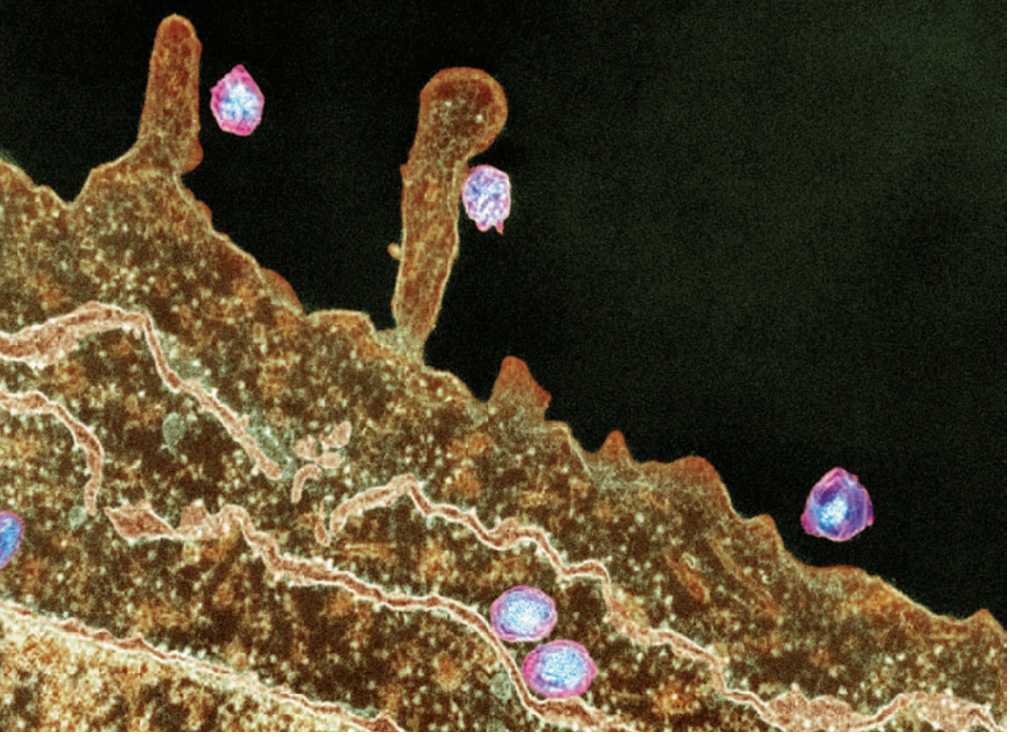

THOMAS DEERINCK, NCMIR/SCIENCE/PHOTO LIBRARY.

The hepatitis C virus attacks liver cells, which that can lead to cirrhosis and cancer.

VACCINES

A moving target

The hepatitis C virus has a set of cunning ways to evade immunity, but researchers are turning the immune system on it.

BY MICHAEL EISENSTEIN

The hepatitis C virus (HCV) dodges the immune system with devilish resourcefulness. Its vaunted genetic variability is an obvious advantage in escaping recognition by antibodies and T cells. But the virus also takes the fight directly to the host by actively suppressing the innate immune system, a key early mechanism in response to infection. In parallel, HCV uses diverse stratagems to mask its surface from antibodies that might neutralize infection. Recent evidence suggests that when all else fails, HCV hides — creeping directly from one liver cell to another, without exposing itself to the immune system[1]. "It's a special challenge as a vaccine target, and 75% of patients develop infection for life," says Michael Houghton, a virologist at the University of Alberta in Edmonton, Canada, who co-discovered HCV in 1989.

Given these facts, one might expect HCV vaccine research to be an exercise in futility. But the minority of patients who banish the virus during acute infection offer hope that the immune system might be coaxed into rising to the challenge. "If somebody has recovered from a primary HCV infection, any subsequent infection is much milder, and they tend to clear the virus far more quickly," says Marian Major, a virologist with the US Food and Drug Administration. "This protects the patient from chronic infection, which is the goal we need to meet for any HCV vaccine."

Accordingly, the most aggressively pursued — and clinically advanced — research has focused on the development of therapeutic vaccines that can beef up an otherwise inadequate immune response and treat chronic disease. Prophylactic vaccines are also in development, but they face economic, ethical and social problems, on top of daunting scientific challenges. However, both approaches need to overcome a common problem: HCV is a wily operator and will not be easy to beat.

CALLING IN FOR BACKUP

Several companies are actively testing therapeutic vaccine candidates, most of which use a non-pathogenic viral vector that presents HCV proteins to the immune system. For example, French biopharmaceutical company Transgene, based in Illkirch Graffenstaden, is adapting the vaccinia virus, used in the smallpox vaccine, to provoke an immune response against a trio of HCV targets. In early clinical trials, Transgene's TG4040 vaccine by itself achieved a modest reduction of viral load in chronically infected patients. Transgene recently started a phase II study to further assess TG4040's efficacy in combination with the standard antiviral regimen of interferon-α plus ribavirin.

