



Computer modeling reveals how surprisingly potent hepatitis C drug works

February 19, 2013



LOS ALAMOS, N.M., Feb. 19, 2013—A study by researchers from Los Alamos National Laboratory and a multinational team reveals how daclatasvir, a direct-acting antiviral agent in development for the treatment of hepatitis C virus (HCV), targets one of its proteins and causes the fastest viral decline ever seen with anti-HCV drugs – within 12 hours of treatment.

Chronic infection with hepatitis C virus affects about 150 million people worldwide. It is the leading cause of cirrhosis, liver cancer and liver transplants and results in some 350,000 deaths worldwide every year.

The team's work reveals that daclatasvir has two primary modes of action against HCV and also provides a more accurate estimate of the HCV half-life. Until 2011, treatment options were limited and offered modest effectiveness; fewer than half of

treated patients were fully cured of the virus. In the last decade, active research on understanding the mechanisms of HCV replication resulted in the discovery of direct acting antivirals targeting all stages of the viral replication process.

The new mathematical analysis of the rapid viral decline observed after one dose of daclatasvir reveals that the drug blocks two stages of the viral lifecycle and that the HCV half-life in serum is four times shorter than previously thought according to a study published in *Proceedings of the National Academy of Sciences USA*.

The NS5A protein within the hepatitis virus is a specific target for drug development. The first NS5A inhibitor, daclatasvir, developed by Bristol Myers Squibb, showed one of the most potent effects in combating HCV; one dose led to a thousand-fold decrease in viral levels within about 12 hours. Oddly, however NS5A has no known enzymatic functions making it difficult to understand its mode of action and design optimal drug combinations.

“Unraveling how this drug could cause such a rapid drop in the amount of virus in an infected person’s blood could greatly enhance our ability to design optimal drug therapies and ultimately cure this disease,” said Alan Perelson, senior author on the paper and a senior fellow at Los Alamos National Laboratory.

A mathematical method called “viral kinetic modeling” aims to characterize the main mechanisms that govern the virologic response to treatment. It is instrumental in understanding HCV pathogenesis and in guiding development of a variety of anti-HCV agents.

Until now, viral kinetic models did not take into account the intracellular events during viral replication and infected cells were considered as “black boxes” whose viral production was partially shut down by treatment.

The researchers demonstrated that understanding the effects of daclatasvir *in vivo* requires a novel modeling approach that incorporates drug effects on the HCV intracellular lifecycle. They used this new model to characterize the viral kinetics during daclatasvir therapy and they showed that this compound efficiently blocked two distinct processes, namely the synthesis of new viral genomes (like other antivirals) but also the release of the virus from infected cells.

As a consequence of this unique mode of action, the viral decline observed during treatment with daclatasvir allowed for more precise estimation of the HCV half-life in serum, about 45 minutes, instead of the previously estimated 2.7 hours. This implies that the daily viral production; and thus the risk of mutations conferring drug resistance, is four times larger than previously thought.

About the team

The study is by researchers Alan S. Perelson from Los Alamos National Laboratory, Susan L. Uprichard and Natasha Sansone from University of Illinois at Chicago; Harel Dahari, Thomas Layden and Scott J. Cotler from Loyola University, Chicago; Richard Nettles from Bristol-Myers Squibb and Jeremie Guedj from Institut National de la Santé et de la Recherche Médicale, France.

The research was funded by National Institutes of Health, the National Science Foundation and the University of Illinois Walter Payton Liver Center Guild.

Link to paper online: [“Modeling shows that the NS5A inhibitor daclatasvir has two modes of action and yields a shorter estimate of the hepatitis C virus half-life.”](#)

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