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New Drug Target May Cause HIV to Knuckle Under

The researchers, led by Hughes investigator Michael F. Summers at UMBC, used nuclear magnetic resonance (NMR) spectroscopy to determine the three-dimensional structure of the HIV nucleocapsid binding to the virus' genetic material, RNA. NMR helps scientists construct a picture of a protein by supplying information about the relative distance between individual atoms in the protein.

"This is the first structural information that shows how HIV viral proteins recognize the viral genome," said Summers. He and colleagues from Syracuse University published their work in the January 16 issue of the journal *Science*.

After HIV infects a cell, the HIV nucleocapsid, which is located inside the virus, packages RNA into the core of newly formed infectious viral particles, which then move on to infect other cells. Scientists may be able to design drugs that keep RNA out of the nucleocapsid's grasp, offering a real chance of preventing the virus from spreading, said Summers.

In 1992, Summers' team determined the structure of the HIV nucleocapsid. Other labs showed that the nucleocapsid recognizes and binds to the viral RNA genome. Further research showed that the nucleocapsid recognizes viral RNA by homing in on the packaging domain a small nucleotide

sequence in the viral RNA.

In order to learn more about this critical protein-RNA interaction, Summers' team decided to take a closer look. Working with Philip N. Borer and Lucia Pappalardo at Syracuse, Summers and UMBC colleagues, Roberto N.

De Guzman, Zheng Rong Wu and Chelsea C. Stalling, showed that the nucleocapsid grasps the packaging domain on RNA using two "zinc knuckles." The term zinc knuckle was coined by Summers to describe that portion of the nucleocapsid that requires zinc to function.

The zinc knuckles are an attractive drug target, Summers says, because the nucleocapsid needs zinc atoms in order for it to fold and function properly. "The zinc knuckle domains are intolerant of mutations," Summers said. "They are a good target because it is unlikely that the virus would be able to mutate the zinc knuckle domains to evade an antiviral drug."

Several pharmaceutical companies have already asked Summers to test chemical compounds in their inventory to see if any can pry zinc out of the nucleocapsid. "We have tried a number of different compounds, but none of them has been satisfactory because they remove zinc from a number of different proteins found in cells."

A more specific class of antiviral drugs that aims to knock zinc out of the nucleocapsid protein is now undergoing clinical trials in the United States and the United Kingdom.

Summers believes that the structural data that he and Borer have published in *Science* may offer a blueprint for a new generation of antiviral drugs that compete with RNA for the nucleocapsid binding site.

The work may also provide a helping hand for those working to develop new drugs to treat other retroviruses or leukemia viruses. "The more targets that drug developers have to shoot at, the better the chance that more

effective drugs will be developed," Summers said.