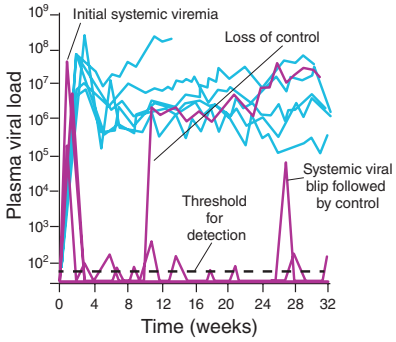

Figure 1 SIV challenge of RhCMV-SIV immunized rhesus macaques. Although all rhesus macaques became infected, half could achieve remarkable control despite occasional ongoing viral blips, with ultimate lack of recoverable virus. The combination of an antibody response with this T cell response might be even more effective at preventing infection and eliminating the virus.

ing widespread seeding of reservoirs and clearly limiting the systemic progressive infection that otherwise ensues. The importance of control in the early phase of infection is underscored by the fact that vaccinated rhesus macaques in which profound containment was not observed showed a level of steady-state viremia indistinguishable from controls[11].

The RhCMV-SIV vaccine clearly did not protect against acquisition of infection, and induction of functional antibody responses must remain a goal of vaccine efforts. But T cells will have to play a part as well, as T cell–B cell interactions are required to initiate and sustain effective B cell immune responses[14]. Notably, many of the licensed vaccines currently used against infectious diseases can prevent infection when antibody levels in the mucosa are sufficiently high; however, given the unlikelihood that an HIV vaccine will have 100% efficacy against acquisition, it is crucial to have effector T cells as a second line of defense to purge any cells that get infected[14]. Natural clearance of HIV infection has not been documented, so we need to outdo natural immune responses, which is the remarkable result achieved by Hansen *et al.*[11].

Whether modified CMV vectors can meet the regulatory challenges involved in administering a persistent replicating virus as a vaccine remains to be determined, and a human CMV vector will have to be attenuated[15]. Moreover, this approach without B cells is unlikely to be enough: only half of rhesus macaques were protected, and there was no effect on acquisition. Yet one thing is certain—the proof of principle has been established. Persistent effector memory responses of the type induced by CMV are able to prevent progressive disease and, possibly, clear infection. At present other vectors in development do not achieve similar persistent effector T cell responses, but this study should prompt additional efforts to do so. In particular, replicating vectors that are not persistent will need to be tested, as they will not face the regulatory hurdles of the CMV-based vaccine. Moreover, there are examples, at least in small-animal models, of replicating vectors inducing high levels of effector T cell responses. More vigorous T cell responses than those achieved with previous T cell–based vaccines[3] may be able to contribute to containment similar to that observed with the RhCMV-SIV vaccination, and large numbers induced by vaccination are likely to be readily accommodated by the T cell compartment without compromising other immune responses[16].

Preventing or limiting the initial infection with antibody responses, and cleaning up systemic infection when it occurs with an effector T cell–based approach, is a paradigm of the immune system[17] and offers the best hope for success. The remarkable level of protection, not prevention, by the candidate T cell–based vaccine used by Hansen *et al.*[11] suggests that clearance of HIV infection may just be possible, which also has implications for current efforts to achieve a cure[18]. With the ongoing global HIV epidemic, these results are good news and offer ample opportunity to build on these exciting advances. The study also underscores that there is no substitute to testing multiple concepts as we continue to search for success. There have been only three vaccine concepts tested in human efficacy trials in the first 30 years of the epidemic[2–4]. Novel concepts such as this deserve to be moved forward in parallel as quickly, efficiently and safely as possible.

COMPETING FINANCIAL INTERESTS
The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturemedicine/.

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■ BEDSIDE TO BENCH

To neutralize or not, a key HIV vaccine question

Thomas J Hope

The goal of developing a vaccine to decrease the sexual transmission of HIV remains one of the highest priorities of public health worldwide. The prevention of new HIV infections would clearly have a tremendous impact on the ability of physicians to deliver quality healthcare. Recently, there have been a number of developments in our understanding of how the immune system responds to HIV and how such responses might be harnessed to develop an effective vaccine[1,2]. But the interpretation of these observations is subject to debate—what is viewed as encouraging by some will lead others to the opposite viewpoint. An active debate of the importance of these results will be invaluable in making sure that future investments in vaccine development advance the field.

