatment-experienced patients. However, the need for enfuvirtide to be injected twice daily and its cost have limited its use. Kay and colleagues now show that a short D-amino-acid peptide that binds to a conserved region of the virus envelope glycoprotein gp41 potentially inhibits HIV entry and might overcome some of these limitations.

HIV entry into CD4⁺ host cells involves sequential interactions between the viral envelope glycoproteins gp120 and gp41, the cellular CD4 receptor and, typically, the CXCR4 or the CCR5 co-receptors. The interaction between gp120 and CD4 triggers a conformational change in gp41 that enables it to fuse the viral and cellular membranes and insert the fusion peptide. This conformation exposes the highly conserved N-trimer region of gp41, which contains a long groove and hydrophobic pocket that can be targeted with peptides and small-molecule inhibitors to prevent virus entry. Indeed, enfuvirtide, a 36-amino-acid peptide, targets the N-trimer but, like other L-peptide drugs, it is sensitive to protease-mediated degradation and thus, has poor pharmacokinetic

properties. The complex strategy needed to synthesize this large peptide chemically is also an important factor contributing to its cost.

It has long been recognized that D-peptide virus-entry inhibitors could offer significant advantages over L-peptide inhibitors as they are resistant to proteases and have the potential to be administered orally. Also, their unique surface geometries could facilitate binding to targets that are not available to L-peptides. By using mirror phage display and structure-assisted design, the authors of this study in *PNAS* have generated an N-trimer pocket-targeted D-peptide with high antiviral potency.

The crystal structure of newly designed D-peptides that were generated against a gp41 N-trimer pocket mimic, IQN17, revealed the main pocket binding residues (dTrp10, dTrp12, dLeu13, dCys5 and dCys14) and suggested that their improved potency could be due to their reduced size (8-mer) and compact hydrophobic core compared with earlier D-peptides. Owing to the trimeric nature of gp41, the authors decided to crosslink the D-peptide that showed the highest affinity (PIE7) to form trimeric inhibitors. This greatly enhanced their potency against the standard HIV-1 laboratory strain HXB2 and primary strains of the virus in single-cycle infectivity assays. These D-peptides are now entering



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preclinical studies for use as topical preventative agents against HIV.

The authors suggest that by further reducing the size of the peptides or the length of the crosslinker, and by investigating the effects of residues flanking the pocket binding residues, it might be possible to design peptides with higher binding affinity and potency. These promising findings warrant further research into the optimization of D-peptides, which may be coming closer to realizing their full therapeutic potential.

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ORIGINAL RESEARCH PAPER Welch, B. D. et al. Potent D-peptide inhibitors of HIV-1 entry. *Proc. Natl Acad. Sci. USA* **104**, 16828–16833 (2007)