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New agent inhibits HCV replication in mouse models—no resistance seen

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Treatments against hepatitis C virus have only been partially successful. A major problem is that antivirals generate drug resistance. Now Seong-Wook Lee of Dankook University, Yongin, Republic of Korea and his collaborators have developed agents that bind to the business end of a critical protein, disabling it so successfully that no resistance has arisen. The research is published in the June 2013 issue of the *Journal of Virology*.

The target protein for the new agents is the NS5B replicase protein, which is the central catalytic enzyme in HCV replication. The researchers developed "RNA aptamers" which bind tightly to the part of that protein that performs the catalysis, disabling the replicase. Aptamers are short nucleic acids or peptides that provide the same level of recognition and binding ability that is common to antibodies.

The aptamers inhibited HCV replication without generating escape mutants, says Lee. Moreover, the aptamers inhibited diverse genotypes of HCV, neither causing toxicity nor inducing innate immunity, he says. Lee notes that in the study, therapeutic quantities of ligand-conjugated aptamer penetrated the liver tissue in the mice, raising the likelihood that therapeutically effective quantities could ultimately be achieved in HCV patients.

Roughly 170 million people worldwide are infected with HCV, says Lee, and it is the major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. There is as yet "no efficient and specific

single regimen against HCV," says Lee. Current treatments are associated with many side effects, partly because rapid generation of drug-resistant virus has forced clinicians to use combinations of several drugs, resulting in greater numbers of side effects in patients than if a single agent could be used. And even with the drug combinations only some patients can generate a sustained antiviral response.

More information: C.H. Lee, Y.J. Lee, S.-W. Lee et al. Inhibition of hepatitis C virus (HCV) replication by specific RNA aptamers against HCV NS5B RNA replicase. J. Virol. June 2013 87:7064-7074; published ahead of print 17 April 2013 ,doi:10.1128/JVI.00405-13