Flu antibody protects against numerous and wide-ranging strains

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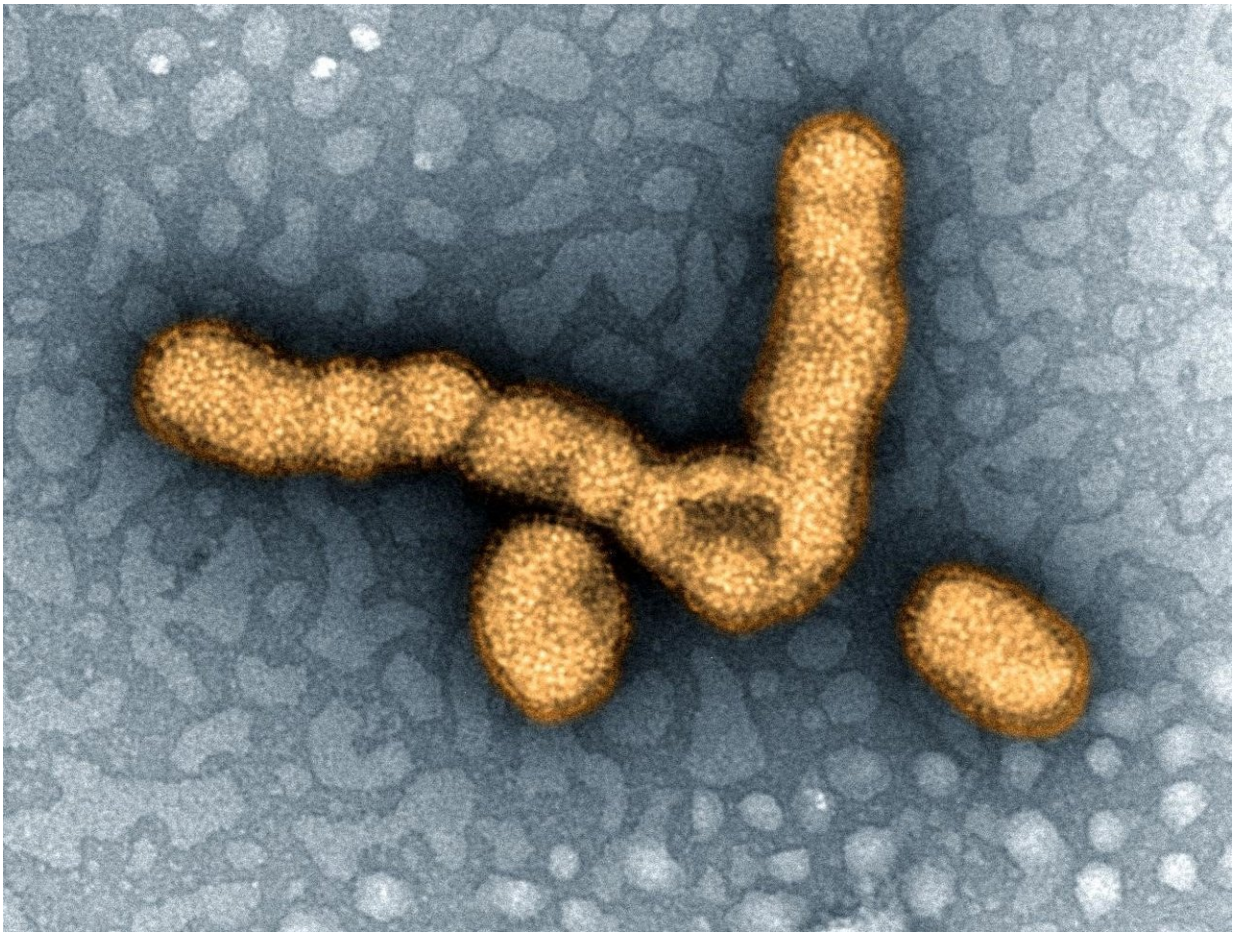


H1N1 influenza virus particles. Credit: NIAID

Researchers have found an antibody that protects mice against a wide

range of lethal influenza viruses, according to a study from Washington University School of Medicine in St. Louis, Icahn School of Medicine at Mount Sinai in New York City, and Scripps Research in La Jolla, Calif. The antibody could serve as a template to aid in design of a universal vaccine that protects against all strains of the virus, and a drug to treat and protect against severe cases of flu, including pandemics.

