Computer-designed proteins programmed to disarm variety of flu viruses

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This is a plastic model of a protein in David Baker's University of Washington lab, where scientists are engineering proteins that disarm flu viruses. Credit: Clare McLean

Computer-designed proteins are under construction to fight the flu. Researchers are demonstrating that proteins found in nature, but that do not normally bind the flu, can be engineered to act as broad-spectrum antiviral agents against a variety of flu virus strains, including H1N1 pandemic influenza.

"One of these engineered proteins has a flu-fighting potency that rivals that of several human monoclonal antibodies," said Dr. David Baker, professor of biochemistry at the University of Washington, in a report in Nature Biotechnology.

Baker's research team is making major inroads in optimizing the function of computer-designed influenza inhibitors. These proteins are constructed via computer modeling to fit exquisitely into a specific nano-sized target on flu viruses. By binding the target region like a key into a lock, they keep the virus from changing shape, a tactic that the virus uses to infect living cells. The research efforts, akin to docking a space station but on a molecular level, are made possible by computers that can describe the landscapes of forces involved on the submicroscopic scale.

Baker heads the new Institute for Protein Design Center at the University of Washington. Biochemists, computer scientists, engineers and medical specialists at the center are engineering novel proteins with new functions for specific purposes in medicine, environmental protection and other fields. Proteins underlie all normal activities and structures of living cells, and also regulate disease actions of pathogens like viruses. Abnormal protein formation and interactions are also implicated in many inherited and later-life chronic disorders.

Because influenza is a serious worldwide public health concern due to its genetic shifts and drifts that periodically become more virulent, the flu is one of the key interests of the Institutes for Protein Design and its collaborators in the United States and abroad. Researchers are trying to meet the urgent need for better therapeutics to protect against this very adaptable and extremely infective virus. Vaccines for new strains of influenza take months to develop, test and manufacture, and are not helpful for those already sick. The long response time for vaccine creation and distribution is unnerving when a more deadly strain suddenly emerges and spreads quickly. The speed of transmission is accelerated by the lack of widespread immunity in the general population to the latest form of the virus.

Flu trackers refer to strains by their H and N subtypes. H stands for hemagglutinins, which are the molecules on the flu virus that enable it to

invade the cells of respiratory passages. The virus's hemagglutinin molecules attach to the surface of cells lining the respiratory tract. When the cell tries to engulf the virus, it makes the mistake of drawing it into a more acidic location. The drop in pH changes the shape of the viral hemagglutinin, thereby allowing the virus to fuse to the cell and open an entry for the virus' RNA to come in and start making fresh viruses. It is hypothesized that the Baker Lab protein inhibits this shape change by binding the hemagglutinin in a very specific orientation and thus keeps the virus from invading cells.

Baker and his team wanted to create antivirals that could react against a wide variety of H subtypes, as this versatility could lead to a comprehensive therapy for influenza. Specifically, viruses that have hemagglutinins of the H2 subtype are responsible for the deadly pandemic of 1957 and continued to circulate until 1968. People born after that date haven't been exposed to H2 viruses. The recent avian flu has a new version of H1 hemagglutinin. Data suggests that Baker's proteins bind to all types of the Group I Hemagglutinin, a group that includes not just H1 but the pandemic H2 and avian H5 strains.

Recognizing the importance of new flu therapies to national and international security, the Defense Advanced Research Projects Agency and the Defense Threat Reduction Agency funded this work, along with the National Institutes of Health's National Institute for Allergy and Infectious Diseases. The researchers also used the Advanced Photon Source at Argonne National Laboratories in Illinois, with support from the Department of Energy, Basic Energy Sciences.

The methods developed for the influenza inhibitor protein design, Baker said, could be "a powerful route to inhibitors or binders for any surface patch on any desired target of interest." For example, if a new disease pathogen arises, scientists could figure out how it interacts with human cells or other hosts on a molecular level. Scientists could then use protein

interface design to generate a diversity of small proteins that they predict would block the pathogen's interaction surface.

Genes for large numbers of the most promising, computer-designed proteins could be tested using yeast cells. After further molecular chemistry studies to find the best binding among those proteins, those could be re-programmed in the lab to undergo mutations, and all the mutated forms could be stored in a "library" for an in-depth analysis of their amino acids, molecular architecture and energy bonds. Advanced technologies would allow the scientists to quickly thumb through the library to pick out those tiny proteins that clung to the pathogen surface target with pinpoint accuracy. The finalists would be selected from this pool for excelling at stopping the pathogen from attaching to, entering and infecting human or animal cells.

The use of deep sequencing, the same technology now used to sequence human genomes cheaply, was especially crucial in creating detailed maps relating sequencing to function. These maps were used to reprogram the design to achieve a more precise interaction between the inhibitor protein and the virus molecule. It also enabled the scientists, they said, "to leapfrog over bottlenecks" to improve the activity of the binder. They were able to see how small contributions from many tiny changes in the protein, too difficult to spot individually, could together create a binder with better attachment strength.

"We anticipate that our approach combining computational design followed by comprehensive energy landscape mapping," Baker said, "will be widely useful in generating high-affinity and high-specificity binders to a broad range of targets for use in therapeutics and diagnostics."

Provided by University of Washington