



A comprehensive and critical overview of schistosomiasis vaccine candidates

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Abstract A digenetic platyhelminth *Schistosoma* is the causative agent of schistosomiasis, one of the neglected tropical diseases that affect humans and animals in numerous countries in the Middle East, sub-Saharan Africa, South America and China. Several control methods were used for prevention of infection or treatment of acute and chronic disease. Mass drug administration led to reduction in heavy-intensity infections and morbidity, but failed to decrease schistosomiasis prevalence and eliminate transmission, indicating the need to develop anti-schistosome vaccine to prevent infection and parasite transmission. This review summarizes the efficacy and protective capacity of available schistosomiasis vaccine candidates with some insights and future prospects.

Keywords Schistosomiasis · *Schistosoma* · Vaccine · Candidate vaccines · Protective immunity

Introduction

Schistosomiasis (also referred to as bilharzia) is a parasitic disease caused by trematodes, blood flukes with a sophisticated life cycle involving an intermediate host freshwater snail, and a definitive host (humans or animals). It is a neglected tropical disease (NTD) closely linked to poverty, and infects 240 million people in 74 developing countries

in the tropics and sub-tropics, and 779 million, mostly children are at risk (Loverde 2019; Chisha et al. 2020; Kura et al. 2020). The burden of schistosomiasis in 2016 was estimated at 2 543 364 disability-adjusted life years (DALYs) (World Health Organization 2019). Most of human infections are caused by *Schistosoma haematobium* (endemic in Africa and Middle East), *S. mansoni* (in Central South America, Africa, and Middle East), and *S. japonicum* (in Eastern Asia) (Di Bella et al. 2018). *Schistosoma mansoni* and *S. japonicum* are responsible for chronic hepatic and intestinal fibrosis while *S. haematobium* causes fibrosis in the urinary tract (McManus and Loukas 2008).

There is interrelation between schistosome infection and host immune responses, as worms can live for several decades in contact with products of immune responses circulating in the blood. The study of this interaction can help in disease control by searching for new drug or developing a vaccine (Fonseca et al. 2012). Praziquantel (PZQ, pyrazino-isoquinolone) is the only readily effective drug widely used for the treatment of the three main parasites causing human schistosomiasis. It has good pharmacologic properties such as it can be given as a single oral dose, is usually well tolerated, with low cost and limited side effects (LoVerde 2019). However, schistosome chemotherapy still has some limitations (Kittur et al. 2017; Wiegand et al. 2017). Praziquantel-based mass drug administration programs require several rounds of treatment. Additionally, only a fraction of the target population receives the drug, because preventive chemotherapy for schistosomiasis was found to be still required in 2018 in 52 countries and was received by 19.1 out of 104.8 million adults (18.2%) and 76.2 million out of 124.4 million children attending school (61.2%) (World Health Organization 2019). The coverage of the numerous children that do not

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attend school in poor, rural endemic communities and pre-school age children is certainly much lower. These data explain intensity of infection and morbidity were reduced in several countries, but prevalence and DALYs remain dramatically high (Deol et al. 2019). Indeed, the World Health Organization recommended periodic PZQ treatments only as a short-term measure for the control of morbidity (World Health Organization 2019). Therefore, vaccines, alone or combined with chemotherapy, present the best strategy for long-term control of schistosomiasis (Ross et al. 2002, 2015).

Disappointingly, up to date there is no commercial vaccine available against any of the human schistosomes emphasizing the need for continued efforts towards achieving this elusive goal (Hewitson and Maizels 2014; McManus et al. 2020). Many groups have made recommendations about which vaccine candidate should be developed against schistosomiasis, suggesting that an effective prophylactic vaccine should reduce the morbidity (Siddiqui and Siddiqui 2017), as well as reduce adult worm burden and egg excretion rates by 75% in immunized individuals (Molehin 2020). The current review will present a comprehensive overview on the efficacy of experimental, but unlicensed, vaccines against schistosomiasis in both humans and animals, delineating new formulations of the present candidates or future vaccine discovery.

