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NEW APPROACHES TO DESIGN HIV-1 T CELL VACCINES

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Abstract

Purpose of review—Following the evidence that T cell responses are crucial in the control of HIV-1 infection, vaccines targeting T cell responses were tested in recent clinical trials. However these vaccines showed a lack of efficacy. This review attempts to define the qualitative and quantitative features that are desirable for T cell induced responses by vaccines. We also describe strategies that could lead to achievement of this goal.

Recent findings—Using the yellow fever vaccine as a benchmark of an efficient vaccine, recent studies identified factors of immune protection and more importantly innate immune pathways needed for the establishment of long-term protective adaptive immunity.

Summary—To prevent or control HIV-1 infection, a vaccine must induce efficient and persistent Ag-specific T cells endowed with mucosal homing capacity. Such cells should have the capability to counteract HIV-1 diversity and its rapid spread from the initial site of infection. To achieve this goal, the activation of a diversified innate immune response is critical. New systems biology approaches will provide more precise correlates of immune protection that will pave the way for new approaches in T cell based vaccines.

Keywords

HIV-1 vaccine; Protective T cell; DC targeting

Introduction

The HIV-1 pandemic is one of the leading causes of death worldwide and remains a serious challenge to global public health [1]. Although antiretroviral drugs can control HIV/AIDS progression in many patients, they only succeed in reducing viral loads without completely eliminating the virus [2,3]. The development of an effective HIV-1 vaccine represents the optimal solution for control of the HIV-1 pandemic. While this is a clearly agreed upon goal, its implementation has been a difficult task [4–6]. HIV-1 vaccine studies have led to disappointing results, likely a consequence of the difficulty in generating broadly cross-neutralizing antibodies [7–9]. Recently the focus has shifted towards vaccines that control viral load after infection, thereby reducing secondary transmission [10]. In individuals exposed to HIV-1 yet remaining uninfected, CD8 T cell-mediated immunity was shown to be critical for the resistance to HIV-1 acquisition [11–15]. In non-human primates (NHP), the magnitude and kinetics in the establishment of effector CD8 T cell responses upon exposure to SIV were correlated with the control of acute infection [16–19]. In humans, the initial peak of T cell responses was shown to be temporally associated with a decrease in viremia [20,21].

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Furthermore, the immune selective pressure exerted by T cell responses induced an accumulation of viral mutations concentrated within T cell epitopes [22–25]. These observations that T cell responses are critical in controlling HIV-1 acquisition and infection have led to the development of vaccine strategies targeting T cells that showed promising results when tested in NHP [26–29].

Several candidate HIV-1 vaccines have been tested; however only four of them have reached phase IIb/III (efficacy) clinical trials [30]. The Step and Phambili trials, using as vaccine a replication-incompetent recombinant adenovirus 5 (Ad5) expressing HIV-1 clade B *gag*, *pol* and *nef*, were stopped before completion [6,31–33]. Protective immunity was not observed in highly exposed individuals despite the induction of HIV-specific T cell responses in 80% of the vaccinees. Moreover, the incidence of HIV-1 infection was increased in subgroups of Ad5-preimmunized and uncircumcised male vaccinees [6,34,35]. The more recent RV144 clinical trial in Thailand, based on priming with a canarypox vaccine ALVAC HIV vCP1521 (*env, gag, pol)* and a boost with the HIV-1 gp120 AIDSVAX B/E recombinant protein, showed encouraging results with an overall reduction in HIV-1 acquisition of 31.2% compared to placebo [36,37]. Ag-specific CD4 T cell proliferative responses were measured in 60% of the vaccinees and Ag-specific CD8 T cell responses were detectable in around 20% of the vaccinees by IFN-γ ELISPOT and cytotoxic assays. However, the vaccination had no effect on the CD4 T cell count or viral load in subjects subsequently diagnosed with HIV-1 infection [36]. Despite its low efficacy, this vaccine strategy provides hope that protective immunity against HIV-1 acquisition may be achieved.

A successful vaccine against HIV-1 must overcome several obstacles including the diversity of the virus and the early establishment of latent viral reservoirs [38,39]. The characteristics of HIV-1 and its immunopathology represent a major challenge for immunologists. Moreover, fundamental correlates of immune protection still need to be defined and validated for the design of novel vaccine strategies. In this review, we will examine the T cell immune responses to HIV-1 infection and those elicited by efficient vaccines with the aim of defining desirable T cell characteristics that should be targeted to prevent or control HIV-1 infection. We will focus on vaccine strategies that engage the innate immune compartment due to its crucial role in shaping an efficient T cell response.

How to counter HIV-1 antigenic diversity?

The diversity of circulating viral strains and the rapid generation of viral variants during infection constitute a major obstacle in the development of an HIV-1 vaccine [25,38,40–42]. The antigenic diversity must be represented in the vaccine components to provide broad T cell responses. Indeed, in SIV infection, T cell correlates of protection have been associated with a broader epitope-specific repertoire prior to heterologous SIV challenge [43]. It was shown that HIV-1 infected individuals whose CD8 T cell responses are dominantly and broadly directed against the *gag* protein exhibit lower plasma viral load [44]. To date, only 1 to 3 HIV-1 strain sequences were used in vaccine design and the lack of representation of these actual sequences in the infecting virus isolates could be one of the reasons behind the inefficacy of such vaccines [6,30,33,45]. New strategies were recently developed to improve “immunological coverage” by consensus and optimized mosaic Ags, which assemble synthetically designed antigenic sequences within several clades to generate full-length mosaic HIV-1 proteins (Table 1 and Figure 1) [46]. Studies in NHP showed that T cell responses induced by these mosaic Ags increased the breadth of the response, as Ag-specific T cells were cross-reactive to multiple HIV epitopes and variants [47–49]. However, the specificity of T cells against natural epitopes and the protective effect induced by such vaccines against HIV-1 infection still need to be demonstrated [50–52].

What characterizes an efficient HIV-specific T cell response ?

Live attenuated viruses such as Yellow Fever 17D (YF-17D) or vaccinia virus (VV) are amongst the most efficient vaccines and studying immune responses to these vaccines should reveal correlates of immune protection. YF-17D mimics an acute viral infection and induces innate and adaptive immune responses, with a balanced Th1/Th2 response, leading to a long-term (10 to 60 years) efficient immune protection [53–55]. In HIV-1 infection, the maintenance of proliferative CD4 T cell responses has been associated to the long-term control of HIV-1 infection [56]. However, the role of CD4 T cells in the disease control is still unclear, as the induction of HIV-specific CD4 T cells has also been suggested to enhance HIV-1 infection by providing an activated pool of target cells for viral replication [39,57,58]. Therefore, as the correlates of immune protection against HIV-1 disease progression are mostly demonstrated for CD8 T cell responses, HIV vaccine strategies mainly focused on the induction of strong CD8 T cells responses have been employed and should be pursue (Figure 1) [59–61].

