Scientists design new anti-flu virus proteins using computational methods

May 13 2011

A research article May 12 in *Science* demonstrates the use of computational methods to design new antiviral proteins not found in nature, but capable of targeting specific surfaces of flu virus molecules.

One goal of such protein design would be to block molecular mechanisms involved in cell invasion and virus reproduction.

Computationally designed, surface targeting, antiviral proteins might also have diagnostic and therapeutic potential in identifying and fighting viral infections.

The lead authors of the study are Sarel J. Fleishman and Timothy Whitehead of the University of Washington (UW) Department of Biochemistry, and Damian C. Ekiert from the Department of Molecular Biology and the Skaggs Institute for Chemical Biology at The Scripps Research Institute. The senior authors are Ian Wilson from Scripps and David Baker from the UW and the Howard Hughes Medical Institute.

The researchers note that additional studies are required to see if such designed proteins can help in diagnosing, preventing or treating viral illness. What the study does suggest is the feasibility of using computer design to create new proteins with antiviral properties.

"Influenza presents a serious public health challenge," the researchers noted, "and new therapies are needed to combat viruses that are resistant to existing anti-viral medications or that escape the body's defense

systems."

They focused their attention on the section of the flu virus known as the hemagglutinin stem region. They concentrated on trying to disable this part because of its function in invading the cells of the human respiratory tract.

Their approach was somewhat similar to engineering a small space shuttle with the right configuration and construction, as well as recognizance and interlocking mechanisms, to dock with a troublesome space station and upset its mission. Only these scientists attempted their engineering feat at an atomic and molecular level.

Central to their approach is the ability of biological molecules to recognize certain other molecules or their working parts, and to have an affinity for binding to them at pre-determined locations. This recognition has both physical and chemical bases. Protein-protein interactions underlie many biological activities, including those that disarm and deactivate viruses.

In their report, the researchers described their general computational methods for designing new, tiny protein molecules that could bind to a certain spot on large protein molecules. They took apart some protein structures and watched how these disembodied sections interacted with a target surface. They analyzed particular high-affinity interactions, and used this information to further refine computer-generated designs for interfaces.

"Protein surfaces are never flat, but have many crevices and bulges at the atomic scale," lead author Sarel Fleishman explained. "The challenge is to identify amino acid side chains that would fit perfectly into these surfaces. The fit must be precise both in shape and in other chemical properties such as electrostatic charge. This geometrical and biophysical

problem can be computationally solved, but requires large computational resources."

The researchers made use of a peer-to-peer computing platform called Rosetta@Home for going through the hundreds of millions of possible interactions of designed proteins and the surface of hemagglutinin to solve this challenge.

Following optimization, the designed proteins bound hemagglutinin very tightly.

Through this method, the researchers created two designs for new proteins that could bind to a surface patch on the stem of the influenza hemagglutinin from the 1918 H1N1 pandemic flu virus.

The shortcomings of the approach, due to approximations, meant that the researchers started out with 73 possibilities of which just two were successful.

One of the disease-causing characteristics of the influenza hemagglutinin stem is that it changes shape by refolding when in an acidic environment. This reconfiguration appears to allow the virus reproduce itself inside of cells.

In this study, one of the newly designed proteins was shown to block a conformational change, not only in H1 influenza hemagglutinin, but also in a similar component in H5 avian influenza.

"This finding suggests that this new protein design may have virus-neutralizing effects against multiple influenza subtypes," the researchers reported.

What was unusual about the workable designs was that they had helical

binding modes, roughly shaped like a spiral staircase, rather than the loop binding that naturally occurring antibodies employ.

X-ray crystallography of the proteins complex showed that the actual orientation of the bound proteins was almost identical to the way the binding mode was designed. The modified surface of the main recognition helix on the designed protein was packed into a groove on the desired region of the virus protein.

"Overall, the crystal structure is in excellent agreement with the designed interface," the researchers noted, "with no significant deviations at any of the contact points." The design and the actual formation were nearly identical.

The scientists were encouraged by this finding. Despite their limitations, the design methods, the scientists believe, capture the essential features of the desired protein-protein interaction.

Provided by University of Washington