The major reason for schistosomiasis spread is the inability of the immune system elements to recognize and eliminate migrating larvae and adult worms. Radiation-attenuated (RA) schistosome larvae vaccine has shown capability to induce consistently high protective immune (Th1 and Th2) responses against challenge infection in laboratory animals (Coulson 1997; Street et al. 1999), and revealed that a schistosomiasis vaccine is a real goal, despite that multiple concerns regarding this approach make it unsuitable for use in humans (Coulson 1997). Furthermore, these promising results paved the way for the discovery of different vaccine candidate antigens, irradiated cercariae vaccine-associated *S. mansoni* antigens (IrV) (Soisson et al. 1992, 1993), fatty acid-binding protein (FABP, Sm14), paramyosin, calpain large subunit (Sm-p80), superoxide dismutase (SOD), glutathione-S-transferase (GST), glyceraldehyde 3-phosphate dehydrogenase (SG3PDH), cysteine peptidases (CPs) (Othman and El Ridi 2014; Pearson et al. 2015), the surface membrane antigen, Sm23 (Harn et al. 1985; Reynolds et al. 1992; Koster et al. 1993) and many other antigens (Table 1). Despite the discovery and publication of numerous promising vaccine antigens candidates, only four have shown promises in human clinical trials and were chosen due to access, and protective immunity potential in non-human primates. These recombinant antigens include *S. haematobium* 28-kD GST (rSh28GST) (Boulanger et al. 1999; Johnson

et al. 2003), *S. mansoni* 14-kDa (Sm14) (Moser et al. 1991), *S. mansoni* tetraspanin, a 9-kDa surface antigen, Sm-TSP-2, (Smyth et al. 2003), and *S. mansoni* calpain (Sm-p80) (Siddiqui et al. 1993).













Recently, many of the above-mentioned antigen candidates, including TSP-2, Sm23, GST, Sm29 and calpain, were identified in extracellular vesicles (EVs) of schistosome adult worms, (Kifle et al. 2020a). Extracellular vesicles are membrane-surrounded vesicles that are continually secreted by different types of cells and play an important role in removing unnecessary cell components, cell–cell communication, and inter-cellular transfer of their mRNA, microRNA (miRNA), lipid and protein cargo (Pluchino and Smith 2019). Such close host–parasite interactions suggest EVs may play a role in protection against schistosomiasis (Kifle et al. 2020a; b), allowing the host immune effectors, namely antibodies, to interact with otherwise inaccessible worm cytosolic, tegumental, and surface membrane antigens, and activate immune cells capable of chasing and harming the parasite (El Ridi and Tallima 2013a; b).

Vaccine candidates in clinical trials

28 kDa glutathione S-transferase

Schistosoma haematobium 28 kDa glutathione S-transferase (Sh28GST) vaccine is expressed in the tegument and sub-tegument of adult (Taylor et al. 1988) and larval (Balloul et al. 1985) schistosomes, and is a predominant ESP (Knudsen et al. 2005; Hansell et al. 2008; El Ridi and Tallima 2009, 2013a; El Ridi et al. 2017). It has a main role in fatty acid metabolism and prostaglandin D2 synthesis, and may contribute to the parasite immune evasion (Tebeje et al. 2016). Several studies were made using the recombinant protein (expressed in *Saccharomyces cerevisiae*) in rodents, primates and cattles (Johnson et al. 2003; Capron et al. 2005; Baiocco et al. 2006). The results showed partial protective effect against schistosome infection, significant reduction of the worm burden (40–60%), in addition to significant reduction in female worm fecundity and eggs viability (Boulanger et al. 1991; Xu et al. 1991; Bushara et al. 1993; McNair et al. 1993; Capron et al. 1994). Notably, recombinant *S. haematobium* glutathione S-transferase (rShGST) vaccine mediated high levels of protection associated with intense specific IgG and IgA antibody responses in baboons and patas monkeys (Boulanger et al. 1991, 1995, 1999). Phase 1 trial was designed to investigate the safety and tolerability of two or three subcutaneous injections of 100 µg rSh28GST antigen with Alum as adjuvant in young, healthy, Caucasian male adult volunteers. The vaccine was perfectly safe for use in adults

