Are effector memory T cells the key to an effective HIV/AIDS vaccine?

Louis J Picker

HIV and its nonhuman primate counterpart, SIV, are daunting targets for vaccine development, and for more than 30 years, these lentiviruses have eluded the “tried and true” vaccine approaches that have worked against so many other microbial pathogens. These viruses combine the following: (i) specific molecular adaptations that thwart innate and adaptive immune mechanisms (particularly antibody-mediated neutralization), (ii) massive replication, high mutation rates, genetic malleability, and functional plasticity leading to rapid evolution, and (iii) genetic integration and establishment of latency—all of which conspire to provide for efficient evasion of host anti-viral immunity and persistent, unrelenting infection [1]. Long-term control of a fully pathogenic HIV or SIV is rare—limited to humans or monkeys with particular genetic polymorphisms that either handicap the virus or provide for an unusually effective cellular immune response—and immune clearance of disseminated HIV/SIV infection has long been considered unachievable. However, it has long been hypothesized that these viruses might be more vulnerable to the immune system in the first few days of infection, as immunity would act on a much smaller, less diverse, and more localized viral population. Unfortunately, HIV/SIV vaccines tested to date have not been able to exploit this putative early vulnerability [1]. Antibody (Ab)-targeted vaccines have been foiled by the difficulty in identifying immunogens and delivery vehicles capable of eliciting and maintaining highly effective anti-viral Abs, either broadly neutralizing Abs, or Abs capable of interfering with early infection by other mechanisms. Moreover, none of the T-cell-targeted vaccine strategies investigated

to date have been able to effectively test this “early-intervention” hypothesis, as their elicited memory responses require anamnestic expansion, effector differentiation, and homing to sites of infection for maximal anti-viral activity, and therefore, relative to viral replication kinetics, come “too little, too late” to achieve consistent, stringent viral control [1,2].

If classical memory T-cell responses are effectively too slow to control HIV/SIV infection, the only alternative for a T-cell-targeted vaccine is to identify a persistent vaccine vector that is able to generate and maintain robust, so-called “effector memory” T-cell responses that are constitutively effector-differentiated and are prepositioned in potential sites of early HIV/SIV replication. To achieve such responses with a vaccine, we turned to Cytomegalovirus (CMV), which over millions of years of coevolution with its mammalian hosts has achieved what might be termed the “Goldilocks” level of viral persistence: not too much replication that would induce T-cell exhaustion, not too little replication that would allow induced T-cell responses to return to resting (central memory) state, but rather just the right amount to elicit and indefinitely maintain high-frequency effector-differentiated T-cell responses in both mucosal portals of entry and lymphoid tissues. Over the past decade, we have demonstrated that CMV biology lends itself quite well to vector development, with: (i) ample genome space for exogenous antigen inserts, (ii) the ability to elicit and maintain high frequency, widely distributed, broadly targeted, effector memory CD4⁺ and CD8⁺ T-cell responses (but not antibody responses) to exogenous inserts, and critically, given the ubiquitous nature of CMV

infection, (iii) the ability to superinfect already CMV-infected individuals and elicit robust insert-specific effector memory T-cell responses during superinfection [3–7]. Most importantly, RhCMV vectors expressing the major SIV viral proteins Gag, Pol, Rev/Nef/Tat, and Env have provided unprecedented protection against highly pathogenic SIVmac239 challenge of rhesus monkeys administered via intra-rectal, intra-vaginal, and intravenous routes [3–6]. All told, approximately 50% of RhCMV/SIV-vaccinated monkeys manifest a unique pattern of viral control characterized by a variably sized “blip” of SIV viremia, which was followed by immediate control of plasma viremia to undetectable levels, with the exception of some animals in which occasional low-level plasma viral blips were detected. Protection was binary, either complete or none at all, and was not associated with an anamnestic T-cell response to the vector-encoded SIV antigens, observations indicating that the SIV-specific T cells available at the time of infection either were or were not sufficient to control infection [3–6]. The mechanisms responsible for 50% efficacy are unclear at the time of this writing, but likely reflect either the level of SIV-specific T-cell responses in the portal of SIV entry and sites of early viral spread (see below) or less likely, genetic polymorphisms among the challenged animals. In the initial weeks after challenge, protected monkeys developed *de novo* T-cell responses to an SIV protein (Vif) not in the RhCMV vectors, and indeed, low levels of SIV virus could be detected in the portal of entry (rectum/colon) and sites of early lymphatic (draining lymph nodes) and hematogenous (liver, spleen, bone marrow) viral spread [6]. However, over time, all evidence of SIV

infection (plasma viral blips, cell-associated virus in tissue, SIVvif-specific T-cell responses) waned and ultimately disappeared. After 1.5–3 years, RhCMV/SIV vector-protected monkeys subjected to comprehensive analysis at necropsy were indistinguishable from never-SIV-infected monkeys by ultrasensitive nested quantitative PCR and RT-PCR, exhaustive SIV-inductive coculture analysis, and adoptive transfer to SIV-naïve recipient RM—the first demonstration of immune-mediated clearance of a pathogenic lentivirus [6].

These data confirm the early vulnerability of lentiviral infections to cellular immunity and provide strong proof-of-principle for the “effector memory” T-cell vaccine concept in general and for the CMV vector platform in specific. The CMV vector-associated

“arrest and clear over time” pattern of protection is technically not the same as protection against infection acquisition, but would, in a clinical setting, appear the same: that is, individuals would be less likely to show progressive infection (thus, no symptoms or disease), would be unlikely to transmit infection, and would, over time, be expected to have increasingly low and eventually no risk of relapse. Recent studies indicate that CMV vectors can be dramatically attenuated without loss of immunogenicity or persistence, paving the way for assessment of attenuated HCMV/HIV vectors in humans.

Conflict of interest

OHSU and Dr. Picker have a significant financial interest in TomegaVax, Inc., a company that may

have a commercial interest in the results of this research and technology. The potential individual and institutional conflicts of interest have been reviewed and managed by OHSU.

References

1. Picker LJ, Hansen SG, Lifson JD (2012) *Annu Rev Med* 63: 95–111
2. Haase AT (2005) *Nat Rev Immunol* 5: 783–792
3. Hansen SG, Vieville C, Whizin N *et al* (2009) *Nat Med* 15: 293–299
4. Hansen SG, Powers C, Richards R *et al* (2010) *Science* 328: 102–106
5. Hansen SG, Ford JC, Lewis MS *et al* (2011) *Nature* 473: 523–527
6. Hansen SG, Piatak M Jr, Ventura AB *et al* (2013) *Nature* 502: 100–104
7. Hansen SG, Sacha JB, Hughes CM *et al* (2013) *Science* 340: 6135/1237874