Sm-p80–Based DNA Vaccine Provides Baboons with Levels of Protection against Schistosoma mansoni Infection Comparable to Those Achieved by the Irradiated Cercarial Vaccine

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To date, no vaccine is available to prevent human schistosomiasis. We have targeted a protein of Schistosoma mansoni that plays an important role in the surface membrane renewal process, a mechanism widely believed to be utilized by the parasite as an immune evasion strategy. Sm-p80 antigen is a promising vaccine target because of its documented immunogenicity, protective efficacy, and antifecondity effects observed in both experimental murine and nonhuman primate models of this infectious disease. In the present study, we report that, in a vector approved for human use (VR1020), an Sm-p80–based DNA vaccine formulation confers a 46% reduction in the worm burden in a baboon (Papio anubis) model. Baboons vaccinated with Sm-p80–VR1020 had a 28% decrease in egg production after challenge with the infectious parasite. Sm-p80–VR1020 vaccine elicited robust immune responses to specific antigen Sm-p80, including immunoglobulin (Ig) G, its subtypes IgG1 and IgG2, and IgA and IgM in vaccinated animals. When stimulated in vitro with recombinant Sm-p80, peripheral blood mononuclear cells and splenocytes from baboons vaccinated with Sm-p80–VR1020 produced considerably higher levels of T helper 1 response–enhancing cytokines (interleukin [IL]–2 and interferon-γ) than T helper 2 (Th2) response–enhancing cytokines (IL-4 and IL-10). Peripheral blood mononuclear cells produced a significantly higher number of spot-forming units for interferon-γ than for IL-4 in enzyme-linked immunosorbent spot assays. A mixed T helper 1/T helper 2 type of humoral and T cell responses was generated after immunization with Sm-p80–VR1020. These findings again highlight the potential of Sm-p80 as a promising vaccine candidate for schistosomiasis.

Schistosomiasis is endemic in 76 different countries and is associated with an estimated yearly mortality rate of 280,000 deaths [1]. Estimates also indicate that 207 million people are infected with and an additional 779 million people are at risk of acquiring this neglected tropical disease [2, 3]. Praziquantel-based morbidity control for schistosomiasis has been useful, but there are distinct disadvantages associated with this strategy. These disadvantages include the minimal effect on the reduction in disease transmission and the inherent danger of large-scale drug resistance developing [4–6]. There is now general agreement that durable and sustained reduction in the disease spectrum and in transmission can only be obtained through long-term protection via vaccination linked with chemotherapy [5, 7]. An effective antischistosome vaccine would greatly contribute to the decrease in morbidity associated with
schistosomiasis provided via protective immune responses, leading to reduced worm burdens and decreased egg production [5–10]. To this effect, the high protective and antifecundity efficacy of Sm-p80 in both murine [11–13] and nonhuman primate [14, 15] models clearly indicates that this antigen has great potential as an important vaccine candidate for the reduction of morbidity associated with schistosome infection. In addition, Sm-p80 was originally identified as being involved in the schistosome immune evasion process of surface membrane biogenesis [16–19]; therefore, Sm-p80 is an important functional protein and represents a unique target to invoke protective immunity against schistosome infection. In this preclinical study of vaccine efficacy determination, using an Sm-p80–based DNA vaccine formulation in VR1020 (a vector approved for use in humans), we noted in baboons high levels of reduction in worm burden and egg production that were comparable to levels previously recorded only in association with use of the irradiated cercarial vaccine [20].

MATERIALS AND METHODS

Parasites and animals. Schistosoma mansoni–infected snails (Biomphalaria glabrata) were acquired from the Schistosomiasis Resource Center, Biomedical Research Institute (Rockville, Maryland). Baboons (Papio anubis) that were 5.3–13.6 years of age were obtained from the baboon-breeding colony of the University of Oklahoma Health Sciences Center and housed in facilities accredited by the Association for Assessment and Accreditation of Laboratory Animal Care. Before the experiments were begun, baboons were tested for intestinal and blood parasites and for antibodies that were cross-reactive to Sm-p80; they were found to be negative for both. This study was approved by the institutional animal care and use committee.

