A natural approach for HIV vaccine

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(PhysOrg.com) -- For 25 years, researchers have tried and failed to develop an HIV vaccine, primarily by focusing on a small number of engineered "super antibodies" to fend off the virus before it takes hold. So far, these magic bullet antibodies have proved impossible to produce in people. Now, in research to be published March 15 online by *Nature*, scientists at The Rockefeller University have laid out a new approach. They have identified a diverse team of antibodies in "slow-progressing" HIV patients whose coordinated pack hunting knocks down the virus just as well as their super-antibody cousins fighting solo.

By showcasing the dynamic, natural immune response in these exceptional patients, the research, led by Michel C. Nussenzweig, Sherman Fairchild Professor and head of the Laboratory of Molecular Immunology, suggests that an effective HIV vaccine may come from a shotgun approach using of a wide range of natural antibodies rather than an engineered magic bullet.

"We wanted to try something different, so we tried to reproduce what's in the patient. And what's in the patient is many different antibodies that individually have limited neutralizing abilities but together are quite powerful," says Nussenzweig, who also is a Howard Hughes Medical Institute investigator. "This should make people think about what an effective vaccine should look like."

HIV strains mutate rapidly, making them especially wily adversaries of the immune system. But one element is shared almost universally among the diverging strains — a protein on the envelope of the virus called

gp140 that HIV needs to infect immune cells. Prior research has shown that four randomly engineered antibodies that block the activity of that protein prevent the virus from infecting immune cells in culture, but all attempts to coax the human body into producing those four have failed.

So Johannes Scheid, a visiting student in Nussenzweig's lab who is now a doctoral candidate, turned his attention to the antibodies produced by six people infected with HIV whose immune systems put up an exceptionally strong fight. The patients represent the roughly 10 to 20 percent of HIV patients who are able to control the virus and are very slow to progress to disease. Their immune systems' memory B cells produce high levels of antivirus antibodies, but until now, researchers have known little about the antibodies or how effective they are.

With help from Rockefeller's Center for Clinical and Translational Science and Rockefeller scientists David D. Ho and Jeffrey V. Ravetch, Scheid and colleagues isolated 433 antibodies from these individuals' blood serum that specifically targeted the envelope protein — the chink in HIV's protean armor. He cloned the antibodies and produced them in bulk, mapped which part of the envelope protein each targeted, and gauged how effective each was in neutralizing the virus. In the process, he identified a new structure within the envelope protein — called the gp120 core — that had never been recognized as a potential target for antibodies. "It's the first time that anyone has defined what is really happening in the B cell response in these patients," says Scheid.

Scheid's work shows that it's common for these antibodies to have neutralizing activity, says Nussenzweig. But each antibody alone has limited ability to fight the virus. "Individually, they're not as strong as the Famous Four," says Nussenzweig, referring to the high-profile super antibodies on which several vaccine attempts have been based. But in high concentrations, a combination of the sets of antibodies cloned from the individual patients seemed to act as teams to knock down the virus in

cell culture as well as any single antibody studied to date. These natural antibodies were also able to recognize a range of HIV strains, indicating that their diversity may be an advantage over a single super antibody that focuses on only one part of the virus, which can mutate. The findings suggest that research into vaccines that mimic this natural antibody response could pay off.

Source: Rockefeller University (news : web)