Vaccination by vaccinia virus (Dryvax) or modified vaccinia virus Ankara (MVA) was shown to be particularly efficient in eliciting Ag-specific CD8 T cells with a high degree of polyfunctionality [62]. Following vaccination with YF-17D, Miller et al. showed that more than 10% of total circulating CD8 T cells are activated within 2 weeks [63]. In contrast to persistent viruses as HIV-1 that lead to chronic infection and T cell exhaustion, YF-17D and VV vaccines elicit a rapid expansion of highly specific and polyfunctional Ag-specific CD8 T cell expressing only transient levels of inhibitory receptors including PD-1 and CTLA-4 (Table 1) [62–68]. Importantly, it appears that T cell mediated immune protection is more likely related to the quality than the quantity of Ag-specific T cell responses. Indeed, high levels of HIV-1 responding CD8 T cells could be seen both in progressors and in long term non progressors (LTNPs) [69–73]. During HIV-1 infection, the proportion of polyfunctional CD8 T cells, as evidenced by their capacity to produce several cytokines (IFN-γ, MIP1-β, TNF-α, IL-2), was shown to inversely correlate with viral load [69]. Similarly, the response to HIV-2, which displays a slower disease progression, was characterized by the generation of polyfunctional CD8 and CD4 Ag-specific T cells [74]. Nevertheless, the polyfunctional T cell responses demonstrated in the Step trial was not sufficient to confer any protection [75]. Indeed, if the correlation between T cell polyfunctionality and HIV-1 disease control is now well established, it is still unclear if this feature is sufficient to provide T cell immune protection [51,76–78]. Other parameters such as proliferative capacity and functional sensitivity have also been associated with the efficiency of Ag-specific CD8 T cells to suppress HIV-1 replication [79] (Table 1 and Figure 1). For inducing an efficient CD8 T cell response and a balanced Th1/Th2 response, several critical parameters should be considered as the Ag dose or the vaccine regimen (e.g. heterologous prime-boost strategies) [80–82]. Importantly, valuable correlates of immune protection still need to be defined and will be elucidated by systems biology approaches.

How to induce long-term immune protection?

The generation of a specific immunological memory that can protect individuals throughout their lifespan, represents one of the major features that determines the success of vaccines and strongly depends on the efficiency of the primary effector response [83–85]. Long-lasting immunological memory is based on heterogeneous CD4 and CD8 T cell sub-populations classically divided into the long-lived central memory T cells (TCM) and the effector memory T cells (TEM) [86,87]. YF-17D and VV vaccination result in the rapid and massive expansion of effector CD8 T cells that gradually differentiate into a memory pool providing immune protection for more than 10 years [63]. Furthermore, a progressive downregulation in activation and proliferation markers and effector functions (HLA-DR, CD62L, CD38, Ki-67, Granzyme B) is observed as well as the acquisition of memory markers (CD127 and Bcl-2) [63,67]. While

protective immune responses are generally attributed to central memory T cells, the YF-17D specific memory CD8 T cells have a particular phenotype of effector memory T cells (CD45RA +, CD27+, CCR7−), which are able to maintain a proliferative capacity. Moreover, a recent study by Vezys et al. showed that, upon heterologous prime-boost immunization in mice, CD8 TEM cells exhibit an extensive expansion capacity in response to new infection by Lymphocytic Choriomeningitis Virus (LCMV) compared to TCM [88]. Prolonged Ag presentation might be required to increase the size of the effector memory T cell pool and to elicit a protective immune response as was recently demonstrated for the malaria vaccine in mice [89]. Indeed, the most successful vaccine strategies have been obtained using modified viral vectors (MVA and LCMV) that permit the persistence of Ags [27,29,62,90–93]. Vaccine strategies should promote primarily CD8 persisting TEM. However, the induction of a long-term immune protection by a vaccine might also need the establishment of a central memory T cell pool (Table 1 and Figure 1) [94,95].

How to block HIV-1 dissemination from mucosal tissues?

To counteract HIV-1 infection, a vaccine must induce a robust immune response before the establishment of chronic infection and prior to its sequestration into the latent viral reservoir [2,23]. Defects in CD8 T cell function and survival have been shown to occur within the first few weeks of SIV infection [96,97]. As HIV-1 transmission occurs most commonly through sexual transmission and the first immunopathologic events take place at mucosal sites, vaccine-induced HIV-specific T cell responses that can be recruited rapidly to those sites is critical [12,18,57]. The magnitude and quality of effector CD8 T cells at mucosal sites has been correlated with viral load [18]. Although TCM are considered as the stem cells for the memory pool this subset undergoes expansion only 3 days after re-exposure to their cognate Ag [98]. Moreover, in contrast to TEM, the TCM subset is poorly represented among intraepithelial lymphocytes and in gut associated lymphoid tissue and is mostly localized in the lymph nodes (LN) as dictated by the expression of the LN homing receptor CCR7 [51,99,100]. Therefore, vaccines inducing TEM would promote a rapid response at mucosal sites upon HIV-1 exposure (Table 1 and Figure 1). Masopust et al. recently demonstrated the induction of the transient expression of α4β7 integrin on early specific effector T cells and on memory T cells shortly after their activation by systemic re-stimulation with LCMV in mice, allowing their homing to intestinal and epithelial tissues [99]. Furthermore, a study using SIV mac239(delta)nef immunized animals showed that lung CD8 T cells, unlike peripheral CD8 T cells, suppressed viral replication by up to 80% *in vitro* [101]. These results suggest that this effective vaccine was eliciting functional immunity at mucosal sites with a distinct behavior from circulating cells. The Rhesus CMV, used as a vector for SIV *gag, rev, tat, nef* and *env* when injected subcutaneously, successfully induced multifunctional CD4 and CD8 effector memory T cells in mucosal tissues and provided protection of NHP against repeated low-dose SIV intrarectal challenge [27]. The route of immunization might be of particular importance for early prevention and inhibition of viral dissemination. Few studies have addressed this parameter and its impact is still debated [102].

How to shape HIV-specific T cell responses?

