usual weak spots. The authors' early phase clinical data are promising, indicating that this compound may become a key component of next-generation anti-HCV therapies.

When HCV was discovered in 1989, drugs specifically targeting the viral proteins were expected to reach clinics rapidly. But more than two decades on, patients and physicians are still waiting. The current standard treatment for HCV infection involves weekly injections of pegylated interferon-α, along with twice-daily oral ribavirin. These drugs, both of which are general inhibitors of viral infection, often have serious side effects, including depression and flu-like symptoms. Furthermore, completion of the year-long course of treatment does not always cure the patient, with success depending on characteristics of the virus, such as strain (the viral genotype), as well as host attributes, such as genetic variations[2–4]. The need for further therapeutic options has spurred years of intense research, which are now coming to fruition.

Traditionally, viral enzymes are the prime targets for drug development. Several HCV enzymes are required for the virus's replication, including two proteases (NS2-3 and NS3-4A), a helicase (NS3) and a polymerase (NS5B) (Fig. 1). Of these, NS3-4A and NS5B have garnered the most attention as drug targets, with several candidates showing encouraging results in clinical trials[5,6]. But the rapid and error-prone replication of HCV makes the emergence of drug resistance a significant issue — and mutations that diminish susceptibility to one or more compounds have appeared during *in vitro* and *in vivo* testing[5,6]. To combat resistance, cocktails of antiviral drugs — ideally, drugs with diverse mechanisms of action — will probably be required, and researchers have therefore started looking beyond the viral enzymes.

Gao *et al.*[1] joined the search by using a broad screen of HCV replication to identify potent antiviral compounds. In a strategy designed to focus on new targets, the group selected candidates that decreased HCV replication in cell culture, but showed no inhibitory activity against NS3-4A, NS5B or the virus's helicase in biochemical assays. The identification[7] of a weak, but specific, 'hit' was followed by a touch of serendipity: the authors found that a dimerization product related to the original lead compound had a significantly higher potency. Further optimization produced BMS-790052 (see Fig. 1 of the paper[1] on page 96). This is an agent that at very low concentrations specifically inhibits all of the HCV genotypes tested, making it the most potent inhibitor of HCV replication ever described. But what is its target?

Prolonged culture of the virus in the presence of BMS-790052 provided a clue, as resistance-causing mutations emerged in one of the HCV proteins, NS5A. This hunch was supported when Gao and colleagues used co-precipitation studies to show that BMS-790052 and NS5A could interact.

For researchers, NS5A is something of a mystery. It is known to be an essential component of the viral RNA amplification machinery and a key player in the assembly of the infectious virus particle, with phosphorylation of the protein regulating these two processes[8,9]. But NS5A does not have a known enzymatic activity, and its mechanisms of action during the HCV life cycle are unclear. Crystal structures of NS5A have revealed that it forms dimers[10,11], which may come together into large oligomeric arrays that channel RNA substrates within the cell. Gao *et al.*[1] speculate that the dimeric structure of BMS-790052 allows it to disrupt the NS5A oligomers, initiating a ripple effect of conformational disturbances that could explain the compound's extreme potency.

Early clinical testing of this NS5A inhibitor[1] began with a placebo-controlled trial, in which patients chronically infected with HCV were given a single oral dose of BMS-790052 at various concentrations. The compound seemed safe and well tolerated, and remained at high levels in the blood for 24 hours. Most encouragingly, the highest dose that Gao *et al.*[1] tested led to an almost 2,000-fold decrease in the mean blood levels of HCV RNA after one day, with the levels remaining low for an entire week. Follow-up clinical data, including testing of multiple doses, are anxiously awaited.

These promising results[1] provide a proof of concept for targeting a non-enzymatic property of HCV in the clinic. The jury is still out on how BMS-790052 will perform in longer trials and in combination with other drugs — unfortunately, many candidate antiviral drugs fail at this stage because of adverse side effects. But the impressive potency of BMS-790052 transforms NS5A into a highly attractive target, and

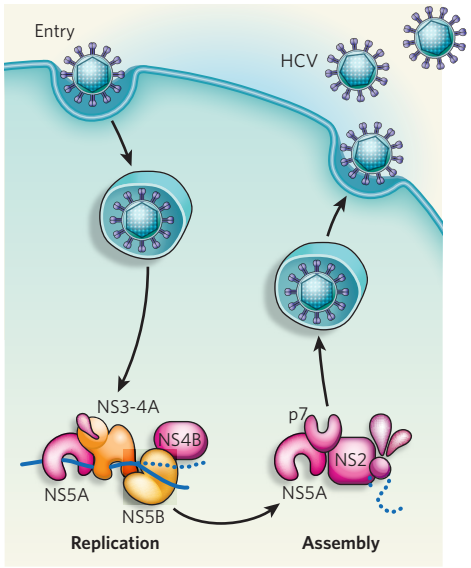

Figure 1 | Life cycle of the hepatitis C virus (HCV). On entering a host cell, HCV replicates using a series of enzymes, which have been the traditional targets for drug development (orange); they include the enzymes NS3-4A and NS5B. Gao *et al.*[1] demonstrate the feasibility of developing inhibitors of HCV proteins with no known enzymatic activity (pink) such as NS5A.

50 YEARS AGO

Health in Industry. By Donald Hunter — The history of occupational disease spreads over many years and, until comparatively recently, ailments like beat knee, 'stagmus', writer's cramp, grocer's itch and cotton-workers' throat were accepted as heavenly or other visitations about which little could be done. With the growth of the industrial revolution the number of diseases multiplied so much in factory, workshop and mine that few industrial workers were able to get through a life-time free from occupational disease ... This interesting book ... describes the genesis of industrial medical services and the way they have developed. Rightly, the author emphasizes that in this field prevention is better than cure, and that responsibility for prevention rests not only upon doctors but also upon the Government, architects, management, trade unions and the workers they represent.
From *Nature* 7 May 1960.

100 YEARS AGO

During the last General Election much was heard about the hard lot of the German workmen and peasants who are compelled to eat black bread, and much political capital was made of it. It may therefore be interesting to inquire how much of a hardship this is from the point of view of nutritiousness and also of tastiness. The so-called black bread is made of rye, and has the property of keeping moist for a much longer time than wheaten bread ... But a consideration of the chemistry of the different breads gives no support to the idea that black bread is an inferior article of diet ... It is good food, nevertheless, and those accustomed to it often actually prefer it ... The political orator is not too particular about his facts so long as he thinks they will serve his turn, and the allegations made about black bread have been, to say the least, wanting in scientific accuracy.
From *Nature* 5 May 1910.

50 & 100 YEARS AGO