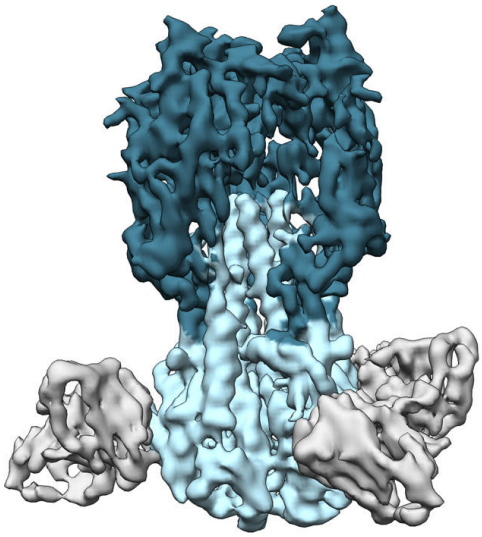

Seasonal flu vaccines induce antibodies against the “head” (slate) of the influenza surface protein hemagglutinin, but a new universal vaccine triggers antibodies (fragments of them shown in gray) that bind to the stalk (light blue) portion. JULIANNA HAN/WARD LAB/SCRIPPS RESEARCH

Innovative universal flu vaccine shows promise in first clinical test

By **Jon Cohen** | Dec. 7, 2020 , 10:20 AM

For epidemiologists, the COVID-19 pandemic has greatly intensified their long-standing nightmare about another virus: the emergence of a new and deadly strain of flu. A universal flu vaccine, effective against any strain of the influenza virus that can infect humans, could protect us from this peril, but progress has been slow. A novel concept for one universal vaccine candidate has now passed its first test in a small clinical trial, its **developers report today** in *Nature Medicine*.

“This is an important paper,” says Aubree Gordon, an epidemiologist at the University of Michigan School of Public Health who studies influenza transmission and vaccines.

The influenza virus rapidly accumulates mutations and easily “reassorts,” or swaps, genes between strains, creating variants that can dodge any past immunity people had acquired naturally or from vaccines. That’s why a new flu vaccine must be developed each year.

Existing flu vaccines contain weakened or inactivated influenza viruses with a mix of hemagglutinins (HAs), the proteins that stud their surfaces. These vaccines primarily aim to trigger antibody responses against HA's top part, or head. Genetic changes in flu viruses rarely alter most of the head. But a small part of the head does reassort, or mutate, frequently, which allows new viral strains to dodge any immune memory and forces flu vaccinemakers to prepare new formulations each year, with updated HAs.

HA's bottom portion, or stalk, is less apt to vary, and epidemiological studies have shown people who have been exposed to an influenza strain and developed antibodies to the stalk can ward off a wide variety of other strains. So, the new universal flu vaccine candidate, one of a handful in development, puts HA's stalk front and center. The study shows for the first time that "you can develop a vaccine strategy that produces stalk-reactive antibodies in humans," says virologist Florian Krammer of the Icahn School of Medicine at Mount Sinai, who co-leads a multi-institutional universal flu vaccines consortium funded by the U.S. National Institute of Allergy and Infectious Diseases and helped develop the candidate tested in the new trial. Other clinical trials testing stalk-based universal flu vaccine candidates have yet to report data.

Targeting the stalk is harder than it sounds, because immune memory cells built up over a lifetime of flu infections react so strongly to the conserved region of HA's head that this response overrides production of antibodies against the stalk. Some researchers have tried to make flu vaccines that only contain HA's stalk, but this fragment is highly unstable. To get around this problem, Krammer and colleagues made what they call chimeric HAs, which link the protein's conserved stalk to unusual heads that are entirely new to the human immune system and don't trigger a person's immune memory. Only low levels of head antibodies are produced, allowing a strong new immune response to stalk to dominate. In essence, the head of the chimera is only there to stabilize the stalk.

Influenza vaccines contain three to four strains of the virus that are classified as group A, which breaks into two other divisions, and group B strains. The researchers developed vaccines made from live, weakened versions of influenza viruses or inactivated viruses bearing chimeric HAs representing only one division of group A. In the trial, 51 participants received the various vaccines and their antibodies were compared with those of 15 people who received placebos. A single shot of vaccine with chimeric HA inactivated

viruses, the researchers report, “induced remarkably high antistalk antibody titers.”

The trial was only a phase I study to establish safety and measure immune responses, which means it didn’t test the ability of the vaccines to protect people from influenza. Still, when the researchers transferred human antibodies triggered by the experimental vaccines into mice and then “challenged” the rodents with the influenza virus, the mice lost far less weight than untreated mice who also were infected, suggesting the antibodies protected them. Immunologist James Crowe, who runs the vaccine center at Vanderbilt University, says the study is “a serious effort” to test the stalk antibody hypothesis and “an important first step.”

Krammer says it will likely take at least 2 years to develop chimeric HAs representing enough other strains from influenza groups A and B to be combined into a universal vaccine. That mix would then be tested in a large-scale, multiyear study designed to show that the vaccine candidate works better than the seasonal vaccine. The seasonal vaccine works fairly well in years when its HA closely matches the variants in circulation, so the chimeric HAs would only show their true power during one of the rarer years when there’s a mismatch.

This “long development path,” Krammer suspects, is the main reason his team lost an initial corporate partner, GlaxoSmithKline, which has another universal flu vaccine in clinical trials. “It’s difficult to get to get a lot of interest for something like this,” Krammer says.

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Jon Cohen

Jon is a staff writer for *Science*.

Email Jon | Twitter

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