Training human antibodies to protect against HIV

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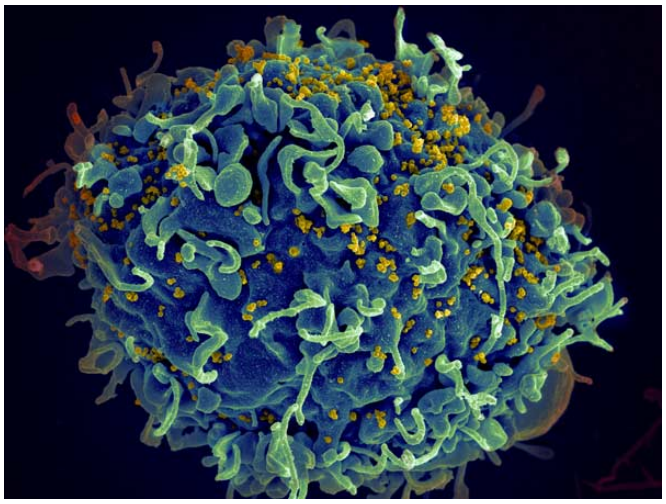

HIV infecting a human cell. Credit: NIH

During HIV infection, the virus mutates too rapidly for the immune system to combat, but some people produce antibodies that can recognize the virus even two years after infection. With an eye towards developing a vaccine, in four related papers from multiple groups publishing September 8 in *Cell* and *Immunity*, researchers describe a multi-step method for "training" the immune system to produce these antibodies in genetically engineered mice.

These broadly neutralizing antibodies can recognize many different iterations of the virus. "They are not capturing only the first or second version of the virus that they ran into," says Michel Nussenzweig, a molecular immunologist at The Rockefeller University and co-senior author on two of the studies. "They retain the ability to catch all of the virus mutations they've seen before."

When produced naturally, these antibodies don't pack enough punch to cure the systemic infection, but they could be strong enough to prevent the infection if induced by a vaccine. As a conceptual test, using mice genetically engineered to simulate the human immune system, Nussenzweig's group devised a way to train the immune system and produce a class of antibodies called PGT121 that react to diverse strains of HIV.

The human immune system contains multiple different precursors, only a few of which could give rise to PGT121 antibodies, so the researchers first had to genetically analyze the antibodies to determine what their naive state likely was. Then, led by immunologist and co-senior author William Schief at the Scripps Research Institute, they created a series of viral protein structures, starting from HIV and working backwards, that could eventually teach the antibodies to recognize multiple forms of the natural HIV.

"The antibody precursors, or what we estimate as their precursors, don't seem to have detectable affinity themselves for the virus," says Schief. "We needed to convert HIV into something stable that would kickstart the process." The development of these structures is highlighted in the *Immunity* paper. At the end of this design process, the researchers had a sequence of modified immunogens to act as stepping stones to guide the antibodies' development.

Nussenzweig's team further tested the iterative training process using genetically engineered mice. Rather than producing the spectrum of antibodies normally found in the mouse immune system, these animals only produced the human precursors that could generate PGT121 antibodies. The researchers started with the first synthetic immunogen developed by Schief that could bind the PGT121 precursor and then tested the mouse serum to see if any antibodies also reacted to the next immunogen in the sequence, getting closer in a step-by-step fashion to natural HIV.

The process worked, and the team successfully

matured a broadly neutralizing antibody in mice that resembled those found in HIV-infected individuals. However, Schief and Nussenzweig emphasize that their work offers a conceptual framework to develop a vaccine, rather than the vaccine itself. "We have done this in a very contrived mouse model," says Nussenzweig. "In a normal mouse—or a normal human—the immune system has a huge repertoire, and the antibody precursors that we're looking for are only a small fraction. If we put the same initial immunogen in a wild-type animal, it's very unlikely that enough of the immunogen would find the right precursors to get the whole thing started."

But, says Schief, "You have to start somewhere. This is a big step forward—we have shown that it's possible to guide antibody maturation from a human germline to produce broadly neutralizing antibodies by vaccination."

Now, with their established principles in hand for HIV vaccine development, the next step is to develop immunogens that have high affinity for the antibody precursors that are actually present in humans (which may differ from the one engineered into the mouse model). This next advance will allow the vaccine to locate and train the right parts of the human immune system in a naturally diverse environment.

A Mouse Model for Quickly Testing HIV Vaccines

In a related *Cell* paper, also publishing September 8, researchers at Boston Children's Hospital and the National Institute of Allergy and Infectious Diseases show how to quickly generate a humanized mouse model for testing new HIV vaccination strategies. In their mouse model, B cells assemble a highly diverse set of HIV antibody precursors that can be taught to produce humanized antibodies capable of neutralizing some HIV viral strains.

"Rather than go through generations of mouse breeding to make models, our approach allows us to quickly delete and replace genomic elements to create changes in B cells," says co-senior author Fred Alt, director of the Program in Cellular and Molecular Medicine at Boston Children' Hospital. "Thus, we can rapidly re-program this mouse model with the intermediate antibody genes selected from the first successful immunizations and expose them to new antigens. We're hoping it will be broadly useful."

"We need to further understand how to engender optimal antibody affinity maturation to evolve the antibody response toward effective virus neutralization," adds Director of the NIAID's Vaccine Research Center John Mascola, also co-senior author on the paper. "But these types of questions can be partially addressed in our humanized mouse models, to help select vaccine antigens and immunization strategies for phase I human studies."

More information: *Cell*, Escolano and Steichen et al.: "Sequential Immunization Elicits Broadly Neutralizing anti-HIV-1 Antibodies in Ig Knock-in Mice" www.cell.com/cell/fulltext/S0092-8674(16)30976-X / DOI: 10.1016/j.cell.2016.07.030

Cell, Briney, Sok, Jardine, Kulp, and Skog et al.: "Tailored Immunogens Direct Affinity Maturation toward HIV Neutralizing Antibodies" www.cell.com/cell/fulltext/S0092-8674(16)31054-6 / DOI: 10.1016/j.cell.2016.08.005

Cell, Tian, Cheng, Chen, Duan and Cheng et al.: "Induction of HIV Neutralizing Antibody Lineages in Mice with Diverse Precursor Repertoires" www.cell.com/cell/fulltext/S0092-8674(16)30975-8 / DOI: 10.1016/j.cell.2016.07.029

Immunity, Steichen, Kulp, Tokatlian, and Escolano et al.: "HIV Vaccine Design to Target Germline Precursors of Glycan-Dependent Broadly Neutralizing Antibodies" www.cell.com/immunity/fulltext … 1074-7613(16)30340-5 / DOI: 10.1016/j.immuni.2016.08.016

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