# HIV-1 Vaccine Development: Progress and Prospects

*Anna R. Thorner, MD, and Dan H. Barouch, MD, PhD*

**Corresponding author**
Dan H. Barouch, MD, PhD
Research East Room 213, Division of Viral Pathogenesis,
Beth Israel Deaconess Medical Center, 330 Brookline Avenue,
Boston, MA 02215, USA.
E-mail: dbarouch@bidmc.harvard.edu

**Current Infectious Disease Reports** 2007, **9:**71–75
Current Medicine Group LLC ISSN 1523-3847


The development of a prophylactic HIV-1 vaccine is a global health priority. It has proven extraordinarily challenging, however, to develop immunogens that elicit broadly reactive HIV-1–specific neutralizing antibodies. As a result, most HIV-1 vaccine candidates in development focus on generating virus-specific cellular immune responses. Both plasmid DNA vaccines and recombinant live vectors have been shown to elicit cellular immune responses, and vaccine candidates based on these technologies are now being evaluated for safety, immunogenicity, and efficacy in advanced phase clinical trials. This review examines the progress and prospects of these vaccine strategies.

## Introduction

Over 40 million people are currently infected with HIV-1, and nearly 5 million new infections occur each year. Therefore, the need for a safe and effective HIV-1 vaccine is paramount, but the scientific challenges associated with its development remain formidable. The virus has evolved effective methods to conceal its envelope (Env) glycoprotein from the immune system, and all attempts to date to generate immunogens that elicit broadly reactive neutralizing antibodies (NAbs) have proven limited. In contrast, it has become possible to generate virus-specific cellular immunity using gene-based vaccines such as DNA vaccines and recombinant live vectors, and a growing number of vaccine candidates based on these approaches are currently in clinical trials.

The extent to which vaccine-elicited cellular immune responses will protect against HIV-1 infection or disease progression in humans, however, remains unclear. Moreover, both DNA vaccines and recombinant live vectors will likely need to be optimized to maximize their potential. In addition, a prophylactic HIV-1 vaccine will need to contend with the extraordinary viral sequence diversity worldwide as well as the capacity of HIV-1 to evade virus-specific immune responses. Hopefully, the recent increase in focus and funding in the HIV-1 vaccine development field will accelerate research that will help solve these challenging problems.

## Immune Control of HIV-1

Substantial evidence demonstrates that adaptive immune responses can partially control HIV-1 replication. Virus-specific CD8+ T lymphocyte responses have been shown to emerge early during acute infection and are believed to contribute substantially to the control of primary viremia [1,2] as well as chronic infection [3]. Consistent with these data, depletion of CD8+ lymphocytes during acute simian immunodeficiency virus (SIV) infection of rhesus monkeys resulted in sustained high levels of primary viremia and rapid clinical disease progression, demonstrating directly the functional significance of these responses [4]. Both HIV-1 and SIV also develop mutations within dominant CD8+ T lymphocyte epitopes during acute and chronic infection [5–9], suggesting that CD8+ T lymphocytes exert substantial selective pressure on the virus. Virus-specific CD4+ T lymphocytes also likely contribute to immune control [10], but these responses are typically weak in HIV-1–infected individuals, in part because the virus preferentially infects and destroys HIV-1–specific CD4+ T lymphocytes [11].

The contribution of virus-specific NAbs to immune control is less well established. NAbs are often directed against historical rather than contemporary virus isolates because of rapid virus escape from NAbs [12,13]. The crystal structures of CD4-bound and unliganded trimeric Env glycoproteins reveal additional strategies used by the virus to avoid host NAbs, including cloaking of the molecular surface by carbohydrates, a recessed CD4 binding site, and creation of the chemokine receptor binding site only after major conformational changes are induced by CD4 binding [14•,15,16]. Moreover, a recent study demonstrated that certain broadly reactive monoclonal antibodies have polyspecific autoreactivity

[17•], perhaps explaining why broadly reactive NAbs are rarely elicited in HIV-1–infected individuals. In particular, this study suggests that the generation of broadly reactive NAbs by vaccination may be limited by tolerance mechanisms. However, the potential importance of vaccine-elicited NAbs should not be underestimated, because adoptive transfer of high titers of broadly reactive monoclonal antibodies has been shown to protect effectively against simian/human immunodeficiency virus (SHIV) transmission in rhesus monkeys [18,19].

