Protection of MN-rgp120–Immunized Chimpanzees from Heterologous Infection with a Primary Isolate of Human Immunodeficiency Virus Type 1


Three chimpanzees immunized with recombinant gp120 from human immunodeficiency virus type 1 (HIV-1) strain MN and 1 control animal were challenged intravenously with a primary isolate of HIV-1SF2. Viral infection was detected in the control animal by viral culture, polymerase chain reaction, and multiple serologic assays beginning 2 weeks after infection. Markers of HIV-1 infection were not detected in any of the gp120-vaccinated animals during 12 months of follow-up. Antisera from the gp120-immunized chimpanzees were unable to neutralize the challenge virus cultured in peripheral blood mononuclear cells (PBMC). These studies demonstrate that immunization with recombinant gp120 derived from a T cell–adapted isolate prevented infection by a heterologous primary isolate of HIV-1. The results suggest that in vitro virus neutralization assays utilizing primary isolates cultured in PBMC may be imperfect indicators of protection in vivo.

The evaluation of candidate human immunodeficiency virus type 1 (HIV-1) vaccines is complicated by the fact that chimpanzees (Pan troglodytes) are the only nonhuman primate species that can be efficiently infected by the virus [1]. Although chimpanzees become persistently infected with HIV-1, they fail to develop the progressive deterioration of the immune system characteristic of AIDS. We previously reported that immunization of chimpanzees with recombinant gp120 from HIV-1IIIB (IIIB-rgp120) protects against intravenous infection with homologous virus [2]. Others have shown that immunization with recombinant HIV-1 envelope glycoproteins alone or in combination with viral peptides can protect against intravenous cell-free or cell-associated challenge with homologous virus [3–5]. A major unanswered question from these studies was whether a monovalent subunit vaccine could protect against heterologous isolates of HIV-1. Early indications from in vitro neutralization studies suggested that antisera to IIIB-rgp120 were extremely limited in their ability to neutralize diverse isolates of HIV-1 [6, 7].

Molecular epidemiologic analysis [8] provided insight into the failure of IIIB-rgp120 to exhibit broad cross-neutralizing activity by showing that the sequence of the principal neutralizing determinant (PND) of gp120 from HIV-1IIIB was unrepresentative of subtype (clade) B viruses. To overcome this problem, a new vaccine was prepared from the MN strain of HIV-1 that possessed a PND sequence typical of ~60% of subtype B viruses circulating in the United States [8]. Preclinical studies demonstrated that MN-rgp120 was a significant improvement over IIIB-rgp120 as shown by its ability to elicit antibodies that neutralized a wide variety of subtype B viruses in vitro [9]. Phase I and II clinical trials confirmed that MN-rgp120 was safe and elicited cross-neutralizing antibodies in humans [10]. Due to the difficulty in preparing a high-titered challenge stock of HIV-1MN [11], it has not been possible to test the efficacy of this vaccine in chimpanzee infectivity studies.

Recently, a new challenge virus derived from HIV-1SF2 (SF2PBMC), another subtype B virus, was prepared and titrated for infectivity in chimpanzees [12]. The culture history of the SF2PBMC challenge stock differed from the HIV-1IIIB stock in that it was prepared from a primary virus (cultured exclusively in peripheral blood mononuclear cells [PBMC]), whereas the HIV-1IIIB stock was prepared from virus adapted to growth in T cell lines. Considerable evidence suggests that the tropism and neutralization sensitivity of primary viruses differ from those of T cell line–adapted viruses [13–15]. In the present studies, we assessed the ability of parenteral immunization with MN-rgp120 to protect chimpanzees from intravenous infection with a heterologous primary isolate of HIV-1.
Materials and Methods

Animals and immunization schedule. Four chimpanzees (6–12 years old) were housed individually at the Southwest Foundation for Biomedical Research (San Antonio, TX). All blood sample collections and inoculations were done under sedation induced by ketamine or telazol (5 mg/kg, intramuscularly) or other drugs as indicated. Two chimpanzees (X140 and X207) received four immunizations of aluminum hydroxide (alum)-adjuvanted MN-rgp120 (300 μg/injection) according to a 0-, 4-, 24-, and 107-week immunization schedule. Another MN-rgp120–immunized chimpanzee (X234) and a control animal (X190) that received adjuvant alone, received three injections according to a 0-, 4-, and 103-week immunization schedule. Thus, the immunizations at 0 and 103 weeks and the virus challenge of X234 and X190 were done at the same time as the 4- and 107-week immunizations and virus challenge of X140 and X207. For purposes of comparison, the data from X234 and X190, which received their primary and secondary immunizations exactly 4 weeks later than X140 and X207, were plotted to coincide with the data from the other 2 animals.

