Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The hunt for a vaccine for hepatitis C virus continues

The past year has been marked by unprecedented successes in the development of several effective vaccines against SARS-CoV-2 within 12 months of discovery of the virus. Alas, the same can not be said for the development of vaccines against hepatitis C virus (HCV), discovered more than 30 years ago. Most recently, Kimberly Page and colleagues reported the results of a randomised trial of a recombinant chimpanzee adenovirus type-3 (ChAd3) vector priming vaccination followed by a recombinant modified vaccinia virus Ankara (MVA) boost that aimed to prevent chronic HCV infection in a high-risk population of recent injection drug users. Both non-replicating viral vectors encoded the non-structural proteins NS3, NS4, NS5A, and NS5B of HCV genotype 1b. Despite producing HCV-specific T-cell responses and lowering peak HCV RNA levels, the vaccine failed to prevent chronic HCV infection.

The development of direct-acting antivirals for HCV means we have the tools to effectively cure patients with chronic HCV. However, many individuals are unaware they are infected with the virus, and the costs of these drugs can limit access. Further, liver damage during chronic HCV infection can persist after viral clearance, and high-risk populations remain at risk of reinfection even after successful treatment. The WHO target of eliminating viral hepatitis by 2030 includes the goal of reducing new HCV infections by 80%. Despite effective treatments, achieving elimination without an HCV vaccine seems unlikely.

There are several reasons why development of an HCV vaccine has proven challenging. HCV is genetically highly diverse. Eight genotypes are currently known, each differing by 30% in nucleotide sequence (by contrast, hepatitis B virus genotypes differ by only 8%). HCV genotypes are further classified into around 90 subtypes with 15% sequence variation. HCV is also adept at avoiding host immune responses. HCV envelope proteins E1 and E2 are the targets of the humoral immune response and thus also a target for vaccines that aim to raise neutralising antibodies against the virus. However, several mechanisms have evolved to avoid such a response. For instance, a hypervariable region of E2 shields more conserved epitopes in the protein from neutralising antibodies, as does glycosylation of the envelope proteins. HCV also exists in the circulation in more than one form, with subviral particles lacking replicative machinery but carrying envelope proteins substantially outnumbering infectious lipoviral particles and acting as decoys for neutralising antibodies. Beyond the peculiarities of the virus itself, research is hindered by a lack of in vitro and in vivo models of infection.

Evidence from individuals who spontaneously clear acute HCV infection suggests that a protective response involves both humoral and cellular immune responses. It thus seems likely that any successful vaccine will need to trigger both types of response. Although the ChAd3-MVA HCV vaccine did not prevent infection, the fact that it stimulated specific T-cell responses, coupled with the success of a similar approach against SARS-CoV-2, suggests that use of non-replicating viral vectors is worth pursuing. While the ChAd3-MVA vaccine targets HCV non-structural proteins, other vaccine candidates target E1 and E2. One candidate, based on a recombinant E1E2 protein, elicited neutralising antibody responses in human studies. The development of mRNA vaccines for SARS-CoV-2, which use the vaccinated individual's own cells to express the spike protein of SARS-CoV-2 and thus trigger an immune response, has garnered much excitement. However, the innate variability of the HCV envelope proteins and our limited knowledge of their protein structure represent obstacles to developing an mRNA HCV vaccine. Further work to define the optimal viral epitopes to target in vaccine development will be essential.

Conducting clinical trials for HCV vaccines can also be challenging—eg, the relatively low incidence of HCV in many industrialised countries necessitates trials being run in the often marginalised populations at high risk of HCV. There is also a relative dearth of funding for research and development of an HCV vaccine. The acute nature of COVID-19 has focused efforts to tackle SARS-CoV-2; by contrast, the chronic nature of HCV, often in marginalised communities, and in combination with the stigma associated with the disease, has left it neglected. We must learn from our colleagues in the AIDS community to be more vociferous in calling for action and investment. It is worth noting that by 2019, there were 39 ongoing HIV vaccine trials; by contrast, just two HCV vaccine candidates have progressed to human trials. Despite the challenges in development of an HCV vaccine, the case for its development is clear; achieving the WHO goals for elimination may depend on it. ■ *The Lancet Gastroenterology & Hepatology*

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For **Page and colleagues' HCV vaccine trial** see *N Engl J Med* 2021; **384:** 541–49

For more on the **recombinant E1E2 vaccine** see *Vaccine* 2010; **28:** 6367–73