Innate immune cells are needed to generate an efficient adaptive immune response. Dendritic cells (DCs) are known to activate naíve T cells to generate effector and memory T cells. Therefore, the types of signals DCs provide to T cells could result in different fates of the subsequent adaptive immune response [103,104]. However, the exact molecules and mechanisms involved in the priming of T cells and in the generation of memory are still unknown. The SIV mac239(delta)nef is the most successful vaccine tested in macaques [105, 106]. The deletion of nef avoids the inhibitory effect of this protein on MHC class I presentation and other negative regulatory mechanisms. Likewise, early activation of innate immunity might

have a major role in modulating the efficacy of the vaccine. YF-17D was shown to infect and activate multiple DC subsets via TLRs 2, 7, 8, and 9, enhancing the presentation of vaccine Ags and the production of pro-inflammatory cytokines [53,54,107]. TLR ligands have been used to increase the frequency of CMV and HIV-specific CD8 T cell responses *in vitro* and also to modulate T cell responses *in vivo* [108–110]. Immunization with *gag* protein conjugated to a TLR7/8 agonist in mice or NHP enhanced the magnitude and quality of *gag*-specific Th1 and CD8 T cell responses [111]. Likewise, the same authors studied the use of different TLR ligands to influence Th1 and CD8 T cell responses in NHP in a prime boost immunization regimen [112]. Longhi et al. demonstrated that TLR3 agonist strongly induces type I IFN production that promotes maturation of DCs and generates CD4 Th1 immunity [113]. Type I interferons have also been shown to dictate clonal expansion, attrition and memory formation of CD8 T cells [114,115]. The fate of CD8 T cells is also dictated by other mechanisms. For example, IL-15 trans-presentation by DCs has been shown to promote effector CD8 T cell survival, while on the other hand, CD137 signaling in DCs could lead to T cell activation induced cell death [116,117]. Deciphering DC signals that dictate the features of T cells is needed for the development of new vaccines. Targeting DCs during vaccination would increase the magnitude but also the quality of the immune response.

The most efficient vectors for HIV-1 vaccine are those that infect and activate DCs such as the Canarypox virus (ALVAC vaccine), the LCMV or MVA [62,91,93,118]. Other viral vectors, virus like particles (VLP) or recombinant viral proteins should be used in combination of costimulatory molecules and TLR ligands to activate DCs and stimulate an efficient immune response (Figure 1). These strategies have already been tested in different models and have shown promising results; for example the incorporation of CD40 ligand into simian-HIV VLP enhanced DC activation and boosted immune responses against HIV-1 [119]. Moreover, the use of an anti-DCs (DEC-205) HIV *gag* fusion antibody vaccine led to an intensified and protective CD4 T cell immunity in mice [120]. Nevertheless, the mechanisms that are used to activate DCs need to be clearly defined and understood as activation of a DC-T cell axis by Ad5 immune complexes has been shown to create an improved environment for replication of HIV-1 in T cells [121].

How to monitor a good protective immune response?

Few T cell assays have been used to analyze T cell responses induced by vaccination strategies and predict vaccine efficacy. They include the commonly used IFN-γ ELISPOT assay, but also tetramer staining, *in vitro* proliferation assays, intracellular cytokine staining assays, staining for markers of activation and cytotoxic related molecules. However, experimental procedures as well as analysis and interpretation still remain controversial as most of these assays have yet to be standardized. Moreover, considering that few memory T cells could be sufficient for a robust secondary immune response, the detection level of these assays should be improved to study the frequencies of memory cells as their frequencies rarely exceed 10^{-3} to 10^{-4} of total T cells. The field has begun to standardize the immuno-monitoring for clinical trials [122–124] and this will help by defining reliable assays to predict vaccine efficacy. In that context, both the IFN-γ ELISPOT as well as polyfunctional T cells failed to predict the unprotective effect of the Step trial [31,75]. New parameters of the induced T cell responses have to be monitored, such as the differentiation status, migration patterns, proliferation potential and survival capacity. For example, the expression levels of transcription factors such as T-bet, Eomes, Blimp-1 and Bcl-6 could be investigated to define the effector and memory CD8 T cell status [125,126]. Moreover T cells should be monitored at mucosal sites, and the capacity of memory T cells to migrate *in situ* should be assessed.

As the very early events in HIV-1 infection in the mucosal sites are not available for study *in vivo*, the impact of vaccines as well as HIV-1 infection have to be studied *in vitro*. Some *in*

vitro models have been already used for mucosal reconstruction to follow virus behavior from its site of entry to the lymph nodes [127]. Randolph et al. have reported a tissue-engineered *in vitro* model to promote autonomous generation and maturation of DCs from PBMCs, without adding exogenous cytokines [128]. In our previous work [53], we found comparable results in the immune responses stimulated by the YF-17D vaccine in this system versus *in vivo* responses after vaccination. Such new models would serve as a surrogate human immune system to elucidate the first events of HIV-1 infection and would enable the testing of the response to a vaccine directly in a human system rather than in animal models.

An effective protection in response to a virus or a vaccine involves a complex polyvalent and coordinated immune response. The recent advances in biotechnological methods, associated with computational tools, permit a quantitative, qualitative and integrated analysis at genomic, proteomic and cellular levels [129,130]. This systems biology approach offers the possibility to examine the immune status of one individual, revealing the complex networks between all of the innate and adaptive immune components over time and to define key molecules and signatures of immune protection (Figure 1) [53,54].

Conclusion

As discussed in this review, some correlates of HIV-1 disease control have been identified and new promising T cell vaccines strategies are emerging [27,29,91,93]. Results from current clinical trials such as HTVN 205 with a prime DNA vaccine containing *gag, pol, env, tat, rev, vpu and a* boost MVA vaccine containing *gag, pol, env* will provide new advances in T cell vaccine development [131]. Key factors of immune protection have also been defined in response to efficient licensed vaccines such as YF-17D [53,54]. Further studies are still needed to understand the underlying mechanisms of immune protection, especially the crucial role of the innate immune system in activating and shaping an efficient T cell response. The characterization of innate and adaptive immune responses in novel *in vitro* models and in highly exposed non-infected individuals should also give important clues to the identification of correlates of immune protection. Furthermore, acute immune responses against other viruses that persist in humans but are naturally controlled should also bring insights in the first immune events that lead to viral control. In all these studies, systems biology approaches would allow for the analysis and integration of innate and adaptive immune responses, providing the tools to build models of immune protection. These findings could then be employed to define composition, dose and administration regimens in novel HIV-1 vaccination strategies. Parameters of immune protection and disease control could be used to assess the efficacy of vaccines in phase I clinical trials. Therefore, more valuable and meaningful data could emerge from phase I studies, avoiding the entry into phase II/III trials without sufficient evidences of vaccine efficacy. New correlates of protection and disease control could emerge and would provide key elements to develop a potent HIV-1 cell vaccine. As many arms of the immune system work in concert, combinations of vaccines that induce effective T cell responses along with neutralizing antibodies or other strategies inducing innate immune responses could achieve successful results [132].