In the past few years, the results of two vaccine trials have transformed much the HIV vaccine field by generating positive and negative results[3,4]. First came the disappointment of the STEP trial vaccine, which used an Ad5 vector to deliver a T cell–based vaccine[3], which generated robust cytotoxic T cell

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responses but failed to show any protection. This was followed by the potential protection from HIV acquisition observed in the RV144 Thai vaccine trial, a result that shocked many in the field. The surprise was due to the fact that it used a combination of vaccines that failed when tested individually[4]. Unlike the STEP trial vaccine, this vaccine generated robust responses of antibodies that bind the HIV envelope protein but did not generate strong cytotoxic T cell responses. However, the antibodies generated did not show the crucial ability to neutralize varied strains of HIV. A vaccine that generates broadly neutralizing antibodies (bnAbs) has been the 'holy grail' of HIV vaccine research since the virus was discovered more than 25 years ago.

The promise of bnAbs was clear. Monoclonal antibodies with broadly neutralizing activity could protect rhesus macaques from vaginal challenge after intravenous injection[5]. Although many years of research yielded only a small number of monoclonal bnAbs, recent advances in technologies have led to an explosion in the identification of new ones. Some of these recently identified bnAbs have the ability to disrupt the infectivity of more that 90% of the HIV variants known worldwide in standard neutralization assays[6]. bnAbs targeting one of several specific sites on the HIV envelope protein can be isolated from the 1% of HIV-infected individuals, the so-called elite neutralizers, who show evidence of broadly neutralizing activity in their blood[7]. This proliferation in the number of example bnAbs has facilitated comparative studies revealing the characteristics that give broadly neutralizing function, which generally fall into several classes that interact with different regions of the envelope protein[8].

Comparison of the binding specificity of monoclonal bnAbs revealed that they focus their binding activity on a small number of regions of the viral envelope and often are polyreactive (sticky)—a beneficial property, as it can increase binding avidity when the low number of envelope spikes in HIV virions prevents simultaneous binding of both arms of the antibody[9]. Sequencing of the genes encoding bnAbs also revealed another rather remarkable characteristic—extensive hypermutation of the variable regions of the antibodies that mediate binding specificity[10]. Hypermutation is a normal function of the antibody response that allows for maturation to achieve optimal binding. Most of the bnAbs contain 80 or more amino acid changes within the heavy and light chains. The extensive hypermutation can lead to the convergent evolution of related sequence[10], structure and envelope-binding specificity from two different heavy chain genes. It is therefore clear that an effective vaccine would need only to present an epitope that will select antibodies with the defined bnAb specificities.

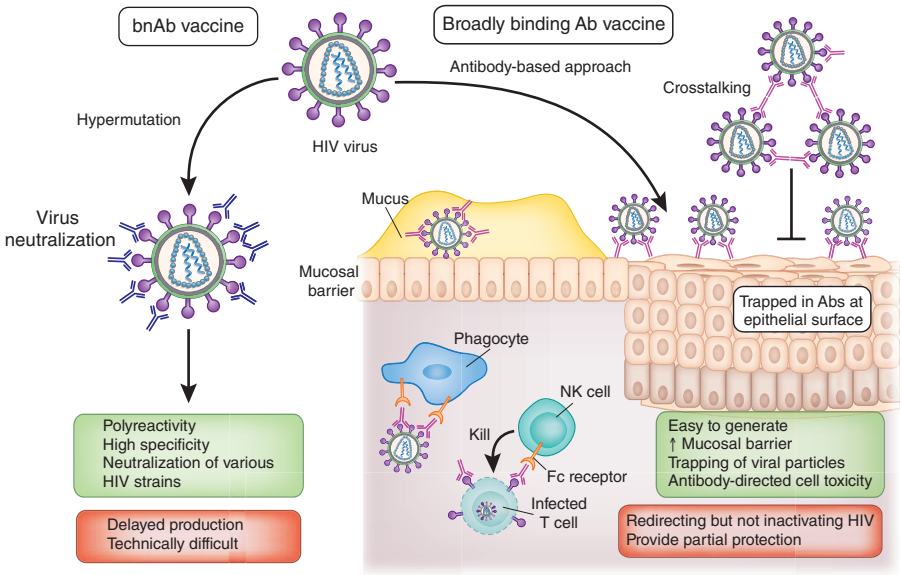

Figure 1 Broadly binding antibodies against HIV infection may efficiently block HIV infection. Although bnAbs could potently block numerous HIV virus strains and prevent infection, their production can be tedious and highly variable among controllers. Despite these pitfalls, a broadly binding Ab vaccine may generate antibodies capable of providing efficacy through different means.

