



# HCV vaccines—back to the future?

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HCV is a huge global problem. Major advances have been made in recent years in the drug therapy for chronic HCV infection (1). If patients have access to such directly acting antiviral agents, there is a very high chance of cure in most settings, even in patients with advanced disease or with previous treatment failures. However, in order to effectively get on top of the epidemic, such therapy is likely only one weapon, as there is still a substantial amount of ongoing transmission and undiagnosed disease, often in populations that are hard to reach. Virologic cure through the new agents does not lead to host immunity, so approaches to prevention of new or repeat infections are still needed. For this reason, a vaccine for HCV still has an important place at the table (2,3).

The classical approach to vaccines has been to use either a live strain with attenuated pathogenicity—as in the case of smallpox vaccine—or to use a killed or inactivated vaccine. Both approaches have been very effective. Live strains—such as the yellow fever vaccine—produce long lasting immunity, and combine typically cellular immunity with humoral responses. While this is advantageous, for many pathogens there is no clear way of safely attenuating the virus, so the risks outweigh the benefits. Inactivated vaccines, for example the Salk polio vaccine, similar to the toxoids used for tetanus, induce a strong antibody response, although the induction of cytotoxic T cells is limited. In the end, the efficacy of the vaccine depends on the dominant form of protection. In the case of HBV vaccines, a recombinant protein approach is highly effective, as the levels of antibody generated are sufficient to provide robust immunity (4). Recombinant protein approaches mimic the killed vaccines in providing a non-replicating

antigen, together with sufficient adjuvant to activate the innate immune responses needed for immunologic priming. For HBV the field is relatively well off as the antibodies represent a clear “correlate of protection”—i.e., their presence predicts efficacy (4). Unfortunately, we do not have very well defined correlates of protection in HCV infection, although there is a wealth of data that innate and adaptive immune responses are important, including a role for T cells. This includes studies of animal models, host immunogenetics, viral evolution and numerous correlative studies in acute and chronic disease, as well as challenge studies (5-7).

For HCV, there have been limited attempts to date to develop preventive vaccines, compared for example to HIV, and there are no simple live-attenuated avenues to explore (3,8,9). HCV is persistent, highly mutable, and difficult to grow in culture. It is also in many patients a relatively poor inducer of immune responses, partly because of its hepatotropism. In common with other complex infections such as HIV and malaria, a viral vector approach has been taken by a few groups, using HCV antigens expressed in the context of another virus, such as a poxvirus or adenovirus. This allows the immunogen to be presented in an optimal form to generate cellular immune responses, and in humans, adenoviral vectors have been shown to be quite effective at priming both CD4+ and CD8+ T cell responses (10,11). Currently a preventive HCV vaccine based on priming with a chimpanzee adenoviral vector expressing HCV non-structural proteins 3-5B, and boosting with a modified vaccinia Ankara (MVA) vector expressing the same proteins is in phase 2 trials in the USA (<https://clinicaltrials.gov/ct2/show/NCT01436357>).

Antibodies also have a role to play in protection against HCV, and in an ideal world a vaccine that induced a high-titre antibody response capable of blocking infection of a wide range of HCV strains—so-called broadly neutralising antibody (bNAbs)—would be very effective. Attempts have been made to generate antibodies using recombinant HCV envelope proteins, and bNAbs have been generated with this approach (12,13). However, high level production of these protein targets is not trivial and so this area is still open for development, including attempts to focus the antibody response on targets within envelope which are highly conserved and block infection (14).

On this background the recent study by Yokokama *et al.* in *Gut* is of interest as it combines new and old approaches to try and induce protective immunity against HCV (15). While it is not possible to routinely culture HCV, certain strains—notably JFH, first generated by Wakita, a co-author on the current study—can replicate in specific cell lines, and this technology has been further developed to allow different genotypes to be cultured (16). The authors were able to make high level stocks of a cell culture strain (HCVcc), purify it and then inactivate it using UV light for safe use as a vaccine. In order to improve its immunogenicity, they combined it with different adjuvants, one the classical alum, and a second, based on stimulation by DNA motifs known as CpG presented in nano-particulate form. CpG motifs bind Toll like receptor 9 (TLR9) and induce strong innate immune activation, enhancing immunogenicity—in particular when presented in nanoparticulate form (17). They analysed immunogenicity of such a vaccine in mice and then in marmosets.

The study showed a number of important features. Animals receiving vaccinations using the alum based vaccine did generate some antibodies against HCV, although the levels of neutralisation were overall quite low. However, using the CpG based nanoparticle adjuvant K3-SPG, the same inactivated HCVcc preparation did induce neutralising antibody which was able to block infection. The levels of neutralisation *in vitro* reached around 60%, so blockade was not complete, but interestingly the sera did block infection by strains bearing envelopes from diverse genotypes, which would be an important attribute of any vaccine. There was also some evidence of T cell responses against components of the vaccine, capable of making interferon-gamma (IFN $\gamma$ ). Analyses of marmoset T cell responses is difficult, so the overall levels of such responses are hard to gauge compared to human studies, but once again they were much more

evident using the CpG based nanoparticle adjuvant K3-SPG. Induction of IFN $\gamma$  in response to HCV antigens does correlate with successful immune control of HCV in many human studies, was an important readout in the challenge studies performed previously using virally vectored vaccines, and remains the major measure immunogenicity in the development of HCV T cell vaccines in human trials (11).

This vaccine approach therefore is in many ways classical, but also relies heavily on the new adjuvant for its immunogenicity. The issue is to assess the potential for protection. This was not addressed in the marmoset model, although such animals can be infected with chimeric HCV/GBV-C viruses and that may be one possible approach (18). Additional pre-clinical models also include transgenic mouse strains which support HCV infection, some of which are immunologically intact (19). Given the lack of a clear correlate of protection, it would be very valuable to have more preclinical data before engaging in human studies. However, if it is possible to scale up and provide a highly robust safety profile for such a vaccine, immunogenicity studies in humans, followed by trials in populations at risk are really the only way to answer the question regarding protection. Possibly the blend of old and new approaches used in this study could pave the way for such future vaccines.

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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