The research is published Oct. 25 in *Science*.

"There are many strains of influenza virus that circulate, so every year we have to design and produce a new vaccine to match the most common strains of that year," said co-senior author Ali Ellebedy, Ph.D., an assistant professor of pathology and immunology at Washington University. "Now imagine if we could have one vaccine that protected against all influenza strains, including human, swine and highly lethal avian influenza viruses. This antibody could be the key to the design of a truly universal vaccine."

Ellebedy discovered the antibody—an immune protein that recognizes and attaches to a foreign molecule—in blood taken from a patient hospitalized with flu at Barnes-Jewish Hospital in St. Louis in the winter of 2017. Ellebedy was working on a study analyzing the immune response to flu infection in humans, in collaboration with the Washington University Emergency Care and Research Core, which was sending him blood samples from consenting flu patients. He quickly noticed that this particular blood sample was unusual: In addition to containing antibodies against hemagglutinin, the major protein on the surface of the virus, it contained other antibodies that were clearly targeting something else.

"At the time we were just starting, and I was setting up my lab so we didn't have the tools to look at what else the antibodies could be targeting," said Ellebedy, who is also an assistant professor of medicine

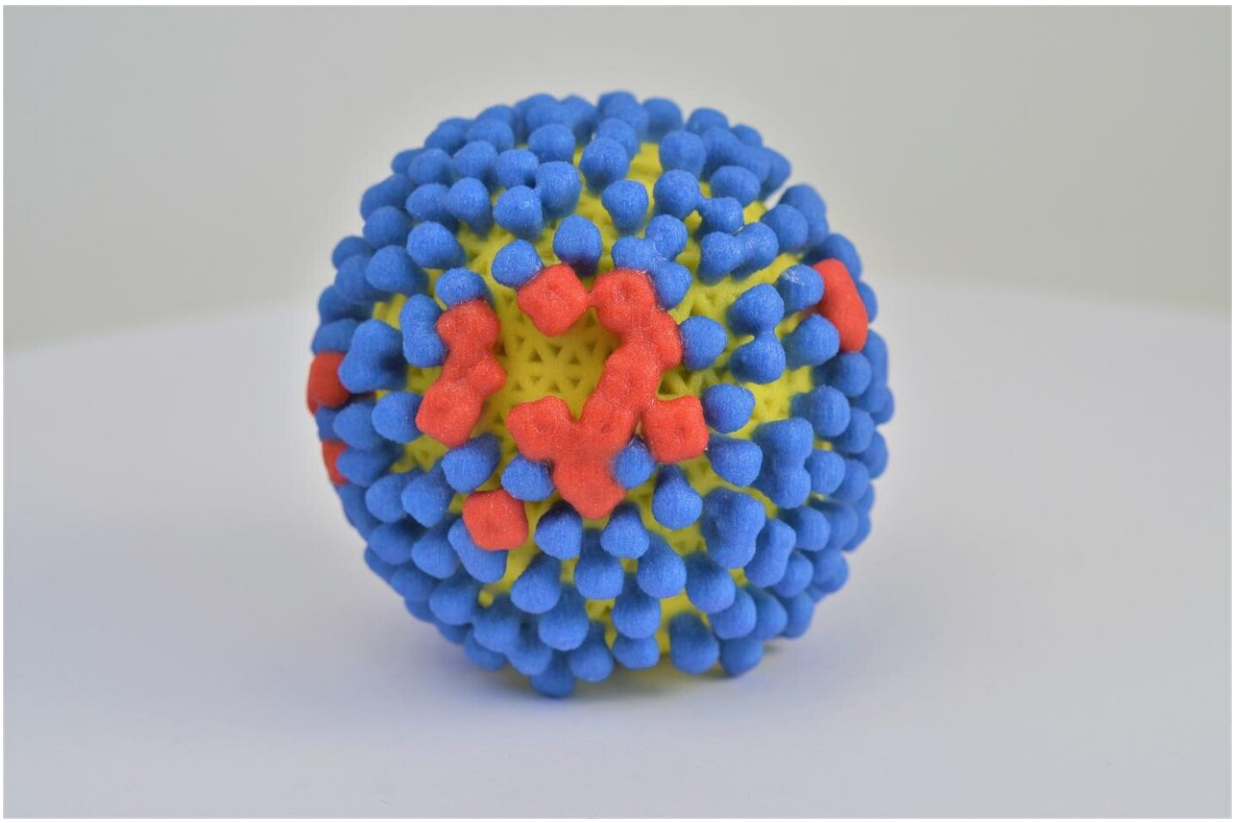
and of molecular microbiology.

