DNA Technology May Revolutionize Flu Vaccine

BY DOUG BRUNK

The way Dr. Joseph Kim sees it, the field of influenza vaccine development could use an extreme makeover.

"Every year, three flu strains are selected by the flu experts around the world, which determines which strains the vaccine makers should make and stock for the coming fall," Dr. Kim, president and CEO of San Diego–based Inovio Biomedical Corp., said in an interview. "They can guess right, or they can guess wrong; but every year, you have to change the vaccine. You can't stockpile from the previous year, because the flu strains could change."

Scientists don't accept this approach for most other common vaccines, he noted, including the one for measles, mumps, and rubella. "That doesn't get changed from year to year, but our society has accepted the fact that the one for influenza does," he said.

Dr. Kim would like to change that paradigm.

Since 2005, he and his associates at Inovio have been developing DNA-based influenza vaccines capable of providing broad protection against existing as well as newly emerging, unknown seasonal and pandemic influenza strains. To design vaccines, the company developed a process known as SynCon, a way of targeting consensus proteins from multiple strains of H1N1, H2N2, H3N2, and H5N1, "which have collectively caused greater than 90% of all seasonal and pandemic flu events in people in the last 100-plus years," Dr. Kim said. "We felt that those were very good targets."

What separates Inovio's SynCon approach from that of other DNA vaccine manufacturers is that the SynCon vaccines demonstrate potential to protect against new strains of influenza that do not specifically match the vaccine.

"So, if the 2009 H1N1 virus mutates, there is no plan B," Dr. Kim said. "There is no backup option; 2009 swine flu could be a big problem or not. No one can predict accurately."

Origins of an Alternative

DNA-based influenza vaccines began to draw serious attention about 6 years ago, when infectious diseases experts around the globe expressed concern about a pandemic of H5N1 influenza virus, noted Dr. William Schaffner, chair of the department of preventive medicine at Vanderbilt University, Nashville, Tenn.

"That galvanized the international community," he said. "Since that time, the United States government and private capital have gone into research to develop more improved influenza vaccines and to improve the vaccine technology. There has been more research into those areas in the past 5 or 6 years than there has been in the previous 50 years. That's stunning."

The concept of DNA vaccines first emerged in the early 1990s, when researchers discovered that immunizing animals with plasmids—a circular string of DNA that encodes for a specific antigen or vaccine target—generates vaccine responses.

"The beauty of this technology is speed," said Vijay B. Samant, president and CEO of San Diego–based Vical, which develops DNA vaccines. "It's not cell culture. It's not egg-based. It's simple fermentation and two purification steps. It does not require the manufacturer to handle the pathogen. All it needs is a gene sequence; that's good enough for us to make the vaccine."

"Instead of delivering the viruses themselves in some form, you're taking a very simple plasmid, which is a circular string of DNA, and you're putting in a genetic blueprint designed for a specific target, in this case hemagglutinin," Dr. Kim explained. "Once you inject that into muscle cells or skin cells, it uses our own cellular machinery to manufacture those proteins as antigens, and presents them in a customized way. It's like mimicking viral infection without the side effects and replication. DNA vaccines can never replicate. They do not infect; they do not cause disease, ever."

Delivery Poses Challenges

Until recently, Dr. Kim and other researchers in the field faced a barrier to the advancement of DNA vaccines: inefficient delivery.

However, a technology developed in the 1990s known as in vivo electroporation is proving to be an effective way to deliver DNA vaccines.

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DR. KIM

Electroporation works like this: After a DNA vaccine is injected into the upper arm or into skin, a short, controlled electrical pulse is delivered into that tissue, either from the same needle or from a surrounding needle. This brief pulse of current "coaxes the cell membranes to open up their pores," Dr. Kim said. "That brings in the DNA. We remove the electric field and the pores close up. This has been shown in animal species to be effective in up to a 1,000-fold increase in DNA vaccine uptake. The whole procedure takes a couple of seconds."

Not all DNA vaccine manufacturers are using electroporation as a delivery method. Vical, the first company to produce a vaccine against the pandemic influenza A(H1N1) virus after initial reports of outbreaks in Mexico, uses a patented adjuvant known as Vaxfectin, "which does an amazing job of protecting the DNA before it enters the skeletal muscle cells," Mr. Samant said. "Being a proinflammatory, it attracts the immune system toward the site of the injection to facilitate creation of the right immune response and immune memory."