Serum collection and serologic assays. Blood was collected at monthly or bimonthly intervals, and serum was obtained by letting clots form for ≥2 h at room temperature. After the tubes were centrifuged at 3000 g, serum was stored at −20°C in cryovials. Serum was assayed for antibodies to MN-rgp120, antibodies to synthetic gp120 V3 domain peptides corresponding to sequences from the gp120 V3 domain, and antibodies able to inhibit the binding of MN-rgp120 to cell surface CD4 as described previously [2, 9, 16, 17]. End-point titers of antibody binding to gp120 and V3 peptides were determined using 3-fold serial dilutions of antisera. The end-point dilution titer was defined as the last dilution that produced an optical density value two times higher than the mean of 1:50-diluted normal chimpanzee sera. Antibody titers were calculated by a computer program that interpolated values between antibody dilutions. The interassay variability of positive control standard sera was ±0.5 wells. Antibodies to HIV-1 were measured by commercial ELISA. An HIV-1 immunoblot assay (Bio-Rad Laboratories, Hercules, CA) was used to identify antibodies to the HIV-1 core proteins (e.g., p17, p24, and p55).

Neutralization assays and viral challenge. In vitro neutralization assays were done by two protocols [18, 19], using T cell–adapted variants of the MN, SF2, and IIIB strains of HIV-1 as well as an SF2

PBMC primary isolate challenge virus (prepared by J. Levy, University of California Medical School, San Francisco, and provided by A. Schultz, Division of AIDS, NIH, Bethesda, MD).

The assay that measured the kinetics of virus neutralizing (VN) antibody formation was done in MT4 cells and relied on a colorimetric indicator dye that measured virus (HIV-1)–induced cytopathicity [19]. The virus neutralization assay that measured cross-neutralizing antibody activity was done in A55 cells and used reverse transcriptase activity as an indicator of reduction in infectious titer relative to normal control sera [10, 18]. The assay for detection of virus neutralization of the primary virus isolate was similar to that used for the prototype laboratory-adapted isolates [10, 18], except that human PBMC rather than the A55 cell line were used to support viral replication. In both, the criterion for neutralization was a 10-fold reduction in infectious titer of the virus when compared with normal chimpanzee sera. In brief, several dilutions of the sera were incubated in duplicate with serial 4-fold dilutions of virus for 1 h before addition of activated PBMC (final well concentration, 2 × 10⁶ cells/mL). Cells were cultured in 96-well U-bottom microtiter plates by periodic addition of fresh interleukin (IL)-2–containing medium. On day 12 after infection, supernatants from each well were tested for the presence of reverse transcriptase activity [10, 18], a criterion for successful infection in each well.

Infectious titer for each treatment group was calculated using the Reed and Muench formula. Neutralization titers were estimated from multiplicity curves plotting the surviving virus fraction (V/V₀) versus serum dilution. The neutralization titers were defined as the reciprocal of the serum dilution interpolated to reduce infectious titer by 10-fold (V/V₀ = 0.1). PBMC were prepared from 10 normal human donors by banding lymphocytes in lymphocyte separation medium (Organon Teknika, Durham, NC). The cells were activated for 2 days with mononclonal antibodies to CD3 (12F6; provided by J. Wong, Harvard Medical School, Boston) and CD28 (clone L293; Becton Dickinson, Mountain View, CA), each at 0.1 μg/mL, and a cell density of 2 × 10⁶/mL in RPMI 1640 containing 20% fetal calf serum and 5% IL-2. The chimpanzee challenge inoculum was prepared from three vials of fresh virus, which were pooled, diluted in PBS, and distributed among four syringes. An aliquot of the challenge virus was used to calculate the TCID₅₀ of virus in the final dilution.