Recent advances in our understanding of the early immunopathologic events of acute HIV-1 infection have had major implications for the development of HIV-1 vaccination strategies. The gut-associated lymphoid tissue (GALT) has been shown to be a major site of viral replication during acute infection [20], and it has been estimated that over half of memory CD4+CCR5+ T lymphocytes are depleted within the first 4 to 10 days of infection, thus setting the stage for progressive immunodeficiency [21•,22•]. Importantly, effective vaccination strategies in rhesus monkeys have been reported to limit the loss of gut-associated memory T lymphocytes following SIV challenge [23•], and clinical protection was correlated with the preservation of central memory CD4+ T lymphocytes in this model [24•].

## Traditional Vaccine Strategies

Traditional vaccine strategies with a proven track record for affording clinical protection against other viral infections include live attenuated viruses, whole killed viruses, and protein subunits. Unfortunately, all of these strategies have encountered significant limitations as vaccine approaches for HIV-1. Live attenuated SIV affords considerable protection against SIV challenges in rhesus monkeys [25], but significant safety concerns have precluded the advancement of live attenuated viruses into clinical trials [26,27].

Inactivated or killed viruses were reported early in the HIV-1 vaccine effort to protect monkeys against SIV infection, although later studies suggested that this finding was an experimental artifact [28,29]. Moreover, an inactivated virus vaccine showed no substantial benefit in HIV-1–infected patients [30]. Similarly, recombinant Env gp120 protein immunogens manufactured by the biotechnology company VaxGen (Brisbane, CA, USA) showed no efficacy in the first and only prophylactic phase 3 vaccine efficacy trials completed to date [31]. These approaches likely failed as a result of their inability to generate broadly reactive NAb responses as well as their inability to elicit potent virus-specific CD8+ T lymphocyte responses. Substantial investigation is currently underway to develop improved HIV-1 Env immunogens, although none of these strategies have been clearly successful yet in generating broad NAbs. A detailed discussion of these ongoing research efforts is beyond the scope of this review.

## Novel Vaccine Strategies

Given the apparent limitations of traditional vaccine approaches, the focus of HIV-1 vaccine development efforts has largely shifted to novel vaccine strategies that can generate HIV-1–specific cellular immune responses. These novel modalities involve gene-based vaccines, including plasmid DNA vaccines and recombinant live vector-based vaccines. In nonhuman primate studies, these vaccines have been shown to elicit virus-specific cellular immune responses and afford partial protection against both SIV and SHIV challenges [24•,32–34]. Rhesus monkeys vaccinated with these immunogens were not protected against infection, but they controlled both peak and setpoint viral loads significantly better than did control animals following challenge. If these vaccines afford similar efficacy in humans, and if the reduction of viral loads is durable, then such vaccines could have two important consequences: they may slow clinical disease progression in infected individuals, and they may also reduce transmission to other individuals, which could result in a substantial population benefit. It is important to note that the majority of clinically licensed vaccines against other pathogens also do not afford sterilizing immunity against infection but rather aim to protect against clinical disease.

However, it is unclear whether rhesus monkey challenge studies will accurately predict HIV-1 transmission in humans. In particular, rhesus monkey challenge studies typically utilize extremely high doses of SIV or SHIV delivered either by the intravenous route or by a mucosal route. In contrast, HIV-1 infection of humans is far less efficient with transmission frequencies of less than 1 in 200 exposures, although individuals with acute HIV-1 infection or concurrent sexually transmitted diseases have substantially higher transmission frequencies [35]. Given the differences between experimental SIV/SHIV infection of rhesus monkeys and natural HIV-1 transmission in humans, the degree to which the current T cell–based vaccines will protect against HIV-1 infection in humans remains an open question that will only be resolved by clinical vaccine efficacy studies.

DNA vaccines have proven immunogenic in preclinical studies, but their immunogenicity in humans has appeared limited. Moreover, the requirement for large doses, often as high as 4 to 5 mg per injection, will likely result in manufacturing and cost challenges in terms of DNA vaccine delivery. Nevertheless, DNA vaccines are promising candidate vaccines as part of heterologous prime-boost regimens, as they prime effectively for subsequent boosts with live vectors [33,34]. Other strategies aimed at augmenting DNA vaccine–elicited immune responses include the addition of adjuvants such as plasmid cytokines [32,36] and the use of in vivo electroporation [37].

