

# Can engineered immune cells stop AIDS?

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Twenty years after its introduction, gene therapy still holds great promise as a way to harness the insidious power of viruses such as human immunodeficiency syndrome (HIV). But scientists have yet to solve a vexing problem: developing an efficient transport system that is capable of delivering therapeutic payloads to specific cells.

As challenging as the problem has been, researchers in the USC Viterbi School of Engineering may be turning a corner. With support from a \$13.9 million grant from the Bill and Melinda Gates Foundation, a multi-institutional team of scientists, including Pin Wang of the USC Mork Family Department of Chemical Engineering and Materials Science, is exploring a completely new way of manipulating the body's natural defense system.

"Rather than focusing on conventional vaccines that boost the immune system, we are experimenting with a way to help the immune system produce antibodies that can neutralize the virus," says Wang. "If we can design a modified virus that will deliver these antibodies to chosen cells, we will be able to insert DNA that will help rather than harm cells."

Viruses are efficient carriers or transport vehicles in the body because they are naturally able to penetrate cells, inserting the genetic material they contain into their new host. By itself, a virus cannot reproduce; it must infect a cell and take control of the host's machinery to make copies.

HIV also possesses an unusual structure and a keen ability to hide from

antibodies in a sugar-coated shield. The shield has very few open spaces on its surface, Wang says, which makes it virtually impossible to penetrate. And because the virus also has an uncanny ability to hide, HIV often goes virtually unnoticed by neutralizing antibodies that are roaming the body in search of foreign invaders.

Faced with such a clever adversary, Wang wants to synthetically alter the HIV invaders and use their hollow shells as delivery vehicles to insert DNA that will counteract the infection.

The "Cadillac" of this gene delivery system is an HIV-based "lentiviral vector," a type of retrovirus that uses the backbone of a virus to infect both dividing and nondividing cells. Wang says lentiviral vectors are very efficient delivery vehicles for human cells.

Collaborators on his project are targeting hematopoietic stem cells -- the bone marrow cells that form blood cells -- to create B lymphocytes. The researchers want to reprogram these bone marrow cells by adding genes that will instruct the cells to produce rare antibodies such as B12, 4E10, 2G12 and 2F5. Wang says these antibodies are known to neutralize the virus.

"In laboratory tests, we remove harmful genes coding for the HIV virus and engineer the backbone, or spine, of virus so that it is no longer replicable " he says. "Once manufactured recombinantly, this modified virus -- the lentiviral vector -- becomes a natural delivery system that can transport useful genes into cells without causing illness."

Although the gene delivery technique looks promising, researchers are still working on ways to manipulate these elusive bone marrow cells and get them to generate "designer immune cells." Another problem seems to be making sure lentiviral vectors target only hematopoietic stem cells, and not other types of cells, to achieve the desired targeted delivery.

With a group of USC biomedical engineering students and Caltech biologists, Wang is experimenting with CD20 as a target antigen for human B cells. His strategy, published in the August 1, 2006 issue of *Proceedings of the National Academy of Sciences*, targets the human B cells only. After two years of experimentation, the team has been able to demonstrate that they can specifically target human B cells in mice.

"Possibly the most important implication of the work is that gene therapy could now be carried out as an inexpensive procedure, able to be considered even in the less-developed world," Wang and his coauthors wrote.

That's good news for the World Aids Foundation, which announced on World AIDS Day (Dec. 1, 2006) that the disease is on the rise again. More than 39 million people around the world are now infected with HIV, the foundation reported.

"I think we are finally on the right track," Wang says. "If scientists can find a way to genetically engineer immune cells to neutralize HIV, we may be able to develop immunotherapy for HIV-Infected people, as well as find ways to prevent it all together."

Source: University of Southern California

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