Detection of HIV-1 after challenge. Serum and cells were collected bimonthly for the first 4 months after viral challenge and monthly from 4 to 9 months after challenge. A final sample was obtained from each animal 12 months after challenge. Several assays were used to detect HIV-1 infection after challenge. A cocultivation assay, similar to that described previously [2, 7], was used to quantitate cell-associated virus in PBMC. In brief, 10⁶ chimpanzee PBMC, with or without stimulation with phytohemagglutinin (PHA; 1 mg/mL) for 3 days, were cocultured with an equal number of 3-day-old human PHA–stimulated blast cells. Cell culture supernatants were collected weekly for 4 weeks. Viral replication was determined by a p24 antigen capture ELISA (Coulter, Hialeah, FL). We used a commercial polymerase chain reaction (PCR) assay to detect viral RNA in plasma (Roche Biomedical Laboratories, Research Triangle Park, NC) to measure plasma viremia, and a nested DNA PCR assay similar to that described previously [2] was used to monitor proviral DNA in PBMC. Briefly, follic gradient–purified chimpanzee leukocytes were washed twice in isotonic PBS, lysed at 6 × 10⁶ cells/mL in PCR buffer (50 mM KCl, 10 mM TRIS-HCl [pH 8.3], 2.5 mM MgCl₂, 0.1 mg/mL gelatin, 0.45% Nonidet P-40, 0.45% Tween 20, and 100 μM/μL proteinase K), and incubated at 55°C for 1 h and at 95°C for 10 min to inactivate the proteinase K.

We prepared synthetic primers corresponding to the long terminal repeat (LTR) region of HIV-1SF (LTR-A, 5′-AAAGTCTTCCCTGGATTTGCAAAATTAC; -B, 5′-TAACCAAGAGAAGAGCTCAACGGCAGGAAAG; -C, 5′-GACCTTTGATGGTATTGCTCCAAAGT; -D, 5′-CTCTCGAAGGATCCCGAGGGAAGTG). The cell lysate (50 μL) was added to 50 μL of a mixture containing PCR elongation buffer (50 mM KCl, 10 mM TRIS-HCl [pH 8.3], 2.5 mM MgCl₂, 0.05 mg/mL gelatin, 0.225% Nonidet P-40, 0.225% Tween 20, 0.1 mg/mL proteinase K), and incubated at 55°C for 1 h and at 95°C for 10 min to inactivate the proteinase K.
HIV-I SF2. Animals were immunized with 300 μg of alum-formulated MN-rgp120 at 0, 4, 24, and 107 weeks (X140 [●] and X207 [■]) or 0, 4, and 103 weeks (X234, ▲). Control animal (XI90, ○) was immunized with alum adjuvant alone on same schedule as X234. Data from X234 and X190, which received primary and secondary immunizations exactly 4 weeks later than X140 and X207, were plotted to coincide with data from latter animals. Blood was taken at times indicated, and serum was analyzed for antibodies to MN-rgp120. All animals were challenged intravenously on same day with 1 mL of 1:40-diluted (748 TCID50 U) of HIV-1SF2 that was passaged exclusively in peripheral blood mononuclear cells and previously titered for infectivity in chimpanzees. A, Antibody titers (log10) to MN-rgp120 detected by ELISA. B, Antibody titers to synthetic peptide corresponding to V3 domain of HIV-I measured by ELISA [2, 9, 17].

Figure 1. Serologic and virologic characterization of antisera from 4 immunized chimpanzees before and after intravenous challenge with HIV-1SF2. Animals were immunized with 300 μg of alum-formulated MN-rgp120 at 0, 4, 24, and 107 weeks (X140 [●] and X207 [■]) or 0, 4, and 103 weeks (X234, ▲). Control animal (XI90, ○) was immunized with alum adjuvant alone on same schedule as X234. Data from X234 and X190, which received primary and secondary immunizations exactly 4 weeks later than X140 and X207, were plotted to coincide with data from latter animals. Blood was taken at times indicated, and serum was analyzed for antibodies to MN-rgp120. All animals were challenged intravenously on same day with 1 mL of 1:40-diluted (748 TCID50 U) of HIV-1SF2 that was passaged exclusively in peripheral blood mononuclear cells and previously titered for infectivity in chimpanzees. A, Antibody titers (log10) to MN-rgp120 detected by ELISA. B, Antibody titers to synthetic peptide corresponding to V3 domain of HIV-I measured by ELISA [2, 9, 17].
was measured in an assay previously used to measure VN antibodies in MN-rgp120–immunized humans [10, 18]. In general, the reverse transcriptase assay was more sensitive than the MT4 assay and consistently yielded 2- to 5-fold higher neutralization titers. Antisera from all 3 immunized chimpanzees, obtained 2 weeks after the final immunization, possessed neutralizing activity against HIV-1 strains MN, SF2, and IIIB (table 1). The neutralizing titers against HIV-1SF2 were 3- to 6-fold lower (1:366–1:37) than those against HIV-1MN (1:214–1:366), whereas the titers to HIVIIIB (1:20) were lower than those against the other 2 viruses.

