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Research on killer HIV antibodies provides promising new ideas for vaccine design

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New discoveries about the immune defenses of rare HIV patients who produce antibodies that prevent infection suggest a novel direction for designing new vaccines. Researchers at Rockefeller University and colleagues have now made two fundamental discoveries about the so called broadly neutralizing anti-HIV antibodies, which effectively keep the virus at bay. By detailing the molecular workings of a proven immune response, the researchers hope their work will ultimately enable them to similarly arm those who are not equipped with this exceptional immunological firepower. The findings are reported in the Sept. 30 issue of the journal *Nature*.

"Nobody yet can make a vaccine that elicits these broadly neutralizing antibodies, but here are patients who can do it, so let's understand how," says Michel C. Nussenzweig, Sherman Fairchild Professor and head of the Laboratory of Molecular Immunology. "That's the theme in this work. The reason the research community is not making this vaccine is not that we're not good engineers. We are. The reason is that we don't understand how these patients produce these antibodies, and that's what we're figuring out. If we know how they're doing it, we might learn how to reproduce it."

HIV strains mutate rapidly, making them notoriously evasive targets for the immune system. In particular, the HIV envelope spike, called gp160, is the site of a host of mutations that obstruct the few elements that all of the virus strains share. Prior research has shown that only four super antibodies block the activity of that protein in a broad range of HIV

strains, neutralizing the virus. But all attempts to coax the human body into producing those four have failed.

Last year, in experiments reported in *Nature*, the Nussenzweig lab showed that a diverse group of broadly neutralizing antibodies cloned from 433 B cells of six slow progressing HIV patients were as capable of knocking down a broad range of HIV strains as any one of the super antibodies. The ability to isolate and clone antibodies from B cells was first worked out by the lab in a pioneering 2003 paper in Science. Now, having applied that method to the B cells in HIV patients with high titers of broadly neutralizing antibodies, the new research explores in more detail what their antibodies target and how they attack.

In work to be published Sept. 30 in *Nature*, postdoc Hugo Mouquet, Nussenzweig and colleagues found a surprising result. Most antibodies are traditionally thought to bind to their target, or antigen, in a bivalent fashion, meaning they get a firm grip by taking hold of two specific handles. But HIV virions do not allow for that possibility because the gp160 spikes are too far apart. Therefore, antibodies to the virus are handicapped because they can only use one of their two high affinity arms to recognize the viral spike. The researchers found that on average 75 percent of the anti-gp160-HIV antibodies in their large collection were selected by the immune system for polyreactivity, a property that allowed the second "free" arm of the antibody to enhance overall affinity by binding to the virion "non-specifically." Generally, the immune system weeds out polyreactive antibodies, even though they are naturally produced in significant quantities, because polyreactive antibodies could in theory attack the body itself.

But the experiments suggest that these "sticky" antibodies may be an opportunistic adaptation to difficult cases such as HIV, in which homotypic bivalent bonding may not be an option. This particular cadre of polyreactive antibodies takes a long time - years - to develop in slow

progressing HIV patients, and much remains to be discovered about that process, but the researchers believe that vaccine designed to elicit antibodies that mimic these properties could be a promising strategy to beat the deadly virus.

In related research published in August in The *Journal of Experimental Medicine*, visiting student John Pietzsch, Nussenzweig and colleagues mapped the target of the largest single group of neutralizing antibodies found in HIV-infected patients with broadly neutralizing serologic activity. These antibodies including one of the recently described super antibodies, targeted a previously undefined region of the HIV envelope protein, a region that is nearby but distinct from the site targeted by previously described super antibodies. By mutating individual amino acids of this target and discovering that the result was an impotent virus, they showed that the largest group of broadly neutralizing antibodies targets a region on the HIV envelope spike that is indispensable for infection.

"The largest group of the HIV neutralizing antibodies was unmapped - this group might have been specific for a number of different sites on the virion," Nussenzweig says. "But they are directed to a single core epitope on the viral spike, near the CD4 binding site. Our findings extend the footprint of what a neutralizing antibody can see."

This site, a core element of the HIV envelope spike that is shared by a full range of HIV strains, is an attractive new target that should be considered for vaccine design, the scientists say, and they are working on how to attack it.
Nussenzweig, whose lab has only in the last couple of years begun working on HIV antibodies, says, "We're making basic discoveries about how antibodies work by studying a disease in patients. We could not do this work in a model organism."