Of the live vaccine vectors, poxviruses have been studied most extensively. Safety concerns associated with vaccinia virus have led to the development of attenuated poxviruses, including ALVAC, MVA, and NYVAC. ALVAC vectors

failed to meet predetermined criteria of immunogenicity to proceed with efficacy trials as a single modality, although a phase 3 trial is currently underway in Thailand assessing the efficacy of priming with ALVAC and boosting with the VaxGen gp120 protein. MVA vectors were shown to have limited immunogenicity in phase 2 studies sponsored by the International AIDS Vaccine Initiative, although in recent studies, administration of MVA or NYVAC vectors following a DNA prime have appeared more immunogenic.

Substantial efforts over the past several years have been devoted to the development of adenovirus vectors as candidate vaccines for both HIV-1 and other pathogens. Vector comparison studies in rhesus monkeys have shown that replication-incompetent, recombinant adenovirus serotype 5 (rAd5) vectors are more immunogenic than many other vaccine modalities, including DNA, MVA, and other vectors [34,38]. Moreover, rAd5 vectors can be produced in large quantities and thus could potentially be manufactured as a practical vaccine. It is possible, however, that pre-existing anti-Ad5 immunity in human populations, particularly in the developing world, may limit the utility of this vaccine vector [39–42]. Consistent with these concerns, early clinical trial data shows that anti-Ad5 immunity suppresses the immunogenicity of rAd5 vaccine vectors in humans [38], although the extent to which this suppression will be a practical clinical limitation will be determined by ongoing clinical trials.

Potential solutions to this problem include escalating the dose of rAd5, priming with DNA prior to boosting with rAd5, and developing novel rAd vectors. Novel rAd vectors in development include rare human serotype rAd vectors [40,43,44], nonhuman primate rAd vectors [45,46], and capsid chimeric rAd vectors [47,48•]. Rare serotype rAd vectors have been shown to evade anti-Ad5 immunity but have appeared less immunogenic than rAd5 vectors in preclinical studies to date [43,44]. In contrast, we have recently reported that a chimeric rAd5 vector, in which the hexon hypervariable regions (HVRs) were exchanged with the corresponding regions from Ad48, retained rAd5 immunogenicity but effectively evaded anti-Ad5 immunity, suggesting the potential utility of the chimeric vector approach [48•].

Other viral vectors are also being developed, including adeno-associated virus (AAV), vesicular stomatitis virus (VSV), Semliki forest virus (SFV), Venezuelan equine encephalitis virus (VEE), and herpes simplex virus (HSV). Bacterial vectors in development include attenuated enteric bacterial vectors such as Salmonella and Shigella and mycobacterial vectors such as bacille Calmette-Guérin (BCG), although the immunogenicity of these prototype bacterial vectors appears lower than that of viral vectors.

## Current Clinical Vaccine Development Programs

Three vaccine candidates are currently in advanced clinical evaluation. A phase 3 trial evaluating the efficacy of an ALVAC prime, VaxGen gp120 boost regimen is currently underway in Thailand ($n$ = 16,000), and results are expected to become available in 2009.

The more potent rAd5 vector-based vaccine developed by Merck & Co. Inc. (Whitehouse Station, NJ, USA) and the DNA prime, rAd5 boost vaccine developed by the U.S. National Institutes of Health (NIH) Vaccine Research Center (VRC) are currently in phase 2 trials, both in collaboration with the HIV Vaccine Trials Network. The Merck rAd5 vector expressing clade B Gag, Pol, and Nef immunogens is currently being evaluated in phase 2b proof-of-concept studies ($n$ = 3000). Phase 2b studies are powered to assess for vaccine efficacy, but they are smaller and more flexible than phase 3 licensure studies. The objective of phase 2b proof-of-concept studies is to evaluate immune correlates of protection in humans, which will provide valuable guidance for the further optimization and evaluation of vaccine candidates. Prevention of HIV-1 infection as well as reduction of peak and setpoint viral loads will be evaluated as endpoints in these studies.

The NIH VRC has developed a DNA prime, rAd5 boost vaccine expressing clade A/B/C Env genes as well as clade B Gag and Pol genes. This vaccine is currently being evaluated in phase 2a safety and immunogenicity studies, and a phase 2b proof-of-concept study with this vaccine candidate is likely to begin in the coming months. While the field awaits the results of these large phase 2 studies, novel vectors are also being evaluated in preclinical studies and in phase 1 clinical trials.