DNA vaccine constructs and verification of protein expression in mammalian cells. The full-length coding sequence of the large subunit of S. mansoni calpain (Sm-p80) [12, 13, 15, 21] was subcloned into BamHI/BglII sites of VR-1020 (Vical). The resultant construct was designated as Sm-p80–VR1020. Expression of Sm-p80–VR1020 was determined by transient transfection in COS-7 [14] and CHO K1 cells [12, 13, 15, 21]. The expressed products in COS-7 and CHO K1 cells were analyzed via polyacrylamide gel electrophoresis and Western blotting, as described elsewhere [12, 13]. For DNA vaccination, plasmid DNA was isolated via the conventional alkaline lysis method. The plasmid DNA was further purified on Sepharose CL4B columns. The purified DNA was then ethanol precipitated and resuspended in sterile, endotoxin-free saline.

Baboon vaccinations, parasite challenge, and worm and egg burden determinations. Six baboons in the experimental group were initially immunized with 500 μg of Sm-p80–VR1020 (prepared in phosphate-buffered saline). In our previous studies involving the baboon model, this dose was found to be optimal for eliciting protective immunity [14]. At weeks 4, 8, and 12, animals received a booster dose of 500 μg of Sm-p80–VR1020. For the control group, 6 baboons were immunized with 500 μg of the control plasmid DNA VR1020 (prepared in phosphate-buffered saline) [14, 15]. Baboons in the control group received a booster dose of 500 μg of VR1020 at weeks 4, 8, and 12. In both groups, all plasmid DNA was injected intramuscularly in the quadriceps. At week 16, baboons from both of the groups were challenged with a total of 1000 cercariae of S. mansoni, as described elsewhere [14]. Eight weeks after challenge, the baboons were euthanized, and adult parasites were recovered. The reduction in the worm burden was calculated as described elsewhere [14]. Liver and intestine samples were used to determine the number of eggs present in baboons from both groups [14].

Collection of blood and isolation of peripheral blood mononuclear cells. Blood samples obtained from baboons were collected just before the first immunization, at the time of every booster immunization (ie, at 4, 8, and 12 weeks), and 4 weeks after the final immunization (ie, before challenge at [16 weeks]). Serum collected from these samplings was used in enzyme-linked immunosorbent assays (ELISAs) [14]. Using Histo-paque-1077 (Sigma-Aldrich), highly enriched populations of peripheral blood mononuclear cells (PBMCs) were isolated from the baboon blood.

Antibody assays. Serum samples obtained from each animal were used to determine antibody levels/titers for immunoglobulin (Ig) G, IgG subtypes (IgG1–IgG4), IgM, IgA, and IgE antibodies, as described elsewhere [14, 15, 22].

Peripheral blood mononuclear cells and splenocyte proliferation assays. Splenocytes were isolated from the macerated spleens of individual baboons, which had been obtained after the animals were euthanized. PBMCs from the 2 groups of baboons were isolated as described above. For the in vitro proliferation assays, the concentration of recombinant protein and the incubation period were first optimized. A standard assay was then developed as follows: in a 96-well flat-bottom plate, 5 × 10^5 PBMCs or splenocytes in 200 μL per well were stimulated with either 0.5 μg of concanavalin A (ConA) or 1.2 μg of recombinant Sm-p80 or with 1.2 μg of ovalbumin, and they were incubated at 37°C in an atmosphere of 5% carbon dioxide. After 48 h of incubation, an aliquot of the supernatant was removed for the estimation of cytokine production, and the remainder was used for the [3-(4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide] (MTT) assay, as described elsewhere [14].

Estimation of cytokine production by proliferating PBMCs and splenocytes. Using the baboon Th1/Th2 ELISA Panel Kit (U-cyT ech), production of cytokines (interleukin [IL]–2, IL-4, IL-10, and interferon [IFN]–γ) by the proliferating PBMCs and splenocytes was estimated as described elsewhere [14].
**Enzyme-linked immunosorbent spot assay.** An enzyme-linked immunosorbent spot (ELISpot) assay was used to estimate the number of cells secreting IL-4 and IFN-γ after in vitro stimulation with recombinant Sm-p80. In brief, PBMCs isolated from individual baboons were seeded (3 × 10^5 cells/100 μl/well) on 96-well precoated plates (anti–IFN-γ or anti–IL-4; U-cyTech). The cells were stimulated with either 0.5 μg of ConA or 1.2 μg of recombinant Sm-p80 or with 1.2 μg of ovalbumin, and they were incubated at 37°C for 48 h in an atmosphere of 5% carbon dioxide. Spot-forming units denoting single cells were counted using an ELISPOT Bioreader 5000 (ImmunoBioSystem). The number of antigen-specific spot-forming units per well was calculated by subtracting its individual background value (buffer control well without antigen) by use of methods described in detail elsewhere [14].

