Researcher invents molecule that stops SARS

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A Purdue University researcher has created a compound that prevents replication of the virus that causes SARS and could lead to a treatment for the disease.

"The outbreak of SARS in 2003 led to hundreds of deaths and thousands of illnesses, and there is currently no treatment," said Arun Ghosh, the Purdue professor that led the molecular design team. "Although it is not currently a threat, there is the concern that SARS could return or be used as a biological weapon. It is important to develop a treatment as a safeguard."

According to the Centers for Disease Control and Prevention, the virus can be transmitted through coughing or sneezing, and the infection can quickly spread from person to person. SARS, or Severe Acute Respiratory Syndrome, spread through two dozen countries over a period of a few months before it was contained. A total of 8,098 people worldwide became ill and 774 died.

In addition to its ability to block the SARS virus, the molecular compound that inhibits the virus provides new insights into a group of proteins found in a range of diseases including childhood croup, herpes and cancer, Ghosh said.

"The molecular inhibitor we developed is very potent against the SARS virus by binding to and blocking the use of a specific protein, called papain-like protease, or PLpro, involved in viral replication and evasion of the immune system," said Ghosh who has a joint appointment in

chemistry and medicinal chemistry and molecular pharmacology. "This is the first design and discovery of an inhibitor for this class of proteins. We are hopeful that this will open the door to new treatments for other diseases as well."

Ghosh's group teamed with a research group led by Andrew Mesecar at the University of Illinois at Chicago. The National Institutes of Health infectious disease biodefense program selected the team and funded the research that has been published in the online version of the journal *Proceedings of the National Academy of Sciences*.

Mesecar's team screened more than 50,000 chemical compounds for the necessary properties to both block the virus and have the potential to become viable drug treatments.

"Only two of the compounds we tested were identified as having the properties researchers believed could become drugs," said Mesecar, a professor of medicinal chemistry and pharmacognosy. "Using those two compounds, Arun Ghosh and his team increased the potency by almost two orders of magnitude."

Ghosh, who invented the HIV drug darunavir that entered the market in 2007, specializes in improving the treatment properties of molecular inhibitors through structure-based design.

"The design of this inhibitor was a challenge because we did not know the structure of the compound, which shows us how an inhibitor works and what parts need to be amplified or changed," Ghosh said.

Kiira Ratia, a graduate student at the University of Illinois, provided a breakthrough when she captured the X-ray structure of the inhibitor molecule bound to the protein. The structure confirmed that the inhibitor would be a good candidate for drug development because it showed that

the inhibitor did not bond too strongly to the protein, Ghosh said.

"This was the first time the structure was revealed and we could see that the inhibitor filled the active site of the protein without using strong covalent bonds," he said. "This is very important for development of a therapeutic treatment because it means there is less of a chance for adverse side effects or toxicity, and the treatment can be easily reversed."

Often a protein involved in the disease process also plays a role in regular human biological processes. A safe and effective treatment needs to block enough of the protein to cripple the disease while not completely eliminating the protein from a person's system. It also must work through interactions that are easily reversed by ending treatment, he said.

The inhibitor has only been tested in the laboratory. It must be developed into a drug treatment and evaluated by the U.S. Food and Drug Administration before it could be used by patients, Ghosh said.

In addition to Ghosh and Mesecar, co-authors of the paper detailing this work include, Ratia, Scott Pegan, Wentao Fu, Michael E. Johnson, Melissa Coughlin and Bellur S. Prabhakar from the University of Illinois; Jun Takayama from Purdue University; and Katrina Sleeman and Srendranath Baliji from Loyola University Chicago Stritch School of Medicine.

The team is evaluating the potential to design similar inhibitors for cancer and continues to work with the SARS inhibitor to create even more effective compounds.

Source: Purdue University