In addition to exploring the immunogenicity of naturally occurring antigen sequences, novel antigens aimed at broader coverage of worldwide virus sequence diversity are also being developed. Antigens derived from a variety of virus isolates as well as synthetically derived consensus sequences are currently being evaluated in preclinical studies. It is hoped that the best vectors eventually will be paired with the best inserts in the development of improved future clinical vaccine candidates.

## Conclusions

Preclinical and clinical development of HIV-1 vaccine candidates hopefully will be accelerated by the recent establishment of the Global HIV/AIDS Vaccine Enterprise (GHAVE), which has provided increased focus and funding to establish consortia of investigators aimed at solving key scientific obstacles confronting HIV-1 vaccine development [49,50••]. Currently, optimism in the field is renewed, based in part on the tangible progress in developing rAd vector–based vaccines that effectively elicit HIV-1–specific cellular immune responses in humans. It is important to realize, however, that no vaccine has previously been developed or licensed based on cellular immune responses, and thus major scientific, regulatory, and logistic challenges are undoubtedly ahead for T cell–based vaccines. Current phase 2b proof-of-concept

studies are evaluating the efficacy of these approaches, and these studies should give a relatively rapid assessment of vaccine efficacy as well as important data regarding immune correlates of protection in humans. Meanwhile, basic research efforts will continue to develop improved T lymphocyte immunogens that optimize vaccine coverage of worldwide viral diversity, vectors that elicit improved cellular immune responses, and hopefully novel Env antigens that will improve the breadth of elicited NAbs.

## Acknowledgments

The authors wish to acknowledge support from the NIH (AI066305, AI066924, AI058727, AI060368), the Bill & Melinda Gates Foundation, and the Doris Duke Charitable Foundation.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance


1. 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, **68:**6103–6110.
2. Pantaleo G, Demarest JF, Soudeyns H, et al.: **Major expansion of CD8+ T cells with a predominant V beta usage during the primary immune response to HIV.** *Nature* 1994, **370:**463–467.
3. Musey L, Hughes J, Schacker T, et al.: **Cytotoxic-T-cell responses, viral load, and disease progression in early human immunodeficiency virus type 1 infection.** *N Engl J Med* 1997, **337:**1267–1274.
4. Schmitz JE, Kuroda MJ, Santra S, et al.: **Control of viremia in simian immunodeficiency virus infection by CD8+ lymphocytes.** *Science* 1999, **283:**857–860.
5. Allen TM, O'Connor DH, Jing P, et al.: **Tat-specific cytotoxic T lymphocytes select for SIV escape variants during resolution of primary viraemia.** *Nature* 2000, **407:**386–390.
6. Evans DT, O'Connor DH, Jing P, et al.: **Virus-specific cytotoxic T-lymphocyte responses select for amino-acid variation in simian immunodeficiency virus Env and Nef.** *Nat Med* 1999, **5:**1270–1276.
7. Barouch DH, Kunstman J, Kuroda MJ, et al.: **Eventual AIDS vaccine failure in a rhesus monkey by viral escape from cytotoxic T lymphocytes.** *Nature* 2002, **415:**335–339.
8. Price DA, Goulder PJ, Klenerman P, et al.: **Positive selection of HIV-1 cytotoxic T lymphocyte escape variants during primary infection.** *Proc Natl Acad Sci U S A* 1997, **94:**1890–1895.
9. Moore CB, John M, James IR, et al.: **Evidence of HIV-1 adaptation to HLA-restricted immune responses at a population level.** *Science* 2002, **296:**1439–1443.
10. Rosenberg ES, Billingsley JM, Caliendo AM, et al.: **Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia.** *Science* 1997, **278:**1447–1450.
11. Douek DC, Brenchley JM, Betts MR, et al.: **HIV preferentially infects HIV-specific CD4+ T cells.** *Nature* 2002, **417:**95–98.
12. Richman DD, Wrin T, Little SJ, Petropoulos CJ: **Rapid evolution of the neutralizing antibody response to HIV type 1 infection.** *Proc Natl Acad Sci USA* 2003, **100:**4144–4149.
13. Wei X, Decker JM, Wang S, et al.: **Antibody neutralization and escape by HIV-1.** *Nature* 2003, **422:**307–312.
14. • Chen B, Vogan EM, Gong H, et al.: **Structure of an unliganded simian immunodeficiency virus gp120 core.** *Nature* 2005, **433:**834–841.

