Advancing a vaccine to prevent human schistosomiasis

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ABSTRACT

Several candidate human schistosomiasis vaccines are in different stages of preclinical and clinical development. The major targets are Schistosoma haematobium (urogenital schistosomiasis) and Schistosoma mansoni (intestinal schistosomiasis) that account for 99% of the world’s 252 million cases, with 90% of these cases in Africa. Two recombinant S. mansoni vaccines – Sm-TSP-2 and Sm-14 are in Phase 1 trials, while Smp80 (calpain) is undergoing testing in non-human primates. SH2GST, also known as Bilhvx in advanced clinical development for S. haematobium infection. The possibility remains that some of these vaccines may cross-react to target both schistosome species. These vaccines were selected on the basis of their protective immunity in preclinical challenge models, through human immune-epidemiological studies or both. They are being advanced through a combination of academic research institutions, non-profit vaccine product development partnerships, biotechnology companies, and developing country vaccine manufacturers. In addition, new schistosome candidate vaccines are being identified through bioinformatics, OMICS approaches, and moderate throughput screening, although the full potential of reverse vaccinology for schistosomiasis has not yet been realized. The target product profiles of these vaccines vary but many focus on vaccinating children, in some cases following mass treatment with praziquantel, also known as vaccine-linked chemotherapy. Several regulatory pathways have been proposed, some of which rely on World Health Organization prequalification.

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Schistosomes are snail-transmitted, water-borne parasitic platyhelminths (order Trematoda) that are found in fresh water bodies in low- and middle-income countries. Current estimates from the Global Burden of Disease Study 2010 (GBD 2010) suggest that 252 million people are infected with schistosomes, 90% of whom live in sub-Saharan Africa [1]. The World Health Organization (WHO) reports that in 2014 at least 258 million people worldwide required frequent and regular preventive treatment for schistosomiasis [2]. Recently though, the disease even emerged in Europe on the French island of Corsica [3]. Globally two-thirds of the cases are infected with Schistosoma haematobium (the cause of urogenital schistosomiasis), one-third with Schistosoma mansoni (the cause of intestinal schistosomiasis), and 1% with Schistosoma japonicum or Schistosoma mekongi (the causes of intestinal schistosomiasis in East Asia). Schistosomiasis, together with hookworm and leishmaniasis, rank as those neglected tropical diseases with the highest disease burden as defined by disability-adjusted life years (DALYs) [1]. While the GBD 2010 estimated that the world lost 3.3 million DALYs from schistosomiasis in 2010 [1], other estimates suggest that DALYs lost may even be an order of magnitude higher if chronic morbidities such as malnutrition, inflammation, and pain are also taken into consideration [4,5]. In addition, there is some evidence that S. haematobium may represent an important risk factor for HIV/AIDS acquisition because of the mucosal inflammation and ulceration caused by genital schistosomiasis in tens of millions of girls and women [6,7]. In addition to S. haematobium–HIV co-infections, S. mansoni and malaria co-infections are also widespread in Africa, and may result in synergistic effects [8]. Schistosomes reproduce by asexual reproduction in freshwater snails and are released in large numbers as infective larvae. In water, these cercariae penetrate the skin of a human
host, transforming into schistosomulae that migrate through the bloodstream and lungs to the liver where they become adult male-female schistosomes. In the host’s mesenteric or bladder venules, the adult schistosomes release their eggs into the tissues before some make their way into the feces or urine. Upon contact with fresh water, the eggs hatch and give rise to miracidia that enter the intermediate hosts, snails.

The pathogenesis of human schistosomiasis begins when eggs destined for exit out of the body through feces or urine, instead become embedded in the tissues of the human intestine or bladder. These trapped eggs subsequently induce inflammation, granulomas, and fibrosis leading to a number of clinical sequelae including hepatic fibrosis and hepatosplenomegaly, hematuria, bladder fibrosis and obstruction, hydroureterosis and chronic renal disease. *S. haematobium* ova can also elicit vaginal or cervical inflammation (so-called “sandy patches”) that increases the risk of HIV/AIDS acquisition, such that schistosomiasis is considered an important co-factor in Africa’s AIDS epidemic [6]. Moreover, infection with *S. haematobium* is strongly associated with squamous cell carcinoma of the bladder [9]. Chronic schistosomiasis, in addition, can lead to many other sequelae as well, especially in children, including but not limited to anemia, chronic pain, malnutrition, growth failure and cognitive deficits [4,5].

Strategies to control schistosomiasis center on Mass Drug Administration (MDA) of an acetylated quinoline-pyrazine known as praziquantel (PZQ). While less than 20% of children who need PZQ MDA actually receive regular treatments, the fact that the prevalence of schistosomiasis may have increased over the last two to three decades [10], suggests that MDA with PZQ alone will not be adequate for the global elimination of schistosomiasis. Indeed, a survey of almost 400 experts on neglected tropical diseases concluded that schistosomiasis may not be eliminated through current approaches [11]. A major reason is that MDA does not interrupt transmission and does not prevent schistosome reinfection. With the added potential for the emergence of PZQ resistance [12,13], there is thus an urgent need for vaccines as an alternative approach to lower the disease burden, limit transmission and mitigate the morbidity of schistosomiasis [14,15].