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References

1. WHO. 2009 global summary. 2009. Available from: http://www.who.int/hiv/data/2009_global_summary.gif
2. Chomont N, El-Far M, Ancuta P, et al. HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation. Nat Med 2009 Aug;15(8):893–900. [PubMed: 19543283]
3. Shen L, Peterson S, Sedaghat AR, et al. Dose-response curve slope sets class-specific limits on inhibitory potential of anti-HIV drugs. Nat Med 2008 Jul;14(7):762–6. [PubMed: 18552857]
4. Berkley SF, Koff WC. Scientific and policy challenges to development of an AIDS vaccine. Lancet 2007 Jul 7;370(9581):94–101. [PubMed: 17617277]
5. Burton DR, Desrosiers RC, Doms RW, et al. HIV vaccine design and the neutralizing antibody problem. Nat Immunol 2004 Mar;5(3):233–6. [PubMed: 14985706]
6. Sekaly RP. The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development? J Exp Med 2008 Jan 21;205(1):7–12. [PubMed: 18195078]
7. Mascola JR, Montefiori DC. The role of antibodies in HIV vaccines. Annu Rev Immunol 2010 Mar; 28:413–44. [PubMed: 20192810]
8. Flynn NM, Forthal DN, Harro CD, et al. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. J Infect Dis 2005 Mar 1;191(5):654–65. [PubMed: 15688278]
9. Pitisuttithum P, Gilbert P, Gurwith M, et al. Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand. J Infect Dis 2006 Dec 15;194(12):1661–71. [PubMed: 17109337]
10. Watkins DI, Burton DR, Kallas EG, et al. Nonhuman primate models and the failure of the Merck HIV-1 vaccine in humans. Nat Med 2008 Jun;14(6):617–21. [PubMed: 18535579]
11. Stranford SA, Skurnick J, Louria D, et al. Lack of infection in HIV-exposed individuals is associated with a strong CD8(+) cell noncytotoxic anti-HIV response. Proc Natl Acad Sci U S A 1999 Feb 2;96 (3):1030–5. [PubMed: 9927688]
12. Clerici M, Salvi A, Trabattoni D, et al. A role for mucosal immunity in resistance to HIV infection. Immunol Lett 1999 Mar;66(1–3):21–5. [PubMed: 10203030]
13. Fowke KR, Nagelkerke NJ, Kimani J, et al. Resistance to HIV-1 infection among persistently seronegative prostitutes in Nairobi, Kenya. Lancet 1996 Nov 16;348(9038):1347–51. [PubMed: 8918278]
14. Rowland-Jones S, Sutton J, Ariyoshi K, et al. HIV-specific cytotoxic T-cells in HIV-exposed but uninfected Gambian women. Nat Med 1995 Jan;1(1):59–64. [PubMed: 7584954]
15. Cohen J. AIDS vaccine research. HIV natural resistance field finally overcomes resistance. Science 2009 Dec 11;326(5959):1476–7. [PubMed: 20007880]
16. Schmitz JE, Kuroda MJ, Santra S, et al. Control of viremia in simian immunodeficiency virus infection by CD8+ lymphocytes. Science 1999 Feb 5;283(5403):857–60. [PubMed: 9933172]
17. Reynolds MR, Rakasz E, Skinner PJ, et al. CD8+ T-lymphocyte response to major immunodominant epitopes after vaginal exposure to simian immunodeficiency virus: too late and too little. J Virol 2005 Jul;79(14):9228–35. [PubMed: 15994817]
18**. Li Q, Skinner PJ, Ha SJ, et al. Visualizing antigen-specific and infected cells in situ predicts outcomes in early viral infection. Science 2009 Mar 27;323(5922):1726–9. This study shows the establishment of Ag-specific effector CD8 T cell response during acute SIV infection in mucosa. [PubMed: 19325114]
19. Wilson NA, Reed J, Napoe GS, et al. Vaccine-induced cellular immune responses reduce plasma viral concentrations after repeated low-dose challenge with pathogenic simian immunodeficiency virus SIVmac239. J Virol 2006 Jun;80(12):5875–85. [PubMed: 16731926]
20. Koup RA, Safrit JT, Cao Y, et al. Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type 1 syndrome. J Virol 1994 Jul;68 (7):4650–5. [PubMed: 8207839]
21. Borrow P, Lewicki H, Hahn BH, et al. Virus-specific CD8+ cytotoxic T-lymphocyte activity associated with control of viremia in primary human immunodeficiency virus type 1 infection. J Virol 1994 Sep;68(9):6103–10. [PubMed: 8057491]

22. Phillips RE, Rowland-Jones S, Nixon DF, et al. Human immunodeficiency virus genetic variation that can escape cytotoxic T cell recognition. Nature 1991 Dec 12;354(6353):453–9. [PubMed: 1721107]

23. Goonetilleke N, Liu MK, Salazar-Gonzalez JF, et al. The first T cell response to transmitted/founder virus contributes to the control of acute viremia in HIV-1 infection. J Exp Med 2009 Jun 8;206(6): 1253–72. [PubMed: 19487423]

24. Goulder PJ, Altfeld MA, Rosenberg ES, et al. Substantial differences in specificity of HIV-specific cytotoxic T cells in acute and chronic HIV infection. J Exp Med 2001 Jan 15;193(2):181–94. [PubMed: 11148222]

25. Salazar-Gonzalez JF, Salazar MG, Keele BF, et al. Genetic identity, biological phenotype, and evolutionary pathways of transmitted/founder viruses in acute and early HIV-1 infection. J Exp Med 2009 Jun 8;206(6):1273–89. [PubMed: 19487424]

26. Casimiro DR, Wang F, Schleif WA, et al. Attenuation of simian immunodeficiency virus SIVmac239 infection by prophylactic immunization with dna and recombinant adenoviral vaccine vectors expressing Gag. J Virol 2005 Dec;79(24):15547–55. [PubMed: 16306625]

27**. Hansen SG, Vieville C, Whizin N, et al. Effector memory T cell responses are associated with protection of rhesus monkeys from mucosal simian immunodeficiency virus challenge. Nat Med 2009 Mar;15(3):293–9. Hansen et al. developed a Rhesus CMV vector that primed and maintained efficient specific CD4 and CD8 effector memory T cells. [PubMed: 19219024]

28. Brandler S, Lepelley A, Desdouits M, et al. Preclinical studies of a modified vaccinia virus Ankara-based HIV candidate vaccine: antigen presentation and antiviral effect. J Virol 2010 May;84(10): 5314–28. [PubMed: 20219934]

