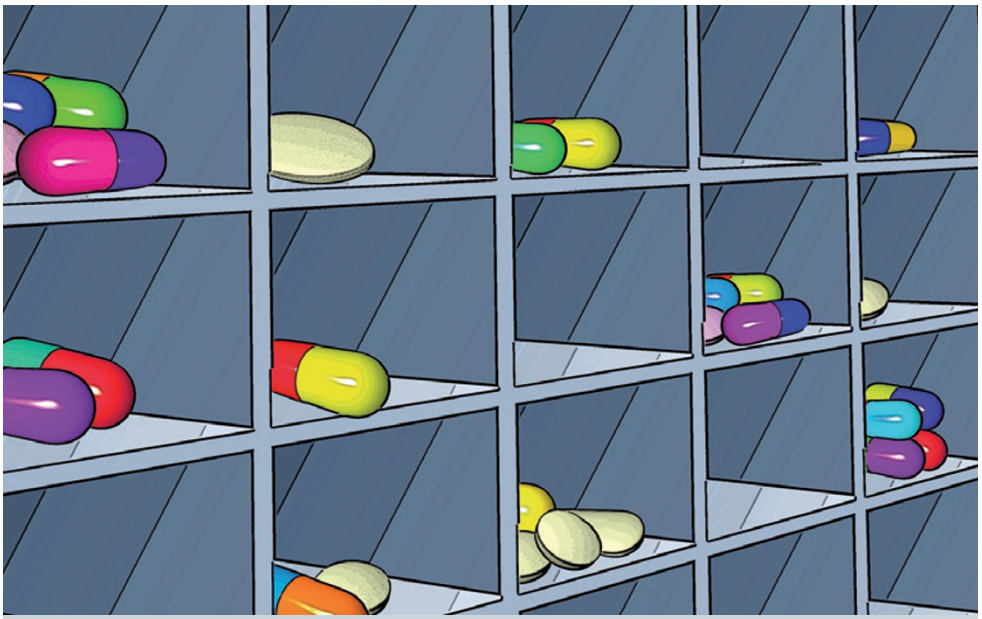

S.Harris/NPG

ANTIVIRAL DRUGS

# Searching the store cupboard for low-cost HCV drugs

Although several highly effective therapies for hepatitis C virus (HCV) infection have recently been approved, their high cost is a barrier to usage in many of the regions that are most affected by the virus. A new study of a large database of approved drugs suggests that repurposing an over-the-counter antihistamine might help to address this issue.

Liang and colleagues performed a cell-based quantitative high-throughput screen of a comprehensive library of approved drugs that was compiled by the US National Institutes of Health's Chemical Genomics Center. They tested for activity against HCV genotype 2a and confirmed hits in a cell-based HCV infection assay. Of the ~3,800 small-molecule entities in the library, antagonists of the $H_1$ histamine receptor containing a cyclizine moiety were found to have greatest potency against HCV. Following a secondary confirmation assay, chlorcyclizine hydrochloride (CCZ) — a first-generation antihistamine approved in the 1940s for allergy treatment — was selected for further testing.

> "CCZ showed synergistic antiviral activity with various classes of established HCV drugs"

There are seven major HCV genotypes, which are divided into several subtypes that show region-specific variation and require different treatment regimens. In human hepatoma cells infected with HCV chimeric-genotype viruses, CCZ significantly reduced intracellular and extracellular viral RNA levels, suggesting pan-genotype activity. Various *in vitro* assays showed that the drug does not affect virus replication, but instead probably inhibits a late stage of entry into the cell — a mode of action the authors propose could prevent viral entry into uninfected cells during hepatocyte turnover, as well as cell-to-cell spread.

Importantly, CCZ showed synergistic antiviral activity with various classes of established HCV drugs, including ribavirin, interferon-α and direct-acting antivirals such as sofosbuvir, suggesting the potential for combination regimens that lower the chance of resistance.

Next, Liang and co-workers investigated the pharmacokinetic characteristics of CCZ. Intraperitoneal injections of CCZ led to high levels of drug exposure in the liver compared with those in the plasma — an important distribution profile given HCV infection and replication occurs only in hepatocytes. However, the drug was also found to cross the blood–brain barrier, raising the potential for adverse effects that would need to be addressed in future development efforts.

To test drug efficacy *in vivo*, transgenic immunodeficient mice infected with HCV genotype 1b or 2a were injected daily with CCZ for 4 weeks and 6 weeks, respectively. Importantly, time-dependent reductions in serum HCV titres were observed over the full course of treatment, indicating no emergence of drug-resistant virus.

Together, the results identify CCZ as an affordable candidate for the treatment of HCV infection that warrants further investigation alone and in combination with existing drugs, and also identify it as a starting point for further optimization.

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**ORIGINAL RESEARCH PAPER** He, S. *et al.* Repurposing of the antihistamine chlorcyclizine and related compounds for treatment of hepatitis C virus infection. *Sci. Transl. Med.* **7**, 282ra49 (2015)