Toward 'universal' vaccine: Scientists describe antibodies that protect against large variety of flu viruses

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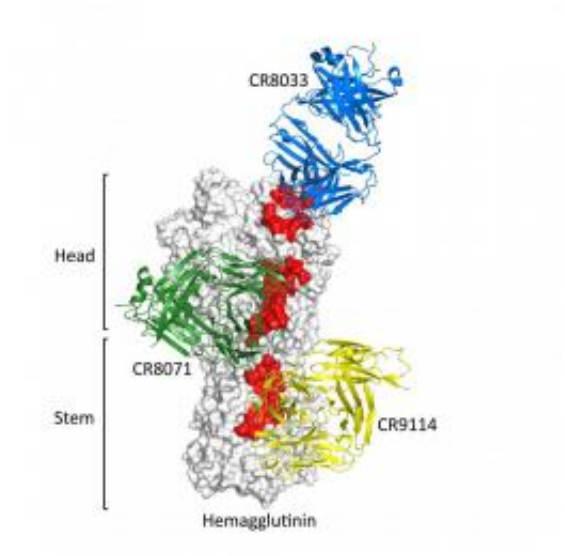

A team led by scientists at the Scripps Research Institute and Crucell Vaccine Institute has described three human antibodies that provide broad protection against influenza B virus strains. The work was published in *Science* Express, the advance online issue of the journal *Science*, on Aug. 9, 2012. Image courtesy of the Wilson lab, the Scripps Research Institute

A team led by scientists at The Scripps Research Institute and Crucell Vaccine Institute in the Netherlands describes three human antibodies that provide broad protection against Influenza B virus strains. The same team had previously reported finding broadly neutralizing antibodies

against Influenza A strains.

The isolation of the new broadly neutralizing antibodies, which was reported the journal *Science*'s advance online edition, Science Express, on August 9, paves the way for researchers to develop a universal antibody-based flu therapy for use in severe infections or to protect hospital staff during an outbreak. Importantly, these antibodies may provide key clues to the design of an active universal flu vaccine —designed to protect long-term against flu viruses, not just against the current season's strains.

"To develop a truly universal flu vaccine or therapy, one needs to be able to provide protection against influenza A and influenza B viruses, and with this report we now have broadly neutralizing antibodies against both," said Ian A. Wilson, the Hansen Professor of Structural Biology at Scripps Research, who was senior investigator for the new study with Crucell's Jaap Goudsmit and Robert Friesen.

One of the newly discovered antibodies will be of special interest to flu researchers, because it appears to protect against essentially all influenza B and influenza A strains. "It's the only one in the world that we know of that has been found to do this," said Wilson.

Looking for the Missing Pieces

Influenza B viruses are considered less dangerous than Influenza A viruses, and have been less intensively studied because they have less capacity to mutate into deadly pandemic strains. However, influenza B viruses account for a significant part of the annual flu illness burden in humans.

To find broadly protective antibodies against Influenza B, the team at Crucell generated a large collection of flu antibodies from the immune

cells of volunteers who had been given a seasonal flu vaccine. The researchers then screened this collection for antibodies that could bind to a wide variety of influenza B strains.

Three of the antibodies they found in this manner—CR8033, CR8071, and CR9114—protected mice against normally lethal doses of the two major influenza B strains. CR9114 also protected mice against influenza A viruses, including the H1N1 subtype that killed about 17,000 people in a 2009 pandemic. The fact that these antibodies protected against a variety of flu strains suggested they mark functionally important sites, or "epitopes," on the virus that are relatively unchanging (conserved) from one flu strain to the next.

Wilson's team at Scripps Research characterized the newly discovered antibodies' binding sites on influenza viruses using electron microscopy and X-ray crystallography techniques. They found that CR8033 binds to a highly conserved epitope—a functionally important site—on the "head" of the hemagglutinin protein, a structure that studs the outer coat of flu viruses and allows the viruses to stick to vulnerable cells. CR8071 binds to the base of the hemagglutinin head. Most antibodies that bind to the hemagglutinin head and neutralize influenza do so by blocking the virus's attachment to host cells.

"The unique thing about these two antibodies is that they neutralize flu viruses chiefly by preventing virus particles from exiting infected cells," said Nick Laursen, a research associate in Wilson's laboratory who was a lead author of the study.

A Weak Point on the Virus

Antibody CR9114 turned out to bind to a site on the hemagglutinin stem. "It prevents the hemagglutinin protein from undergoing the shape-change needed for the virus to fuse to the outer membrane of a host

cell," said Cyrille Dreyfus, a Wilson lab research associate who also was a lead author of the study. "This appears to be a real weak point of the virus, because this epitope is highly conserved among influenza A subtypes as well as influenza B."

Wilson notes that in a study published in 2009 his laboratory determined the structure of another Crucell antibody that broadly neutralizes influenza A viruses by binding to essentially the same site on the hemagglutinin stem—but in a subtly different way, so that it fails to get a grip on influenza B viruses, too. "With some tweaking of that antibody's binding domains, we might have been able to get a broader effect like CR9114's," Wilson said.

The viral epitope to which CR9114 binds will now be studied extensively by researchers as a target for vaccines and therapies, because it is the only one found so far that is broadly vulnerable to neutralization on both influenza A and B viruses.

Remarkably, CR9114 performed poorly against influenza B viruses in initial lab-dish tests known as microneutralization assays, which test the ability of an antibody to protect cells from viral infection. Yet CR9114 was clearly effective under more realistic conditions in mice, even at low doses. Because it attacks the stem rather than the head of flu virus hemagglutinins, CR9114 also failed to show effects in a widely used test known as the hemagglutinin-inhibition assay.

"As we move towards design of a universal flu vaccine, we need to find more inclusive assays to screen for antibodies such as CR9114, which may be highly effective but have novel mechanisms for neutralization that cannot be detected by the current methods used in influenza vaccine development," Goudsmit said.

More information: "Highly conserved protective epitopes on

Influenza B viruses," *Science*, 2012.

Provided by Scripps Research Institute