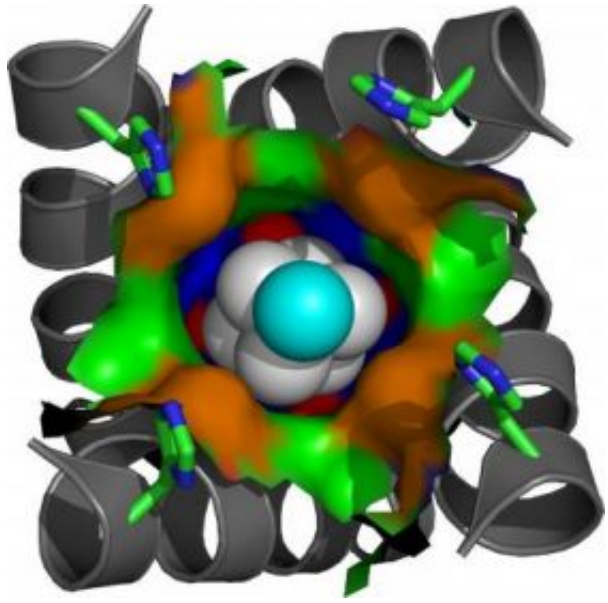
Penn researchers discover new target for preventing and treating flu

January 30 2008



Structure of amantadine inside viral binding site. Credit: William F. DeGrado, PhD, University of Pennsylvania School of Medicine

Emerging subtypes of influenza A virus hold the potential to initiate a world-wide epidemic in the next few years, according to World Health Organization officials. However, almost all type A influenza viral strains have become resistant to amantadine and rimantadine, two drugs that make up one of only two classes used to treat the flu.

Researchers at the University of Pennsylvania School of Medicine have now provided a new strategy for designing drugs that target the resistant

viral strains by solving the three-dimensional structure of a viral protein called the M2 proton channel. This protein is the molecular receptor for these drugs. This study is published in the Jan. 31 issue of the journal *Nature*.

The M2 protein is located in the viral envelope, forming a long, narrow channel that allows the flow of protons into the viral interior, an essential step for infection. Amantadine sits in this channel and blocks the flow of protons, thus halting infection. In non-resistant viruses, amantadine acts like a cork lodged deep in the channel.

“We know that resistance to amantadine is caused by a mutation in the virus M2 protein, but we did not know how this mutation caused resistance,” explains senior author William F. DeGrado, PhD, Professor of Biochemistry and Biophysics. “Now we do – the mutation changes the shape of the channel so amantadine can no longer do its job."

The structure revealed that there is a pocket in the channel next to the location where amantadine fits that is conserved in all influenza A viruses. This newly discovered space could be the target for new drugs. "Inhibitors that target this cavity adjacent to two highly conserved amino acids in M2 might reclaim the M2-blocking class of drugs so that ongoing endemic outbreaks and future pandemics of this deadly virus might be prevented and treated," says DeGrado.

"The crystal structures of influenza M2 with and without the anti-influenza drug help us understand the molecular basis of drug resistance, which is a serious problem in treating the flu," said Jean Chin, PhD, who oversees grants on membrane proteins at the National Institute of General Medical Sciences, which in part funded this research. "The findings will inform scientists working to design the next generation of antivirals."

The M2 protein was crystallized so that its structure could be examined under different conditions. This allowed the Penn research team, which included Amanda Stouffer, Rudresh Acharya, David Salom, Cinque Soto, Luigi Di Costanzo, Steven Stayrook, Vikas Nanda, and Anna Levine, to determine the structure of the crystallized protein using a technique called x-ray crystallography.

The pure protein crystal was bombarded with x-rays so that the position of each atom in relation to its neighboring atoms in the crystal would show up as an array of black spots. From the pattern of thousands of spots, the structure of the protein can be graphically visualized using computer imaging technology.

The next step is to design new compounds that plug the M2 channel by fitting into the newly discovered larger cavity. The Penn research group is currently engaged in these studies.

Source: University of Pennsylvania School of Medicine