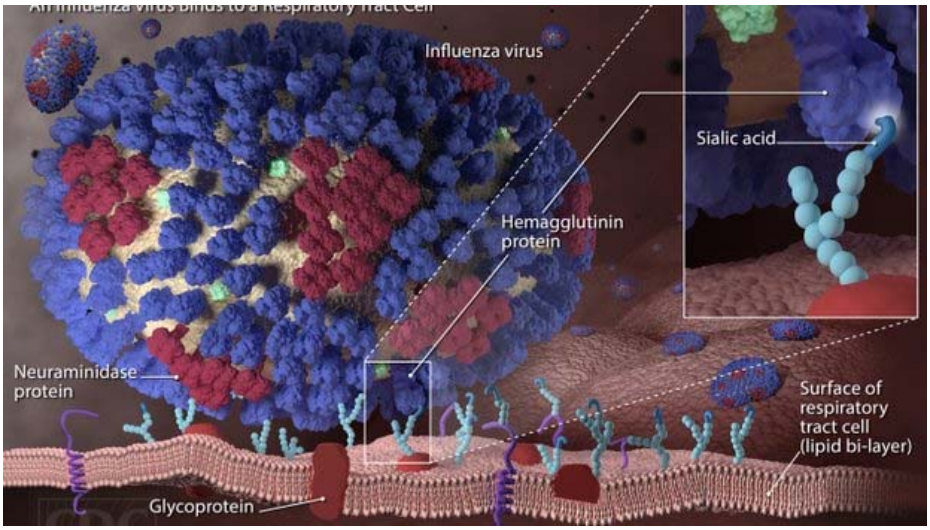
Flu virus weak spot found by Scripps Research scientists

By Bradley J. Fikes (/staff/bradley-fikes/) 10 a.m. Feb. 10, 2013



This graphic depicts influenza infection. A viral protein called hemagglutinin binds to the sialic acid receptors on the surface of a human respiratory tract cell. The structure of hemagglutinin fits the sialic acid receptors like Velcro. Once virus is attached to the cell, it is then able to enter and infect the cell. This marks the beginning of a flu infection. — *Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (NCIRD)*

LA JOLLA — As the world sneezes, wheezes and aches through the latest flu season, scientists from The Scripps Research Institute report what could be a key discovery for fighting the virus (http://www.virology.ws/influenza-101/) in its many forms.

In a new study, the scientists said they have found out how to neutralize the flu's most notorious advantage, namely its ability to mutate around vaccines and drugs. This could lead to new methods to prevent infections, and to reduce their severity.

By seizing on a tiny molecular weakness shared by many Type A and some Type B viruses, the scientists have demonstrated in the lab how the flu's ability to infect people can be thwarted. Moreover, the research applies to crossover infections from avian flu, a major concern in recent years.

While drugs based on this research are years away, the findings represent a major conceptual advance in the frustrating battle against influenza, say scientists who have examined the study.

The key to this advance comes from recognizing the importance of a tiny cavity in a protein (http://www.rcsb.org/pdb/101/motm.do?momID=76) the virus uses to infect human cells. Blocking this cavity prevents the virus from penetrating cells, said study leader Ian Wilson (http://www.scripps.edu/research/faculty/wilson) of Scripps, who has been working on a universal flu vaccine for years.

While the virus, as always, mutates to thwart this blockage, the mutant viruses become incapable of infecting human cells. They appear to be "dead-end mutations," the study stated.

The study was published Sunday (http://www.nature.com/doifinder/10.1038/nsmb.2500) in the journal Nature Structural and Molecular Biology. Wilson, chair of the department of Integrative Structural and Computational Biology at Scripps, is the study's senior author. Rui Xu of Wilson's lab is the first author.

Enduring threat

The study is specific to flu viruses, and doesn't apply to other viruses such as HIV, Wilson said. HIV, the virus that causes AIDS, also mutates at a ferocious pace, making development of a vaccine to prevent or treat infection difficult. HIV also has a corresponding site that is targeted by antibodies but, unlike influenza viruses, that site is much larger and more amenable to being specifically blocked by antibodies.

While influenza is not as dangerous as AIDS, it represents a much wider public health problem, because the virus spreads much more readily.