Table 1 Major schistosome vaccine candidates

Vaccine candidates in clinical trials	Experimental forms	Experimental models	Conclusions	Clinical trials	References
Sh28GST	Recombinant Sh28GST		Partial protection with a significant reduction in female worm and egg burden	Reached Phase 1, 2, and 3 in human. showed to be safe to use and highly immunogenic	Boulanger et al. 1991 Xu et al. 1991
Sm14	Recombinant Sm14		High protection, reduction in female worm burden and fecundity	Reached phase 1 and 2 in human. showed to be safe, long lasting efficacy, phase 3 is planned	Tendler et al. 1995, 1996 Varakdo et al. 2004
TSPs	Recombinant TSP-1 Recombinant TSP-2		Significant protection against TSP-2 but not TSP-1	Reached phase 1, in human. showed to be safe immunogenic. phase 2 was undertaken	Tran et al. 2006 Curti et al. 2013
Vaccine candidates in pre-clinical trials					
Sm-p80	Whole molecule DNA Prime-boost r Sm-p80		High protection, reduction in female worm burden and fecundity	Approved for Phase 1 clinical trial in human	Siddiqui et al. 2005a,b Zhang et al. 2018a,b
Vaccine candidates in experimental trials					
Surface membrane candidate vaccines					
Sm23	Whole molecule PcDNA PcDNA+ rSm23 MAP construct		Significant protection but less antifecundity effect	Did not reach clinical trials	Da'dara et al. 2001 Da'dara et al. 2003
SG3PDH	rSG3PDH SG3PDH peptides MAP construct SG3PDH+SmCB1+ SmCL3		Showed a promising results, induced high protection (Th1 and Th2)	Did not reach clinical trials	El Ridi et al. 2001a, b Veprek et al. 2004
Tegument candidate vaccines					
Sm29	recombinant Sm29 Sm29 derived peptide Sm29/Sm14		Partial protection, significant reduction in female worm and egg burden	Did not reach clinical trials	Cardoso et al. 2006, 2008; Alves et al. 2015
Cytosolic candidate vaccines					
Paramyosin	Whole molecule DNA vaccine Peptide Partial recombinant		Partial protection, significant reduction in female worm and egg burden	Did not reach clinical trials	Lamar et al. 1986 Pearce et al. 1988
Excretory/Secretory proteins					
SmCB	Recombinant SmCB		High protection (Th1 and Th2 response)	Did not reach clinical trials	Riccardi et al. 2015, 2016
SmCB1 alone or +SG3PDH/PRX-MAP	Active recombinant CB1 inactive recombinant CB1		High protection against <i>S.mansoni</i> and <i>S.hematobium</i> infection	Did not reach clinical trials	El Ridi et al. 2014 Tallima et al. 2015
FhCL1 alone or +SG3PDH/PRX-MAP	Active recombinant CL1 inactive recombinant CL1		High protection against <i>S.mansoni</i> and <i>S.hematobium</i> infection	Did not reach clinical trials	El Ridi et al. 2014 Tallima et al. 2015
SmCL3+SmCB1 alone or combined with rSG3PDH	Enzymatically active SmCL3 and SmCB1		High protection against <i>S.mansoni</i> and <i>S.hematobium</i> infection	Did not reach clinical trials	Tallima et al. 2017a, b

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Sm Schistosoma mansoni, *Sh Schistosoma hematobium*, *Fh Fasciola hepatica*, *G3PDH*, glyceraldehyde 3-phosphate dehydrogenase, *GST* glutathione-S-transferase, *TSPs* tetraspanin; *CB*, cathepsin B, *CL* cathepsin L, *PRX* Peroxidase, *MAP* Multiple antigen peptide

and highly immunogenic, inducing interleukin (IL)-5 and IL-13, absence of IgE, and predominance of IgG1 antibodies capable of inhibiting the enzymatic activity of the immunogen (Riveau et al. 2012). Safety, tolerability and immunogenicity of the vaccine were also demonstrated in adults and children residing in endemic regions (Mo et al. 2014). rShGST is the only schistosomiasis antigen that has reached Phase 3 clinical trials. In Phase 3, 250, 6–9 years-old Senegalese children, were cured of schistosome infection and randomized to receive three subcutaneous injections of either rSh28GST/Alhydrogel (Bilhvax group) or Alhydrogel alone (control group) with four-week intervals, and then a booster one year after the first injection. The vaccine protective capacity was evaluated by recurrence of natural infection within approximately two years following PZQ treatment on week 44, 8 weeks before the booster injection (on week 52). Children immunized with rSh28GST showed elevated levels of specific IgG1, IgG2, and IgG4 antibody but a lack of IgG3 and IgA isotypes. In human populations, acquired immunity is linked with IgG3 and IgA antibodies to Sh28GST. Failure in achieving protection against urinary schistosomiasis might be due to the antibody isotype issue (Riveau et al. 2018) or to the confounding impact of the PZQ treatment before the first and last immunization (Alsallaq et al. 2017).

