Prospects improve for long-lasting flu vaccine

Each year, vaccine companies gamble on the flu strain they expect to make the most people sick in the coming season and develop a new influenza vaccine to protect against it. The strategy involves a risky calculus, so researchers have turned to targeting nonmutating components of the virus with an eye to forging a universal flu vaccine capable of providing lasting protection from a single shot.

"The hope is that if we make and develop a vaccine based on these conserved [regions], then the vaccine would last longer than just one year," says Peter Palese, a virologist at Mount Sinai School of Medicine in New York.

Last month, for example, Palese and his colleagues reported that injecting mice with a synthetic peptide derived from the conserved portion of a particular viral protein induced cross-reactive immunity against a trio of divergent flu strains (*Proc. Natl. Acad. Sci. USA* **107**, 18979–18984, 2010). A similar approach was also adopted earlier this year by researchers who engineered bacteria to express a viral protein and observed that it also provided protection against flu infections in mice (*Proc. Natl. Acad. Sci. USA* **107**, 13701–13706, 2010).

Both of these strategies targeted the hemagglutinin protein—the 'H' in H1N1—which helps the flu virus enter cells. More specifically, the newer vaccines target the relatively stable stalk of the hemagglutinin protein; in contrast, most seasonal flu jabs are directed against the molecule's head, which is about ten times more variable.

In another tactic, a team led by Gary Nabel, director of the Vaccine Research Center at the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, vaccinated mice and ferrets with plasmid DNA encoding complete hemagglutinin, followed by a booster shot containing a disabled cold virus also encoding the same protein. Reporting this summer, the researchers showed that this consecutive immunization strategy yielded broadly neutralizing and protective antibodies that were directed against the protein's conserved stem (*Science* **329**, 1060–1064, 2010).

But there are other flu proteins that remain relatively constant that researchers are also trying to target. Two of the leading candidates are nucleoprotein, which is involved in viral replication, and the matrix-2 protein, an ion channel protein found in the viral envelope of every influenza type A strain.

istockphoto

Less is more: Immunologists strive to develop a universal, enduring flu shot.

Previous research had shown that immunizing with either protein on its own provided partial protection against diverse flu strains, but now scientists have combined the two proteins into a single dose to elicit rapid and lasting protection. "What you need is synergism," says Hildegund Ertl, director of the Wistar Institute Vaccine Center in Philadelphia. "It's a no brainer. Two immune responses perform better than one immune response."

In September, Ertl and her colleagues reported that the nucleoprotein fused to an engineered cold virus expressing part of the matrix-2 protein taken from three different strains triggered a strong and cross-reactive immune response (*Mol. Ther.* doi:10.1038/mt.2010.202, 2010). Independently, a month later a team led by Suzanne Epstein, associate director for research at the US Food and Drug Administration's Office of Cellular, Tissue and Gene Therapies in Rockville, Maryland, reported that mice vaccinated through the nose with a different cold virus expressing conserved portions of both proteins were protected from diverse viral challenge for close to a year (*PLoS One* **5**, e13162, 2010).

Wayne Marasco, an immunologist at the Dana-Farber Cancer Institute in Boston who is developing vaccines targeted at both hemagglutinin and the protein neuraminidase, expects some amalgam of approaches to be the most effective. "Viruses are very clever, and putting all your eggs in one basket is going to be problematic," he says. One combinatorial approach that has already completed a phase 1 human trial is being developed by Vical, a San Diego biotech with a plasmid-based vaccine that targets hemagglutinin, nucleoprotein and the matrix-2 protein (*Vaccine* **16**, 2565–2572, 2010).

But Nabel, who co-wrote a commentary about universal flu vaccines on page 1389 of this journal, warns that such multiprotein approaches can sometimes lead to reduced immune responses against each of the antigens. "When you do combinations of vaccines, you can't be guaranteed that the whole is equal to the sum of the parts, let alone greater," he says.

Regardless of which conserved proteins researchers choose to target, none of the experimental vaccines currently being advanced would be truly universal, notes Richard Compans, a virologist at the Emory Vaccine Center in Atlanta, because the products under development only target parts of influenza type A viruses, but not influenza type B, the other viral type typically targeted by seasonal flu jabs. "We would still need to do something to incorporate a protective component against that virus as well," he says.

Elie Dolgin

© 2010 Nature America, Inc. All rights reserved.