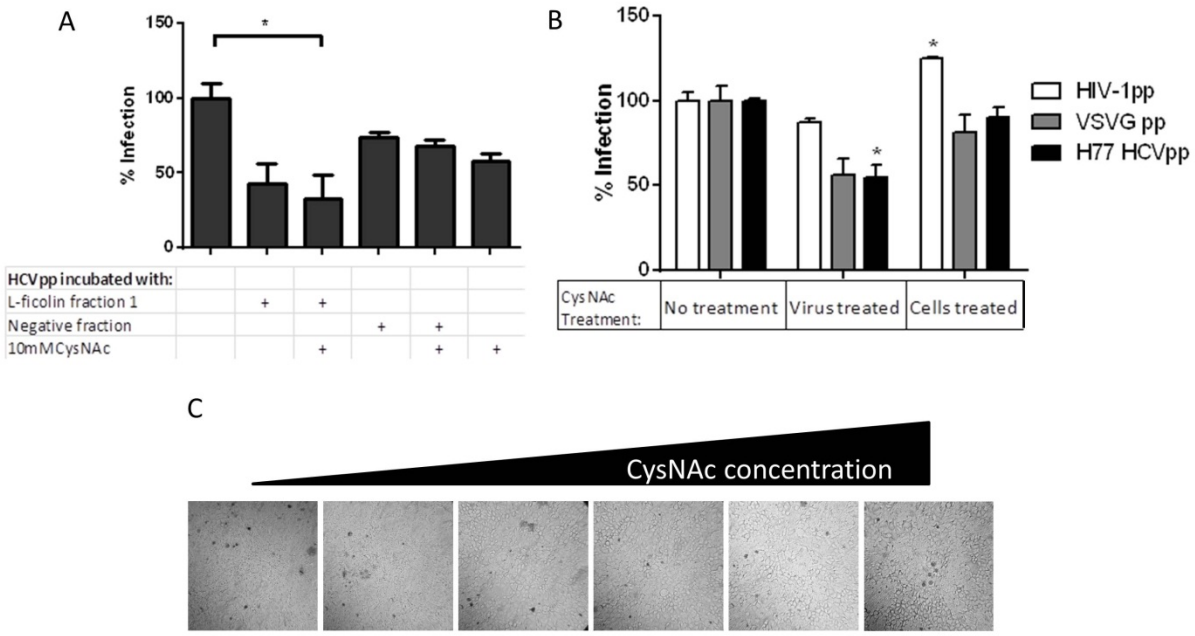
**Supplementary methods**

*Effect of L-ficolin ligands on viral entry.* To determine inhibition of neutralization of HCVpp entry by L-ficolin ligands, L-ficolin (or a negative control) was pre-incubated with either 10mM CysNAc for one hour prior to incubation with pseudoviruses and infection of Huh7 cells. After 4 hours' infection, media was removed and replaced with fresh media in the absence of ligands. Further experiments incubated 10mM of CysNAc with HCV, VSV or HIV-1 pseudoviruses, or target cells, for one hour before infection. Infection was determined by luciferase assay as described above. Cell cytotoxicity of CysNAc was assessed by incubating serially diluted CysNAc (10, 5, 2.5, 1.25 & 0.625mM) in DMEM for 24 hours with Huh7 cells before staining with trypan blue and inspection of the cell monolayer with a phase-contrast microscope.

*Patient samples.* Serum samples were obtained with ethical approval from the Trent HCV Cohort Study (MREC/98/3/55) and were retrieved from -80$^{o}$C storage after only one freeze-thaw cycle.

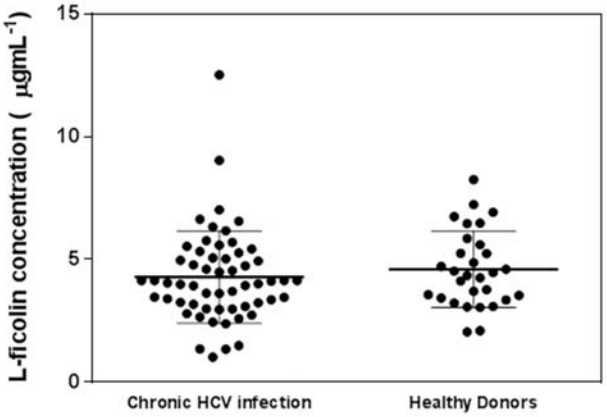
*Quantification of functional L-ficolin binding.* Binding activity of recombinant L-ficolin was determined by ELISA. Microtiter plates (Nunc) were coated with 1 mgmL$^{-1}$ bovine serum albumin (BSA) in phosphate buffered saline (PBS). Following overnight incubation at 4˚C, samples were incubated with 100 µL 0.1% acetic anhydride in methanol. Wells were blocked with PBS, 0.05% Tween 20 (PBS-Tween), containing 5% milk. After three washes with TBS (10 mM Tris–HCl, 140 mM NaCl, pH 7.4), containing 0.05% Tween 20 and 5 mM $CaCl_2$, serum, or recombinant L-ficolin was added. After washing, biotin-labeled anti-human L-ficolin antibody (GN5, 0.5µg/mL) was added for 2 hours. Wells were washed and incubated with a 1:5000 dilution of a streptavidin-alkaline phosphatase conjugate (Sigma). Following a further three washes with TBS–Tween, binding was visualized with pNPP substrate (Sigma). Absorbance was measured at 405nm. L-ficolin levels were quantified from a standard curve generated from a serum with defined L-ficolin concentration, as previously described [1].

Supplementary Figure 1.




**Supplementary Figure 1. Effect of CysNAc on neutralization of HCV pseudoparticles.** A) Neutralization assays using HCVpp representing strain H77 were performed with L-ficolin in the presence or absence of 10mM CysNAc, previously demonstrated to inhibit binding of L-ficolin to HCV E2. While neutralization was observed in the preparation containing L-ficolin, CysNAc unexpectedly did not inhibit neutralization, but augmented it. A similar effect of the presence of CysNAc was observed when incubating with a negative control preparation that had little effect on entry, demonstrating that the inhibition of entry by CysNAc was independent of the action of L-ficolin. Significant neutralization was observed with L-ficolin, as determined by One-way ANOVA (* $p<0.05$). B) Incubation of CysNAc with pseudoparticles possessing either HCV or VSV glycoproteins inhibited entry, but no effect was observed when incubated with HIV-1 pseudoparticles. Incubation of target cells with CysNAc resulted in increased HIV-1pp entry (One-way ANOVA; * $p<0.05$). C) Huh7 cells were incubated with increasing concentrations of CysNAc and then stained with trypan blue to assess toxicity of this compound on the cells. No appreciable cell death occurred as a result of increased CysNAc concentration, but changes in cell morphology and size were observed with increasing CysNAc concentration.

Supplementary Figure 2.




**upplementary Figure 2. Concentration of circulating serum L-ficolin.** The concentration of L-ficolin was assayed in 40 HCV-infected individuals and 30 HCV RNA/antibody-negative healthy donors. Serum L-ficolin concentrations ranged between 1-12.5µg/mL. The median value for healthy controls was 4.6µg mL-1 (S.D. ±1.5) and 4.2µg mL-1 (S.D. ±1.9) in chronic HCV infections. No significant difference between the groups was evident.