The crystal structure of an unliganded gp120 core reveals key ways that the Env protein evades the immune system.

15. Kwong PD, Wyatt R, Robinson J, et al.: **Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody.** *Nature* 1998, **393:**648–659.
16. Wyatt R, Kwong PD, Desjardins E, et al.: **The antigenic structure of the HIV gp120 envelope glycoprotein.** *Nature* 1998, **393:**705–711.
17. • Haynes BF, Fleming J, St Clair EW, et al.: **Cardiolipin polyspecific autoreactivity in two broadly neutralizing HIV-1 antibodies.** *Science* 2005, **308:**1906–1908.

Two broadly reactive NAbs exhibit autoimmune polyspecificity, suggesting that the generation of certain broad NAbs may be limited by tolerance mechanisms.

18. Baba TW, Liska V, Hofmann-Lehmann R, et al.: **Human neutralizing monoclonal antibodies of the IgG1 subtype protect against mucosal simian-human immunodeficiency virus infection.** *Nat Med* 2000, **6:**200–206.
19. Mascola JR, Stiegler G, VanCott TC, et al.: **Protection of macaques against vaginal transmission of a pathogenic HIV-1/SIV chimeric virus by passive infusion of neutralizing antibodies.** *Nat Med* 2000, **6:**207–210.
20. Veazey RS, DeMaria M, Chalifoux LV, et al.: **Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection.** *Science* 1998, **280:**427–431.
21. • Mattapallil JJ, Douek DC, Hill B, et al.: **Massive infection and loss of memory CD4+ T cells in multiple tissues during acute SIV infection.** *Nature* 2005, **434:**1093–1097.

Mucosal CD4+ T lymphocytes are rapidly depleted within the first few days of acute SIV infection.

22. • Li Q, Duan L, Estes JD, et al.: **Peak SIV replication in resting memory CD4+ T cells depletes gut lamina propria CD4+ T cells.** *Nature* 2005, **434:**1148–1152.

As in [21•], mucosal CD4+ T lymphocytes are rapidly depleted within the first few days of acute SIV infection.

23. • Mattapallil JJ, Douek DC, Buckler-White A, et al.: **Vaccination preserves CD4 memory T cells during acute simian immunodeficiency virus challenge.** *J Exp Med* 2006, **203:**1533–1541.

Vaccination with a DNA prime, rAd5 boost regimen partially preserves gastrointestinal CD4+ T lymphocytes following SIV challenge.

24. • Letvin NL, Mascola JR, Sun Y, et al.: **Preserved CD4+ central memory T cells and survival in vaccinated SIV-challenged monkeys.** *Science* 2006, **312:**1530–1533.

Vaccination with a DNA prime, rAd5 boost regimen preserves central memory CD4+ T lymphocytes and slows clinical disease progression following SIV challenge.

25. 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, **258:**1938–1941.
26. Baba TW, Jeong YS, Pennick D, et al.: **Pathogenicity of live, attenuated SIV after mucosal infection of neonatal macaques.** *Science* 1995, **267:**1820–1825.
27. Learmont JC, Geczy AF, Mills J, et al.: **Immunologic and virologic status after 14 to 18 years of infection with an attenuated strain of HIV-1. A report from the Sydney Blood Bank Cohort.** *N Engl J Med* 1999, **340:**1715–1722.
28. Murphey-Corb M, Martin LN, Davison-Fairburn B, et al.: **A formalin-inactivated whole SIV vaccine confers protection in macaques.** *Science* 1989, **246:**1293–1297.
29. Stott EJ: **Anti-cell antibody in macaques.** *Nature* 1991, **353:**393.
30. Kahn JO, Cherng DW, Mayer K, et al.: **Evaluation of HIV-1 immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549 x 10(6)/L CD4 cell counts: A randomized controlled trial.** *JAMA* 2000, **284:**2193–2202.

