SOUTHWESTERN NEWS

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NEW DRUGS RESTORE IMMUNE RESPONSE BLOCKED BY HEPATITIS C VIRUS IN HUMAN CELLS

DALLAS – April 17, 2003 – A new generation of drugs restores the immune response blocked by the hepatitis C virus, reducing the virus to nearly undetectable levels in a matter of days, according to researchers at UT Southwestern Medical Center at Dallas and UT Medical Branch at Galveston.

"We found that the new protease inhibitors could actually prevent the virus from blocking this immune response and basically restore the innate antiviral response in human cells," said Dr. Michael Gale, assistant professor of microbiology at UT Southwestern and senior author of the study, published online today in *Science* Express. "Our conclusion is that these new drugs will have a dual efficacy."

Protease inhibitors, which are already undergoing clinical trials as therapies to treat chronic hepatitis C infections, target the enzymatic activity of the viral protease. Protease, an enzyme that can split a protein into component peptides, is required to process viral proteins into their functional forms.

"If you block the protease, it neutralizes the virus and restores the host response to infection, allowing the cell to clear the virus naturally," said Gale, the Nancy Cain and Jeffrey A. Marcus Scholar in Medical Research, in Honor of Dr. Bill S. Vowell. "That type of mechanism of the drug was completely unexpected."

Hepatitis C virus, which is primarily transmitted by intravenous drug use, blood transfusions or blood products, as well as through sexual contact, affects 4 million people in the United States, making it the most common blood-borne infection in the nation. Hepatitis C virus is the leading cause of cirrhosis and liver cancer and accounts for more than 8,000 U.S. deaths annually.

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The purpose of the study was to determine why hepatitis C virus is so persistent in human cells. Eighty-five percent of individuals exposed to the virus develop chronic infections that are unresponsive to therapy. Seventy percent of those with chronic infections develop chronic liver disease, and nearly 3 percent with long-term infections die of related illnesses, according to the Centers for Disease Control and Prevention.

Gale and his colleagues discovered that the virus persists, in part, because it blocks the innate immune response of infected cells.

"We believe that is a major reason why hepatitis C virus causes chronic infection," Gale said.

Two different protease inhibitor drugs are in different stages of clinical trials. The drugs will likely be evaluated in more detail considering these findings, Gale said.

"As opposed to just studying how much the drug knocks down the virus, now we will evaluate how the drug impacts the host cell's response to the infection," he said.

Dr. Stanley Lemon, dean of medicine at UTMB and director of its National Institutes of Health-funded hepatitis research center, noted that protease inhibitors active against the AIDS virus have revolutionized the treatment of that disease.

"These new findings with hepatitis C virus suggest that protease inhibitors will become an important addition to existing interferon treatments for hepatitis C and that they will have equal if not greater impact on the treatment of this important form of liver disease," he said.

The lead author of the study was Eileen Foy, a student in UT Southwestern's Medical Scientist Training Program. Other authors from UT Southwestern were Dr. Chunfu Wang, postdoctoral researcher in microbiology, and Rhea Sumpter Jr., student research assistant in microbiology. Other UTMB contributors were Dr. Kui Li and Dr. Masanori Ikeda, from the department of microbiology and immunology.

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