All 4 animals were challenged on the same day (week 111) with 1 mL of a 1:40 dilution of an HIV-1SF2 challenge stock that had previously been titered for infectivity in chimpanzees [12]. The virus was aliquoted from the same stock of SF2 PBMC that had successfully infected 6 chimpanzees at the Southwest Foundation for Biomedical Research (unpublished data). On the day of challenge, XI40 had an HIV-1MN neutralization titer of 1:40, whereas X207 and X234 had neutralization titers of 1:80 (figure 2B). Titration of an aliquot of the challenge virus in PHA-activated human PBMC that had successfully infected 6 chimpanzees at the Southwest Foundation for Biomedical Research (unpublished data). The virus could be neutralized by a selected high-titer reference sera from an HIV-1-infected human (table 1).

Several assays were used to monitor the animals for signs of infection after viral challenge. By use of a virus cocultivation assay, HIV-1 was detected in PBMC from control animal XI90 2, 4, and 6 weeks after challenge. Samples collected monthly from weeks 8 to 20 after challenge were negative for plasma viremia by virus cocultivation assays; these became positive at week 41 after challenge but were culture-negative at week 20.

### Table 1. Neutralization of T cell–adapted and primary isolates of HIV-1 by sera from MN-rgp120–immunized chimpanzees.

<table>
<thead>
<tr>
<th>Neutralization titers of HIV strains</th>
<th>MN</th>
<th>SF2</th>
<th>IIIB</th>
<th>SF2_PBMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>X140</td>
<td>214</td>
<td>37</td>
<td>20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>X207</td>
<td>366</td>
<td>125</td>
<td>20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>X234</td>
<td>366</td>
<td>65</td>
<td>20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>X190</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>HIV-1 (positive control)*</td>
<td>4090</td>
<td>4144</td>
<td>828</td>
<td>200–400</td>
</tr>
</tbody>
</table>

NOTE: Neutralization of T cell–adapted viruses was done in AA5 cells; HIV-1SF2 challenge stock was cultured in CD3- and CD28-activated human peripheral blood mononuclear cells. Neutralization titers represent antibody dilution required to reduce HIV-1 infectivity by 90% (IFN/IN = 0.1) relative to normal sera controls.

* Neutralization of HIV-1 by selected high-titer reference sera from HIV-1–infected human.

† Range of neutralization titers from multiple experiments on different days.

Figure 2. Functional evaluation of antisera from chimpanzees immunized with MN-rgp120 or alum alone as in figure 1. Antisera were tested for ability to inhibit 125I-labeled MN-rgp120 binding to surface of CD4 cells (A) or to inhibit HIV-1MN infectivity of MT4 cells (B). Data in A represent reciprocal of serum dilutions giving IC50 of labeled MN-rgp120 binding to cell surface CD4 [16, 17]. Data in B represent reciprocal of serum dilutions giving 50% decrease in virus infectivity of HIV-1MN in MT4 cells measured as described in [19]. Open, cross-hatched, shaded, and solid bars represent animals X140, X207, X234, and X190, respectively.
The MN-rgp120-immunized animals were negative throughout 12 months of follow-up by this assay (table 2). Serologic evidence of viral infection was indicated in immunoblots in which antibodies to the p17 and p24 core antigens were first observed in the control animal 6 weeks after challenge (table 2; figure 3); the antibodies persisted for 12 months after challenge. Immunoblot reactivity consistent with HIV-1 infection was not seen in any of the immunized animals during the 12-month postchallenge follow-up period. Sera from X234 had immunoblot reactivity to an unknown protein with a mobility midway between gp120 and p55 at 3 and 6 months after challenge. This reactivity did not correspond to any known HIV-1-derived proteins and was not present on immunoblot strips from other manufacturers (data not shown).