Phase I Trials Begin

On Oct. 1, 2009, the U.S. Navy awarded Vical a contract to support a phase I clinical trial of its vaccine against H1N1 influenza. "Our goal is to get that trial done by later this year," Mr. Samant said.

In a virus challenge and protection study of Inovio's SynCon H1N1 vaccine, mice were injected with the H1N1 virus that caused the 1918 Spanish flu. Mice that received the H1N1 vaccine were completely protected from the virus, whereas all of the unvaccinated animals died within 1 week.

In 2010, the SynCon H5N1 vaccine will undergo human testing in healthy volunteers, followed by tests in combination with the SynCon H1N1 vaccine. Addition of H2N2 and other strains could soon follow.

Potential Pitfall

"If we are correct, we can revolutionize how flu vaccines are made and delivered," Dr. Kim said.

One potential pitfall of the DNA vaccine technology is the impending backlash from vaccine naysayers, cautioned Dr. Schaffner.

"We have a hardcore group of vaccine skeptics," he said. "This is a group of people who look askance at vaccines, are dubious about their benefits, and are concerned about how they're manufactured and what's in them. Any innovation, whether it is the addition of an adjuvant, or a new technology such as this, will come to their attention and draw some of their skepticism and opposition. We have to brace for this."

Dr. Schaffner disclosed that he has been a consultant for various vaccine manufacturers. He also is a member of a data safety committee for Merck for experimental vaccines. ■

Heart Failure Patients Need Better Influenza Protection

BY DIANA MAHONEY

BOSTON — Patients with heart failure do not maintain protective levels of antibody titres following influenza vaccination, leaving this already at-risk population even more vulnerable to influenza-related complications, according to a study presented at the annual scientific meeting of the Heart Failure Society of America.

To determine whether heart failure patients sustain postvaccination influenza seroprotection throughout the flu season, Orly Vardeny, Pharm.D., of the University of Wisconsin at Madison, and colleagues evaluated 62 heart failure patients (median age 57) and 40 healthy controls (median age 49) during the 2006-2007 and 2007-2008 influenza seasons. The investigators measured serum antibody production via hemagglutination inhibition assay before influenza vaccination and 2-4 weeks and 6 months after vaccination, and compared antibody titers to individual vaccine viral strains after flu season to measure the persistence of antibody response.

All participants showed early antibody seroprotection, defined as postvaccination hemagglutination inhibition (HAI) antibody titer greater of at least 40, with similar rates of seroconversion between the heart failure patients and the healthy controls. Antibody titers decreased over time in both groups throughout the influenza season, said Dr. Vardeny. But the decreases observed among the healthy controls did not drop below the threshold of protective levels, whereas those observed in the heart failure patients did, "which made the heart failure patients more susceptible to influenza," she said.

Specifically, titer levels to the A(H3N2) viral strain fell from a peak of 320 to 60 post season in the healthy controls and from 160 to 30 in the heart failure patients, and titer levels to the A(H1N1) strain fell from 160 to 80 in the healthy controls and from 60 to 30 in the heart failure patients, Dr. Vardeny reported. Titers to the less virulent B-type strain fell similarly in both groups, she noted.

In a study published earlier this year, Dr. Vardeny and her colleagues identified differences in immune responses to influenza vaccination in heart failure patients compared to healthy controls. The investigators determined that patients with heart failure had higher vaccine-induced interleukin-10 concentrations, suggesting a different cytotoxic T-lymphocyte phenotype for vaccine responses, and that heart failure patients mounted a less vigorous antibody immune response to the newest vaccine viral strain than did the healthy controls (J. Card. Fail. 2009;15:368-73).

The findings may help explain the reduced efficacy in heart failure patients of the vaccine targeting the more powerful influenza A strain and they highlight the need for a solution, said Dr. Vardeny. "It's clear that people with heart failure, who are already at risk for influenza-related complications, need better protection against influenza," she said. Possible solutions that should be considered include higher doses of the vaccine, which might offer season-long seroprotection, or mid-season booster shots, she suggested.

Dr. Vardeny reported having no financial relationships to disclose. ■