Two New Antibodies Found to Cripple HIV

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Findings Reveal an Achilles Heel on the Virus for AIDS Vaccine Researchers to Exploit

NEW YORK, NY, LA JOLLA and SAN FRANCISCO, CA, SEATTLE, WA, September 3, 2009—Researchers at and associated with the International AIDS Vaccine Initiative (IAVI), at The Scripps Research Institute, and at the biotechnology companies Theraclove Sciences and Monogram Biosciences have discovered two powerful new antibodies to HIV that reveal what may be an Achilles heel on the virus. They published their work in Science this week.

Researchers will now try to exploit the newfound vulnerability on the virus to craft novel approaches to designing an AIDS vaccine. Moreover, the global collaboration and process that led to the discovery of the two new broadly neutralizing antibodies (bNAbs) are likely to produce more such antibodies, which may in turn reveal additional vulnerabilities of HIV, adding still more vitality to the effort to develop a vaccine against AIDS.

“The findings themselves are an exciting advance toward the goal of an effective AIDS vaccine because now we’ve got a new, potentially better target on HIV to focus our efforts for vaccine design,” said Wayne Koff, senior vice president of research and development at IAVI. “And having identified this one, we’re set up to find more, which should further accelerate global efforts in AIDS vaccine development.”

Broadly neutralizing antibodies to HIV are produced by a minority of HIV-infected individuals and are distinct from other antibodies to HIV in that they neutralize a high percentage of the many types of HIV in circulation worldwide. It is widely believed that to prevent HIV infection an AIDS vaccine would need to teach the body to produce these powerful antibodies before exposure to the virus. Animal experiments suggest that conceptually such a vaccine would work. Before this finding only four antibodies to HIV had been discovered that were widely agreed to be broadly neutralizing.

The two newly discovered bNAbs, called PG9 and PG16, are the first to have been identified in more than a decade and are the first to have been isolated from donors in developing countries, where the majority of new HIV infections occur. Moreover, previously identified bNAbs against HIV have functioned by binding to places on HIV that have proven difficult to exploit by means of vaccine design.

“These new antibodies, which are more potent than other antibodies described to date while maintaining great breadth, attach to a novel, and potentially more accessible site on HIV to facilitate vaccine design,” said Dennis Burton, professor of immunology and microbial science and scientific director of the IAVI Neutralizing Antibody Center at The Scripps Research Institute in La Jolla, California. Professor Burton is also a member of the newly established Ragon Institute of MGH, MIT and Harvard. “So now we may have a better chance of designing a vaccine that will elicit such broadly neutralizing antibodies, which we think are key to successful vaccine development.”

Breadth of neutralization is important because any effective AIDS vaccine must provide protection from a diverse range of the most prevalent types of HIV circulating worldwide. High potency suggests that such antibodies will not have to be produced by the body in very large quantities to confer protection.
The two new antibodies target a region of the viral spike used by HIV to infect cells. The viral spike glycoproteins, termed gp120 and gp41, are highly variable and have evolved to thwart immune attack. But biochemical studies suggest that PG9 and PG16 target regions of gp120 that do not change, which probably accounts for their breadth of neutralization. Now researchers at the IAVI-organized Neutralizing Antibody Consortium (NAC), a scientific network focused on designing vaccines capable of eliciting broadly neutralizing antibodies, will turn their attention to studying the molecular structure of PG9 and PG16 and that of the region they target on the HIV spike. They will use this information to try to devise immunogens—the active ingredients of vaccines—that elicit similar antibodies.

How they were discovered

The methods by which PG9 and PG16 were isolated are themselves proving instructive. Their identification represents the first success of an ongoing global hunt launched by IAVI in 2006 to find new bNAbs to support the rational design of novel AIDS vaccine candidates. The effort, named Protocol G, is unprecedented in scale and distinguished by its emphasis on identifying antibodies that neutralize subtypes of HIV circulating primarily in developing countries. IAVI's clinical research partners have collected blood specimens from upward of 1,800 HIV-infected volunteers from IAVI-supported clinical research centers in seven sub-Saharan countries as well as from centers in Thailand, Australia, the United Kingdom and the United States.

All samples were sent to Monogram Biosciences, which, working with researchers at IAVI's AIDS Vaccine Design and Development Laboratory in New York City and the IAVI Neutralizing Antibody Center at The Scripps Research Institute, screened the sera for broadly neutralizing activity. Researchers historically have sought bNAbs in serum by testing whether antibodies from such samples bind to soluble versions of gp120 and gp41. It turns out that PG9 and PG16, however, bind to soluble forms of the proteins very weakly, if at all. The antibodies were detected only because a micro-neutralization assay developed by Monogram in partnership with IAVI measuring their ability to block HIV infection of target cells was run in parallel with the standard binding assays used for screening. This has significant implications for the future screening of bNAbs.

"If you think of it as a fishing expedition," said Christos Petropoulos, chief scientific officer and vice president of virology research and development at Monogram Biosciences, "we and the rest of the field were previously using the wrong bait in the search for HIV-specific broadly neutralizing antibodies. Together with colleagues at IAVI, we reasoned that the best approach to identifying antibodies with the most potent and broad neutralizing activity was to screen directly for their ability to block HIV infection. To do this we developed a new, specialized test known as the micro-neutralization assay, which has opened up new avenues for exploration of additional donors for similar antibodies."

