DNA Technology May Revolutionize Flu Vaccine

BY DOUG BRUNK

The way Dr. Joseph Kim sees it, influenza vaccine development needs 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," 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." He wants 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.

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 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."

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.

"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," said Dr. Schaffner.

The concept of DNA vaccines first emerged in the early 1990s, when academic scientists 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 viruses, "you're taking a very simple plasmid . . . and you're putting in a genetic blueprint designed for a specific target, in this case hemagglutinin," Dr. Kim explained. Once injected, "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.

Electroporation works like this: After a DNA vaccine is injected via syringe into the upper arm or into skin, a short, controlled electrical pulse is delivered directly into that tissue. This "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."

Not all DNA vaccine manufacturers are using electroporation.

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."

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DR. KIM

Phase I Trials Begin

In October, 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.

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. "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 has been a consultant for various vaccine manufacturers. He also is a member of a data safety committee for Merck for experimental vaccines. ■