**Statistical analyses.** The significance between 2 groups was calculated using a t test for independent samples that was performed using the SPSS computer program (version 13.0; SPSS Inc.). Bonferroni adjustments were included for multiple comparisons, to reduce the risk of reaching false conclusions based on chance. P values obtained using these methods were considered to be significant if they were <.05.

**RESULTS**

**Protein expression of Sm-p80–VR1020 in COS-7 and CHO K1 cells.** Before starting vaccination with Sm-p80–VR1020, the constructs were first characterized and tested for protein expression in COS-7 and CHO K1 cells. Expression of Sm-p80 was observed by Western blotting performed using an anti-Sm-p80 antibody [14]. A distinct 80-kDa band was detected in lysates of COS-7 (Figure 1A) and CHO K1 cells (Figure 1B) that were transiently transfected with Sm-p80–VR1020. No such band was detected in COS-7 or CHO K1 cells transfected with VR1020 alone (data not shown).

**Reduction in worm burden and egg production in baboons after vaccination with Sm-p80 in a naked DNA immunization protocol.** The protective and antifecundity effect of the Sm-p80 DNA construct was examined via 4 intramuscular injections. Baboons immunized with Sm-p80–VR1020 demonstrated a 46.35% reduction in worm burden, compared with baboons that received only the control plasmid VR1020 (Figure 2A and Table 1). In addition, in the control group of baboons, the worm types (prevalence) were found to be as follows: single males (38.31%), single females (17.74%), and paired worms (43.93%). In the experimental group, the worm types (prevalence) were as follows: single males (43.56%), single females (19.47%), and paired worms (19.47%). No immature worms were recovered in any of the 2 groups. The distinct antifecundity effect of this vaccine regimen was also observed in the present study (Figure 2B). Baboons vaccinated with Sm-p80–VR1020 demonstrated a 27.97% reduction in egg production (in the liver and intestine) (Table 1). These differences in the reductions in the worm burden (P < .005) and egg counts (P < .05) of the Sm-p80–VR1020 and control VR1020 groups were found to be statistically significant. In addition, Sm-p80–VR1020 DNA vaccine was tolerated optimally; baboons from both control and experimental groups did not display any negative behavioral or clinical manifestations. Furthermore, the baboons in both groups did not produce any anti-DNA antibodies (data not shown).

**Antibody response to Sm-p80 in immunized baboons.** High levels of Sm-p80–specific antibody titers were obtained for total IgG (Figure 3A) and its subtypes IgG1 (Figure 3B) and IgG2 (Figure 3C) in serum samples obtained from baboons immunized with Sm-p80–VR1020, compared with immunized control animals. Moderate levels of IgA (Figure 3D) and IgM (Figure 3E) were also observed in the serum samples of the vaccinated group of animals. IgG3 and IgG4 reactivities were not detected in any of the vaccinated animals. Also, no detectable levels of Sm-p80–specific antibodies (total IgG, IgG subtypes, IgA, and IgM) were detected in the group of animals immunized with control plasmid DNA (VR1020). Titers of total IgG antibodies in the Sm-p80–VR1020 group started to increase at week 4, and at week 12 they reached the highest level for all of the 6 baboons (end-point titer, 51,200 for 2 baboons and 25,600 for 4 baboons) (Figure 3A). In the Sm-p80–VR1020 group, almost equal levels of antibodies were observed for the IgG subtypes IgG1 and IgG2 (Figure 3B and 3C). The IgG1 titer in the group vaccinated with Sm-p80–VR1020 showed an increase at week 4, reaching peak levels at week 12 in all 6 animals (end-point titer, 6400); at week 16, the titers decreased

