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Inhibition of hepatitis C virus in chimeric mice by sshRNAs: Sequence analysis of surviving virus shows added selective pressure of combination therapy

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It was previously shown that a cocktail of two short synthetic shRNAs (sshRNAs) targeting the internal ribosome entry site of hepatitis C virus (HCV) formulated with lipid nanoparticles was able to suppress viral replication in chimeric mice infected with HCV GT1a by up to 2.5 log₁₀. Viral load remained about 1 log₁₀ below pre-treatment levels 21 days after the end of dosing. HCV viral RNA amplified from serum of treated mice after the 21-d follow-up period was sequenced. Viral RNA from the HCV sshRNA-treated groups was altered in sequences complementary to the sshRNAs and nowhere else in the sequenced region, while the viruses from the control group that received an irrelevant sshRNA had no mutations in that region. The ability of the most commonly-selected mutations to confer resistance to the sshRNAs was confirmed in vitro by introducing those mutations into HCV-luciferase reporters. The most frequent mutations selected by sshRNA treatment within the sshRNA target sequence were at the most polymorphic residues as identified from an analysis of available clinical isolates. These results demonstrate a direct antiviral activity with effective HCV suppression, and confirm an RNAi mechanism of action. It is concluded that either a potent sshRNA against a highly conserved HCV target sequence or a combination of 2 sshRNAs against two different target regions could be effective against HCV infection when combined with antiviral agents having different mechanism(s) of action, but a cocktail comprising more than two sshRNAs would be required in any treatment relying on sshRNAs alone.

Biography

Brian H Johnston is Founder and CEO of SomaGenics, which invents and develops RNA-based therapeutics and diagnostic tools. He holds a BA in Chemistry from Pomona College, a PhD in Biophysical Chemistry from UC Berkeley, and performed Postdoctoral research at UC San Francisco and MIT. He subsequently moved to SRI International, where he was a founding Director of the Nucleic Acids Program before starting SomaGenics. He is author of some 56 research publications and reviews and has been a Principal Investigator or Co-investigator of research grants totaling \$20 million. He has held faculty appointments at MIT, Stanford, and the University of Paris.

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