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# Vaccine Pulse

WITH A NEW DELIVERY TECHNOLOGY, DNA-BASED VACCINES MAY JUST GET A SHOT IN THE ARM

by Chael Needle

**W**hile traditional vaccines have successfully used various versions of a virus to give the body a head start in recognizing an antigen and forming an immune response in the form of antibodies, a new generation of vaccine candidates is looking to tap the potential of antigen-coded DNA fragments to elicit immune responses against diseases for which vaccine development has stalled, such as cancers and chronic infectious diseases like HIV. DNA-based vaccines are thought to be less expensive to manufacture as well as more amenable to accelerated development than traditional vaccines, but it is their potential for increased clinical benefit due to the induction of cell-mediated immune responses and expanding the self-teaching power of the immune system that has captured the attention of the research community.

"It just makes so much sense to be able to use your own immune system to be able to fight disease, once you have it, and even more sense to use your immune system to be ready to fight it in case it does show up," says Avtar Dhillon, MD, director, president, and CEO of Inovio Biomedical, a company dedicated to developing multiple DNA-based immunotherapies for various targets, including hepatitis C and HIV.

To make a DNA-based vaccine, you deliver DNA into human tissue, predominantly muscle, and allow the muscle to produce a component of the virus or cancer—one or more proteins uniquely related to a specific virus or cancer but do not function or permit replication. "By identifying a key protein, whether it's in cancer, like a PMSA [prostate member specific antigen], or from a virus such as gag, pol, or nef in the case of HIV, putting the DNA that codes for these proteins into the muscle or skin, letting those tissues make the protein, and then letting that protein trigger specific antibody and T-cell responses, you now have an immune system that's highly charged to attack what it has been trained to attack. The vaccine has fired up both sides of the

immune system—the antibodies *and* the T cells—and now [they] are looking for that target protein..." he says.

A new approach is necessary, he notes, in part because the traditional approach was limited in its ability to keep up with the ever-evolving HIV. "So what we look for are proteins that are not only stable through different clades and strains, and that are not going to evolve significantly over many, many years...[T]he other thing we look at is how broadly are they seen in different strains or clades. That allows us to be able to make broader vaccines that can be useful for years and years and in many geographic locations rather than having to constantly change them..." he says.

Inovio has wed an innovative delivery technology called electroporation to DNA-based vaccines and other immunotherapies. Using controlled, millisecond electrical pulses to create permeability in the cell membrane, electroporation has been shown to dramatically enhance the uptake of injected biological materials, such as the DNA, by 1,000 times or more.

Electroporation is a delivery technology that has potential across multiple targets. "If you look at all the steps involved, it's only the final result that is different. And the final result is different because you are going after different targets. The delivery technology platform evolved out of a response to a need for better immune responses and fewer side effects from DNA-based vaccines that did not rely on this delivery method. "Not only have we overcome the side effects and the [delivery] issues, we have shown tremendous augmentation of the immune response to the antigens encoded by the DNA, which is exactly what you want. Now what we are seeing is fantastic antibody responses and T-cell responses that are suggestive of being able to reach therapeutic and preventative potential." Inovio's research has attracted pharmaceutical, academic, governmental and other HIV/AIDS-related research agencies, and the company extended the licensing of its proprietary devices to the International



AIDS Vaccine Initiative (IAVI). The biotech has also attracted some of the community's top researchers, including Dr. David Weiner, one of the leaders in cutting-edge DNA vaccine research.

Having already established electroporation as safe and tolerable, researchers are forging ahead, looking at different cancers, CMV, and biodefense targets. A prostate cancer trial at the University of Southampton in the UK using electroporation to deliver DNA coded for the PSMA antigen has shown some very good T-cell and antibody responses, notes Dr. Dhillon. Additionally, a trial in Sweden is studying hepatitis C virus, logging promising early results that show not only T-cell and antibody responses but a reduction in viral load. Trials using electroporation that are successful will bode well for establishing proof of concept for the delivery system, and DNA vaccines for multiple potential targets, including HIV. Says Dr. Dhillon: "In my opinion, based on the type of immune responses we have seen, it's just a matter of sort of tweaking the DNA and making sure that you have the right protein. Once you overcome the first hurdle—DNA delivery and induction of pathogen-specific antibody and T cells—in my opinion eighty percent of the battle is won..."

Chael Needle wrote about treatment updates presented at the International AIDS Conference in the September issue.

PHOTO COURTESY INOVIO