Moving ahead an HIV vaccine

Despite remarkable advances in managing disease progression in people infected with HIV, an effective vaccine to prevent infectivity and stop the HIV epidemic remains an unmet clinical need. The genetic variability of the virus and the poor natural immune response—humoral and cellular—generated against HIV are hurdles that pose challenges to vaccine development. In 'Bench to Bedside', Bruce Walker, Rafi Ahmed and Stanley Plotkin examine a study in rhesus macaques where a vector-based viral vaccine that elicits a persistent and rapid T effector cell response to SIV antigens results in control of the infection. Although only 50% of the rhesus macaques controlled the infection, this *in vivo* finding stresses how outdoing the natural immune cellular response can prove effective to clear systemic viruses. But a humoral response will still remain the 'holy grail' to avoid HIV infection and transmission. In 'Bedside to Bench' Tom Hope peruses recent vaccine trials to propose how to best achieve an effective antibody response against HIV by discussing the perks and perils of non-neutralizing versus broadly neutralizing antibodies.

■ BENCH TO BEDSIDE

Use both arms to beat HIV

Bruce D Walker, Rafi Ahmed & Stanley Plotkin

The best chance to curb the HIV epidemic lies in the development of an effective vaccine, yet this remains the greatest unmet need as the epidemic continues unabated and the virus claims new victims worldwide[1]. The intense variability of HIV, its ability to infect immune cells and its rapid establishment of latent infection through integration into the host genome all represent major challenges. Indeed, two human efficacy trials of candidate vaccines have failed[2,3], whereas the third showed modest efficacy[4].

The pendulum continues to swing in terms of how to overcome these challenges. The failure of an antibody-based vaccine for HIV[2] led to an almost exclusive focus on T cell–based vaccines, and a T cell–based vaccine failure has swung it back again[3]. The protection reported in the Thai trial[3], and the fact that the poxvirus-protein combination induced antibodies rather than $CD8^+$ T cells, has further reinforced this view. Although there is certainly reason to be hopeful, as broadly neutralizing antibodies have now been detected in infected humans[5–9], inducing such responses with a vaccine has not yet been possible, nor is it clear how to do so[10]. Interestingly, non-neutralizing antibodies may have been important to the outcome of the Thai trial.

But is it really a question of B cells versus T cells, or is there reason to champion parallel approaches to induce both antibodies and T cells? A recent study by Hansen *et al.*[11] provides the best evidence to date that vaccine-induced T cells have something substantial to contribute. The study investigates a new concept in the HIV field, namely the use of live replicating and persistent recombinant cytomegalovirus (CMV) vectors to deliver vaccine antigens. The rationale for this approach stems from the fact that systemic spread of infection and establishment of life-long viral reservoirs occurs extremely rapidly, and that traditional T cell–based vaccine approaches that primarily induce expandable T cell memory populations may therefore not be sufficient: there may not be the luxury of time to allow for sufficient expansion and migration of effector T cells to sites of infection[12].

The results of the study are striking. Rhesus CMV vectors expressing SIV proteins (RhCMV-SIV), were administered to rhesus macaques alone or in combination with Ad5-SIV vectors that in previous vaccine studies did not prevent acquisition but partially controlled viremia after infection[13]. The RhCMV-SIV vectors were highly immunogenic for T cell responses—more so than any other vectors reported to date—but not for SIV-specific antibodies. And although they did not protect against acquisition of infection (an outcome thus far only associated with antibodies), subsequent durable control was achieved in 13 of 24 rhesus macaques vaccinated with these vectors[11]. The characteristics of this control were remarkable and implicate an active immunologic mechanism: occasional systemic blips of viremia appeared during the first 6 months, as high as 100,000 RNA copies per milliliter, but were largely absent by one year (**Fig. 1**). The levels of viremia in these rhesus macaques were insufficient to elicit detectable neutralizing antibodies to the infecting SIV but did elicit $CD8^+$ T cell responses to SIV antigens not present in the vaccine—clear evidence that there was productive infection. Given the initial plasma viral loads and subsequent viral blips, it is likely that systemic infection also occurred in the vaccinated animals. Thus, it seems that the CMV-induced SIV-specific $CD8^+$ T cells not only reduced the initial infection but also controlled systemic infection at later time points.

The study provides a clear immunologic correlate of protection against disease, in that amounts of vaccine-induced SIV-specific $CD8^+$ T cells were associated with subsequent resolution of viremia. However, once control was firmly established, viremia was maintained at undetectable levels, despite depletion of $CD4^+$ or $CD8^+$ T cells[11]. Perhaps most striking, attempts to recover infectious virus at necropsy from the RhCMV-SIV–immunized rhesus macaques were not successful—a level of viral control not found during prolonged treatment or in elite controllers—despite initial peak viremia in excess of 10 million RNA copies per milliliter in some of the successfully vaccinated rhesus macaques.

How should these findings affect our thinking as we go forward with attempts to make an effective HIV vaccine, and what are the limitations of this approach? The evidence suggests that the presence of effector $CD8^+$ and possibly $CD4^+$ T cells may be sufficient to tip the balance, not by preventing acquisition but possibly by limit-

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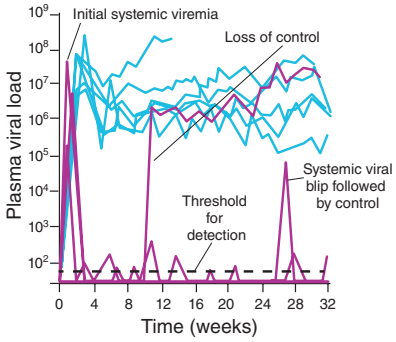

Figure 1 SIV challenge of RhCMV-SIV immunized rhesus macaques. Although all rhesus macaques became infected, half could achieve remarkable control despite occasional ongoing viral blips, with ultimate lack of recoverable virus. The combination of an antibody response with this T cell response might be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