***Schistosoma mansoni* 14 kDa fatty acid binding protein**

Schistosoma mansoni 14 kDa (Sm14) fatty acid binding protein (FABP) is located in the basal lamella of the tegument and gut epithelium (Brito et al. 2002; Tendler and Simpson 2008). Schistosomes lack an oxygen-dependent pathway for the synthesis of fatty acids and sterols. Hence, they are entirely dependent on the host by using Sm14 to absorb and transport fatty acids from the host (Tendler and Simpson 2008; Tebeje et al. 2016). Sm14 is, hence, considered a good target for development of an effective vaccine against schistosomiasis. Its recombinant form (rSm14) showed significant protective immunity against *S. mansoni* in outbred Swiss mice and New Zealand White rabbits (60–95%). In addition, it induced immune cross protection against *Fasciola hepatica* infection. So, it is potentially used against different infections and has great appeal in terms of human and animal health (Tendler et al. 1995, 1996; Tendler and Simpson 2008; Santini-Oliveira et al. 2016). Otherwise, outbred Swiss mice immunized once with rSm14-Bacillus Calmette-Guerin (rSm14-BCG) and challenged with *S. mansoni* cercariae showed reduction (48%) in worm burden that was analogous to that obtained by vaccination with rSm14 protein (Varaldo et al. 2004).

Hence, the antigen was allowed to move forward to clinical trials to assess its safety and immunogenicity on

humans. In Phase 1a and 1b trials (2011–2014), rSm14 was formulated with glucopyranosyl lipid adjuvant (GLA) adjuvant in an oil-in-water emulsion and used to immunize 20 male and 10 female volunteers from a non-endemic area for schistosomiasis in Rio de Janeiro state, Brazil. Results showed no adverse events related to the vaccine, which elicited significant increase in Sm14-specific total IgG, with no IgE observed at any time, and stimulated both Th1 and Th2 cytokines (Tendler et al. 2015; Santini-Oliveira et al. 2016). Accordingly, the results supported this product as a safe, strongly immunogenic vaccine against schistosomiasis, and paved the way for follow-up phase 2 trials (2015–2017). In phase 2a trial, rSm14 vaccine was safe with long lasting immunogenicity when administrated to 30 male adults from endemic area for both *S. mansoni* and *S. haematobium* in Senegal River Basin (Tendler et al. 2018). Accordingly, Phase 2b and phase 3 trials are planned (McManus et al. 2020).

<https://clinicaltrials.gov/ct2/show/NCT03041766>

<https://clinicaltrials.gov/ct2/show/NCT03799510>

Tetraspanins

A family of tetraspanins (TSPs) is highly expressed in the *S. mansoni* tegument membranocalyx, and outermost membrane of the intra-mammalian stages of the parasite, apparently accessible to the immune system elements; the portion readily exposed to the host immune system is the extracellular loop (van Balkom et al. 2005; Braschi et al. 2006; Braschi and Wilson 2006; Wilson 2012). *Schistosoma mansoni* TSPs (Sm-TSP-1 and Sm-TSP-2) play important roles in tegument stability, development, or maturation (Tran et al. 2006, 2010). IgG1 and IgG3 (no IgE) antibodies isolated from naturally immune individuals recognized TSP-2, not TSP-1, when compared to antibodies from chronically infected or naïve individuals (Correa-Oliveira et al. 1989, 2000; Tran et al. 2006; Loukas et al. 2007). As well, TSP-2 conferred high level of protection in mice with generation of IgG antibodies, which correlated positively with protective immunity in naturally resistant people. Therefore, efficacy trials have focused on the TSP-2 antigen reflecting its use as schistosomiasis vaccine (Pearson et al. 2015; Hotez et al. 2019).

Vaccination of CBA/CaH mice with rSm-TSP-2 formulated with adjuvant conferred high levels of protective immunity against challenge infection with *S. mansoni*, characterized by reduction of 57% and 64% in adult worm and liver egg burdens, respectively. While immunization with rTSP-1 resulted in lesser protective immunity than rTSP-2 represented by 34% and 52% reduction in adult worm and liver egg burdens, respectively (Tran et al. 2006). Along with ShGST and Sm14, TSP-2 has reached the clinical trial phase 1 and showed that the TSP-2/alum

(Al) hydrogel in formulation with or without an aqueous GLA formulation (GLA-AF) was well tolerated and safe to use for humans when administrated to healthy young adults who reside in non- *S. mansoni*-endemic area (Keitel et al. 2019). Furthermore, phase 1b dose-escalation study has been undertaken to assess the safety and immunogenicity of Sm-TSP-2 with or without AP 10-701 (new nomenclature of GLA-AF) in healthy Ugandan adults (Keitel et al. 2019) <https://clinicaltrials.gov/ct2/show/NCT03910972>.