1. Biological feasibility for vaccine development

Immunity as a result of natural exposure to a pathogen is often taken as evidence of the biological feasibility for vaccine development. In the case of human schistosomiasis, rates and intensity of infection tend to diminish with age, especially after puberty. However, it is unclear if acquired immunity is solely responsible for this observation. Furthermore, the likelihood that such immunity is partly due to an IgE-mediated mechanism complicates strategies that try to mimic natural immunity. The goal of immunization, therefore, may not be sterilizing immunity but the long-term reduction of both ova burden in the host tissues and excretion from the host, leading to diminished pathogenicity and reduced transmission, respectively.

The feasibility of schistosomiasis vaccines has been demonstrated in a series of proof-of-concept studies where mice and non-human primates (NHPs) were immunized with radiation-attenuated cercariae, and were found to be protected (with efficacies of >80%) against percutaneous schistosomal challenge [16–18]. Vaccinated mice exhibited both cellular and humoral immune responses to lung-stage parasites [19], and under some circumstances, the co-administration of the cercarial vaccine with interleukin-12 adjuvant improved protective immunity [20,21]. Although an attenuated cercarial vaccine may not be a viable approach in humans due to a number of factors including feasibility of production, quality control, and safety, it represents a model for identifying meaningful correlates of immunity, particularly for the design of a recombinant immunogen.

2. General approaches to vaccine development for low- and middle-income country markets

Schistosomes do not multiply in the human host, and most of the pathology comes as a consequence of the deposition of schistosome eggs in the tissues that lead to end-organ damage associated with fibrosis, inflammation, and bleeding. Current vaccine development strategies aim to prevent schistosome infection and/or reduce ova burden through the interruption of parasite reproduction. Thus, among the major vaccine targets are the migrating schistosomulum stages as well as adult females.

In the 1990s, an independent, WHO/TDR-sponsored evaluation of six *S. mansoni* vaccine candidates in preclinical development found that none achieved better than 40% efficacy in reducing worm load.

Since then the maturing of several new technologies, including OMICs (e.g., genomics, proteomics, transcriptomics), microarrays, and immunomomic profiling, have helped in the identification of promising new target schistosome antigens [22–24]. However, both inadequate funding and infrastructure for vaccine development have slowed the translation of these antigen discovery technologies to the clinic. Indeed the overall pipeline of human schistosomiasis vaccines currently in clinical trials is extremely modest especially when considering the high disease burden of schistosomiasis and its potential role in Africa’s AIDS epidemic.

For *S. haematobium*, a single candidate molecule, Sh28GST (Bilhax), a schistosome glutathione S-transferase common to the schistosomula and adult stages, is believed to currently be undergoing testing. Early phases 1 and 2 clinical trials conducted in Niger and Senegal have demonstrated an acceptable safety profile and induction of high IgG3 antibody titers that have neutralized Sh28GST activity and reduced egg-production, an effect that could lead to decrease urinary tract pathology and transmission [25,26]. A phase 3 trial to evaluate if the vaccine candidate and PZQ administration would delay pathologic relapses of the *S. haematobium* infection in infected children was conducted from 2009 to 2012, but no results have been reported yet [27].

There are two vaccine candidates for intestinal schistosomiasis caused by *S. mansoni* in early stage clinical testing. The first comprises the extracellular domain of an integral membrane *S. mansoni* surface protein, Sm-TSP-2, that is found by IgG1 and IgG3 antibodies from individuals that have cleared infection [28]. Preclinical studies in mice have shown that immunization with this protein subunit substantially reduces worm burden. This immunogen has been successfully expressed in yeast (Pichia pastoris) for scale-up cGMP production [29,30], and is currently in phase 1 trials in Houston, Texas, USA. A second vaccine candidate in clinical testing is based on Sm-14, a fatty acid binding protein from *S. mansoni*, and it was announced that this vaccine will undergo phase 1 trials in Brazil [31]. While not yet in clinical development, Smp80 (calpain) has demonstrated efficacy in NHP challenge studies, and will also likely advance to the clinic [32]. As Asian schistosomiasis caused by *S. japonicum* is an important zoonosis, there is increased interest here in developing a veterinary vaccine for water buffalo, cattle, and pigs as a potential means toward blocking a transmission to humans [33].

Because several of the antigens under investigation are highly conserved among different species, there is some optimism for advancing a pan-schistosome vaccine, especially for *S. mansoni* and *S. haematobium* co-infection, prevalent in sub-Saharan Africa. In addition, because of the geographic overlap between schistosomiasis and hookworm disease, there have also been early
considerations to develop a multivalent vaccine that targets both helminths [34]. The general approach would then be to target school-aged children in hyperendemic areas with broadly immunogenic and durable vaccines of relatively low cost and extended shelf-life. An additional potential benefit would be the reduction of HIV/AIDS transmission through the prevention of urogenital schistosomiasis [7].