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Instead of using a vector, the Swedish company ChronTech Pharma, based in Huddinge, Sweden, vaccinates patients with naked DNA molecules encoding HCV genes. DNA vaccines are considerably cheaper to manufacture than vector-based vaccines, although their track record is patchy. But, by using an electrical current to pulse DNA directly into muscle tissue, ChronTech has been able to markedly improve DNA uptake while eliciting a strong local immune response. "For patients who went through the vaccine trial and were then put onto standard care, their virus disappeared very rapidly, and they also had an unusually high cure rate," says ChronTech co-founder Matti Sällberg, a viral immunologist at the Karolinska Institute in Stockholm. Indeed, five of six patients treated with ChronVac-C in conjunction with a standard drug regimen successfully eliminated HCV infection (relative to about half of all patients with existing drugs alone), and in March the company received approval for a phase II trial.

Both Transgene's and ChronTech's vaccines stimulate the cellular immune response — the first stage of the adaptive immune response, which kicks in after innate immunity (see 'HCV versus the immune system'). In the cellular immune response, killer T cells destroy infected liver cells when they recognize surface features, known as epitopes, that indicate the presence of virus. Cellular immunity seems to be the front line in preventing progression of acute infection. "Spontaneous resolvers are those who elicit early and broad cellular immune responses against multiple epitopes," says Houghton.

After the cellular immune response comes the humoral response, in which B cells secrete antibodies that can bind to and possibly neutralize HCV. The importance of humoral immunity in beating back acute HCV infection remains murky. "We need to learn a lot more about whether neutralizing antibodies are important," says Genevieve Inchauspé, head of the Infectious Diseases Department at Transgene. Helper and killer T-cell-oriented therapies have shown some effectiveness in humans, and there is evidence that HCV might encounter problems in eluding T-cell recognition[2]. Although the virus can acquire mutations that allow it to escape many immune-system traps, the mutations it requires to avoid T cells are detrimental and "actually reduce viral fitness", says Sällberg.

Yet even the best therapeutic vaccine candidates induce reactions that fall far short of those of spontaneous resolvers. Most ongoing trials therefore add these experimental therapies to the current standard treatment, but the existing regimen is notable for its nasty side effects. "The ultimate goal would be to be able to replace interferon and ribavirin with a vaccine," says Inchauspé, "or perhaps reduce the

therapy: make it shorter with fewer injections." She adds that patient interest is high enough that Transgene completed recruitment for its phase II trial ahead of schedule.

PREPARED FOR THE WORST

As safer and more effective drugs approach the marketplace, thus covering the therapeutic front in the battle against HCV, many vaccine developers are trying to address the traditional objective of vaccines: preventing disease from taking hold in the first place.

While working at the biotechnology firm Chiron, later acquired by Swiss pharmaceutical firm Novartis, Houghton managed the team that developed the first preventive HCV vaccine candidate, based on an injection of purified recombinant viral envelope proteins. This Chiron/Novartis vaccine was designed to elicit the production of antibodies while stimulating helper T cells, which in turn stimulate killer T cells and thus promote cellular immunity. In preclinical studies, significantly fewer vaccinated animals exhibited chronic infection relative to unvaccinated controls after exposure to HCV[3]. In phase I trials, human volunteers responded to vaccination with a strong helper T-cell response while producing detectable levels of antibodies with the capacity to neutralize diverse viral subtypes[4].

Although Novartis developed a plan for a phase II trial to assess the vaccine's protective efficacy, work lost momentum after Houghton's departure in 2007. Development was ultimately suspended, largely owing to financial considerations. "Although I believe it could work with 70–80% efficacy, it's a difficult and expensive vaccine to make," says Houghton. He would like to continue to develop and refine the approach in his new lab, with an eye towards future clinical trials.

