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Inhibiting Viral Infection with Backbone-Modified Peptides

Many viral pathogens are enveloped viruses; a lipid bilayer (the “envelope”) encloses the viral genome. Infection by an enveloped virus requires fusion of the envelope with the target cell membrane, to enable the viral genome to enter the cytoplasm. For viruses that use a type I entry mechanism, including HIV and coronaviruses, the bilayer fusion process is orchestrated by a single viral surface protein. This fusion protein exists initially as compactly folded trimer. After the target cell has been recognized, the trimer undergoes profound conformational rearrangements that are thought to drive fusion of the envelope and cell membrane. Peptides derived from a key region of the fusion protein, the “C-terminal heptad repeat” (HRC) domain, can interfere with these rearrangements and inhibit viral infection. The AIDS drug enfuvirtide works in this way.

We have sought to address a key liability of conventional peptide-based fusion inhibitors, their susceptibility to degradation by proteases. Our approach is to replace a subset of the α-amino acid residues with β-amino acid residues, to generate α/β-peptide inhibitors. The challenge in this approach is to retain the recognition behavior of original α-peptide toward the susceptible intermediate form of the fusion protein trimer while diminishing the recognition behavior toward protease active sites. Development of α/β-peptide fusion inhibitors for HIV and other viruses will be described, along with first steps toward SARS-CoV-2 inhibitors.