29**. Liu J, O'Brien KL, Lynch DM, et al. Immune control of an SIV challenge by a T-cell-based vaccine in rhesus monkeys. Nature 2009 Jan 1;457(7225):87–91. This study shows that durable partial immune control of a pathogenic SIV challenge can be achieved by an improved T-cell-based vaccine regimen in the absence of a homologous Env antigen. [PubMed: 18997770]

30. Barouch DH, Korber B. HIV-1 vaccine development after STEP. Annu Rev Med 2010;61:153–67. [PubMed: 20059334]

31. Buchbinder SP, Mehrotra DV, Duerr A, et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet 2008 Nov 29;372(9653):1881–93. [PubMed: 19012954]

32. Cohen J. AIDS research. Promising AIDS vaccine's failure leaves field reeling. Science 2007 Oct 5;318(5847):28–9. [PubMed: 17916696]

33. Corey L, McElrath MJ, Kublin JG. Post-step modifications for research on HIV vaccines. AIDS 2009 Jan 2;23(1):3–8. [PubMed: 19050380]

34. Hutnick NA, Carnathan DG, Dubey SA, et al. Baseline Ad5 serostatus does not predict Ad5 HIV vaccine-induced expansion of adenovirus-specific CD4+ T cells. Nat Med 2009 Aug;15(8):876–8. [PubMed: 19620962]

35. O'Brien KL, Liu J, King SL, et al. Adenovirus-specific immunity after immunization with an Ad5 HIV-1 vaccine candidate in humans. Nat Med 2009 Aug;15(8):873–5. [PubMed: 19620961]

36. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med 2009 Dec 3;361(23):2209–20. [PubMed: 19843557]

37. Cohen J. HIV/AIDS research. Beyond Thailand: making sense of a qualified AIDS vaccine "success". Science 2009 Oct 30;326(5953):652–3. [PubMed: 19900904]

38. Barouch DH. Challenges in the development of an HIV-1 vaccine. Nature 2008 Oct 2;455(7213): 613–9. [PubMed: 18833271]

39. Virgin HW, Walker BD. Immunology and the elusive AIDS vaccine. Nature 2010 Mar 11;464(7286): 224–31. [PubMed: 20220841]

40. O'Connor DH, Allen TM, Vogel TU, et al. Acute phase cytotoxic T lymphocyte escape is a hallmark of simian immunodeficiency virus infection. Nat Med 2002 May;8(5):493–9. [PubMed: 11984594]

41. Hu SL, Abrams K, Barber GN, et al. Protection of macaques against SIV infection by subunit vaccines of SIV envelope glycoprotein gp160. Science 1992 Jan 24;255(5043):456–9. [PubMed: 1531159]

42. Kawashima Y, Pfafferott K, Frater J, et al. Adaptation of HIV-1 to human leukocyte antigen class I. Nature 2009 Apr 2;458(7238):641–5. [PubMed: 19242411]
43. Martins MA, Wilson NA, Reed JS, et al. T-cell correlates of vaccine efficacy after a heterologous simian immunodeficiency virus challenge. J Virol 2010 May;84(9):4352–65. [PubMed: 20164222]
44. Kiepiela P, Ngumbela K, Thobakgale C, et al. CD8+ T-cell responses to different HIV proteins have discordant associations with viral load. Nat Med 2007 Jan;13(1):46–53. [PubMed: 17173051]
45. Gaschen B, Taylor J, Yusim K, et al. Diversity considerations in HIV-1 vaccine selection. Science 2002 Jun 28;296(5577):2354–60. [PubMed: 12089434]
46. Fischer W, Perkins S, Theiler J, et al. Polyvalent vaccines for optimal coverage of potential T-cell epitopes in global HIV-1 variants. Nat Med 2007 Jan;13(1):100–6. [PubMed: 17187074]
47. Wang S, Kennedy JS, West K, et al. Cross-subtype antibody and cellular immune responses induced by a polyvalent DNA prime-protein boost HIV-1 vaccine in healthy human volunteers. Vaccine 2008 Jul 23;26(31):3947–57. [PubMed: 18724414]
48. Barouch DH, O'Brien KL, Simmons NL, et al. Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys. Nat Med 2010 Mar;16(3):319–23. [PubMed: 20173752]
49. Santra S, Liao HX, Zhang R, et al. Mosaic vaccines elicit CD8+ T lymphocyte responses that confer enhanced immune coverage of diverse HIV strains in monkeys. Nat Med 2010 Mar;16(3):324–8. [PubMed: 20173754]
50. Speiser DE, Baumgaertner P, Voelter V, et al. Unmodified self antigen triggers human CD8 T cells with stronger tumor reactivity than altered antigen. Proc Natl Acad Sci U S A 2008 Mar 11;105(10): 3849–54. [PubMed: 18319339]
51. Appay V, Douek DC, Price DA. CD8+ T cell efficacy in vaccination and disease. Nat Med 2008 Jun; 14(6):623–8. [PubMed: 18535580]
52. Kastenmuller W, Gasteiger G, Gronau JH, et al. Cross-competition of CD8+ T cells shapes the immunodominance hierarchy during boost vaccination. J Exp Med 2007 Sep 3;204(9):2187–98. [PubMed: 17709425]
53**. Gaucher D, Therrien R, Kettaf N, et al. Yellow fever vaccine induces integrated multilineage and polyfunctional immune responses. J Exp Med 2008 Dec 22;205(13):3119–31. Systems biology approach was used to reveal key transcription factors that coordinate the induction of both arms of the immune system in response to YF-17D vaccine. [PubMed: 19047440]
54**. Querec TD, Akondy RS, Lee EK, et al. Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans. Nat Immunol 2009 Jan;10(1):116–25. Using a systems biology approach, this study identifies early gene signatures that predict CD8 T cell or humoral responses to YF-17D vaccine. [PubMed: 19029902]
55. Pulendran B. Learning immunology from the yellow fever vaccine: innate immunity to systems vaccinology. Nat Rev Immunol. 2009 Sep 18;
56. Rosenberg ES, Billingsley JM, Caliendo AM, et al. Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia. Science 1997 Nov 21;278(5342):1447–50. [PubMed: 9367954]
57**. Li Q, Estes JD, Schlievert PM, et al. Glycerol monolaurate prevents mucosal SIV transmission. Nature 2009 Apr 23;458(7241):1034–8. This study demonstrates that mucosal pDCs and inflammation recruit CD4 T cells to fuel viral expansion during acute SIV infection. [PubMed: 19262509]
58. Douek DC, Brenchley JM, Betts MR, et al. HIV preferentially infects HIV-specific CD4+ T cells. Nature 2002 May 2;417(6884):95–8. [PubMed: 11986671]
59. Tatsis N, Fitzgerald JC, Reyes-Sandoval A, et al. Adenoviral vectors persist in vivo and maintain activated CD8+ T cells: implications for their use as vaccines. Blood 2007 Sep 15;110(6):1916–23. [PubMed: 17510320]
60. Shiver JW, Emini EA. Recent advances in the development of HIV-1 vaccines using replication-incompetent adenovirus vectors. Annu Rev Med 2004;55:355–72. [PubMed: 14746526]
61. Feinberg MB, Moore JP. AIDS vaccine models: challenging challenge viruses. Nat Med 2002 Mar; 8(3):207–10. [PubMed: 11875482]

