

JULY 12, 1996

## Researchers Provide Picture of HIV-1 Coat Protein

For the first time, researchers have peered deep inside the human immunodeficiency virus (HIV-1) and described a fragment of the egg-like shell that envelops the virus' genetic material.

"Any scientist who wants to develop a new drug that interferes with HIV needs to know what the virus looks like," said Michael F. Summers, an HHMI investigator at The University of Maryland Baltimore County (UMBC). "We've provided the first look at one of HIV's closely-held secrets."

In a report in the July 12, 1996, issue of *Science*, Summers, Rossitza K. Gitti, Brian M. Lee, and Jill Walker, all of HHMI at UMBC, and colleagues from the University of Utah offer a molecular snapshot of a fragment of the HIV-1 capsid (CA) protein—the shell that contains HIV-1 RNA and other enzymes the virus needs to infect cells and multiply.

Aside from its crucial importance to HIV, this protein has been the subject of an all-out assault by structural and molecular biologists because it seemed similar to plant virus proteins that scientists had successfully disrupted. Such disruption renders the virus unable to infect plants. "We have felt that if we knew the structure of this protein in HIV-1, it would make it easier to design similar drugs that target the CA protein and possibly keep HIV from infecting cells," Summers said.

For six years, Summers' lab has stalked the structure of the HIV-1 CA protein. During that time, the group described in detail two other structural proteins from HIV-1. Until recently, however, they had been frustrated by attempts to unveil HIV-1 CA.

Part of the problem, Summers explained, is that his group focused on getting a picture of the entire protein. That proved difficult because HIV-1 contains about 2,000 copies of CA. These copies stick together to form a shell inside the virus. "You end up with a sample that is too big for study with nuclear magnetic resonance (NMR) methods used in our lab," Summers said.

The breakthrough came when Summers and his colleagues realized that halving the protein would provide much more manageable samples. Again, they performed NMR studies, which build a picture of a protein based on the distance between its hydrogen atoms. The researchers were stunned to find

that the CA protein looked unlike anything in the protein structure databases routinely consulted by scientists.

"For years people had hypothesized that it would be composed predominantly of the  $\beta$ -sheet motif common to other viruses," Summers said. "We found that CA is almost entirely composed of  $\alpha$ -helices and is unlike any previously discovered viral coat protein."

The secret of the CA structure may also whisper something to drug designers. Nestled within the CA fragment is the binding site of cyclophilin A, a protein found in most blood cells. Scientists at Columbia University have shown that if cyclophilin A is absent, HIV-1 cannot infect cells. "We now have a detailed picture of the cyclophilin A binding site (on CA)," Summers said. "That information should be crucial to scientists who are designing antiviral agents based on inhibiting cyclophilin A's interaction with HIV-1."