Recently, TSPs were found to be localized in adults *S. mansoni* and *S. haematobium* tegument vesicles, not on the surface membrane (Schulte et al. 2013; Sotillo et al. 2015), supporting a mechanism of action via release in EVs (i.e. ESP) (Sotillo et al. 2016; Samoil et al. 2018; Kifle et al. 2020a; Mekonnen et al. 2020). The study of Mekonnen et al. (2020) reported that ShTSP-2 conferred a highly significant protection against heterologous challenge (*S. mansoni*) model of infection. However, it is not clear how the ability of anti-TSP antibodies to block vesicle uptake by host target cells explains the potential of TSPs as promising anti-fluke vaccine (Kifle et al. 2020b).

Vaccine candidate in pre-clinical trials

Sm-p80

Sm-p80 is the large subunit (heavy chain) of the *S. mansoni* calcium-activated neutral protease, calpain (Siddiqui and Siddiqui 2017), immunolocalized in different schistosome life stages at the inner membrane of the tegument and underlying musculature (Braschi and Wilson 2006). It is an excretory-secretory product (ESP) released upon larvae skin invasion and during migration in the lung (Knudsen et al. 2005; Hansell et al. 2008; El Ridi and Tallima 2009, 2013a; El Ridi et al. 2017), and was predominant in adult worms-derived EVs (Kifle et al. 2020a). Calpain helps the worm escape the immune response by surface membrane turnover, by degradation of fibronectin, and inhibiting blood clot formation around the worm (Siddiqui et al. 1993; Kumagai et al. 2005; Wang et al. 2017). Despite calpain location on the inner side of the surface membrane of schistosome, it represents a target for vaccine development. It has been tested for efficacy in different forms, like prime boost, recombinant (r), or DNA based forms and showed significant protection capacity, had remarkable efficacy in fecundity reduction, and reduced the egg-induced pathology with transmission blocking potential in rodents and baboons (Siddiqui et al. 1993; Siddiqui

et al. 2003a, b, 2005a; Ahmad et al. 2009a, b, c; Zhang et al. 2010, 2014; Karmakar et al. 2014a; Le et al. 2018). Of note, Sm-p80 ortholog expressed in the tegument of *S. japonicum* and *S. haematobium* adult worms significantly conferred cross-species protection in rodents and baboons against *S. mansoni*, *S. japonicum*, and *S. haematobium* infections (Zhan et al. 2014; Karmakar et al. 2014b, c; Molehin et al. 2017).

Findings in both mice and baboons have confirmed that Sm-p80 vaccine-based protection involves antibodies and type 1 cytokines (Torben et al. 2011). Immunization of C57BL/6 mice and olive baboons with Sm-p80 combined with GLA adsorbed on aluminum hydroxide (Sm-p80 + GLA-alum) resulted in worm burden reduction by 39–44%, and production of Sm-p80-specific total IgG and IgG subtypes (IgG1, IgG2a, IgG2b and IgG3), with an elevation in Th1 cytokines IFN- γ , IL-2 and TNF- α (Zhang et al. 2018a). Furthermore, in double-blind preclinical trial, olive baboons immunized with Sm-p80/GLA-SE (GLA suspended in a stable squalene-based oil-in-water emulsion, SE) showed considerable reduction in adult female worms (93.4%) and remarkable reduction in tissue egg load (89.9%). Of note, a considerable decrease in schistosome egg excretion in feces of vaccinated baboons, combined with more than 80% reduction in egg maturation and viability documented the parasite transmission-blocking potential of the vaccine (Zhang et al. 2018b). Immunization with Smp80 + CpG-oligodeoxynucleotide (CpG-ODN) adjuvant reduced liver egg burdens by 38.0% and egg load in small and large gut by 72.2% and 49.4%, respectively, in baboons. Furthermore, significant production of Sm-p80-specific antibodies was detected in immunized baboons (Siddiqui et al. 2018). These promising results supported Sm-p80 vaccine has now been approved for Phase 1 clinical trials to begin in early-mid 2021 (Molehin 2020; Tsuji 2020).

Sm-p80 protection was attributed to ADCC, which is impossible as the molecule is not located on the apical lipid layer of the worm surface membrane, and even so, would not be accessible by antibodies (Zhang et al. 2001; Ohta et al. 2004; Ahmad et al. 2009a, b, c; Zhang et al. 2010; Siddiqui and Siddiqui 2011; Torben et al. 2012; Karmakar et al. 2014a). The Sm-p80 immunogen may interact with vaccine-induced specific antibodies, leading to activation of effector cells and release of inflammatory mediators. Calpain was recently found to be enriched in EV (Kifle et al. 2020a), and when it interacts with antibodies, calpain/antibody complexes can be internalized by the host and may enhance the production of arachidonic acid, and immune cells activation and trafficking (Kifle et al. 2020b).