He sent three of the antibodies with unknown targets to co-senior author Florian Krammer, Ph.D., a microbiology professor at the Icahn School of Medicine at Mount Sinai. An expert on neuraminidase—the other protein on the surface of the influenza virus—Krammer tested the antibodies against his extensive library of neuraminidase proteins. At least one of the three antibodies blocked neuraminidase activity in all known types of neuraminidase in flu viruses, representing a variety of human and nonhuman strains.

"The breadth of the antibodies really came as a surprise to us," Krammer said. "Typically, anti-neuraminidase antibodies can be broad within a subtype, like H1N1, but an antibody with potent activity across subtypes was unheard of. At first, we did not believe our results. Especially the ability of the antibodies to cross between influenza A and influenza B viruses is just mind-boggling. It is amazing what the human immune system is capable of if presented with the right antigens."

Neuraminidase is essential to flu virus replication. The protein cuts newly formed viruses free of infected cells so they can move on and infect new cells. Tamiflu, the most widely used drug for severe flu infection, works by inactivating neuraminidase.

To find out whether the antibodies could be used to treat severe cases of flu, Krammer and colleagues tested them in mice given a lethal dose of influenza virus. All three were effective against many strains, and one antibody—called 1G01—protected mice against all 12 strains tested, representing all three groups of human flu virus, as well as avian and other nonhuman strains.



Influenza viruses, like the model shown here, display several kinds of surface proteins on their exteriors. Credit: NIAID

"All the mice survived, even if they were given the antibody 72 hours after infection," Ellebedy said. "They definitely got sick and lost weight, but we still saved them. It was remarkable. It made us think that you might be able to use this antibody in an intensive care scenario when you have someone sick with flu and it's too late to use Tamiflu."

Tamiflu must be administered within 24 hours of symptoms. A drug that could be used later would help many people diagnosed after the Tamiflu window has closed. But before the researchers could even think of designing such a drug based on the antibody, they needed to understand how it was interfering with neuraminidase.

They turned to co-senior author Ian Wilson, DPhil, a noted structural biologist at Scripps Research. Wilson and Xueyong Zhu, Ph.D., a staff scientist in his lab, mapped the structures of the antibodies while they were bound to neuraminidase. They found that the antibodies each had a loop that slid inside the active site of neuraminidase like a stick between gears. The loops prevented neuraminidase from releasing new virus particles from the surface of cells, thereby breaking the cycle of viral production in cells.

"We were surprised how these antibodies managed to insert a single loop into the conserved active site without contacting the surrounding hypervariable regions, thereby achieving much greater breadth against the neuraminidase of different influenza viruses than we have seen before," Wilson said.

The structures showed that the antibodies provide such broad protection because they target parts of the active site of the neuraminidase protein that is much the same across distantly related flu strains. Even minor changes to that part of the protein could abolish its ability to do its job, thereby preventing the virus from replicating.

The researchers are working on developing new and improved treatments and vaccines for influenza based on antibody 1G01, which has been patented by Washington University.

"Neuraminidase has been ignored as a vaccine candidate for a long time," Ellebedy said. "These antibodies tell us that it should not have been overlooked. Now that we know what a broadly protective antibody to neuraminidase looks like, we now have an alternative approach to start designing novel vaccines that induce antibodies like this. And that could be really important if we are going to figure out how to design a truly universal vaccine."

More information: "Broadly protective human antibodies that target the active site of influenza virus neuraminidase" *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aay0678

Provided by Washington University School of Medicine