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RESEARCHERS DEVELOP A NEW METHOD FOR IMMUNIZATION USING A "GENE GUN"

DALLAS--March 12, 1992--Researchers at The University of Texas Southwestern Medical Center at Dallas are using a "gene gun" to shoot DNA-coated microprojectiles directly into the cells of animals, provoking an immune response to the proteins generated by the foreign DNA. The researchers say this technique may lead to new ways of immunizing individuals against viral infections; at the very least, it is a new way of manipulating the immune system and of changing the genetic constitution of cells.

"This is so new that we don't know all the possible applications for this technique," said Dr. Stephen Johnston, associate professor of internal medicine and biochemistry at UT Southwestern. "A lot of our colleagues thought the idea was a little crazy when they first heard what we were attempting because the premise was so simple. It's a new angle in approaching the immune system."

Johnston, along with Cornell University collaborators Dr. John Sanford and research associate Michael DeVit, created the hand-held device after years of tinkering. This group also helped to develop a somewhat similar, but larger device, that is currently being used by plant molecular biologists to increase the growth potential of crops.

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THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER
OFFICE OF MEDICAL INFORMATION
5323 HARRY HINES BOULEVARD DALLAS, TEXAS 75235-9060
TELEPHONE (214) 688-3404 FAX (214) 688-8252

CONTACT: Lynn Gentry
(214) 688-3404

Johnston and Dr. De-Chu Tang, assistant instructor of internal medicine at UT Southwestern, have now used their gun in genetic immunization experiments. Their research findings are reported in the March 12 issue of Nature.

According to the article, they inoculated mice in their ears with gold pellets coated with DNA fragments from a human gene. Nearly 88 percent of the mice produced antibodies against the protein produced by the human growth hormone gene. Based on these early findings, they postulated that it might be possible to provoke immune responses to viral infections, such as the one that causes acquired immune deficiency syndrome, or AIDS.

The gun, or "wand," as Johnston calls it, is about the same size and shape as a soft-drink can. It uses high-pressure helium gas to propel tens of thousands of microscopic DNA-coated pellets. The pellets are made of gold because it is dense enough to penetrate the cells and it is biologically inert. The pellets travel at about the same speed as a bullet fired from a high-powered rifle, about 3,000 feet per second, but the wand is designed so that much of the pressure is deflected away from the target, minimizing the damage done by the blast of helium. The pellets penetrate 10 to 20 cell layers deep, according to Johnston, and despite their speed, they do not destroy the cell membranes because the membranes quickly reseal themselves.

He said no specific cellular target within cells has to be selected for the gene transfer process to work because once the DNA is inside a cell, it is recognized as DNA and carried into the nucleus. In some instances, the DNA is incorporated into the cell's own DNA and the interloper begins generating the protein it was designed to produce. As these foreign proteins make their way to the cell surface and present themselves as antigens, the body's immune system produces antibodies to the foreign proteins, even though the animal's own cells are making them. Johnston said only 10 to 20 percent of the cells

in a bombarded area will express the particular gene introduced, but that is still enough to provoke an immune response.

Once the body has dealt with the invader, a few members of the immune system, called memory cells, will retain their knowledge of the battle and act as sentries against future attacks by the same virus. A second infection by the real virus would then be dealt with more swiftly and thoroughly; thus the researchers call their technique "genetic immunization."

Conventional vaccines are created by isolating a particular virus or protein of the virus and inoculating an animal with it. Once the animal has been exposed to the protein, the animal's memory cells will be able to initiate another immune response if the animal is exposed to the virus in the future. Johnston said genetic immunization is different from the conventional method in that DNA, rather than a protein, is injected. Also, genetic immunization probably exposes the animal to the foreign protein for a longer period of time than the conventional vaccination. Injected proteins also are cleared from the body quicker.

"Our immunization technique may have advantages over the standard immunization method because it more closely resembles a natural infection and may stimulate a stronger immune response," said Johnston. "We've also measured a much more sustained immune response, apparently because daughter cells from the original cell may carry the foreign gene fragment with them through each successive generation to keep the immune system stimulated longer." Because some viruses might require a sustained immune response in order to eradicate an infection, Johnston feels this aspect of genetic immunization might be clinically significant.

"Vaccinating an individual against AIDS would involve selecting the DNA fragment or fragments that are responsible for provoking an immune response to the virus and inoculating an individual with those fragments," said Johnston.

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"There's probably years of work to be done before this or other clinical applications could be attempted."

Johnston said they will continue refining their genetic immunization technique for use in humans. In the future, he speculated, the gene gun might be used to treat various cancers, certain forms of arthritis or even to enhance the outcome of vascular surgery by injecting genes that will help blood vessels remain unclogged.

The research was supported by grants from the National Institutes of Health, the Perot Family Foundation and the Moss Heart Trust.

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NOTE: The University of Texas Southwestern Medical Center at Dallas comprises Southwestern Medical School, Southwestern Graduate School of Biomedical Sciences, Southwestern Allied Health Sciences School, affiliated teaching hospitals and outpatient clinics.