The virus mainly infects cells lining the airways, which means that any flu virus in the air, such as from sneezing, is a major infection

threat. In San Diego County, 30 people have died from the flu this season, the county's Health and Human Service Agency said last week.

Moreover, influenza periodically erupts into global pandemics that cause great loss of life worldwide. The worst pandemic, from 1918-1919 (http://www.flu.gov/pandemic/history/1918/the_pandemic/index.html), caused an estimated 50 million deaths, about 675,000 of which were in the United States. About 20 to 40 percent of the global population became ill.

A second pandemic struck in 1957-1958, causing the deaths of nearly 70,000 Americans.

The virus causes such devastation by its method of attachment to cells. It uses a linking protein that docks with sugars called sialic acids (http://www.ncbi.nlm.nih.gov/books/NBK20724/). These sugars bristle from cell surfaces in humans and other animals. Sialic acids play important roles in immunity and, according to recent research, perhaps human evolution.

Once docked with the sialic acids, the virus injects itself into cells. The protein's attachment sites mutate rapidly, making new vaccines necessary each year.

The cavity is found at the "head" of this flu protein, called hemagglutinin (http://www.rcsb.org/pdb/101/motm.do?momID=76), where the attachment occurs. Unlike many other parts of the virus, this cavity doesn't change, Wilson said. That fact suggests the cavity's structure is important to the virus.

Viral Velcro

The study is very significant, said sialic acid experts Miriam Cohen (http://cmm.ucsd.edu/gagneux/gagneux/miriam.html) and Pascal Gagneux (http://biomedsci.ucsd.edu/faculty/faculty_descrip.aspx?id=263) of UC San Diego. Gagneux authored a 2011 study (http://www.pnas.org/content/early/2011/10/06/1102302108.full.pdf+html) suggesting that sialic acid played a role in the emergence of forms of malaria that target humans, and in human/chimp speciation (http://ucsdnews.ucsd.edu/newsrel/health/20111010SugarOrigin.asp).

"This is extremely promising work, as it suggests a way that one could produce a drug or design a vaccine, that essentially corners this perpetual moving target so that all that can evolve are noninfectious progeny," Cohen and Gagneux wrote in an email.

"This new discovery does provide a new molecular scaffold on which to base the designing of potential drugs that efficiently block the binding of a broad variety of influenza A viruses, including viral strains from bird hosts, which represent an eternal reservoir for these viruses in the wild."

Cohen and Gagneux said drugs developed from this approach could cause fewer side effects than Tamiflu, which targets a complementary viral protein, called neuraminidase (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC525087/). While hemagglutinin brings flu viruses into cells, neuraminidase causes newly formed flu viruses to be released from infected cells.

"Humans have their own neuraminidase enzymes with important roles in immunity, fertilization and brain function, possibly opening up side effects of neuraminidases," they wrote. " In contrast humans do not have hemagglutinin-like proteins, making hemagglutinin a very promising drug target."

Hemagglutinin links with numerous sialic acid molecules on the cell surface. By themselves, these attachment sites are weakly binding, but together they tightly bind the virus to cells, "like Velcro," Wilson said, using the same analogy as Cohen and Gagneux.

The body responds to this viral invasion, or to flu vaccines, by producing antibodies, large protein molecules. These antibodies latch onto the various viral attachment sites — the Velcro — getting in between the virus and the cells. But these sites mutate rapidly.

So Wilson and his collaborators looked to clues from nature to find "broadly neutralizing" antibodies that showed success against many flu strains. He found three such antibodies, all of them attaching to this particular cavity.

Because the cavity doesn't change shape when the virus mutates, the attachment creates a physical blockage that the virus can't evade, except by losing its sialic acid attachments, Wilson said. Since these attachments are the only way it can grab onto human cells, the mutated virus can't infect people.

These broadly neutralizing antibodies share a characteristic formation that allows them to thrust a narrow arm deep into the viral protein. Wilson said that is important, because this formation allows the antibodies to avoid the highly mutable bumps and protrusions around this vulnerable site that block most antibodies from attaching.

Other authors of the paper were Ryan McBride and James C Paulson of Scripps, and Jens C Krause and James E Crowe Jr. of Vanderbilt University Medical Center, Nashville, Tennessee.