Monkey-infecting virus may provide part of future HIV vaccine

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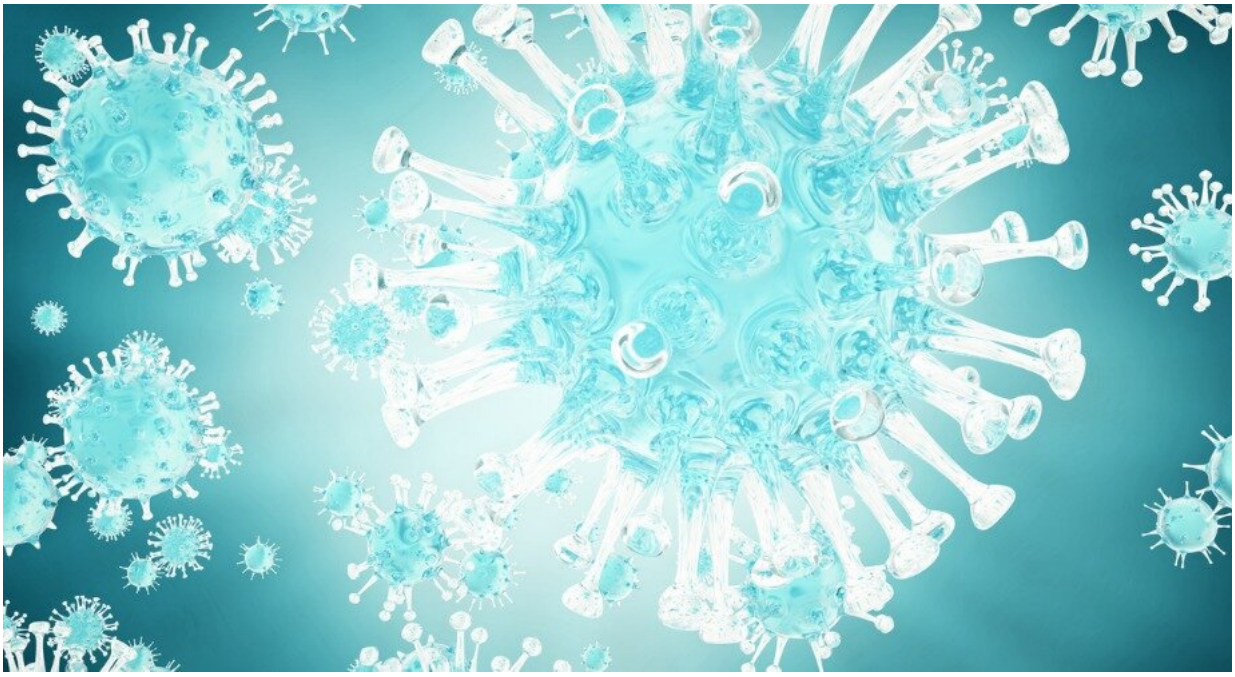

Credit: Scripps Research

A protein from Simian Immunodeficiency Virus (SIV), which can infect monkeys and apes, has shown promise as a potential component of a vaccine against Human Immunodeficiency Virus (HIV), in a new study from scientists at Scripps Research in La Jolla, California.

Chimpanzee SIV, which can cause an AIDS-like disease in the natural

host, is the virus that "jumped" to humans and evolved into HIV roughly a century ago in Africa. SIV's outer-envelope protein, Env, shares a key structure with HIV's Env; that and other properties make SIV Env attractive as a potential component of a future vaccine against HIV infection. In the study, published in the May 21 issue of *Cell Reports*, the Scripps Research scientists found that inoculating mice with SIV Env proteins elicited antibodies that neutralize infection against multiple HIV strains.

"We've shown here that one can use shapes from chimpanzee-infecting SIV to stimulate the production of antibodies against the human-infecting HIV," says co-senior author Dennis Burton, Ph.D., the James and Jessie Minor Chair in Immunology in the Department of Immunology and Microbiology at Scripps Research. "It's a simple but inspired strategy, reminiscent of the use of cowpox virus to immunize against smallpox virus over 200 years ago, and should help us in making an HIV vaccine."

Despite medications that can control HIV and reduce transmission, the disease remains a leading cause of death and a health threat to millions worldwide. Approximately 37 million people worldwide were living with HIV at the end of 2017, according to the Centers for Disease Control and Prevention. A vaccine for HIV would help prevent infection and control the spread of disease.

The traditional approach to designing a viral vaccine is to use a weakened or engineered version of the virus as the "immunogen" that stimulates the immune system to produce protective antibodies. But that doesn't work against HIV. The AIDS-causing virus rapidly mutates its outermost structures during infection, constantly creating new strains or variants that can evade antibodies produced against prior variants. A vaccine based on one HIV strain encountered in the past would be ineffective against virtually all versions of HIV a person would be likely

to encounter in the future.

As an alternative approach, Burton's group and others want to design HIV vaccines that focus the antibody response on the few truly vulnerable parts of the virus. These vulnerable viral structures, or "broadly neutralizing epitopes," are so important to HIV's ability to infect cells and replicate that they vary by a limited amount from one strain to the next. It's a challenging strategy because these structures normally are well concealed by the virus.

Moreover, the antibodies that can fasten to these epitopes tend to have unusual shapes, and essentially are difficult for the immune system to produce; they are found only rarely in HIV-infected people, and even then, usually at low levels.

Burton and colleagues hope to overcome those hurdles by using a primary injection plus a series of booster shots, all with distinct immunogens, to gradually force the production of antibodies that fasten tightly to broadly neutralizing epitopes—while minimizing the usual, wasted production of antibodies against non-vulnerable sites on the virus. SIV Env has seemed a potentially good immunogen in such a vaccine because it has a broadly neutralizing epitope, the V2-Apex, that is nearly identical to its counterpart on HIV Env, yet has little similarity otherwise.

"In a multi-stage and multi-component HIV vaccine strategy, we would like to elicit antibody responses to the broadly neutralizing epitope shared between sequential immunogens, while minimizing the off-target responses to other epitopes," says Raiees Andrabi, Ph.D., a postdoctoral research associate in the Burton lab who was first author of the study.

Andrabi and colleagues engineered a stable stand-alone version of SIV Env—a three-part "trimer" structure normally supported by the viral

outer membrane—from a chimpanzee-infecting SIV strain close to human HIV. Using mice engineered by collaborators at Duke University to be capable of producing the necessary antibodies, they showed that inoculating with the SIV Env trimers twice over four weeks elicited the desired, narrowly targeted antibody response to the HIV V2-Apex. The antibody response was capable of neutralizing several HIV isolates; adding a booster inoculation using HIV Env trimers made the HIV-neutralizing response even broader.

"This suggests that the antibody responses were developing along favorable pathways," Andrabi says.

The laboratory of co-senior author Andrew Ward, Ph.D., professor in the Department of Integrative Structural and Computational Biology at Scripps Research, meanwhile used cryo-electron microscopy to map for the first time the atomic structure of the SIV Env trimer. The team analyzed the map to discover the structural differences between SIV and HIV Env trimers.

The scientists' SIV Env trimer has been approved by the U.S. National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH) as a candidate HIV vaccine, and the development of a larger-scale manufacturing process for it is now underway, Andrabi says. The team hopes to begin the human safety trials within the next few years.

More information: Raiees Andrabi et al, The Chimpanzee SIV Envelope Trimer: Structure and Deployment as an HIV Vaccine Template, *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.04.082

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