Chemists track how drug changes, blocks flu virus

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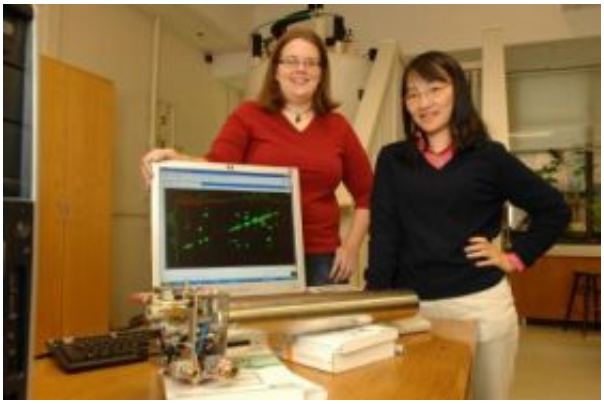

Mei Hong, Iowa State's John D. Corbett Professor in Chemistry, and Sarah Cady, a graduate student in chemistry, are using solid-state nuclear magnetic resonance spectroscopy to study how an anti-virus drug affects influenza A. The technique uses the equipment in front of and behind the researchers. It is similar to the magnetic resonance imaging technology that takes pictures of soft tissues in the body. Photo by Bob Elbert/Iowa State University

An anti-virus drug attacks influenza A by changing the motion and structure of a proton channel necessary for the virus to infect healthy cells, according to a recently published research paper by two Iowa State University chemists.

Mei Hong, Iowa State's John D. Corbett Professor in Chemistry, and Sarah Cady, a graduate student in chemistry, are studying the effects of the antiviral drug amantadine on influenza A. That's the type of flu bug

that most commonly makes people sick and the one that has caused the most serious flu epidemics.

Their findings appear in the Feb. 5 edition of the *Proceedings of the National Academy of Sciences.*

Hong said the findings are particularly important because mutations of the type A virus are resistant to amantadine treatment.

“In the last few years, amantadine resistance has skyrocketed among influenza A viruses in Asia and North America, making it imperative to develop alternative antiviral drugs,” Hong and Cady wrote in their paper.

To develop those drugs, Hong said researchers first need to understand exactly how amantadine stops the flu virus.

First, some background about how a flu virus infects a healthy cell: A virus begins the process by attaching itself to a healthy cell. The healthy cell surrounds the flu virus and takes it inside the cell through a process called endocytosis. Once in the cell, the virus uses a protein called M2 to open a channel to the healthy cell. Protons from the healthy cell flow through the channel into the virus and raise its acidity. That triggers the release of the virus’ genetic material into the healthy cell. The virus hijacks the healthy cell’s resources and uses them to reproduce and spread the virus.

If the M2 proton channel is blocked, the process doesn’t work and a virus can’t infect a cell and spread.

Hong and Cady studied the proton channel with the help of solid-state nuclear magnetic resonance spectroscopy – a technique similar to the magnetic resonance imaging technology that takes pictures of soft tissues in the body. The technology enabled them to discover and describe the

motion and structure of the M2 proton channel in virus cells. They studied the channel when cells were treated with amantadine and when they were not.

Hong said the study made three findings:

-- First, the M2 protein is in constant motion, changing among various conformations, and amantadine treatment changes the rate of motion and reduces the number of possible conformations the protein can adopt.

-- Second, the structure of the protein changes most prominently at two places facing the channel interior when cells are treated with amantadine.

-- And third, the tilt and orientation of the protein's helices are subtly changed by amantadine.

And all that blocks the ability of a virus to infect a healthy cell.

"We didn't know that before," Hong said. "And now that makes it very clear what we should study next."

Hong's next step is to examine how mutant versions of the virus are able to resist the flu-stopping changes caused by amantadine. Hong said that study will depend on winning research funding and recruiting graduate students interested in chemistry with biological applications.

Source: Iowa State University