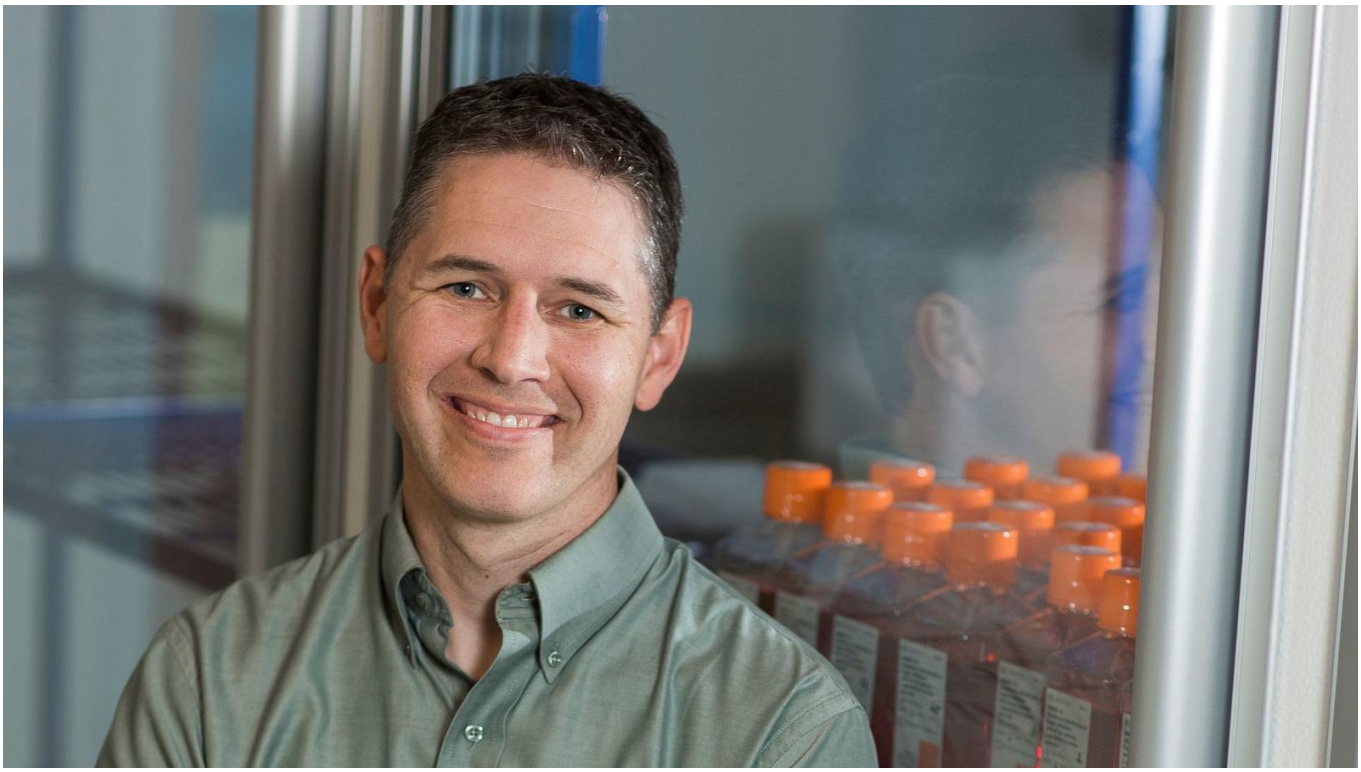
Powerful HIV-neutralizing response possible in most people, study by San Diego researchers finds



Shane Crotty, a vaccine researcher at the La Jolla Institute for Allergy & Immunology. (LIAI)

By **Bradley J. Fikes**

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In an advance toward an effective HIV vaccine, San Diego researchers have shown how cells vital to stopping the virus can be made to multiply. The study will help guide upcoming vaccine trials.

While HIV is treatable by many drugs, millions in impoverished countries can't afford them, especially in Sub-Saharan Africa. So public health officials say a vaccine to block transmission is the best hope for control, and possibly eradication of HIV and AIDS.

But after decades of effort, no truly effective HIV vaccine has been developed. So researchers have been studying the virus and the immune system to understand why.

The new study focuses on how to train the immune system to make more of certain antibody-making cells, called B cells. Arising from a "naive" state, these cells go through repeated stages of growth and mutation to learn how to make effective antibodies.

But only about one in a million precursor B cells are capable of maturing into cells that make effective antibodies against HIV. It had been unclear if that minute amount was enough, or whether the immune systems of most people are simply incapable of mounting an effective response.

The new study indicates promoting this effective response is possible under the right conditions. It was published Dec. 26 in the journal *Immunity,* and is available at j.mp/hivbnab.

Using a mouse model, the researchers found it's possible to coax these rare precursor cells to mature and proliferate into producers of antibodies that neutralize a broad range of HIV strains. Specifically, these cells can mature into cells that make a particularly promising class of antibodies called VRC01.

In a Darwinian process, the cells must outcompete the far more numerous precursor B cells that can mature into those making ineffective antibodies. This initial or "priming" process must be followed by additional steps to allow the developing B cells to home in onto the precise antibody response to neutralize HIV.

Understanding what takes place will help researchers determine how well new HIV vaccines are guiding the immune response, said vaccine researcher Shane Crotty of the La Jolla Institute for Allergy & Immunology, a lead author of the study.

The study gives a stronger scientific basis for developing neutralizing antibody vaccines, said Dr. Anthony Fauci, director of the National Institute of Allergy & Infectious Diseases.

"It's really an excellent study and it's taking us another step closer to understanding how we might ultimately elicit very elusive broadly neutralizing antibodies," Fauci said.

In the mice, the population of potentially useful precursor B cells was expanded, a necessary step but not sufficient to develop an effective antibody response. Turning naive B cells into those capable of making broadly neutralizing antibodies takes multiple steps. So a vaccine would require multiple immunizations, each step nudging these B cells toward final maturation into those that make the broadly neutralizing antibodies.

This convoluted process is necessary because HIV is covered with decoy structures that aren't found in other viruses. By the time the immune system has latched onto these decoy sites, the virus has mutated away. By contrast, the parts of the virus vulnerable to broadly neutralizing antibodies are well hidden.

Infected people can eventually make these broadly neutralizing antibodies, after years of trial and error. By then, the virus is too well established to eradiate. So the main problem is how to design an HIV vaccine to compress this years-long immune learning process into just a few months.

And that requires understanding what is going on in the immune system at a molecular level after HIV

he proper molecules to stimulate an immune response, or immunogen, Fauci said.

“And the reason this paper is so important is it's telling you that you have to develop an immunogen that specifically targets these germline B cell precursors to get them going, and then by subsequent immunizations coax them along on the pathway to a broadly neutralizing antibody,” Fauci said. “So it's exceedingly important to the field of immunogen design.”

Germline B precursor cells are the original immune cells the body starts out with.

One of those vaccine approaches is led by William Schief of The Scripps Research Institute. His strategy involves unshielding the vulnerable viral site so it’s visible to the B cells.

“Our data are consistent with the idea that his vaccine idea really may work because it looks like people really do have these B cells,” Crotty said.

Research funding included grants from NIAID, CHAVI-ID, the international AIDS Vaccine Initiative with support from United States Agency for International Development, the Ministry of Foreign Affairs of the Netherlands and the Bill & Melinda Gates Foundation.

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