

## Research

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# Small interfering RNA targeted to stem-loop II of the 5' untranslated region effectively inhibits expression of six HCV genotypes

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## Abstract

**Background:** The antiviral action of interferon alpha targets the 5' untranslated region (UTR) used by hepatitis C virus (HCV) to translate protein by an internal ribosome entry site (IRES) mechanism. Although this sequence is highly conserved among different clinical strains, approximately half of chronically infected hepatitis C patients do not respond to interferon therapy. Therefore, development of small interfering RNA (siRNA) targeted to the 5'UTR to inhibit IRES mediated translation may represent an alternative approach that could circumvent the problem of interferon resistance.

**Results:** Four different plasmid constructs were prepared for intracellular delivery of siRNAs targeting the stem loop II-III of HCV 5' UTR. The effect of siRNA production on IRES mediated translation was investigated using chimeric clones between the gene for green fluorescence protein (GFP) and IRES sequences of six different HCV genotypes. The siRNA targeted to stem loop II effectively mediated degradation of HCV IRES mRNA and inhibited GFP expression in the case of six different HCV genotypes, where as siRNAs targeted to stem loop III did not. Furthermore, intracytoplasmic expression of siRNA into transfected Huh-7 cells efficiently degraded HCV genomic RNA and inhibited core protein expression from infectious full-length infectious clones HCV 1a and HCV 1b strains.

**Conclusion:** These *in vitro* studies suggest that siRNA targeted to stem-loop II is highly effective inhibiting IRES mediated translation of the major genotypes of HCV. Stem-loop II siRNA may be a good target for developing an intracellular immunization strategy based antiviral therapy to inhibit hepatitis C virus strains that are not inhibited by interferon.

## Background

Hepatitis C virus (HCV) is a major blood-borne human pathogen [1]. It is estimated that more than 170 million people worldwide have been infected with hepatitis C [2].

The majority of infected individuals develop life long chronic infections since only a fraction of people infected with HCV develop immunity and clear the virus infection [3]. Chronic hepatitis C virus infection can results in long-