31. 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, **191:**654–665.
32. Barouch DH, Santra S, Schmitz JE, et al.: **Control of viremia and prevention of clinical AIDS in rhesus monkeys by cytokine-augmented DNA vaccination.** *Science* 2000, **290:**486–492.
33. Amara RR, Villinger F, Altman JD, et al.: **Control of a mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine.** *Science* 2001, **292:**69–74.
34. Shiver JW, Fu TM, Chen L, et al.: **Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity.** *Nature* 2002, **415:**331–335.
35. Pilcher CD, Fiscus SA, Nguyen TQ, et al.: **Detection of acute infections during HIV testing in North Carolina.** *N Engl J Med* 2005, **352:**1873–1883.
36. Sumida SM, McKay PF, Truitt DM, et al.: **Recruitment and expansion of dendritic cells in vivo potentiate the immunogenicity of plasmid DNA vaccines.** *J Clin Invest* 2004, **114:**1334–1342.
37. Otten G, Schaefer M, Doe B, et al.: **Enhancement of DNA vaccine potency in rhesus macaques by electroporation.** *Vaccine* 2004, **22:**2489–2493.
38. Shiver JW, Emini EA: **Recent advances in the development of HIV-1 vaccines using replication-incompetent adenovirus vectors.** *Annu Rev Med* 2004, **55:**355–372.
39. Casimiro DR, Chen L, Fu TM, et al.: **Comparative immunogenicity in rhesus monkeys of DNA plasmid, recombinant vaccinia virus, and replication-defective adenovirus vectors expressing a human immunodeficiency virus type 1 gag gene.** *J Virol* 2003, **77:**6305–6313.
40. Vogels R, Zuijdgeest D, van Rijnsoever R, et al.: **Replication-deficient human adenovirus type 35 vectors for gene transfer and vaccination: efficient human cell infection and bypass of preexisting adenovirus immunity.** *J Virol* 2003, **77:**8263–8271.
41. Kostense S, Koudstaal W, Sprangers M, et al.: **Adenovirus types 5 and 35 seroprevalence in AIDS risk groups supports type 35 as a vaccine vector.** *AIDS* 2004, **18:**1213–1216.
42. Sumida SM, Truitt DM, Lemckert AA, et al.: **Neutralizing antibodies to adenovirus serotype 5 vaccine vectors are directed primarily against the adenovirus hexon protein.** *J Immunol* 2005, **174:**7179–7185.
43. Barouch DH, Pau MG, Custers JH, et al.: **Immunogenicity of recombinant adenovirus serotype 35 vaccine in the presence of pre-existing anti-Ad5 immunity.** *J Immunol* 2004, **172:**6290–6297.
44. Lemckert AA, Sumida SM, Holterman L, et al.: **Immunogenicity of heterologous prime-boost regimens involving recombinant adenovirus serotype 11 (Ad11) and Ad35 vaccine vectors in the presence of anti-ad5 immunity.** *J Virol* 2005, **79:**9694–9701.
45. Farina SF, Gao GP, Xiang ZQ, et al.: **Replication-defective vector based on a chimpanzee adenovirus.** *J Virol* 2001, **75:**11603–11613.
46. Fitzgerald JC, Gao GP, Reyes-Sandoval A, et al.: **A simian replication-defective adenoviral recombinant vaccine to HIV-1 gag.** *J Immunol* 2003, **170:**1416–1422.
47. Nanda A, Lynch DM, Goudsmit J, et al.: **Immunogenicity of recombinant fiber-chimeric adenovirus serotype 35 vector-based vaccines in mice and rhesus monkeys.** *J Virol* 2005, **79:**14161–14168.
48.• Roberts DM, Nanda A, Havenga MJ, et al.: **Hexon-chimaeric adenovirus serotype 5 vectors circumvent pre-existing anti-vector immunity.** *Nature* 2006, **441:**239–243.

Chimeric Ad vectors represent a potential strategy to solve the problem of pre-existing anti-Ad5 immunity.

49. Klausner RD, Fauci AS, Corey L, et al.: **Medicine. The need for a global HIV vaccine enterprise.** *Science* 2003, **300:**2036–2039.
50.•• **The Global HIV/AIDS Vaccine Enterprise: scientific strategic plan.** *PLoS Med* 2005, **2:**e25.

Consortia of investigators have been formed to attempt to solve key scientific obstacles facing HIV-1 vaccine development as part of the Global HIV/AIDS Vaccine Enterprise.