62. Precopio ML, Betts MR, Parrino J, et al. Immunization with vaccinia virus induces polyfunctional and phenotypically distinctive CD8(+) T cell responses. J Exp Med 2007 Jun 11;204(6):1405–16. [PubMed: 17535971]

63*. Miller JD, van der Most RG, Akondy RS, et al. Human effector and memory CD8+ T cell responses to smallpox and yellow fever vaccines. Immunity 2008 May;28(5):710–22. This study analyzes the fate of Ag-specific CD8 T cell response in response to YF-17D vaccine. [PubMed: 18468462]

64. Trautmann L, Janbazian L, Chomont N, et al. Upregulation of PD-1 expression on HIV-specific CD8 + T cells leads to reversible immune dysfunction. Nat Med 2006 Oct;12(10):1198–202. [PubMed: 16917489]

65. Day CL, Kaufmann DE, Kiepiela P, et al. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature 2006 Sep 21;443(7109):350–4. [PubMed: 16921384]

66. Petrovas C, Casazza JP, Brenchley JM, et al. PD-1 is a regulator of virus-specific CD8+ T cell survival in HIV infection. J Exp Med 2006 Oct 2;203(10):2281–92. [PubMed: 16954372]

67. Akondy RS, Monson ND, Miller JD, et al. The yellow fever virus vaccine induces a broad and polyfunctional human memory CD8+ T cell response. J Immunol 2009 Dec 15;183(12):7919–30. [PubMed: 19933869]

68. Co MD, Kilpatrick ED, Rothman AL. Dynamics of the CD8 T-cell response following yellow fever virus 17D immunization. Immunology 2009 Sep;128(1 Suppl):e718–27. [PubMed: 19740333]

69. Betts MR, Nason MC, West SM, et al. HIV nonprogressors preferentially maintain highly functional HIV-specific CD8+ T cells. Blood 2006 Jun 15;107(12):4781–9. [PubMed: 16467198]

70. Emu B, Sinclair E, Favre D, et al. Phenotypic, functional, and kinetic parameters associated with apparent T-cell control of human immunodeficiency virus replication in individuals with and without antiretroviral treatment. J Virol 2005 Nov;79(22):14169–78. [PubMed: 16254352]

71. Migueles SA, Sabbaghian MS, Shupert WL, et al. HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors. Proc Natl Acad Sci U S A 2000 Mar 14;97(6):2709–14. [PubMed: 10694578]

72. Saez-Cirion A, Lacabaratz C, Lambotte O, et al. HIV controllers exhibit potent CD8 T cell capacity to suppress HIV infection ex vivo and peculiar cytotoxic T lymphocyte activation phenotype. Proc Natl Acad Sci U S A 2007 Apr 17;104(16):6776–81. [PubMed: 17428922]

73. Owen RE, Heitman JW, Hirschkorn DF, et al. HIV+ elite controllers have low HIV-specific T-cell activation yet maintain strong, polyfunctional T-cell responses. AIDS 2010 May 15;24(8):1095–105. [PubMed: 20400885]

74. Duvall MG, Precopio ML, Ambrozak DA, et al. Polyfunctional T cell responses are a hallmark of HIV-2 infection. Eur J Immunol 2008 Feb;38(2):350–63. [PubMed: 18200635]

75. Casimiro, DMJ. The STEP Trial: A Pathway Toward Understanding the Biological Basis for the Vaccine Efficacy Results. Available from: http://www.hvtn.org/fgm/1107slides/McElrath.pdf

76. Almeida JR, Price DA, Papagno L, et al. Superior control of HIV-1 replication by CD8+ T cells is reflected by their avidity, polyfunctionality, and clonal turnover. J Exp Med 2007 Oct 1;204(10): 2473–85. [PubMed: 17893201]

77. Belyakov IM, Kuznetsov VA, Kelsall B, et al. Impact of vaccine-induced mucosal high-avidity CD8 + CTLs in delay of AIDS viral dissemination from mucosa. Blood 2006 Apr 15;107(8):3258–64. [PubMed: 16373659]

78. Betts MR, Harari A. Phenotype and function of protective T cell immune responses in HIV. Curr Opin HIV AIDS 2008 May;3(3):349–55. [PubMed: 19372989]

79. Almeida JR, Sauce D, Price DA, et al. Antigen sensitivity is a major determinant of CD8+ T-cell polyfunctionality and HIV-suppressive activity. Blood 2009 Jun 18;113(25):6351–60. [PubMed: 19389882]

80. Brown SA, Surman SL, Sealy R, et al. Heterologous Prime-Boost HIV-1 Vaccination Regimens in Pre-Clinical and Clinical Trials. Viruses 2010 Feb 1;2(2):435–67. [PubMed: 20407589]

81. Harari A, Bart PA, Stohr W, et al. An HIV-1 clade C DNA prime, NYVAC boost vaccine regimen induces reliable, polyfunctional, and long-lasting T cell responses. J Exp Med 2008 Jan 21;205(1): 63–77. [PubMed: 18195071]

82. Estcourt MJ, Ramsay AJ, Brooks A, et al. Prime-boost immunization generates a high frequency, high-avidity CD8(+) cytotoxic T lymphocyte population. Int Immunol 2002 Jan;14(1):31–7. [PubMed: 11751749]

83. Obar JJ, Khanna KM, Lefrancois L. Endogenous naive CD8+ T cell precursor frequency regulates primary and memory responses to infection. Immunity 2008 Jun;28(6):859–69. [PubMed: 18499487]

84. Schmidt NW, Podyminogin RL, Butler NS, et al. Memory CD8 T cell responses exceeding a large but definable threshold provide long-term immunity to malaria. Proc Natl Acad Sci U S A 2008 Sep 16;105(37):14017–22. [PubMed: 18780790]

85. Castellino F, Galli G, Del Giudice G, et al. Generating memory with vaccination. Eur J Immunol 2009 Aug;39(8):2100–5. [PubMed: 19637203]

