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Team Identifies Novel Hepatitis C Inhibitors

By Eric Sauter

Scientists from the Scripps Florida campus of The Scripps Research Institute and their colleagues at Boston University have described their discovery of several novel drug-like inhibitors of the hepatitis C virus (HCV). These new inhibitors have the potential to substantially widen the current options to treat HCV infection.

The research, from the laboratory of Professor Donny Strosberg of Scripps Florida, supported by members of the Scripps Florida Lead Discovery Division directed by Peter Hodder, and colleagues from Boston University, will be published in an upcoming print edition of the journal *ASSAY and Drug Development Technologies* and appeared in the December 15, 2009 print edition of the journal *Bioorganic & Medicinal Chemistry Letters*.

With more than 130 million people infected worldwide by HCV, new therapeutic strategies are urgently needed for this blood-borne disease, which is the main cause, with hepatitis B, of liver cancer, according to the National Cancer Institute.

Using a new fluorescence-based assay, the scientists were able to identify four small-molecule inhibitors of dimerization of the viral core protein. In this process, which is essential to the survival of the virus, the core protein binds to itself and related proteins to form the viral capsid, the outer lipid-encapsulated protein shell that protects the virus's genetic material like an eggshell protects its yolk sack.

"The fact that is so exciting is that no one has really considered the core protein as a viable target in HCV—in HIV, yes, but not HCV," said Strosberg. "With this study, there is now no good reason why researchers shouldn't go after the HCV core protein."

One of the problems in developing drugs for HCV is that it mutates at such prodigious rates; mutations in viral enzymes tend to lead to increased drug resistance.

By targeting the interactions of the core protein with itself and with other proteins, Strosberg and his colleagues have sought to reduce the problem of rapid mutation—because the core protein mutates much less than the other HCV proteins, and because mutations that affect the interface between core and itself or other proteins would be more likely to deactivate the virus anyway. Core proteins orchestrate the assembly and release of the infectious virus, as well as the disassembly of viral particles upon entering host cells.

Significantly, the new compounds not only inhibited dimerization of the core but also inhibited propagation of HCV in isolated hepatoma cells.

The New Assay

In a study that appeared in the *Journal of General Virology* earlier this year, Strosberg and his colleague described how peptides (molecules of two or more amino acids that are the building blocks of proteins) derived from the HCV core protein also inhibited its dimerization. Peptides however, are difficult to administer orally, unstable in the blood circulation, and are therefore difficult to use therapeutically.

The new assay goes one step further, allowing Strosberg and his colleagues to identify the three times smaller molecules with potential to interfere with the core protein function in the virus.

"While there is no similarity structurally between these new small molecule inhibitors and the peptides, functionally they behave precisely the same way," Strosberg said. "We developed an assay to screen small



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molecules that is robust and capable of revealing useful compounds that block protein-protein interactions and production of the virus."

Protein-protein interactions, which involve such key physiological actions as signal transduction and protein assembly, are highly desirable drug discovery targets, not only for HCV, but also for other viral infections because inhibitors of these protein associations have been shown to lack many clinical complications, such as the adverse side effects of recombinant therapeutic proteins. However, designing small molecules that inhibit protein-protein interaction remains problematic for a number of reasons, primarily because proteins are so large—interactions are thought to often take place over a wide area and conformation/site-selectivity is difficult to engineer.

"We always look for the simplest solution," Strosberg said. "We knew from our peptide study that we could split the core protein and use only one part that we knew still allowed the dimerization process. That simplified the process because the core protein is sometimes difficult to work with."

Next, Strosberg and his team uncovered a domain on the core protein—what they call "a hot spot"—that was essential for the interaction that creates the capsid and allows the virus to function.

"Since we had already established a proof-of-concept that certain peptides could disrupt capsid formation, we left the peptide world and moved into the small-molecule world," he said. "We developed the high-throughput version of the assay. That's what the industry always wants to know first—can you move from a peptide to a small-molecule and can you find inhibitors among screen large collections?"

From there, the team screened small-molecule compounds that could potentially disrupt the protein-protein gears that create the viral capsid, using the protein library and high-throughput screening technology available at Scripps Florida. For initial screening, Strosberg and his colleagues used a relatively small library containing nearly 2,250 indoline alkaloid-type compounds, produced by their colleagues at Boston University.

These studies revealed the four promising compounds described in the study. "These new compounds definitely put us closer to the 'El Dorado' of finding viable protein-protein inhibitors for HCV," said Strosberg.

The small molecule inhibitor study made clear that three of the newly discovered inhibitors are relatively non-toxic compounds that could be the basis for the development of new anti-HCV drugs or could be used in combination with other compounds such as interferon on HCV targets other than the virus's core protein.

"These small-molecule candidates are quite promising," Strosberg said. "We continue to study the binding of these compounds with the HCV core protein and hope to design even more potent inhibitors based on their structures."

The first author of the *ASSAY and Drug Development Technologies* study, "A Time-Resolved Fluorescence-Resonance Energy Transfer Assay for Identifying Inhibitors of Hepatitis C Virus Core Dimerization," is Smitha Kota of The Scripps Research Institute. In addition to Strosberg, others authors include, Louis Scampavia, Timothy Spicer, Virginia Takahashi, and Peter Hodder of The Scripps Research Institute, and Aaron Beeler, John Snyder and John Porco of The Center for Chemical Methodology and Library Development, Boston University. See <http://www.liebertonline.com/doi/full/10.1089/adt.2009.0217?cookieSet=1>.

The first author of the *Bioorganic & Medicinal Chemistry Letters* study, "New Small Molecule Inhibitors of Hepatitis C Virus," is Wanguo Wei of The Center for Chemical Methodology and Library Development, Boston University; the corresponding author is John K. Snyder, also of Boston University. In addition to Strosberg, other authors include Smitha Kota and Virginia Takahashi of The Scripps Research Institute; and Cuifang Cai of Boston University. For more information, see [Pub Med](#).

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