Further evidence of HIV-1 infection in X190 was shown by commercial HIV-1 ELISA (figure 4): Anti-HIV-1 antibodies, which were detected 6 weeks after infection, have continued to increase over time. By PCR, proviral DNA was detected in PBMC from X190 4 weeks after challenge and at all subsequent time points (12, 16, 20, 41, and 52 weeks after challenge). In contrast, proviral DNA was not detected in any of the MN-rgp120-vaccinated animals. Virion-associated viral RNA in the plasma was first detected in X190 2 weeks after infection and reached a maximum concentration at postinfection week 6; thereafter, the levels declined and were undetectable by 12 weeks after challenge. Plasma virion-associated RNA was not detected in any of the vaccinated animals during this period. The kinetics of the antibody response to MN-rgp120 and to the V3 domain was consistent with HIV-1 infection in animal X190 but not in the other animals. Anti-MN-rgp120 and V3 titers progressively increased after challenge in X190 (figure 1) but progressively decreased in immunized animals X140, X207, and X234. At 12 months (week 164) after challenge, the MN-rgp120 titer in the infected control (X190) increased...
to 3.91 \(\log_{10}\), whereas the titers in the MN-rgp120 animals had fallen to \(\sim 3.1\). Overall, the kinetics of viral replication and seroconversion in this experiment were similar to those seen in previous chimpanzee challenge experiments, indicating that the HIV-1SF2 challenge stock exhibited infectivity comparable to that of the HIVIIIb challenge stock used in previous studies [2, 7].

**Discussion**

Previous studies have demonstrated that subunit vaccines prepared against HIVIIIb can protect against homologous challenge with cell-free or cell-associated virus administered by intravenous infusion [2–5]. The present studies were done to determine whether immunization with a monovalent subunit vaccine, MN-rgp120, could elicit an immune response that protected against intravenous challenge with cell-free virus from a heterologous HIV-1 primary isolate. Although both HIV-1MN and HIV-1SF2 are classified as clade B viruses [20], their envelope glycoprotein sequences differ by \(\sim 18\%\) at the amino acid level [20]. The sequence variation between HIV-1SF2 and -1MN is typical of that expected among subtype B viruses in vaccine field trials. The V3 domain sequences of gp120 from HIV-1MN and -1SF2 both contain the consensus PND sequence, IGPGRAF, found in \(\sim 60\%\) of subtype B viruses from North America and western Europe [8, 20]. Cross-reactive antibodies to this common PND sequence may in part account for the protection from heterologous challenge. Passive immunization studies in chimpanzees have shown that monoclonal antibodies to the V3 domain of gp120 are sufficient to protect against HIV-1 infection [21]. However, studies of hybridomas raised against MN-rgp120 have demonstrated that this antigen can elicit neutralizing antibodies to a variety of non-V3 neutralizing epitopes [17].

Another important issue addressed in the present study was whether a vaccine prepared from a T cell–adapted HIV-1 strain could protect against a primary HIV-1 isolate (i.e., viruses passaged exclusively in PBMC). In this regard, it was surprising that all of the MN-rgp120–immunized chimpanzees were protected from infection even though none possessed antibodies that could neutralize the PBMC-grown challenge virus. A possible explanation is that the protection from HIV-1 infection we observed may be similar to that obtained with feline leukemia virus vaccines. In the latter, the protection elicited by immunization with a recombinant envelope glycoprotein vaccine failed to correlate with significant concentrations of VN antibodies [22]. Another possibility may be that protection is mediated by other immune mechanisms (e.g., cytotoxic T lymphocytes [CTL]). However, protection mediated by CTL seems unlikely, since protein antigens in alum adjuvants are poor inducers of CTL activity [23] and because strategies designed to elicit CTL responses (e.g., recombinant vaccinia virus vaccines) have not provided protection from HIV-1 in the chimpanzee [24, 25]. A more likely explanation for the inability of the PBMC neutralization assay to predict protection in vivo is that the conditions of infection in the in vitro PBMC assay are not representative of in vivo conditions of infection. Productive HIV-1 infection of CD4 cells occurs only in activated T cells [26–28], and infection of resting T cells results in incomplete reverse transcription and abortive HIV-1 infection [29, 30]. Since \(<1\%\) of T cells are normally activated in vivo, most interactions between virus and CD4 cells probably result in unproductive infections. In contrast, in vitro propagation of HIV-1 in PBMC requires conditions in which the vast majority of T cells are activated by potent mitogens and cytokines [26–28] (e.g., PHA and IL-2). Thus, the probability of virions encountering cells that can sustain productive infections is at least 2–3 orders of magnitude greater in vitro than it is in vivo. In addition to providing a better substrate for viral infection, PBMC activation by PHA induces the synthesis of growth factors (e.g., tumor necrosis factor), growth factor receptors, adhesion molecules, and transcription factors [31] that enhance viral replication and infectivity [32–34]. Moreover, the concentration of virus used for neutralization in vitro is markedly disproportionate to the concentration of virus used for in vivo infectivity studies. Although each chimpanzee in this study received \(\sim 750\) TCID\(_{50}\) of HIV-1, the virus was immediately diluted into a blood volume of \(\sim 5\) L, resulting in a concentration of 0.14 TCID\(_{50}\)/mL, a concentration at least 1000-fold lower than that (100 TCID\(_{50}/0.2\) mL) used in in vitro virus neutralization assays. Taken together these observations support the concept that the conditions of infection in the in vitro primary virus PBMC neutralization assays provide the virus with a variety of growth advantages that are not available to viruses during experimental HIV-1 infection in vivo.

