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An Achilles' Heel in the AIDS Virus

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An Achilles' Heel In the AIDS Virus

By Mark Schoofs

Scientists using a powerful mathematical tool previously applied to the stock market have identified an Achilles heel in HIV that could be a prime target for AIDS vaccines or drugs.

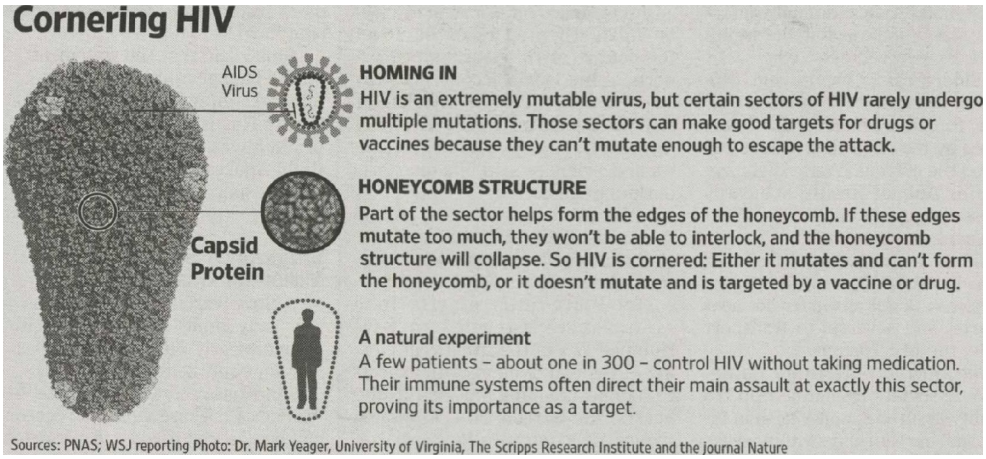
The research adds weight to a provocative hypothesis—that an HIV vaccine should avoid a broadside attack and instead home in on a few targets. Indeed, there is a rare group of patients who naturally control HIV without medication, and these "elite controllers" most often assail the virus at precisely this vulnerable area.

"This is a wonderful piece of science, and it helps us understand why the elite controllers keep HIV under control," said Nobel laureate David Baltimore. Bette Korber, an expert on HIV mutation at the Los Alamos National Laboratory, said the study added "an elegant analytical strategy" to HIV vaccine research.

"What would be very cool is if they could apply it to hepatitis C or other viruses that are huge pathogens—Ebola virus, Marburg virus," said Mark Yeager, chair of the physiology department at the University of Virginia School of Medicine. "The hope would be there would be predictive power in this approach." Drs. Baltimore, Korber and Yeager weren't involved in the new research.

One of the most vexing problems in HIV research is the virus's extreme mutability. But the researchers found that there are some HIV sectors, or groups of amino acids, that rarely make multiple mutations. Scientists generally believe that the virus needs to keep such regions intact. Targeting such sectors could trap HIV.

The study was conducted at the **Ragon Institute**, a joint enterprise of Massachusetts General Hospital, the Massachusetts Institute of Technology and Harvard University. The institute was founded in 2009 to convene diverse groups of scientists to work on HIV/AIDS and other diseases.



Two of the study's lead authors aren't biologists. Arup Chakraborty is a professor of chemistry and chemical engineering at MIT, though he has worked on immunology, and Vincent Dahirel is an assistant professor of chemistry at the Université Pierre et Marie Curie in Paris. They collaborated with Bruce Walker, a longtime HIV researcher who directs the Ragon Institute. Their work was published Monday in the Proceedings of the National Academy of Sciences.

To find the vulnerable sectors in HIV, Drs. Chakraborty and Dahirel reached back to a statistical method called random matrix theory, which has also been used to analyze behavior of stocks. While stock market sectors are well-defined, the Ragon researchers didn't know what viral sectors they were looking for.

So they defined the sectors purely mathematically, using random matrix theory to sift through most of HIV's genetic code for correlated mutations, without reference to previously known functions or structures of HIV. The segment that could tolerate the fewest multiple mutations was dubbed sector 3 on an HIV protein known as Gag.

Previous research by Dr. Yeager and others had shown that the capsid, or internal shell, of the virus has a honeycomb structure. Part of sector 3, it turns out, helps form the edges of the honeycomb. If the honeycomb suffered too many mutations, it wouldn't interlock, and the capsid would collapse.

For years, Dr. Walker had studied rare patients, about one in 300, who control HIV without taking drugs. He went back to see what part of the virus these "elite controllers" were attacking with their main immune-system assault. The most common target was sector 3.

Dr. Walker's team found even immune systems that fail to control HIV often attack sector 3, but they tend to devote only a fraction of resources against it, while wasting their main assault on parts of the virus that easily mutate to evade the attack. That suggested what the study's authors consider the paper's most important hypothesis: A vaccine shouldn't elicit a scattershot attack, but surgical strikes against sector 3 and similarly low-mutating regions of HIV.

"The hypothesis remains to be tested," said Dan Barouch, a Harvard professor of medicine and a colleague at the Ragon institute. He is planning to do just that, with monkeys. Others, such as Oxford professor Sir Andrew McMichael, are also testing it.

The Ragon team's research focused on one arm of the immune system that attack other cells HIV has infected. Many scientists believe a successful HIV vaccine will also require antibodies that attack a free-floating virus. Dr. Chakraborty is teaming with Dennis Burton, an HIV antibody expert at the Scripps Research Institute in La Jolla, Calif., to apply random matrix theory to central problems in antibody-based vaccines.