Study describes a better animal model to improve HIV vaccine development

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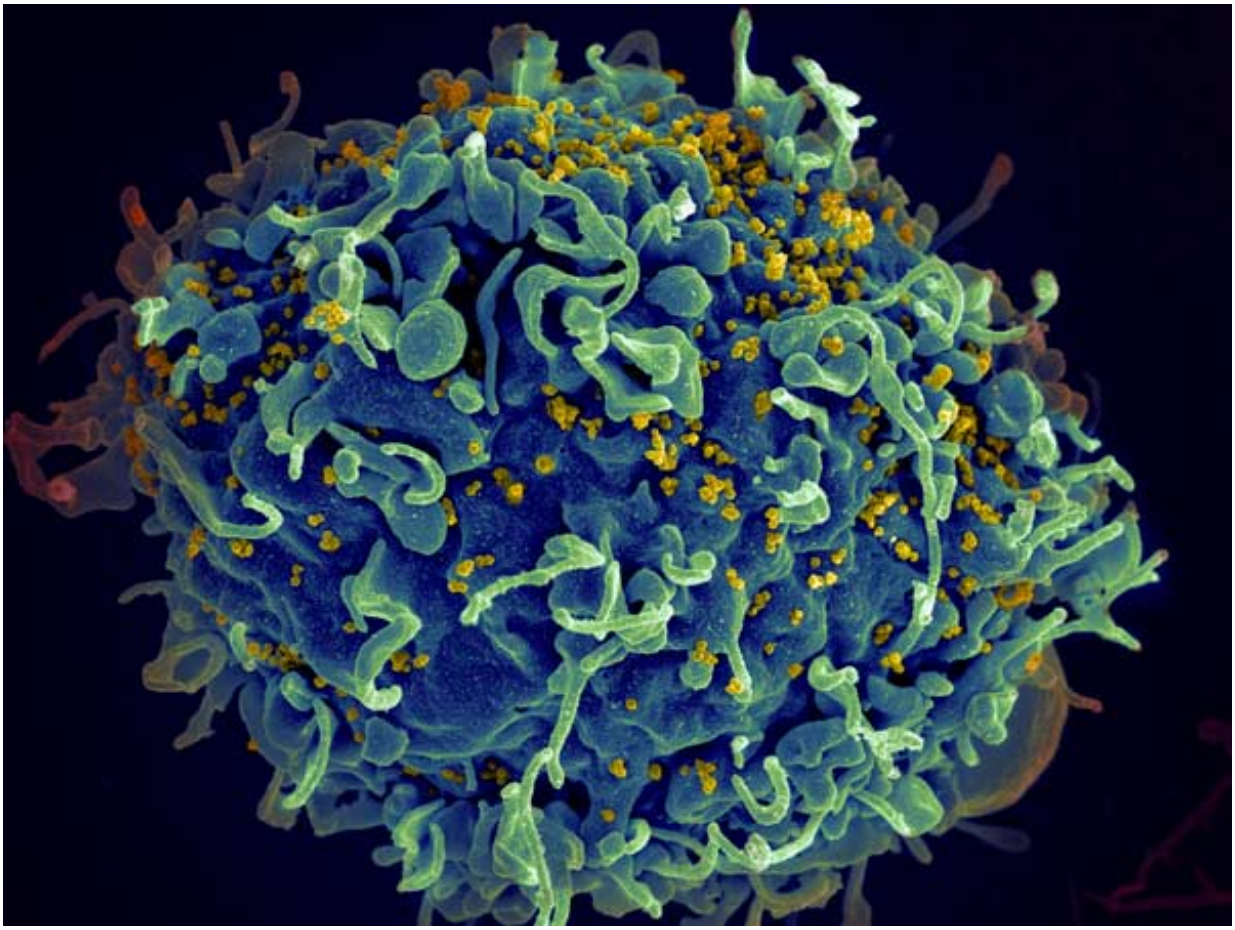

HIV infecting a human cell. Credit: NIH

Vaccines are usually medicine's best defense against the world's

deadliest microbes. However, HIV is so mutable that it has so far effectively evaded both the human immune system and scientists' attempts to make an effective vaccine to protect against it. Now, researchers from the Perelman School of Medicine at the University of Pennsylvania have figured out how to make a much-improved research tool that they hope will open the door to new and better HIV vaccine designs. George M. Shaw, MD, PhD, a professor of Hematology/Oncology and Microbiology, and Hui Li, MD, a research assistant professor of Hematology/Oncology, published their results in the early online edition of the *Proceedings of the National Academy of Sciences*.

An ideal preventive vaccine works by presenting non-infectious components or a weakened form of a microbe to the host's immune cells to prime the system for future contact with the invader. This allows the immune system to mount an attack against a microbe it has already seen.