The relevance of the SF2\(_{\text{PBMC}}\) challenge stock to viruses transmitted in human populations has been the subject of much debate. Historical opinion suggests that the infection induced in chimpanzees by the SF2\(_{\text{PBMC}}\) stock might be more transient than that induced by other viruses. Our results fail to support this concept. In fact, the kinetics of infection and seroconversion in SF2\(_{\text{PBMC}}\)-infected chimpanzees were indistinguishable from those in HIVIIIb-infected chimpanzees (unpublished data) [2, 7]. The fact that virus could be recovered from X190 9 months after challenge demonstrates that the SF2\(_{\text{PBMC}}\) challenge stock induces a persistent infection. Another concern regarding the relevance of the SF2 challenge stock relates to its growth and neutralization phenotype. Primary HIV-1 isolates can exhibit several distinct phenotypes with respect to tropism, syncytia formation, and sensitivity to inactivation by antibodies and recombinant soluble CD4 [13–15, 35]. The present studies demonstrate that the SF2\(_{\text{PBMC}}\) challenge stock was more resistant to antibody-mediated neutralization than the T cell–adapted variant of HIV-1SF2. Preliminary analysis of the SF2\(_{\text{PBMC}}\) challenge stock (unpublished data) suggest that it possesses a syncytium-inducing CD4-sensitive phenotype. Thus, it remains to be determined whether MN-rgp120 can protect against viruses possessing a CD4-resistant, non-syncy-
tium-inducing phenotype. Since a titrated chimpanzee challenge stock with these properties has yet to be described, it will likely be several years before an appropriate challenge virus will be available to resolve this issue.

There is also concern that the animals apparently protected from HIV-1 infection may have experienced a transient infection or may harbor apparent infections in cells (e.g., tissue macrophages, follicular dendritic cells) that are poorly represented in peripheral blood. Although we cannot completely rule out these possibilities, we think them unlikely since both transient and persistent infection of noncirculating cells should stimulate the formation of antibodies to HIV-1 core proteins, which are more abundant and more immunogenic than the envelope glycoproteins. Previous experience has shown that a vaccine that delayed or induced partial protection of chimpanzees from HIV-1 infection resulted in full seroconversion to viral proteins within 7 months of viral challenge [3]. Although our protocol did not provide for the collection and analysis of lymph node biopsies to detect noncirculating infected cells, such a protocol is under consideration for future studies.

The present studies and reports by others [36, 37] suggest that immunization with MN-rgp120 can protect chimpanzees from heterologous infection with a primary HIV-1 isolate. However, we cannot be certain that protection of chimpanzees accurately predicts protection of humans from natural HIV-1 infection and disease. Given that HIV-1 is typically nonpathogenic in chimpanzees, this system is not a perfect model for human HIV-1 infection and pathogenesis. However, previous experience suggests that chimpanzee infectivity experiments can be reliable indicators of vaccine efficacy, even when the challenge virus fails to induce disease. In the case of the hepatitis B virus (HBV), protection of chimpanzees from HBV infection accurately predicted vaccine efficacy even though HBV, like HIV-1, was unable to induce disease [38]. In the absence of in vitro or in vivo assays that duplicate the conditions of infection or disease progression, it is not possible to reliably calculate the probability of success for candidate HIV-1 vaccines. As with most other vaccines, the correlates of protective immunity cannot be defined prospectively and can only be determined through retrospective analysis of data from vaccine efficacy trials in humans. The fact that MN-rgp120 has shown efficacy in an animal model that has been a valid predictor of protection of humans from infection by some strains of HIV-1.

Acknowledgments

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