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GLADSTONE INSTITUTE OF VIROLOGY AND IMMUNOLOGY NEWS

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GLADSTONE SCIENTISTS LINK HEPATITIS C VIRUS INFECTION TO FAT ENZYME IN LIVER CELLS

Discovery points to a potential new strategy for treating the disease

SAN FRANCISCO, CA—October 10, 2010—Scientists at the Gladstone Institute of Virology and Immunology (GIVI) have found that an enzyme associated with the storage of fat in the liver is required for the infectious activity of the hepatitis C virus (HCV). This discovery may offer a new strategy for treating the infection.

More than 160 million people are infected throughout the world, and no vaccine is available to prevent further spread of the disease. Current treatments are not effective against the most common strains in the US and Europe. The study, published in the journal *Nature Medicine*, shows that the enzyme DGAT1 is a key factor in HCV infection. With several potential DGAT1 inhibitors already in the drug-development pipeline, a treatment for HCV may be possible in the near future.

“Our results reveal a potential ‘Achilles heel’ for HCV infection,” said Melanie Ott, MD, PhD, senior author on the study. “Several DGAT1 inhibitors are already in early clinical trials to treat obesity-associated diseases. They might also work against HCV.”

At first glance, the HCV lifecycle is fairly simple. The virus enters the cell. One large protein is produced and cut into several smaller viral enzymes and proteins that build the virus. The RNA genome is copied, and the new RNAs and structural proteins are used to make new virus particles that are released into the blood stream to infect more cells. These processes were thought to occur at specialized membranes inside the cell. However, recently it has been shown that fat droplets are critically involved.

Fat droplets, which store fat in cells, have become a hot new topic in biology. DGAT1 is one of the enzymes that help to form fat droplets. The Gladstone team, led by Eva Herker, PhD, discovered that HCV infection and viral particle production are severely impaired in liver cells that lack DGAT1 activity.

“DGAT enzymes produce the fat that is stored in the droplets that are important for HCV replication, so we wondered if inhibiting those enzymes might disrupt the viral life cycle,” said Dr. Herker. “We found that HCV specifically relies on one DGAT enzyme, DGAT1. When we inhibit DGAT1 with a drug, the liver still produces fat droplets through another DGAT enzyme but these droplets cannot be used by HCV.”

The team sought to identify which step in the HCV lifecycle requires DGAT1. They found that DGAT1 interacts with one viral protein, the viral nucleocapsid core protein, required for viral particle assembly. The core protein normally associates with the surface of fat droplets but cannot do so when DGAT1 is inhibited or missing in infected cells.

Researchers at Gladstone Institute of Cardiovascular Disease had previously cloned DGAT1.

Charles Harris, Robert V. Farese, Jr. and Katrin Kaehlcke were part of the Gladstone team. Celine Hernandez, Arnaud Charpentier and Arielle Rosenberg supported the research from the Universite Paris Descartes.

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Melanie Ott’s primary affiliation is with the Gladstone Institute of Virology and Immunology, where she is associate investigator and where her laboratory is located and her research is conducted. She is also an associate professor of medicine at UCSF.

Gladstone Institutes is a nonprofit, independent research and educational institution, consisting of the Gladstone Institute of Cardiovascular Disease, the Gladstone Institute of Virology and Immunology, and the Gladstone Institute of Neurological Disease. Independent in its governance, finances and research programs, Gladstone shares a close affiliation with UCSF through its faculty, who hold joint UCSF appointments.