But in the case of fighting AIDS, HIV's ability to rapidly mutate, especially its outer coat protein—the envelope—poses a special challenge to vaccine development. So too does the fact that the envelope is coated with host derived sugars that the human immune system cannot recognize as foreign. These and other features of HIV have stymied vaccine development for over 30 years.

Despite these obstacles, substantial progress in HIV vaccine development has been made, and a number of promising candidate vaccines are in development. However, still another hurdle to progress has been the absence of a good animal model in which to test HIV vaccines. The immune systems of small animals like mice, rabbits, and guinea pigs are too different from the human immune system to be helpful.

Rhesus monkeys are primates whose immune system is much closer to that of humans, but HIV cannot infect or replicate in monkeys. To

overcome this obstacle, researchers developed chimeric simian-human immunodeficiency viruses (SHIVs), genetically engineered viruses containing the envelope of HIV but with other viral components from simian immunodeficiency virus (SIV), which naturally infects monkeys. SHIVs thus seemed to have the best of both worlds: They carried the envelope of HIV and they replicated in monkeys, causing AIDS-like disease.

But there was still one catch—one unforeseen problem with SHIVs. The only HIV envelopes that would allow SHIVs to infect rhesus monkeys were those that were adapted in artificial ways to bind to the rhesus CD4 molecule, the primary receptor for HIV. As a byproduct of this adaptation, the SHIVs lost their natural defenses to antibodies. This rendered the SHIVs of little value to HIV vaccine research.

Now, Shaw, Li, and their colleagues have found a way to overcome these obstacles and to make a much better SHIV - one that closely mimics HIV infection in humans.

"We found that changing a single amino acid in the envelope coat protein of naturally occurring HIV strains led to dramatic differences in the ability of SHIVs to infect monkeys, while at the same time retaining the native-like features of the virus envelope and its interaction with the human immune system," Shaw said.

"This is an enabling discovery for the HIV vaccine field because it allows scientists for the first time to study in a controlled and reproducible manner the interaction of natural HIV envelope proteins with monkey B lymphocytes, which are stimulated to make protective antibodies," Li said.

The Envelope is Key

Many viruses, including flu and HIV, are covered by a protective membrane called an envelope. Embedded in this envelope are viral and host proteins and sugars. The viral envelope fuses with the host cell, allowing the viral genes to enter the host cell and replicate.

The HIV outer envelope is covered by host sugar molecules, making it hard for the host immune system to recognize the virus as foreign. For a vaccine to target the virus, it must elicit antibodies that get past this sugar shield and bind to viral specific proteins. This is where the new SHIVs come in - they express an envelope that closely mimics ones found on naturally occurring HIV strains. As such, the new SHIVs can be used as a test system to elicit protective antibodies in monkeys and as challenge viruses to determine if vaccine elicited antibodies are protective against HIV infection.

In the *PNAS* study, Li and Shaw hypothesized that changing the binding affinity of the HIV envelope to rhesus monkey CD4, the primary receptor for HIV, would be the key to successful SHIV design. However, this strategy must be done without altering the natural protective features of the envelope. To test this hypothesis they examined the evolutionary history of all types of HIV-related immunodeficiency viruses that naturally infect humans and subhuman primates to look for amino acids under strong positive selection pressure as viruses spread from one primate species to another.

They zeroed in on one amino acid out of about 850 that comprise the viral envelope. This amino acid, called "Env375," turned out to be the key. "Changing this one amino acid in HIV to resemble variants found in SIV enhanced the entry of SHIVs into monkey CD4 T cells by a thousand-fold," Li said. "It was like night and day."

Moving quickly forward on the heels of this discovery, Li and Shaw have created a set of "designer SHIVs" that contain HIV envelopes of

particular research interest. These HIV envelopes in the context of human infection have elicited broadly neutralizing antibodies, the ultimate goal of HIV vaccine research.

The team infected rhesus macaques with the "designer SHIVs" and closely monitored them for the development of neutralizing antibodies. They have already observed in numerous infected animals that the SHIV virus and host antibody response are evolving in ways that closely resemble human infection by HIV-1.

"These results have given us hope that the new SHIVs will indeed be a game-changer for HIV vaccine research," Shaw said. The SHIVs replicated persistently at concentrations comparable to HIV-1 levels in humans and elicited neutralizing antibody responses typical of HIV-1.

"We identified rhesus macaque CD4 binding as a critical determinant for productive SHIV infection in the monkeys and Env375 mutations that influence this," Shaw said. "This discovery represents a novel and generalizable strategy for constructing SHIVs with envelope glycoproteins of particular interest, including those that elicit broadly neutralizing antibodies in humans or ones that bind particular B cell receptors."

The group's next steps include evaluating the molecular pathways by which the HIV envelope and the corresponding neutralizing antibodies co-evolve in humans and in rhesus macaques, leading to the development of protective broadly neutralizing antibodies. By using this approach, Li and Shaw hope to use SHIV infections of rhesus macaques as a guide to successful vaccine development for HIV in humans.

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