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Roadmap reveals shortcut to recreate key HIV antibody for vaccines

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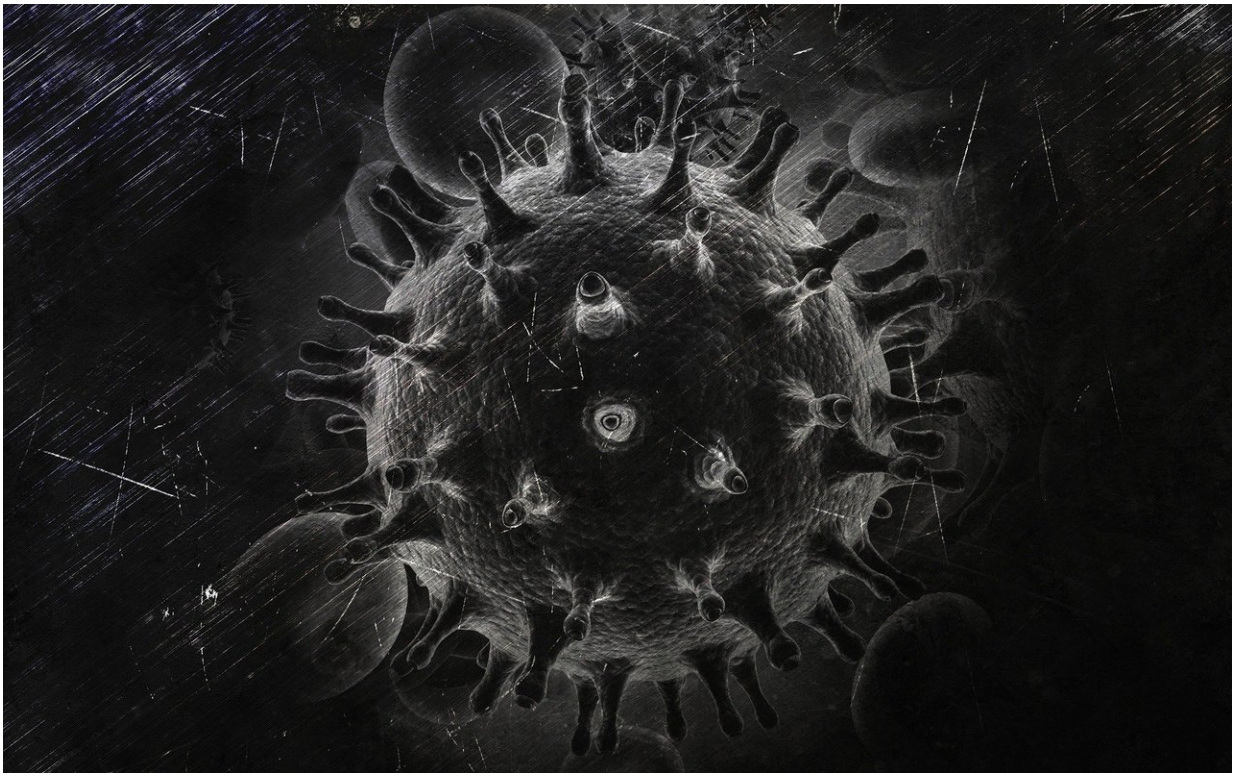

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HIV evades the body's immune defenses through a multitude of mutations, and antibodies produced by the host's immune system to fight HIV also follow convoluted evolutionary pathways that have been challenging to track.

This complexity has made it difficult for researchers to develop a preventive HIV vaccine that elicits effective antibodies similar to those that evolve in some people living with HIV. This is a task akin to retracing a traveler's exact journey knowing only the destination, with few clues to the myriad possible origins and routes.

Now, a team led by Duke Human Vaccine Institute researchers, publishing online Dec. 11 in the journal *Immunity*, reported that they have filled in a portion of the roadmap toward effective neutralization of HIV, identifying the steps that a critical HIV antibody takes to develop and maintain its ability to neutralize the virus.

In their study, lead author Mattia Bonsignori, M.D., and colleagues focused on a particular class of broadly neutralizing antibodies known as VRC01, which targets a conserved region of the HIV envelope called the CD4 binding site. This antibody lineage has long been considered a critical component of a protective vaccine-induced immune response because of its ability to neutralize a vast majority of HIV variants, despite their diversity.

"These broadly neutralizing antibodies undergo a long and convoluted maturation process," said Bonsignori, a member of the Duke Human Vaccine Institute. "There has been extensive study of them in the field, but until now, we have not been able to start at the unmutated ancestors—the origin—because it's been so difficult to retrace the sequence of the many mutations, deletions and changes."

The researchers extrapolated the un-mutated common ancestor of the VRC01 lineage and reconstructed the maturation pathways that resulted in the broadest antibodies and those that would be detrimental to HIV transmission.

Using that roadmap, the researchers then found that it's possible for this

class of antibodies to get to broad neutralization using a strategic detour along their developmental pathway. This detour is essentially a shortcut around what had been a major impediment that blocked previous attempts to induce the antibodies' neutralizing properties.

"That was where everyone was stuck—we knew that if we could figure out how to engage the ancestor antibodies, we would be on our way," Bonsignori said. "But we always hit this roadblock, where a particular sugar on HIV envelope blocked the development of the antibody during the early stages of antibody maturation, and everything got stuck."

Bonsignori said the solution is to bypass that sugar, slipping around this impediment rather than trying to blast through it.

"What we found by reconstructing the different pathways was that you can get to the end using an easier route," Bonsignori said. "Now we can use this information to design immunogens that will properly engage the immune system to circumvent this roadblock."

Provided by Duke University Medical Center

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