# Scientists advance universal flu vaccine

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A universal influenza vaccine - so-called because it could potentially provide protection from all flu strains for decades - may become a reality because of research led by scientists from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

In experiments with mice, ferrets and monkeys, the investigators used a two-step immunization approach to elicit infection-fighting antibodies that attacked a diverse array of influenza virus strains. Current flu vaccines do not generate such broadly neutralizing antibodies, so they must be re-formulated annually to match the predominant virus strains circulating each year.

The research, led by NIAID scientist Gary J. Nabel, M.D., Ph.D., appears online ahead of print July 15 issue of Science Express.

"Generating broadly neutralizing antibodies to multiple strains of influenza in animals through vaccination is an important milestone in the quest for a universal influenza vaccine," says NIAID Director Anthony S. Fauci, M.D. "This significant advance lays the groundwork for the development of a vaccine to provide long-lasting protection against any strain of influenza. A durable and effective universal influenza vaccine would have enormous ramifications for the control of influenza, a disease that claims an estimated 250,000 to 500,000 lives annually, including an average of 36,000 in the United States."

In parallel experiments with mice, ferrets and monkeys, Dr. Nabel and

his colleagues first primed the animals' immune systems with a vaccine made from DNA encoding the influenza virus hemagglutinin (HA) surface protein. After being primed with DNA vaccine, the mice and ferrets received a booster dose of the 2006-2007 seasonal influenza vaccine or a vaccine made from a weakened cold virus (an adenovirus) containing HA flu protein. Monkeys were boosted with the seasonal flu vaccine only.

This prime-boost vaccine stimulated an immune response to the stem of the lollipop-shaped hemagglutinin of influenza virus. Unlike HA's head—which mutates readily, allowing the virus to become unrecognizable to antibodies—the stem varies relatively little from strain to strain. In principle, Dr. Nabel explains, antibodies generated against the stem of HA should be able to recognize and neutralize multiple flu strains.

Although the DNA in the priming vaccine was derived from a 1999 circulating flu virus, all the animals made antibodies capable of neutralizing virus strains from several other years. Mice and ferrets produced antibodies not only against virus strains dating from before 1999, including a strain that emerged in 1934, but also against strains that emerged in 2006 and 2007.

Moreover, although the prime-boost vaccines were both made from H1 subtypes of influenza A virus, the antibodies they generated neutralized other influenza subtypes, including H5N1 (avian influenza) virus. This indicates that a prime-boost strategy potentially could confer immunity to many or all subtypes of influenza A, says Dr. Nabel.

In another set of experiments, the scientists measured how well the prime-boost vaccine protected mice and ferrets from infection with deadly levels of flu virus. Three weeks after receiving the boost, 20 mice were exposed to high levels of 1934 flu virus, and 80 percent survived.

Mice receiving DNA only, seasonal flu vaccine only or a sham prime-boost vaccine all died.

The researchers saw similar results when they tested several prime-boost combinations in ferrets, which are considered a good animal model for predicting flu vaccine efficacy in humans. All four ferrets that received a DNA prime-seasonal boost were protected from infection with a 2007 virus strain, while all six ferrets that received the DNA prime-cold virus boost combination were protected from the 1934 influenza virus.

Collaborators on these studies included Terrence Tumpey, Ph.D., of the Centers for Disease Control and Prevention.

"We are excited by these results," says Dr. Nabel. "The prime-boost approach opens a new door to vaccinations for influenza that would be similar to vaccination against such diseases as hepatitis, where we vaccinate early in life and then boost immunity through occasional, additional inoculations in adulthood."

Trials of prime-boost influenza vaccines assessing safety and ability of the vaccine to generate immune responses are already under way in humans, Dr. Nabel adds. The information from the new research will be valuable in selecting candidates to move forward into large-scale trials, he says. "We may be able to begin efficacy trials of a broadly protective flu vaccine in three to five years."

**More information:** C-J Wei, et al. Induction of broadly neutralizing H1N1 influenza antibodies by vaccination. Science DOI: 10.1126/science.1192517 (2010).

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