Scientists devise approach that stops HIV at earliest stage of infection

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Their study, which appears this week in the online Early Edition of the Proceedings of the National Academy of Sciences (PNAS), may re-energize attempts to create a preventive/therapeutic vaccine against HIV, say the authors. To date, more than a dozen candidate vaccines, which have attempted to raise immunity against the spiky proteins on the viral envelope, have all failed in clinical testing.

The investigators have created devices they call glycodendrons that are designed to do two things at once: inhibit the transport of HIV from where it traditionally enters the body, preventing it from moving deeper inside where it can infect immune cells; and set up an immune antibody response to a unique carbohydrate structure on the surface of the virus.

“This paper is about a new direction in HIV vaccine design,” said the study’s lead investigator, Scripps Research Chemistry Professor Chi-Huey Wong. “Results we have so far are very promising.”

To date, he says the devices have been able to stimulate the immune system of mice to induce antibodies against HIV surface glycoprotein, and, in laboratory studies, have been able to block the virus from infecting immune cells.

Targeting One Multi-Purpose Area on HIV

This new approach capitalizes on two recent findings in the field of HIV

research. One is the discovery that HIV takes a Trojan horse approach to reach cells it needs to infect deep inside the human body. Scientists have described how, when the virus enters the body through sexual contact, it hitches a ride with the dendritic cells of the immune system that stand guard for invaders at the mucosal lining of tissues. The virus outsmarts these cells, however, and latches onto a particular receptor protein, known as DC-SIGN, on the dendritic cells. By sticking to these immune system fighters, HIV manages to evades immune detection while the dendritic cells travel to the ultimate goal of the virus: immune T-Cells in the lymphoid system, which HIV then invades, setting up a deadly infection that spreads.

The second discovery is that an antibody exists that can signal immune destruction of the virus. The antibody, 2G12, protects people who have it against HIV progression, but very few of those who are infected put up such an immune reaction, said the study's first author, Sheng-Kai Wang, a graduate student in Wong's laboratory. Scientists at Scripps Research have defined the details of the action of the antibody and found that recognizes a dense cluster if sugars on one region of the virus's spiky protein coating—which is, strikingly, the same area that HIV uses to bind to the DC-SIGN protein on dendritic cells.

Earlier, Scripps Research Professor Dennis Burton, a co-author of this study, and Wong designed and tested synthetic constructs to mimic the clusters of sugars recognized by 2G12 that could form a vaccine. Wong invented a process he calls programmable one-pot synthesis that allows him to quickly assemble many types of carbohydrate structures by placing a large number of chemical building blocks into a reaction vessel to make sequential chemical reactions.

So the Scripps Research team built a dendron structure that can bind to the DC-SIGN protein, preventing HIV from doing so, and which also mimics the sugar clusters that 2G12 binds to, prompting the immune

system to produce destructive antibodies to the viral coat. “The sugar structure is able to inhibit HIV from binding to DC-SIGN on dendritic cells in vitro," Wong said. "But to become a vaccine, as tested in mice, the sugar structure has to be attached to a carrier as the sugar structure alone is too small and too weak to be used as a vaccine. The sugar-carrier conjugate will also inhibit HIV from binding to DC-SIGN.”

The researchers say the next step in the research is to test if the dendron antibody can target the surface coating of different kinds of HIV strains in order to evaluate the potential of the vaccine strategy.

Source: Scripps Research Institute