A schistosomiasis vaccine could be developed either as a standalone technology or used as a companion technology alongside MDA. Towards this goal Bergquist and colleagues have made cogent arguments for shaping a “vaccine-linked chemotherapy” strategy that would initially implement MDA with PZQ followed by immunization to prevent reinfection [35].

3. Technical and regulatory assessment

The pathway toward regulatory approval of these vaccine candidates will likely require at least a 40% reduction of worm burden. The schistosome antigens and prototype vaccine formulations currently in early clinical testing induce 30–70% reductions in worm burden or egg production and have succeeded to increase viability in laboratory animals. The challenge though remains in the translation of these antigens into humans and maintain a similar or superior protection through formulation with novel adjuvants, including the use of Toll-like receptor agonists such as synthetic lipid A molecules. The immune correlates of protection for a schistosomiasis vaccine are thought to be observable in IgG1 and IgG3 antibody recognition of the antigens. The standard animal model for screening potential antigens has been the mouse model used to test the efficacy of schistosomiasis vaccines, but SmP80 is now also undergoing extensive testing in NHPs [36].

Several additional factors must be taken into consideration for a successful vaccine development in low- and middle-income countries including the choice of antigen and target species (e.g., *S. haematobium*, *S. mansoni* or both), production feasibility and cost per dose. Careful antigen and adjuvant selection, cutting edge immunogen design based on potential immune correlates, and robust efficacy in laboratory animal models will not be sufficient for a successful vaccine if cGMP manufacturing of the vaccine product is not feasible [12]. Currently, recombinant vaccines for NTDs are thus mostly produced in low-cost bacteria or yeast expression systems. It will also be important to select the appropriate adjuvant and delivery platform to stimulate the correct immune response. An additional challenge here has been the limited availability of adjuvants with regulatory approval for use in humans.

4. Status of vaccine R&D activities

The vaccine candidates currently in clinical trials are listed in Tables 1 and 2. Some of the progress in developing these promising vaccine candidates has come from screening schistosome OMFs databases through DNA microarray profiling, proteomics, glycomics, and immunomics have helped identify promising immunogens [22–24,37]. Further significant advancement has been achieved through the successful application of RNA interference (RNAi) technology, which in the case of *Sm-TSP-2* allowed investigators to ascribe specific functions to the molecule and its role in parasite survival [38]. Complexities of advancing true reverse vaccinology approaches (as was successfully done for meningococcus) include large genome sizes, and the requirement for eukaryotic expression systems, as well as cumbersome laboratory animal model systems.

5. Likelihood for financing

According to the public search tool, G-Finder, between 2007 and 2013, approximately $27 million in funding was awarded for schistosomiasis vaccine research and development (R&D), primarily from major public sector funding agencies such as the Australian National Health and Medical Research Council (NHMRC), France’s *Institut national de la santé et de la recherche médicale* (INSERM), the Brazilian Ministry of Health’s Department of Science and Technology (DECIT), the European Commission, and the US National Institutes of Health (NIH) [41]. Through a group of philanthropic donors, including the Michelson Medical Research Foundation and the Blavatnik Family Foundation the Sabin Vaccine Institute Product Development Partnership (Sabin PDP) has also funded schistosomiasis vaccine R&D efforts to a total of approximately US$1.25 million, with additional NIH support for toxicology testing and for the phase 1 trial. New and increased financing from major funders will be critical to advance these candidate vaccines.

Conflicts of interest

Several of the authors are investigators and patent holders on vaccines against hookworm and other neglected tropical diseases and are in part supported by grants to develop these vaccines; and are in part supported by grants to develop these vaccines.

Table 1

<table>
<thead>
<tr>
<th>Parasite species targeted</th>
<th>Vaccine</th>
<th>Major antigens/adjuvants</th>
<th>Sponsor</th>
<th>Status</th>
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<tbody>
<tr>
<td><em>Schistosoma haematobium</em></td>
<td>Bilhvx</td>
<td>Shi28GST (28-kDa recombinant glutathione-S-transferase)</td>
<td>Institut Pasteur and INSERM</td>
<td>Completed Phase 2 and 3 trials in West Africa (results pending) [15,27].</td>
</tr>
<tr>
<td><em>Schistosoma mansoni</em></td>
<td>Sm-TSP-2</td>
<td>Sm-TSP-2 (9-kDa recombinant tetraspanin) Alhydrogel® + GLA</td>
<td>Sabin Vaccine Institute Product Development Partnership/NAID, NIH/Baylor College of Medicine Vaccine and Treatment Evaluation Unit</td>
<td>Initiated Phase 1 trial in 2014 at Baylor College of Medicine [39].</td>
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<tr>
<td><em>S. mansoni</em></td>
<td>Sm-14</td>
<td>Sm-14 (14-kDa recombinant fatty acid binding protein) with the adjuvant GLA</td>
<td>Oswaldo Cruz Foundation (Fiocruz) Orofino</td>
<td>Ongoing phase 1 trial [40]. Phase 2 trials are planned for 2015 in Brazil and Africa.</td>
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Table 2

<table>
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<tr>
<th>Candidate name/identifier</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tr>
<td>Sm-TSP-2</td>
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<td>Sm-14</td>
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<td>CT-SOD</td>
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