DURHAM, N.C. -- In laboratory tests that may lead to a new class of AIDS drug, researchers at Duke University Medical Center have used a simple peptide molecule to stop the human immunodeficiency virus (HIV) from infecting human immune cells in culture. HIV is the virus that causes AIDS.

The peptide was synthesized to mimic a key part of the HIV infection machinery, found on the outside of the virus particle. When mixed with HIV, the peptide plugged itself into that mechanism and halted the infection process.

The peptide could represent a new class of drugs that disarms the virus before it can further infect human cells in HIV-positive patients, said the researchers. Most AIDS drugs now available are designed to work inside infected cells, and none has completely succeeded.

The research, reported in the Nov. 1 issue of the Proceedings of the National Academy of Sciences, is also a step forward in understanding how the virus works, say the scientists.

"This is a highly promising discovery. It gives us a new way to think about designing therapeutic drugs to prevent the spread of infection," said Dani Bolognesi, director of Duke's Center for AIDS Research and one of the report's authors. "In addition, it gives us a new tool to study the structure of the virus and how it works."

In their studies, the researchers were attempting to understand the structure of a portion of the protein coat surrounding the virus. Their experiment consisted basically of designing and building artificial peptides, which are pieces of protein, and mixing them in laboratory cultures of HIV and human immune cells.

The virus did not infect the immune cells because, the researchers believe, the peptides interfered with entry of the virus into the cells.

Duke's artificial peptide blocked HIV transmission in two ways: between the virus and non-infected human immune cells, and between infected human immune cells and non-infected immune cells.

Bolognesi said that, although the peptide completely blocked viral infection, the research team can only theorize why it works. "We think we know why it works, but much
more experimentation is needed before an accurate model is built."

The Duke scientists took a structural approach to understanding how the virus works. The AIDS research team, led by Thomas Matthews, has, for many years, studied the outermost components of the virus particle, often called the viral envelope. They have tried to understand how this envelope interacts with a target immune cell before, during, and after the infection process.

The Duke team primarily studied two glycoproteins -- proteins linked to sugar molecules -- known as gp120 and gp41. Proteins, the working molecules of a cell, are usually made up of hundreds of amino acids, the basic chemical building blocks of life.

On the virus envelope, the combination of gp120 and gp41 form spikes shaped like mushroom stalks that stick out from the viral body; in this analogy, gp120 is the mushroom "cap" and gp41 is the "stem."

The researchers knew that gp120 acts as a "docking mechanism" for the virus -- binding tightly to receptors on immune cells targeted for infection, holding the virus in contact with the cell. The gp41 stem holds the gp120 cap to the surface of the virus, and also plays a major role in the entry of the virus into the cell, said the Duke researchers.

Each HIV particle is coated with about 100 of these mushroomlike glycoprotein combinations, organized into discrete clusters of two to four units around the surface of the virus. This non-random association of envelope glycoproteins into clusters is a feature HIV shares with many other enveloped viruses, such as viruses that cause the flu.

The scientists believe the clustering phenomenon is important in the early stages of virus infection; specifically in its role of penetrating target cells to allow entry of the virus' lethal genetic material.

In trying to understand how gp41 operates, the scientists designed synthetic peptides, or pieces of protein they think is part of the envelope structure, to see if the peptide and the natural protein interact.

Based on predictions of how the virus worked, the Duke team sought a peptide, called a "leucine zipper," that they believed to be an active site of gp41. Leucine zippers are so named, because they feature a repeating leucine amino acid. The "zippers" are actually spiral-like coiled peptides that zip together with other identical coils.

Believing the leucine zippers must play a role in allowing HIV to change its shape to infect cells, the researchers sought the coils on the gp41 stem.

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They manufactured a sequence of 38 amino acids based on what they thought the HIV coil would be like.

"This was an unusual approach, and a bit of a gamble, because no one really knows how the virus works," said Matthews. He said the different disciplines represented on the Duke team helped in forming a picture of HIV infection; Matthews is a virologist, Bolognesi is a microbiologist, Terrence Oas is a biochemist, and first author Carl Wild, a postdoctoral researcher in Matthews' lab, studies protein structure.
To the surprise of the researchers, the gamble paid off, said Bolognesi. Their first attempt at mixing the peptide with HIV and uninfected cells resulted in total blockage of HIV infection.

"We were confident that there was a leucine zipper at work on the viral envelope; it just made sense," said Wild. "But we had no idea that it was this powerful."

Disbelieving the results, the scientists repeated the experiments many times, with the same outcome.

Also, when the researchers flooded a mixture of infected and uninfected cells with the synthetic peptides, the HIV transmission process was stopped.

Based on their findings, the Duke team has constructed a tentative model of how gp41 might work (see attached diagram), and how the synthetic peptide blocks the process. However, they believe the model will likely evolve after further experimentation.

Bolognesi said that much more research is needed before the Duke peptide could be considered a candidate for a drug. Alternately, a drug might be designed that would dissolve the coil structure on gp41, inactivating the virus, said Bolognesi.

The research was funded by grants from the National Institute of Allergy and Infectious Disease.

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