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**Figure 1.** Protein expression of Sm-p80 in COS-7 and CHO K1 cells. A Western blot of Sm-p80 obtained after transient transfection of the DNA construct, Sm-p80–VR1020, in COS-7 cells (A) and CHO K1 cells (B). This Sm-p80–VR1020 construct was used in the vaccination experiments.
Figure 2. Adult worm burden distribution (A) and egg load per gram of liver and intestine (B) of individual baboons in groups of animals immunized with control plasmids, VR1020 (n = 6), or Sm-p80–VR1020 (n = 6). Both the reduction in worm burden (*P < .005) and the reduction in egg counts (*P < .05) were statistically lower in vaccinated animals.

to some degree (Figure 3B). IgG2 antibody titers gradually started to increase at week 8 and reached a peak at week 16 (end-point titer, 6400 in 1 animal and 3200 in 4 animals) (Figure 3C). IgA antibody titers started to increase at week 8 and reached their maximal levels at week 16 (end-point titer, 6400 in 4 animals and 3200 in 2 animals) (Figure 3D). Similarly, in the group vaccinated with Sm-p80–VR1020, IgM titers had increased by week 8, peaked at week 12 (end-point titer, 3200) and then decreased by week 16 (Figure 3E). No IgE, IgG3, or IgG4 antibodies were detectable in vaccinated animals (data not shown).

**T cell proliferative responses and cytokine production in vaccinated baboons.** As ascertained by stimulation indices obtained via MTT assays, the rate of proliferation of PBMCs and splenocytes from the Sm-p80–VR1020 group was 56.4% and 37.8% higher, respectively, than that noted in the VR1020 controls, after stimulation in vitro with the Sm-p80 recombinant protein. However, Sm-p80–driven proliferation of PBMCs and splenocytes was markedly lower than the stimulation induced by ConA. As shown in Table 2, the high degree of proliferation by splenocytes was also correlated with IFN-γ and IL-2 production. Splenocytes from the Sm-p80–VR1020 group produced >8-fold higher levels of IL-2 and >9-fold higher levels of IFN-γ, compared with splenocytes from the VR1020-immunized controls. IL-4 and IL-10 production by splenocytes was negligible in both groups (Table 2). Similarly high levels of proliferation of PBMCs from the Sm-p80–VR1020 group were also correlated with IFN-γ and IL-2 production; IL-2 was produced at a >82-fold higher level, and IFN-γ was produced at a >13-fold higher level, compared with levels noted in the VR1020-immunized controls (Table 2). These results were confirmed by ELISPOT analysis of the proliferating PBMCs in response to in vitro stimulation by recombinant Sm-p80. The spot-forming unit counts for individual baboons are shown in Tables 3 (IL-4) and 4 (IFN-γ). In these studies, an average of 22-fold more spot-forming units was detected for IFN-γ, compared with IL-4, in baboons vaccinated with Sm-p80–VR1020.

**DISCUSSION**

Previous data from our laboratory [11–16, 21] and that of other investigators (data on *S. mansoni* [23, 24] and on *S. japonicum* [25, 26]) clearly demonstrate that calpain (Sm-p80) is a potentially valuable vaccine candidate for the reduction of morbidity associated with schistosomiasis. In our continual efforts...
Figure 3. Titers of anti–Sm-p80 antibodies in immunized baboons. Enzyme-linked immunosorbent assay was performed with serum samples obtained (every 4 weeks) from each baboon in the respective vaccine groups (VR1020 and Sm-p80–VR1020). Total immunoglobulin (Ig) G (A), IgG1 (B), IgG2 (C), IgA (D), and IgM (E) in serum samples collected every 4 weeks from individual control (JE37, WE62, TR16, JO12, and MA12) and vaccinated (MO34, RO34, LO27, CH40, BA33, and PR57) baboons. Data are the mean of 3 experiments ± the standard error.

to improve the protective and antifecundity efficacy of Sm-p80, in this preclinical study, we used a vaccination regimen that included a vector that is approved for human use (VR1020) and an animal model (baboon) that currently represents the most relevant nonhuman primate model of human clinical manifestations of the disease schistosomiasis [10]. The baboon can serve as a useful bridge between mouse and human studies [27] and may represent a better predictor of the situation in humans [10]. In addition, the DNA vaccine approach has shown promise in a wide array of prophylactic vaccine strategies—for example, against bacteria and viruses [28] and, perhaps to a higher level, against several parasitic diseases [29, 30].
Thus, in the present study, a logical and sagacious step was taken to test the most consistent Sm-p80-based DNA vaccine formulation in a baboon model before embarking on clinical trials in humans.