86. Lanzavecchia A, Sallusto F. Understanding the generation and function of memory T cell subsets. Curr Opin Immunol 2005 Jun;17(3):326–32. [PubMed: 15886125]

87. Wherry EJ, Teichgraber V, Becker TC, et al. Lineage relationship and protective immunity of memory CD8 T cell subsets. Nat Immunol 2003 Mar;4(3):225–34. [PubMed: 12563257]

88. Vezys V, Yates A, Casey KA, et al. Memory CD8 T-cell compartment grows in size with immunological experience. Nature 2009 Jan 8;457(7226):196–9. [PubMed: 19005468]

89. Cockburn IA, Chen YC, Overstreet MG, et al. Prolonged antigen presentation is required for optimal CD8+ T cell responses against malaria liver stage parasites. PLoS Pathog 6(5):e1000877. [PubMed: 20463809]

90. Grandpre LE, Duke-Cohan JS, Ewald BA, et al. Immunogenicity of recombinant Modified Vaccinia Ankara following a single or multi-dose vaccine regimen in rhesus monkeys. Vaccine 2009 Mar 4;27 (10):1549–56. [PubMed: 19168105]

91**. Flatz L, Hegazy AN, Bergthaler A, et al. Development of replication-defective lymphocytic choriomeningitis virus vectors for the induction of potent CD8+ T cell immunity. Nat Med 2010 Mar;16(3):339–45. Flatz et al. generated a replication-defective Lymphocytic Choriomeningitis Virus vector, that elicited efficient CD8 and Th1 CD4 T cells as well as a humoral response to vaccine antigens. [PubMed: 20139992]

92. Aboud S, Nilsson C, Karlen K, et al. Strong HIV-Specific CD4+ and CD8+ T lymphocyte proliferative responses in healthy individuals immunized with a HIV-1 DNA vaccine and boosted with HIV-1 recombinant Modified Vaccinia virus Ankara (MVA). Clin Vaccine Immunol. 2010 May 12;

93. Garber DA, O'Mara LA, Zhao J, et al. Expanding the repertoire of Modified Vaccinia Ankara-based vaccine vectors via genetic complementation strategies. PLoS One 2009;4(5):e5445. [PubMed: 19421328]

94. Letvin NL, Mascola JR, Sun Y, et al. Preserved CD4+ central memory T cells and survival in vaccinated SIV-challenged monkeys. Science 2006 Jun 9;312(5779):1530–3. [PubMed: 16763152]

95. Harari A, Pantaleo G. Understanding what makes a good versus a bad vaccine. Eur J Immunol 2005 Sep;35(9):2528–31. [PubMed: 16106373]

96. Petrovas C, Chaon B, Ambrozak DR, et al. Differential association of programmed death-1 and CD57 with ex vivo survival of CD8+ T cells in HIV infection. J Immunol 2009 Jul 15;183(2):1120–32. [PubMed: 19564339]

97. Mueller YM, Petrovas C, Do DH, et al. Early establishment and antigen dependence of simian immunodeficiency virus-specific CD8+ T-cell defects. J Virol 2007 Oct;81(20):10861–8. [PubMed: 17670818]

98. Whitmire JK, Eam B, Whitton JL. Tentative T cells: memory cells are quick to respond, but slow to divide. PLoS Pathog 2008 Apr;4(4):e1000041. [PubMed: 18404208]

99*. Masopust D. Developing an HIV cytotoxic T-lymphocyte vaccine: issues of CD8 T-cell quantity, quality and location. J Intern Med 2009 Jan;265(1):125–37. This study demonstrates that different routes of immunization lead to the transient expression of mucosal homing receptors shortly after activation of T cells. [PubMed: 19093965]

100. Masopust D, Vezys V, Marzo AL, et al. Preferential localization of effector memory cells in nonlymphoid tissue. Science 2001 Mar 23;291(5512):2413–7. [PubMed: 11264538]

101. Greene JM, Lhost JJ, Burwitz BJ, et al. Extralymphoid CD8+ T cells resident in tissue from simian immunodeficiency virus SIVmac239{Delta}nef-vaccinated macaques suppress SIVmac239 replication ex vivo. J Virol 2010 Apr;84(7):3362–72. [PubMed: 20089651]

102. Holst PJ, Orskov C, Thomsen AR, et al. Quality of the transgene-specific CD8+ T cell response induced by adenoviral vector immunization is critically influenced by virus dose and route of vaccination. J Immunol 2010 Apr 15;184(8):4431–9. [PubMed: 20212099]

103. Haase AT. Targeting early infection to prevent HIV-1 mucosal transmission. Nature 2010 Mar 11;464(7286):217–23. [PubMed: 20220840]

104. Steinman RM. Dendritic cells: understanding immunogenicity. Eur J Immunol 2007 Nov;37(Suppl 1):S53–60. [PubMed: 17972346]

105. Daniel MD, Kirchhoff F, Czajak SC, et al. Protective effects of a live attenuated SIV vaccine with a deletion in the nef gene. Science 1992 Dec 18;258(5090):1938–41. [PubMed: 1470917]

106. Baba TW, Liska V, Khimani AH, et al. Live attenuated, multiply deleted simian immunodeficiency virus causes AIDS in infant and adult macaques. Nat Med 1999 Feb;5(2):194–203. [PubMed: 9930868]

107. Querec T, Bennouna S, Alkan S, et al. Yellow fever vaccine YF-17D activates multiple dendritic cell subsets via TLR2, 7, 8, and 9 to stimulate polyvalent immunity. J Exp Med 2006 Feb 20;203 (2):413–24. [PubMed: 16461338]

108. Lau LL, Jiang J, Shen H. In vivo modulation of T cell responses and protective immunity by TCR antagonism during infection. J Immunol 2005 Jun 15;174(12):7970–6. [PubMed: 15944303]

109. Lore K, Betts MR, Brenchley JM, et al. Toll-like receptor ligands modulate dendritic cells to augment cytomegalovirus- and HIV-1-specific T cell responses. J Immunol 2003 Oct 15;171(8):4320–8. [PubMed: 14530357]

110. Storni T, Ruedl C, Renner WA, et al. Innate immunity together with duration of antigen persistence regulate effector T cell induction. J Immunol 2003 Jul 15;171(2):795–801. [PubMed: 12847247]

111. Wille-Reece U, Wu CY, Flynn BJ, et al. Immunization with HIV-1 Gag protein conjugated to a TLR7/8 agonist results in the generation of HIV-1 Gag-specific Th1 and CD8+ T cell responses. J Immunol 2005 Jun 15;174(12):7676–83. [PubMed: 15944268]