Once the researchers had ranked the top 10% of serum samples in terms of breadth of neutralization, they needed to isolate the actual bNAbs. This can be painstaking work. But Theracrine Sciences, a company that had been working outside the HIV field, had a relevant and unique high-throughput process that it adapted to HIV work with financing from IAVI’s Innovation Fund, which is co-funded by the Bill & Melinda Gates Foundation. The Theracrine team used a system designed to expose the entire repertoire of antibodies from a blood sample obtained from an HIV-infected individual. Antibodies with broadly neutralizing potential were identified from this pool and traced to their corresponding antibody-forming cells. Using recombinant DNA technology, bNAb genes were then isolated from these cells to enable the production of unlimited quantities of the antibody clones for research.

"It is exciting that we were able to use our technology to identify and isolate these new bNAbs, which may offer important clues that could help create an effective AIDS vaccine. Through this strong scientific partnership, we have rapidly delivered promising results," said Matthew Moyle, chief scientific officer and...
senior vice president of Theraclone Sciences. “This project has been a useful demonstration of Theraclone’s antibody discovery platform in infectious disease, and we highly value IAVI’s collaborative approach to solving the AIDS vaccine challenge,” said David Fanning, president and CEO of Theraclone Sciences.

With a large pool of HIV-positive donors from Protocol G now identified whose serum contains HIV-specific broadly neutralizing antibodies, it is likely that this global collaboration will generate more bNAbs that will benefit the vital enterprise of accelerating AIDS vaccine development.

“The story of the discovery of these two new antibodies demonstrates the challenges of AIDS vaccine research but also the power of the collaboration that formed to produce this advance. This is what can happen when you have researchers from the global North and South, from academia and industry, from within and outside the HIV field, working together in a framework to speed innovation,” said Seth Berkley, president and CEO of IAVI. “By working in this manner, I am confident we will continue to move toward solving the AIDS vaccine challenge, one of the greatest scientific and public health challenges of our time.”

*The published study on the two new bNAbs is available online at [www.sciencemag.org](http://www.sciencemag.org).*

ABOUT IAVI

**The International AIDS Vaccine Initiative (IAVI)** is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996 and operational in 24 countries, IAVI and its network of collaborators research and develop vaccine candidates. IAVI was founded with the generous support of the Alfred P. Sloan Foundation, The Rockefeller Foundation, The Starr Foundation and Until There’s A Cure Foundation. Other major supporters include the Bill & Melinda Gates Foundation, the Foundation for the National Institutes of Health, The John D. Evans Foundation, The New York Community Trust, the James B. Pendleton Charitable Trust; the Governments of Canada, Denmark, India, Ireland, the Netherlands, Norway, Spain, Sweden, the United Kingdom and the United States, the Basque Autonomous Government and the European Union, as well as The City of New York, Economic Development Corporation; multilateral organizations such as The World Bank; corporate donors including BD (Becton, Dickinson & Co.), Bristol-Myers Squibb, Continental Airlines, Google Inc., Henry Schein, Inc., Pfizer Inc, and Thermo Fisher Scientific Inc.; leading AIDS charities such as Broadway Cares/Equity Fights AIDS; other private donors such as The Haas Trusts; and many generous individuals from around the world. For more information, see [www.iavi.org](http://www.iavi.org).

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ABOUT THERACLONE SCIENCES
Theraclone Sciences is a Seattle-based discovery-stage biotech focused on the development of novel therapeutic antibodies for the treatment of infectious disease and inflammation. The company’s technology harnesses the power of the human immune system to identify naturally evolved monoclonal antibodies from the blood cells of immunologically relevant human subjects. Recombinant human monoclonal antibodies can be rapidly obtained using our discovery platform and scaled for large-scale industrial production. Such antibody drug candidates may be uniquely important in combating disease and may have potential as therapeutic products that can be administered to a broad patient population. Theraclone is a privately held company with venture investment from ARCH Venture Partners, Canaan Partners, Healthcare Ventures, Amgen Ventures, MPM Capital, and Alexandria Real Estate Investment. For additional information, please visit www.theraclone-sciences.com.

ABOUT MONOGRAM BIOSCIENCES
Monogram Biosciences, Inc. is advancing individualized medicine by discovering, developing and marketing innovative products to guide and improve treatment of serious infectious diseases and cancer. Monogram Biosciences, Inc.’s products are designed to help doctors optimize treatment regimens for their patients that lead to better outcomes and reduced costs. Monogram Biosciences, Inc.‘s technology is also being used by numerous biopharmaceutical companies to develop new and improved anti-viral therapeutics and vaccines as well as targeted cancer therapeutics. More information about Monogram Biosciences, Inc. and its technology can be found on its web site at www.monogrambio.com.

Protocol G collaborating institutions include: MRC/UVRI Uganda Research Unit on AIDS, Uganda Virus Research Institute, Entebbe, Uganda; St. Stephen's AIDS Trust, Chelsea and Westminster NHS Foundation Trust, London UK; NRL, St. Vincent's Institute, Melbourne, Victoria, Australia; Zambia Emory HIV Research Project, Lusaka, Zambia, and the Rwanda-Zambia HIV Research Group, Emory University, Atlanta, GA, USA; Projet San Francisco, Kigali, Rwanda and the Rwanda-Zambia HIV Research Group, Emory University, Atlanta, GA, USA; CeDReS/CHU Treichville, Abidjan, Côte d'Ivoire; Kenya AIDS Vaccine Initiative, College of Health Sciences, University of Nairobi, Nairobi, Kenya; SUNY Downstate Medical Center, Brooklyn, NY, USA; Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa; Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; Department of Retrovirology, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand; Rwanda-Zambia HIV Research Group, Emory University, Atlanta, GA, USA; Institute of Human Virology, Plateau State Human Virology Research Centre, Jos, Nigeria.

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