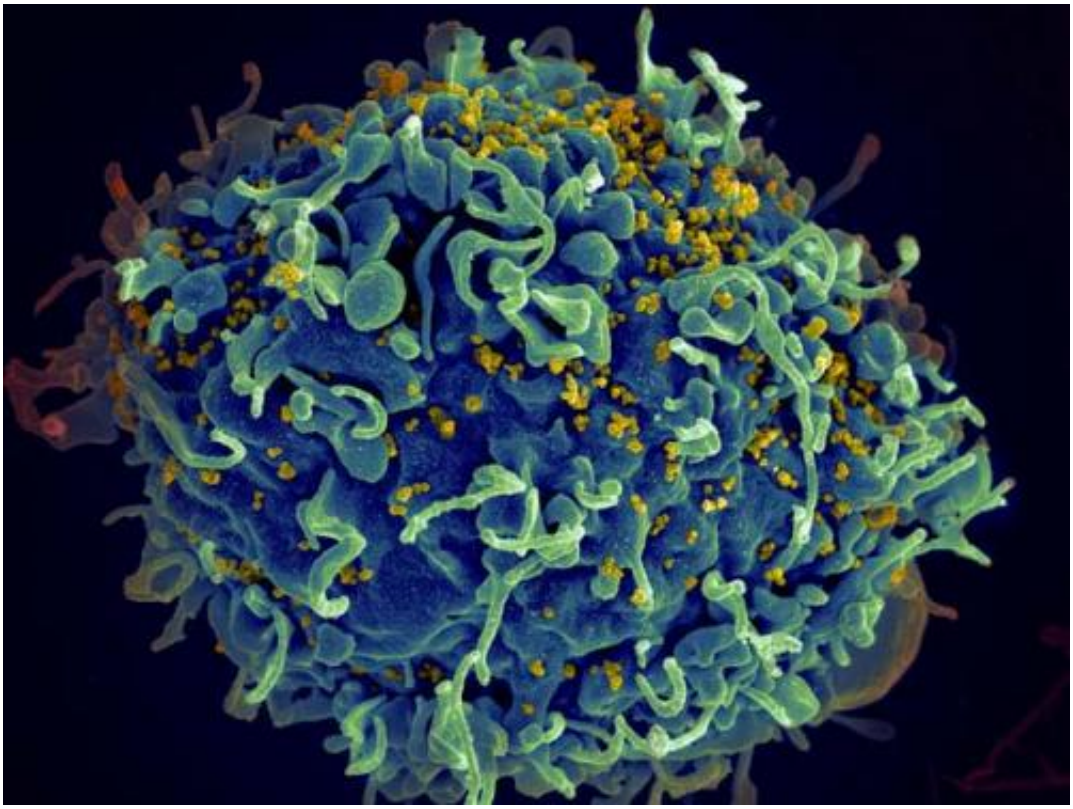
MedicalXpress

'Redesigned' antibodies may control HIV

May 18 2015



HIV, the AIDS virus (yellow), infecting a human immune cell. Credit: Seth Pincus, Elizabeth Fischer and Austin Athman, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

With the help of a computer program called "Rosetta," researchers at Vanderbilt University have "redesigned" an antibody that has increased potency and can neutralize more strains of the AIDS-causing human immunodeficiency virus (HIV) than can any known natural antibody.

Their findings, published online today in *The Journal of Clinical Investigation*, suggest that computer-redesigned antibodies may speed the search for an effective therapy or vaccine for a virus that so far has eluded all attempts to eradicate it.

"There's a consensus (in the HIV field) that the vaccine that works is going to be a designed one," said James Crowe Jr., M.D., director of the Vanderbilt Vaccine Center who led the work with Jens Meiler, Ph.D., associate professor of Chemistry and Pharmacology.

Working with colleagues at The Scripps Research Institute in La Jolla, California, the Vanderbilt researchers began with a "parent" antibody isolated from the blood of an HIV-infected person that was a strong "neutralizer" of HIV in laboratory tests.

The researchers then used the Rosetta computer program, which can predict the structure of a protein from its amino acid sequence, to "redesign" the antibody. By changing a single amino acid, they were able to increase the stability of the antibody when it bound to HIV's envelope protein.

The researchers didn't change the interface between the antibody and the virus. Rather, by increasing its thermodynamic stability, the antibody became more rigid and better able to fit the HIV protein like a lock and key.

"By changing a single amino acid, we made it four times more potent, four times stronger and it also started killing even more HIV strains than the parent antibody," said Crowe, Ann Scott Carell Professor and professor of Pediatrics and of Pathology, Microbiology and Immunology.

The original, isolated antibody is now being produced in great quantities

from a single clone of immune cells, and thus is a "monoclonal" antibody. It currently is being tested in clinical trials. Crowe said the redesigned antibody could be added to the study as a second-generation version.

The field of redesigning antibodies has grown quickly out of the need to treat and prevent debilitating and often-fatal viral infections, and from technological advances that have made it possible to "see" and strengthen the interactions between virus and virus-killing antibodies.

HIV is a wily opponent. Every day it evolves, or alters the envelope protein on its surface, to evade immune detection. A single person infected with HIV carries more variations of the virus than all the influenza strains isolated worldwide, Crowe said. The immune system simply cannot keep up.

In 2013, Scripps scientists led by Ian Wilson, Ph.D., and Andrew Ward, Ph.D., reported in the journal Science the structure of the HIV envelope protein using crystallography and cryo-electron microscopy. "Now we know what it looks like," Crowe said. "We can better understand how to target it."

Last year, Crowe and another colleague at Scripps, William Schief, Ph.D., reported in the journal Nature that "computational protein design" can be used to induce potent neutralizing antibodies of respiratory syncytial virus (RSV), a leading cause of respiratory infections in young children.

"That was the first paper in which people agreed that computer design of a vaccine worked," he said.

Structure and proof of principle in hand, scientists are now using the computer to generate neutralizing antibodies against parts of the

envelope protein that don't change.

Down the road, Crowe said, "if computational design ... can predict how viruses evolve in the future, we could potentially design antibodies and vaccines for viruses before they occur in nature."

Toward that end, Crowe and Meiler have organized the Interface Group, a diverse collaboration of scientists across campus, including an expert in game theory who is modeling the interplay between viruses and the immune system.

"You couldn't have this type of biomedical research," he said, "without that playful, curious aesthetic sense that you get with the Rosetta 'community.'"

More information: Redesigned HIV antibodies exhibit enhanced neutralizing potency and breadth, *J Clin Invest.* 2015. DOI: 10.1172/JCI80693

Provided by Vanderbilt University Medical Center