Scientists map route for eliciting HIV-neutralizing antibodies

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Researchers have traced in detail how certain powerful HIV neutralizing antibodies evolve, a finding that generates vital clues to guide the design of a preventive HIV vaccine, according to a study appearing in *Science Express* this week. The discoveries were made by a team led by the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

"This elegant research brings us another step closer to an HIV vaccine and establishes a potent new technique for evaluating the human immune response to experimental vaccines, not only for HIV, but for pathogens generally," said NIAID Director Anthony S. Fauci, M.D.

The new findings build on last year's discovery reported by VRC scientists of three HIV antibodies, two of which could stop more than 90 percent of known global HIV strains from infecting human cells in the laboratory. Called VRC01, VRC02 and VRC03, these antibodies were found in blood donated for NIAID studies by an HIV-infected North American known as donor 45. In the new paper, scientists report discovering antibodies similar to VRC01 in the blood of two HIV-infected Africans known as donor 74 and donor 0219.

The researchers further discovered that these VRC01-like antibodies all bind to the same spot on HIV in the same way. This suggests that an HIV vaccine should contain a protein replica of this spot, known as the CD4 binding site, to elicit antibodies as powerful as VRC01, according to the researchers. The CD4 binding site is one of the few parts of the

continuously mutating virus that stays the same across HIV variants worldwide, and the virus uses this site to attach to the cells it infects.

The scientists previously found that the genes for VRC01-like antibodies undergo an unusually high number of mutations—70 to 90—between the first draft that codes for a weak antibody and the final version that codes for an antibody that can neutralize HIV. These genes lie in the DNA of immune cells called B cells.

"To make a vaccine that elicits VRC01-like antibodies, we will need to coach B cells to evolve their antibody genes along one of several pathways, which we have now identified, from infancy to a mature, HIV-fighting form," said VRC Director Gary J. Nabel, M.D., Ph.D.

To guide B cells along this extended evolutionary pathway, the scientists first needed to map the route. They began by turning to an existing technology to sequence the collection of B-cell genes that code for all the antibodies created by a person's immune system. This study marks the first time this technology, called deep sequencing, has been used to track the evolution of the antibody response to HIV at the genetic level. The NIH researchers then devised sophisticated bioinformatics techniques to decipher the large library of genetic data produced by deep sequencing.

"We found a way to read the books, or genes, in this library by defining unique characteristics of VRC01-like antibodies," said Peter Kwong, Ph.D., chief of the VRC's structural biology section and co-principal investigator of the study.

Based on their discovery of the common structure and genetic origin of the VRC01-like antibodies, the scientists devised strategies for scanning the B-cell DNA libraries of donor 45 and donor 74. From hundreds of thousands of antibody genes, the scientists first identified thousands that

code for VRC01-like antibodies and then sorted these genes into family trees showing their evolution from their earliest stage into mature forms. The genes that coded for HIV neutralizing antibodies grouped together on the same branches of the trees.

Next, the researchers focused on the gene segment that codes for the part of the VRC01-like antibody that attaches to and neutralizes HIV. Examining this sequence in the genes of the newfound relatives of VRC01 revealed how the sequence changed step by step along one of a few clear paths from its original state into a mature form. A vaccine that elicits VRC01-like antibodies would need to coax the B-cell DNA of immature antibodies to evolve along one of these pathways.

The scientists now aim to create proteins they can deliver through a vaccine to serve as signposts that direct the development of B-cell DNA to produce VRC01-like antibodies.

The new research has far-reaching implications for vaccine development. "As we develop and test new HIV vaccines, it will be possible to analyze not just antibodies in the blood, but also the specific B-cell genes that are responsible for producing antibodies against HIV," said John R. Mascola, M.D., deputy director of the VRC and co-principal investigator of the study. "This information will indicate whether an investigational HIV vaccine in a preclinical or clinical trial is heading in the right direction."

More information: X Wu et al. Focused evolution of HIV-1 neutralizing antibodies revealed by crystal structures and deep sequencing. *Science Express* (online on Aug. 11, 2011).

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