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Press Release

Scripps Research Team Identifies Key Molecules that Inhibit Viral Production

Discovery May Aid in the Development of Anti-Hepatitis C Virus Drugs

JUPITER, FL, March 9, 2009—A team from The Scripps Research Institute has found a way to inhibit viral production of the Hepatitis C virus (HCV). The advance has the potential to accelerate future research on the virus life cycle and to aid in the development of novel HVC drugs.

The research, led by Professor Donny Strosberg of Scripps Florida, was published on March 4, 2009, in the *Journal of General Virology*'s advance, online edition, Papers in Press.

In the new study, Strosberg and his colleagues describe peptides (molecules of two or more amino acids) derived from the core protein of hepatitis C. The team found that these peptides inhibit not only dimerization of the core protein (the joining of two identical subunits), but also production of the actual virus itself.

"We went for the simplest solution, taking a peptide from core to see if we could block the interaction," Strosberg said, "and it did."

The Problem with Hepatitis C

With over 170 million people infected worldwide by HCV, new therapeutic strategies for HVC—a blood-borne disease that affects the liver—are urgently needed.

But one of the critical problems in developing drugs for HCV is that it mutates at such prodigious rates. An RNA virus like hepatitis C can mutate at a rate estimated as high as one million times that of DNA viruses; in contrast, DNA viruses contain an enzyme (polymerase) that acts as something of a proof reader to ensure that newly transcribed DNA strands are the same as the original, helping to reduce mutations.

"In one sense, the ongoing issue with hepatitis C is that there are still so very few drugs to treat the virus and very few tools to study it," Strosberg said. "We set out to develop new tools and to identify a new target – core, the capsid protein. By targeting the interactions of core with itself or other proteins, we could reduce the problem of rapid mutation not only because the core protein mutates significantly less, but also because mutations that would affect the interface between core and itself or other proteins would often be more likely to deactivate the virus, in contrast to mutations in viral enzymes which often lead to increased resistance to drugs."

Recent efforts to develop therapeutic strategies against HCV have concentrated on designing inhibitors that target several of the 10 HCV proteins that comprise the virus, including mostly the non-structural proteins. However, as the study points out, the one HCV structural protein

that has not been targeted yet is the core protein, the one responsible for assembly and packaging of the HCV RNA genome.

The Core of the Matter

Core, the most conserved protein among all HCV genotypes, plays several essential roles in the viral cycle in the host cell; studies have suggested that these core-core or core-other protein interactions can modulate various functions including signaling, apoptosis or programmed cell death, lipid metabolism, and gene transcription.

The core protein is particularly important in the assembly of the hepatitis C nucleocapsid, an essential step in the formation of infectious viral particles; the nucleocapsid is the viral genome protected by a protein coat—the capsid. This core protein plays an essential role in the HCV cycle during assembly and release of the infectious virus, as well as disassembly of viral particles upon entering host cells.

Looking closely at the core interaction with itself, Strosberg developed several novel quantitative assays or tests for monitoring these protein-protein interactions with the specific goal of identifying inhibitors of the core dimerization, which would block virus production.

"People have been dreaming about inhibiting protein-protein interactions, as a new El Dorado for finding novel drug targets," says Strosberg, "but few conclusive studies have emerged, except in the virus-host area."

Inhibition of HCV Production

The new research, however, led to the discovery of two peptides that inhibited HCV production by 68 percent and 63 percent, respectively; a third related peptide showed 50 percent inhibition. When added to HCV-infected cells, each of the three peptides blocked release but not replication of infectious virus; viral RNA levels were reduced by seven fold. Strosberg notes that the efficacy of small molecules like these can often be improved over initial levels.

"After we'd finished our work, we learned that Frank Chisari—one of the leading experts on HCV who works at Scripps Research in La Jolla—had been looking at similar peptides using a very different approach," said Strosberg. "One of his peptides was the same as ours—it also inhibited virus production. It's an incredible coincidence and a confirmation of our study."

The first author of the study, "Peptide Inhibitors of Hepatitis C Core Oligomerization and Virus Production," is Smitha Kota, a member of the Strosberg laboratory at The Scripps Research Institute's Florida campus. Others authors include Carlos Coito, and Guillaume Mousseau of The Scripps Research Institute and J-P Lavergne of the Institut de Biologie et Chimie des Protéines of the CNRS at the University of Lyon, France. See http://vir.sgmjournals.org/cgi/content/abstract/vir.0.008565-0v1.

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1961, it employs approximately 3,000 scientists, postdoctoral fellows, scientific and other technicians, doctoral degree graduate students, and administrative and technical support personnel. Scripps Research is headquartered in La Jolla, California. It also includes Scripps Florida, whose researchers focus on basic biomedical science, drug discovery, and technology development.

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