Researchers isolate new potent and broadly effective antibodies against HIV

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A team of researchers at and associated with the International AIDS Vaccine Initiative (IAVI), The Scripps Research Institute, the biotechnology company Theraclone Sciences and Monogram Biosciences Inc., a LabCorp company, report in the current issue of *Nature* the isolation of 17 novel antibodies capable of neutralizing a broad spectrum of variants of HIV, the virus that causes AIDS.

The new antibodies, large protein molecules that bind to pathogens and flag them for destruction, were isolated from blood serum samples collected in a continuing global search for broadly neutralizing antibodies (bNAbs) launched by IAVI. They should provide researchers with a new set of targets for the design of vaccine candidates that can elicit similar antibodies to protect people from contracting HIV. Some of the bNAbs blocked HIV infection of cells as much as 10 to 100 times as potently as previously discovered bNAbs.

"Most antiviral vaccines depend on stimulating the antibody response to work effectively," said Dennis Burton, a professor of immunology and microbial science and director of the IAVI Neutralizing Antibody Center at The Scripps Research Institute in La Jolla, Calif. Professor Burton, one of the senior authors of the study, is also a member of the Ragon Institute, in Cambridge, Mass. "Because of HIV's remarkable variability, an effective HIV vaccine will probably have to elicit broadly neutralizing antibodies. This is why we expect that these new antibodies will prove to be valuable assets to the field of AIDS vaccine research."

Only a minority of people who are HIV-positive begin to produce bNAbs after several years of infection. Animal studies suggest that such antibodies could block HIV infection if they were elicited by a preventive vaccine. Researchers prize bNAbs because their structural and biochemical analysis can reveal how to achieve a preventive vaccine. Specifically, scientists expect that they can use information about how bNAbs bind to HIV to construct immunogens—the active ingredients of vaccines—that elicit similar antibodies. The potency of bNAbs matter because a highly potent antibody could confer such protection at relatively low levels.

"Solving the neutralizing antibody problem is perhaps the greatest challenge facing the field today," said IAVI's chief scientific officer, Wayne Koff. "IAVI concluded many years ago that unlocking the information stored in bNAbs was going to be essential to the fulfillment of our mission—ensuring the design and development of broadly effective AIDS vaccines. This is why we support several laboratories around the world that are designing novel vaccine candidates on the basis of what we're learning from such antibodies. We have no doubt that these new bNAbs will contribute a great deal to our own immunogen design efforts and, we hope, those of other researchers working on AIDS vaccines."

In that regard, the new bNAbs are encouraging. Many of them bind hitherto unknown molecular structures, or epitopes, on the surface of HIV. This means that they could significantly broaden the target options researchers have in designing vaccines to elicit similar antibodies.

How the antibodies were discovered

The 17 new bNAbs described in the current *Nature* report were isolated from four HIV-positive individuals. The effort, sponsored by IAVI, is unprecedented in scale and distinguished by its emphasis on identifying

antibodies that neutralize subtypes of HIV circulating primarily in developing countries. It had previously yielded three potent bNAbs, two of which, PG9 and PG16, were isolated by this research team in 2009 and described in the journal Science. Another bNAb was subsequently isolated from these samples by researchers at the Vaccine Research Center of the National Institutes of Health, who have also discovered a set of bNAbs from separate blood samples using an entirely different approach.

Both the previous and current studies used Theraclone Science's highly sensitive I-STAR™ technology to isolate the antibodies. The new crop of bNAbs, like PG9 and PG16, was rescued from cell cultures derived from single antibody-producing B cells used for antibody discovery and development. Theraclone Sciences Executive Chair and Interim CEO, Steven Gillis commented, "We're delighted that I-STAR has provided essential support in identifying bNAbs that will contribute to advancing AIDS vaccine development. In this project, and in our own infectious disease and cancer programs, the I-STAR platform continues to demonstrate a remarkably powerful ability to isolate rare antibodies with unique properties. Theraclone values these collaborative opportunities in which I-STAR can be used to help improve treatment for critical diseases."

Monogram Biosciences, which also participated in the discovery of PG9 and PG16, conducted the neutralization assays essential to isolating the new bNAbs. The serum samples from which they were isolated represent the top 1% of all such samples gathered by IAVI and its partners, in terms of the number of HIV variants they neutralize and the potency with which they do so.

"Monogram has developed a highly skilled scientific team capable of taking on a variety of biomedical challenges," said Chris Petropoulos, Vice President, Laboratory Corporation of America Holdings, Research

and Development, Monogram Biosciences. "Their expertise and innovation has been invaluable to the discovery of these new antibodies. This research illustrates the important role different sectors of the research and health care community can play in supporting global health initiatives."

The analysis of the new antibodies also hints at how future vaccines ought to be formulated to maximize their effectiveness. On the basis of their analyses, the authors of the report conclude that AIDS vaccine candidates that seek to effectively harness the antibody response should probably attempt to elicit certain combinations of bNAbs if they are to provide truly comprehensive protection from HIV.

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