Baboons vaccinated with Sm-p80–VR1020 had a 46% reduction in worm burden and a 28% reduction in egg production. These results demonstrated a higher degree of improvement in protective efficacy, compared with vaccination with another Sm-p80–pcDNA3 that exhibited a 38% reduction in the worm burden in baboons [14]. Conversely, the use of the Sm-p80–VR1020 vaccine formulation did not change, in a statistically significant fashion, the antifecundity effects previously recorded [14].

Thus, in the present study, a logical and sagacious step was taken to test the most consistent Sm-p80–based DNA vaccine formulation in a baboon model before embarking on clinical trials in humans. Compared with vaccination with RA vaccine [20], and in another study, 80% protection was achieved after 4 vaccinations with shorter intervals between the final boost and experimental challenge [35]. In addition, 3 exposures to RA vaccine in vervet monkeys resulted in 48% protection; increasing the number to 5 exposures elicited only 39% protection [20]. Even though the RA vaccine approach has served as a reference standard for elucidating the mechanisms of protection, the inconsistent results achieved using this strategy indicate its limited applicability and its inherent impracticality for use in human populations. Compared with

Table 2. Cytokine Production by Splenocytes or Peripheral Blood Mononuclear Cells (PBMCs) Induced by Recombinant Sm-p80 after 48 Hours of Culturing In Vitro

<table>
<thead>
<tr>
<th>Cells, vaccine group</th>
<th>IL-4</th>
<th>IL-10</th>
<th>IL-2</th>
<th>IFN-γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VR1020</td>
<td>52.42 ± 2.42</td>
<td>53.99 ± 5.35</td>
<td>55.33 ± 14.30</td>
<td>72.89 ± 42.93</td>
</tr>
<tr>
<td>Sm-p80–VR1020</td>
<td>54.18 ± 7.14</td>
<td>49.03 ± 9.64</td>
<td>447.01 ± 22.96</td>
<td>692.09 ± 32.73</td>
</tr>
<tr>
<td>PBMCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VR1020</td>
<td>7.91 ± 0.21</td>
<td>0.82 ± 0.61</td>
<td>7.03 ± 0.22</td>
<td>28.02 ± 0.67</td>
</tr>
<tr>
<td>Sm-p80–VR1020</td>
<td>9.65 ± 1.56</td>
<td>0.71 ± 0.23</td>
<td>579.77 ± 51.25</td>
<td>384.21 ± 3.64</td>
</tr>
</tbody>
</table>

NOTE. Data are the mean no. of picograms per milliliter ± standard deviation. IFN, interferon; IL, interleukin.
the defined vaccines used in other studies, Sm-p80–VR1020 vaccine appears to be far superior in its antiworm and anti-fecundity effects, and the regimen used in the present study has attained protection levels that previously could be achieved only by the use of irradiated cercarial vaccine.

Robust immune responses were generated via the immunization of Sm-p80–VR1020 vaccine formulation that included IgG; IgG1 and IgG2 antibody isotypes; IgA; and IgM in vaccinated baboons. Generally, in this study, responses of total IgG and its subtypes (IgG1 and IgG2) increased with each subsequent vaccine booster. IgG3, IgG4, and IgE responses were not detectable. Similarly, in vaccination studies using plague antigen LcrV in baboons [38], and in our previous studies of Sm-p80–pcDNA3 [14], IgG3 and IgG4 were found to be below the detection limits. However it is possible that the nondetection of IgG3 and IgG4 (and IgE) could be the result of the poor cross-reactivity of human reagents being used for the detection of baboon antibody subtypes, because no host-specific secondary antibodies of nonhuman primate origin are available for these subtypes [14]. However, IgM responses to immunization were recorded even though they appeared to be short-lived. A similar finding for IgM levels was also observed when the RA vaccine was used in baboons [39]. Of interest, in this study, modest levels of antibody responses were observed for total IgA; this was not the case in our previous studies of Sm-p80–pcDNA3 vaccine [14]. Generation of Sm-p80–specific IgA antibodies in this study is interesting, because a significant association between IgA responses to soluble worm antigen and resistance to reinfection in humans has been reported. [40]. Similar to findings of previous studies [14], IgE was also not detectable in vaccinated animals in experiments in the present study. As recorded in this study, early emergence with short lives of IgM responses and very low or undetectable levels of IgE was also observed in the “self-curing” S. mansoni–rhesus macaque model [41]. Cumulatively, our data on Sm-p80–specific humoral responses indicate that a mixed T helper 1/T helper 2 type of priming was achieved after vaccination with Sm-p80–VR1020 vaccine.