Unfortunately, selecting binding specificities requiring such extensive hypermutation will clearly require multiple rounds of injections followed by selection for increased affinity in vaccinated individuals. This affinity maturation through selection requires continuous exposure to antigen over extended periods of time during the vaccination protocol. The study of the temporal development of bnAbs in infected individuals reveals that it takes, on average, 2.5 years to develop these protective antibodies[2].

The type of vaccination regimen that can recapitulate the continuous, daily systemic exposure to billions of virions that drives hypermutation in infected individuals is not clear. And only 10–30% of infected individuals will actually develop any of these bnAbs during infection[2]. If bnAbs do not arise within the first 3 years of infection, it does not seem that they can be developed subsequently[2]. This is not good news in the efforts to develop a vaccine that is focused on the goal of generating bnAbs. The identification and characterization of bnAbs has showed the field what humoral response a vaccine strategy must generate while revealing that stimulating such a response seems insurmountable at first glance.

The vaccine field has been focused on neutralizing antibodies since the beginning, and rightly so, as this effort has the greatest promise and must therefore continue. However, there may be an alternative. The recent RV144 Thai vaccine trial generated robust binding antibodies that did not show broadly neutralizing activity in standard assays[4]. On the basis of the outcome of the RV144 Thai vaccine trial, these binding yet non-neutralizing antibodies can potentially inhibit HIV transmission at the barriers of the sexual mucosa by alternative mechanisms (**Fig. 1**). First, they can potentially induce particle crosslinking into large complexes that cannot penetrate the mucosal barriers. Second, they might also potentially trap viral particles within superficial epithelial barriers and the protective mucus of the female reproductive tract. Third, binding antibodies can mediate antigen-specific targeting and killing of infected cells through antibody-directed cell cytoxicity and related mechanisms[11].

There may be other ways binding antibodies might prove to confer protection at mucosal barriers. Such binding antibody responses are readily generated by vaccination with antigens of the type used in the RV144 vaccine trial but have generally been dismissed because they have not protected vaccinated individuals in previous trials[4,12]. But not all antibody responses are the same, and maybe a binding antibody response associated with the right functional activity could generate binding antibodies that provide protection.

Perhaps a crucial question is whether an antibody response can confer protection from virus acquisition in the absence of virus neutralization. The analysis of protective antibody responses generated against human

papilloma virus has yet to identify a clear correlate of protection[13]. Neutralizing antibodies could certainly have a role, but protection is observed when such antibodies do not predominate. Likewise, there is no clear correlate of protective antibody responses for other successful vaccines, suggesting that the answer does not exclusively come from the presence of neutralizing antibodies[14].

This brings us back to the RV144 Thai vaccine trial[4], which having shown minimal, transient protection in the absence of bnAbs or robust T cell responses, hints at a role for antibody responses derived from binding of non-neutralizing antibodies. Although the RV144 Thai trial vaccination approach will not become an efficacious vaccine, many researchers are now collaborating to define the antibody responses generated by this trial. Any unique aspects of these antibodies may point the way toward understanding what is required for a protective binding antibody response. If the characteristics of a protective response are defined, the vaccinologists may develop the necessary antigens to generate binding antibody responses that will function as a protective vaccine in the absence of the generation of the long-sought-after bnAbs. To facilitate this approach, we need to understand the underlying mechanisms behind the transient protection generated by the RV144 Thai vaccine trial. If these mechanisms can be defined, it should be possible to make the function of broadly binding antibodies more efficient—bringing us another step closer to the goal of developing a vaccine that can decrease the spread of HIV by sexual transmission around the world.

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