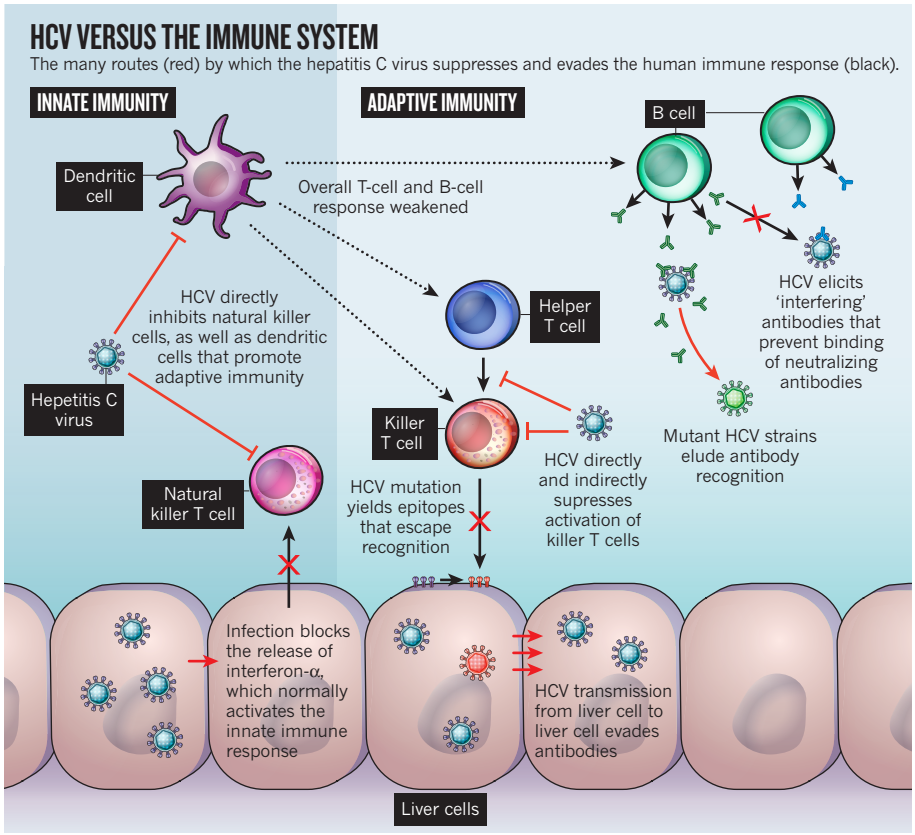
The only other HCV vaccine candidates in the pipeline are from Okairos, a Rome-based biopharmaceutical company that was spun off from drug giant Merck, that recently embarked on phase I trials with two vaccine formulations. Okairos's prophylactic strategy uses two injections — an initial 'prime' and a follow-up 'boost' — that contain distinct viral vectors, each of which expresses the same set of HCV-derived proteins. This combination approach prevents the immune response from focusing its attention on the vector at the expense of the intended target, explains Alfredo Nicosia, chief scientific officer at Okairos. Okairos presented initial data from one trial at this year's International Liver Congress, in Berlin, showing that seven of ten vaccinated volunteers generated a broad T-cell response against peptides derived from a variety of HCV subtypes. This reaction was sustained over the course of a year following the prime injection, and Nicosia is optimistic that this vaccine will be ready for phase II trials later this year.

The motive for developing a prophylactic HCV vaccine is clear: to avoid the need for a toxic, unpleasant and expensive treatment that doesn't always work. A full course of ribavirin and interferon-α costs US$25,000 in the United States. Nevertheless, there is little evidence to suggest an imminent scramble for the largely empty prophylactic marketplace.

One reason may be that the advent of potent new antiviral drugs such as telaprevir (from Vertex Pharmaceuticals, based in Cambridge, Massachusetts) and boceprevir (from Merck, based in Whitehouse Station, New Jersey) offers an efficacy of HCV treatment that removes some of the urgency from developing preventive strategies. Furthermore, because of the relatively inefficient sexual transmission of the virus, most new cases of HCV arise from unsanitary medical practices in the developing world or among injection drug users; the limited financial resources of this target population could be a serious deterrent to companies that might otherwise consider embarking on the expensive and risky journey of vaccine development. Under these conditions, commercial success might depend on the willingness of health regulatory agencies to integrate HCV prevention into the standard vaccination arsenal. Houghton sees it as an open question whether those agencies would recommend a universal HCV vaccine for adolescents, "knowing that it's mainly the product of high-risk behaviours like intravenous drug use."

Even if a vaccine manages to clear those hurdles, navigating through the testing process will be more tricky than usual. HCV is so good at evading the innate immune system that a successful prophylactic vaccine might not prevent acute infection, although, by bolstering adaptive immunity, the vaccine should prevent a chronic infection and subsequent reinfection. This risk of acute infection will add an ethical complication to clinical trials involving prophylactic treatment of patients in high-risk groups. Doctors who monitor these trials would be obliged to warn people who develop an acute infection and offer them prompt access to treatment, directly confounding the study results.

These challenges are not insurmountable and, as a positive example, Houghton points to the vaccine against hepatitis B virus, which also disproportionately affects injection-drug users. He adds that the expertise of investigators at agencies such as the National Institute on Drug Abuse, in Bethesda, Maryland, has been invaluable in HCV vaccine trial planning and recruitment. However, it is important to manage expectations: even a successful vaccine will probably achieve only an efficacy of 70–80% because of HCV's remarkable escape artistry. "It's a race between the vaccine-induced immune response and the virus," says Nicosia, "and we need to tilt it in favour of the former in order to achieve prevention." ■



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1. Brimacombe, C. L. *et al. J. Virol.* **85**, 596–605 (2011).
2. Söderholm, J. *et al. Gut* **55**, 266–274 (2006).
3. Houghton, M. *Immunol. Rev.* **239**, 99–108 (2011).
4. Frey, S. E. *et al. Vaccine* **28**, 6367–6373 (2010).