Proliferation of PBMCs and splenocytes in response to in vitro stimulation with recombinant Sm-p80 resulted in the production of higher levels of T helper 1 response–enhancing cytokines (IL-2 and IFN-γ) than T helper 2 response–enhancing cytokines (IL-4 and IL-10). These observations were reinforced by ELISPOT analyses in which the number of spot-forming units detected for IFN-γ was several-fold higher than that for IL-4 in Sm-p80–induced PBMCs. Similar patterns were observed in previous studies using Sm-p80–pcDNA3 vaccine [14]. These results of PBMC and splenocyte proliferation indicate that Sm-p80–VR1020 vaccine formulation is able to elicit a potent Sm-p80–specific T cell response in baboons, as has been observed in murine [11, 13, 21] and baboon [14] models.

Taken together, it appears that both antibodies and IFN-γ play an important role in the Sm-p80–mediated protective immunity; however, their respective contributions in conferring this protection still need to be elucidated. Furthermore, we have argued that schistosome vaccine candidates should first be exhaustively tested in a nonhuman primate model system before trials in humans should be undertaken [10]. The results of the present study, combined with our previous studies in the nonhuman primate model [14], have provided a proof of concept

<table>
<thead>
<tr>
<th>Vaccine group, baboon</th>
<th>IFN-γ–producing spot-forming units, by stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>VR1020</td>
<td></td>
</tr>
<tr>
<td>JE37</td>
<td>33.25 ± 12.05</td>
</tr>
<tr>
<td>WE62</td>
<td>7.00 ± 1.78</td>
</tr>
<tr>
<td>TR16</td>
<td>14.50 ± 8.50</td>
</tr>
<tr>
<td>JO12</td>
<td>10.50 ± 3.50</td>
</tr>
<tr>
<td>MA96</td>
<td>13.00 ± 5.60</td>
</tr>
<tr>
<td>MG12</td>
<td>7.67 ± 2.40</td>
</tr>
<tr>
<td>Sm-p80–VR1020</td>
<td></td>
</tr>
<tr>
<td>MO34</td>
<td>122.00 ± 34.59</td>
</tr>
<tr>
<td>RO34</td>
<td>14.75 ± 6.24</td>
</tr>
<tr>
<td>LO27</td>
<td>172.00 ± 0.00</td>
</tr>
<tr>
<td>CH40</td>
<td>34.33 ± 15.92</td>
</tr>
<tr>
<td>BA33</td>
<td>10.75 ± 1.49</td>
</tr>
<tr>
<td>PR57</td>
<td>35.50 ± 11.50</td>
</tr>
</tbody>
</table>

NOTE. Data are the mean no. of spot-forming units ± standard error. Detection was performed after PBMCs underwent 48 h of culture in vitro. ConA, concanavalin A.

Table 4. Enzyme-Linked Immunosorbent Spot Assay Detection of Interferon (IFN)–γ–Producing Peripheral Blood Mononuclear Cells (PBMCs) from Individual Baboons
for Sm-p80-based vaccine, and we now believe that this vaccine formulation with further optimization is a step closer to being tested to determine safety and efficacy in humans.

Acknowledgment

We thank David W. Carey for his excellent technical assistance with the baboon studies.

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34. Reid GD, Sturrrock RF, Harrison RA, Tarara RP. Schistosoma haematobium in the baboon (Papio anubis): assessment of protection levels against either a single mass challenge or repeated trickle challenges after vaccination with irradiated schistosomula. J Helminthol 1995; 69:139–47.


