A hairpin to fight HIV

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When a host cell is infected with HIV, the virus brings its own genetic material into the host cell. This cell then replicates, reads the viral RNA, and uses it as a blueprint to produce more viral proteins.

Complete viruses are then released to attack the next cells. A team of researchers from the University of Zurich (Switzerland) and the University of Washington (USA) has now developed a new potential starting point for a drug that could intervene in this deadly cycle. As reported in the journal *Angewandte Chemie*, it involves a hairpin-shaped molecule that imitates the spatial structure of an important viral protein and should thus stop the discharge of viral RNA from the cell nucleus.

An important step in the lifecycle of HIV—and a potential point of attack for treatment—is as follows: The viral RNA produced in the nucleus of the host cell is transported as a long strand out through pores in the cell membrane into the cell's cytoplasm, where it is translated into proteins or packed into a viral shell. This discharge is an active process carried out by a viral protein called Rev.

For this process, many Rev units have to attach to a binding site on the viral RNA, called the Rev-responsive element (RRE). The search for an effective RRE-binding inhibitor has thus far remained unsuccessful.

A small arginine-rich domain consisting of 17 amino acids allows the Rev protein to recognize its binding site, a furrow on the RNA. Once bound to the RNA, this domain adopts a helical form. It is this protein structure that the team led by John A. Robinson and Gabriele Varani

wished to reverse engineer in order to disrupt the binding of Rev to RRE.

The researchers produced a peptide mimetic, a molecule that imitates the structure of the desired peptide. The group has previously shown that alpha-helical peptides can be imitated by something called a alpha-hairpin turn. The researchers attached side chains to the robust scaffold formed by the “hairpin" so that the groups of atoms required for molecular recognition are presented just as they are in the original helical peptide.

A series of screening steps, starting from a small family of cyclic hairpin peptide mimetics, led to the development of a structure that firmly and correctly binds RRE. This compound also has the ability to displace the Rev protein from Rev-RRE complexes.

“Hairpin peptide mimetics are a highly promising new class of drugs," says Robinson. “We hope that it will be possible to develop a drug suitable for HIV treatment based on this foundation?"

Source: John Wiley & Sons, Inc.