112. Wille-Reece U, Flynn BJ, Lore K, et al. Toll-like receptor agonists influence the magnitude and quality of memory T cell responses after prime-boost immunization in nonhuman primates. J Exp Med 2006 May 15;203(5):1249–58. [PubMed: 16636134]

113*. Longhi MP, Trumpfheller C, Idoyaga J, et al. Dendritic cells require a systemic type I interferon response to mature and induce CD4+ Th1 immunity with poly IC as adjuvant. J Exp Med 2009 Jul 6;206(7):1589–602. This study shows that polyinosinic:polycytidylic acid and DC-targeted HIV gag protein vaccine promote the maturation of DCs via the induction of type I IFN. [PubMed: 19564349]

114. Bahl K, Kim SK, Calcagno C, et al. IFN-induced attrition of CD8 T cells in the presence or absence of cognate antigen during the early stages of viral infections. J Immunol 2006 Apr 1;176(7):4284–95. [PubMed: 16547266]

115. Thompson LJ, Kolumam GA, Thomas S, et al. Innate inflammatory signals induced by various pathogens differentially dictate the IFN-I dependence of CD8 T cells for clonal expansion and memory formation. J Immunol 2006 Aug 1;177(3):1746–54. [PubMed: 16849484]

116. McGill J, Van Rooijen N, Legge KL. IL-15 trans-presentation by pulmonary dendritic cells promotes effector CD8 T cell survival during influenza virus infection. J Exp Med 2010 Mar 15;207(3):521–34. [PubMed: 20212069]

117. Zhang B, Zhang Y, Niu L, et al. Dendritic cells and Stat3 are essential for CD137-induced CD8 T cell activation-induced cell death. J Immunol 2010 May 1;184(9):4770–8. [PubMed: 20351189]

118. Engelmayer J, Larsson M, Lee A, et al. Mature dendritic cells infected with canarypox virus elicit strong anti-human immunodeficiency virus CD8+ and CD4+ T-cell responses from chronically infected individuals. J Virol 2001 Mar;75(5):2142–53. [PubMed: 11160718]

119. Zhang R, Zhang S, Li M, et al. Incorporation of CD40 ligand into SHIV virus-like particles (VLP) enhances SHIV-VLP-induced dendritic cell activation and boosts immune responses against HIV. Vaccine. 2010 May 12;

120. Trumpfheller C, Finke JS, Lopez CB, et al. Intensified and protective CD4+ T cell immunity in mice with anti-dendritic cell HIV gag fusion antibody vaccine. J Exp Med 2006 Mar 20;203(3):607–17. [PubMed: 16505141]

121. Perreau M, Pantaleo G, Kremer EJ. Activation of a dendritic cell-T cell axis by Ad5 immune complexes creates an improved environment for replication of HIV in T cells. J Exp Med 2008 Nov 24;205(12):2717–25. [PubMed: 18981239]

122. Britten CM, Janetzki S, Ben-Porat L, et al. Harmonization guidelines for HLA-peptide multimer assays derived from results of a large scale international proficiency panel of the Cancer Vaccine Consortium. Cancer Immunol Immunother 2009 Oct;58(10):1701–13. [PubMed: 19259668]

123. Britten CM, Janetzki S, van der Burg SH, et al. Toward the harmonization of immune monitoring in clinical trials: quo vadis? Cancer Immunol Immunother 2008 Mar;57(3):285–8. [PubMed: 17721782]

124. Janetzki S, Britten CM, Kalos M, et al. "MIATA"-minimal information about T cell assays. Immunity 2009 Oct 16;31(4):527–8. [PubMed: 19833080]

125. Kallies A. Distinct regulation of effector and memory T-cell differentiation. Immunol Cell Biol 2008 May-Jun;86(4):325–32. [PubMed: 18362944]

126. Ahlers JD, Belyakov IM. Memories that last forever: strategies for optimizing vaccine T-cell memory. Blood 2010 Mar 4;115(9):1678–89. [PubMed: 19903895]

127. Hladik F, Sakchalathorn P, Ballweber L, et al. Initial events in establishing vaginal entry and infection by human immunodeficiency virus type-1. Immunity 2007 Feb;26(2):257–70. [PubMed: 17306567]

128. Randolph GJ, Beaulieu S, Lebecque S, et al. Differentiation of monocytes into dendritic cells in a model of transendothelial trafficking. Science 1998 Oct 16;282(5388):480–3. [PubMed: 9774276]

129. Zak DE, Aderem A. Systems biology of innate immunity. Immunol Rev 2009 Jan;227(1):264–82. [PubMed: 19120490]

130. Gardy JL, Lynn DJ, Brinkman FS, et al. Enabling a systems biology approach to immunology: focus on innate immunity. Trends Immunol 2009 Jun;30(6):249–62. [PubMed: 19428301]

131. AVAC. Ongoing trials of preventive HIV/AIDS vaccines worldwide. 2009. Available from: www.avac.org/trials_table.htm

132. Walker LM, Phogat SK, Chan-Hui PY, et al. Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. Science 2009 Oct 9;326(5950):285–9. [PubMed: 19729618]

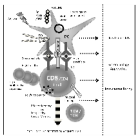

Figure 1.

To elicit an efficient T cell response, a vaccine must target innate immune cells, and in particular the DCs: viral vectors that infect DCs, adjuvants, TLR-ligands or costimulatory molecules should be included in the vaccine composition to improve Ag-presentation and T cell priming. The breadth of the vaccine-induced T cell response can be improved by using optimal vaccine antigens, as mosaic Ags that enhance the recognition of multiple HIV-1 epitopes and variants within theses epitopes by cross-reactivity. Defined as correlates of HIV-1 disease control, the polyfunctionality, proliferative capacity and functional avidity of CD8 T cells should be induced. To achieve a long-term immune protection, HIV-1 T cell vaccine must induce the generation of long-lasting central memory T cells (TCM) and mostly effector memory T cells (TEM) that are more likely to act rapidly in the mucosal site of HIV-1 transmission. The development of novel *in vitro* models, immuno-monitoring and systems biology approaches will provide a comprehensive analysis of the complex networks between both arms of the innate and the adaptive immunity and allow to define precise correlates of immune protection and key targets for an efficient HIV-1 T cell vaccine.

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Table 1

Comparison between the CD8 T cell immune response during HIV-1 infection and an efficient immune response that should be induced by a protective vaccine.

CD8 T cell response characteristics	HIV-1 infection	Ideal Vaccine
Magnitude	Not associated to protection	Moderate or High
Breadth	Narrow/escape mutations	Broad and cross reactive
Avidity	Moderate/low	High
Functionality	Mono-functional responses	Polyfunctional responses
Proliferation	Impaired	Sustained
Memory	Impaired	Sustained
Timing of homing	Too late	Early