

## POTENT INHIBITION OF HCV ENTRY BY CARBOHYDRATE BINDING PROTEINS

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Inhibition of viruses at the stage of viral entry provides a route for therapeutic intervention. HCV envelope is comprised of highly glycosylated proteins E1 and E2 with approximately 4 and 11 N-linked glycosylation sites, respectively. Only high-mannose-type oligosaccharides are associated with these proteins. Since glycans associated HCV envelope glycoproteins play an essential role in protein folding and/or HCV entry, N-linked glycans might be a potential target for the development of new antivirals against HCV. We demonstrated here that antiviral lectins or carbohydrate binding proteins, scytovirin (SVN) (isolated from cyanobacterium *Scytonema varium*) and griffithsin (GRFT) (from the red alga *Griffithsia* sp.), exhibit potent (low nanomolar) anti-HCV activities in both HCV cell culture (HCVcc) and HCV pseudoparticle (HCVpp) assays. Both molecules exhibited the impressively wide therapeutic windows: i.e. the selective indexes of 1,400 and 90,000, respectively. This is the strongest potency observed among the compounds that we ever tested. Both molecules did not show anti-HCV activities in the subgenomic replicon assay, confirming that they act at the viral entry step. Although a number of new drugs begin to show promising results in clinical trials, there are accumulating evidences showing that the emergence of resistance viruses will eventually limit the efficacy. This is due to the extraordinarily high genetic diversity of HCV with rapid viral kinetics, large population size and a quasispecies distribution. As is the case for effective anti-HIV therapy, the combination of multiple drugs with different targets will thus be necessary for the treatment of hepatitis C. The inhibition of viral entry by molecules like SVN and GRFT offers a new opportunity to develop a highly active antiviral combination for HCV therapy. Moreover, these highly potent antiviral lectins will be valuable tools for dissecting the early steps of HCV entry.