New chemically-activated antigen could expedite development of HIV vaccine

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Scientists working to develop a vaccine for the human immunodeficiency virus (HIV) report they have created the first antigen that induces protective antibodies capable of blocking infection of human cells by genetically-diverse strains of HIV. The new antigen differs from previously-tested vaccines by virtue of its chemically-activated property that enables close sharing of electrons and produces strong covalent bonding. Researchers used a mouse model to generate the antibodies. The report by researchers at The University of Texas Health Science Center at Houston is online and will appear in a print issue of the *Journal of Biological Chemistry* in November.

"The complexity of HIV has for long thwarted development of an effective HIV vaccine. Our findings open a new path toward an effective preventative and therapeutic vaccine," said Sudhir Paul, Ph.D., the study's senior author and a professor in the Department of Pathology and Laboratory Medicine at The University of Texas Medical School at Houston. "The new antigen is a prototype vaccine. This prototype successfully eliminates nature's restrictions on the production of broadly-neutralizing antibodies to HIV by the immune system."

Thirty-three million people were living with HIV at the end of 2007, according to the World Health Organization. That same year, nearly 3 million people became newly infected, and 2 million died of acquired immunodeficiency syndrome or AIDS, which occurs at the most advanced stages of HIV infection. Vaccines work by introducing an antigen into the body, which spurs the immune system to produce

antibodies that guard against infection. Previously-tested HIV vaccine candidates stimulated vigorous production of antibodies to the mutable segments of the virus envelope. But, these vaccine candidates did not stimulate the production of antibodies to the regions essential for virus attachment to host T cells, the process that initiates infection.

Scientists in Paul's laboratory used a chemically-activated form of the HIV envelope protein gp120 to stimulate the production of mouse monoclonal antibodies that block infection of cultured human cells by genetically-diverse HIV strains from around the world. Paul said these same antibodies can be found in humans who remain free of AIDS despite long-term HIV infection. "HIV infection itself stimulates production of this class of antibodies, but the amount is too small to control infection. The challenge is to boost production of the protective antibodies in humans using a vaccine."

Because of the genetic variability of HIV, most antibodies fail to stop infection initiated by thousands of different HIV strains responsible for the pandemic. "Dr. Paul's team has developed a revolutionary antibody technology and used it to overcome major obstacles to a vaccine for HIV. They identified antibodies that neutralized 100 percent of strains drawn from the major viral subtypes. Furthermore, they have developed ways to immunize animals to produce them. No previous vaccine candidate has even approached these objectives," said Robert L. Hunter, M.D., Ph.D., professor and chairman of the Department of Pathology and Laboratory Medicine at the UT Medical School at Houston.

The vaccine prototype builds on Paul's earlier discovery that a tiny stretch of amino acids numbered 421-433 in gp120 can serve as the Achilles heel of HIV. "Unlike the changeable regions of its envelope, this region must remain constant to attach to T cells. Equally important, HIV can survive only if the body's immune system fails to produce antibodies to this region. The virus minimizes production of antibodies

to the vulnerable region because it also silences B lymphocytes, the cells responsible for producing antibodies," Paul said. "In nature, microbial antigens stimulate antibody synthesis when they bind antibodies on the surface of B cells by weak noncovalent forces. In the case of HIV, noncovalent binding of its cell attachment site induces a state of B cell tolerance, permitting infection to proceed unchecked. Our covalent vaccination approach breaks the tolerance and stimulates production of antibodies that inactivate the virus."

The tolerance signal is converted to a stimulatory signal because strong covalent binding to the B cells liberates a large amount of energy that is not available in traditional binding reactions, Paul said. Moreover, the prototype vaccine contains two modular antigenic regions. Binding of one region generates a stimulatory signal that overcomes the tolerance signal.

"There is another advantage. B cells have the unique capability of producing antibodies adapted to recognize the chemical groups we placed in the prototype vaccine. The adaptations impart enzyme-like activity to the antibodies, which results in exceptionally stable HIV binding, and sometimes, in catalytic breakdown of the viral coat. Consequently, the antibodies inactivate HIV effectively," Paul said.

"The failure of previous HIV vaccine trials has produced pessimism about the prospect of effective HIV vaccination. Our approach is promising but additional studies are necessary. To expedite development of the vaccine, we must maximize the antibody response and focus it even more at the HIV cellular attachment site," said Yasuhiro Nishiyama, Ph.D., lead author and an associate professor at UT Medical School.

"While the prototype vaccine induces antibodies that neutralize infection of isolated human cells, we must also show that the antibodies prevent

the natural process of infection within the body," said Stephanie Planque, Ph.D., co-author and researcher in Paul's laboratory.

"The induction of antibodies that neutralize infection of human blood cells by diverse strains of HIV from various parts of the world is an important milestone. This is an entirely new vaccination approach that might bypass the natural constraints on developing effective immunity against HIV," said Carl Hanson, Ph.D., study co-author and head of the Retrovirus Diagnostic Section of the Viral and Rickettsial Disease Laboratory of the California Department of Public Health.

More information: The journal article is titled "Towards Effective HIV Vaccination: Induction of Binary Epitope Reactive Antibodies with Broad HIV Neutralizing Activity."

Source: University of Texas Health Science Center at Houston (news : web)