Vaccine candidates in experimental trials

Surface membrane candidate vaccines

Sm23

Surface membrane 23 kDa (Sm23), an integral membrane protein (Rogers et al. 1988), was first identified by Harn and his colleagues as the target of a protective monoclonal antibody. It has been shown to confer protection in naive mice (Harn et al. 1985), and classified as a member of the ‘tetraspanin’ trans-membrane protein family (Wright et al. 1990; Lebel-Binay et al. 1995). Sm23 is exposed on the apical membrane of parasite (Wright et al. 1991); however, in low quantity (Braschi and Wilson 2006), and expressed in the adult tegument (Harn et al. 1985; Oligino et al. 1988).

Efforts have been made to develop an effective vaccine using Sm23 in plasmid DNA (pcDNA), multiple antigenic peptides (MAPs), and recombinant (r) vaccines constructs. High levels of protection were achieved upon Sm23 use in MAP form, based on B and T cell epitopes (Reynolds et al. 1992; Harn et al. 1995). Priming and boosting of C57BL/6 mice with Sm23-pcDNA elicited production of IgG2a and IgG1 antibodies showed statistically significant reduction of 21–44% in worm and egg burdens (Da’Dara et al. 2001); the number of eggs recovered per worm pair did not differ significantly, showing that the Sm23-pcDNA vaccine has no additional anti-fecundity effect. Sm23-pcDNA immunization of C57BL/6 mice followed by boosting with rSm23 formulated with alum did not result in significant reduction in worm burdens, despite it induced higher anti-Sm23 antibodies (IgG1) level than Sm23-pcDNA alone. In addition, mice primed and boosted with rSm23 formulated in alum were also not protected from challenge infection, likely because the protective vaccination using Sm23 is associated with a Th1 immune response (Da’Dara et al. 2003). In a subsequent study, immunization of C57BL/6 mice with Sm23 DNA elicited only 34% protection despite induction of specific antibody responses that were predominately of the IgG2a and IgG2b isotypes (Ganley-leal et al. 2005).

A more recent study revealed a limited number of conformational epitopes on Sm23 and other tegmental proteins have the ability to elicit mouse, rat and human production of serum antibodies against *S. mansoni* infection, but they never influenced schistosomula or adult worm survival suggesting that there is a need to re-evaluate host immune responses to many schistosome antigens (Krautz-Peterson et al. 2017). El Ridi and Tallima (2013a; b) explained that surface membrane antigens may be immunogenic, inducing T and B cell responses, but

antibodies are unable to get access to surface membrane antigens and activate antibody-dependent complement or cell-mediated (ADCC) cytotoxicity. It is remarkable that vaccination with a protein at the host-parasite interface induced only limited reduction in challenge infection parameters. It is because surface membrane antigens are hindered by a sphingomyelin (SM)-based hydrogen-bond network protecting the larval, developing, and adult worms from the host immune effectors (El Ridi and Tallima 2006; Keating et al. 2006; Tallima and El Ridi 2008; Migliardo et al. 2014; El Ridi et al. 2017). Then molecules at the apical surface are not accessible to antibody binding in healthy worms.

The mechanism behind Sm-23-mediated protection may be explained by their presence as ESP or in EVs, exosome-like, 120 k pellet vesicles and microvesicle-like, 15 k pellet vesicles, found to be a reservoir of different vaccine candidates such as, TSPs Sm23, Sm-TSP-1, and Sm-TSP-2 (Kifle et al. 2020a). Recombinant Sm23 and other TSPs extracted from adult *S. haematobium* worms were shown to induce significant protection characterized by reduction in liver (47%, 38% and 41%) and intestinal (47%, 45% and 41%) egg burdens against challenge infection with *S. mansoni*. These results reflect that EVs surface proteins can be used as anti-schistosome vaccine candidates (Mekonnen et al. 2020), provided they evoke critical responses needed for optimal vaccine efficacy (Ganley-leal et al. 2005).

Glucose transporter proteins

Adult schistosomes obtain their glucose from the host blood. Two glucose transporter proteins (GTPs) have been identified in the tegument of *S. mansoni*, SGTP 1 and 4 antigens (Krautz-Peterson et al. 2010; You et al. 2014). SGTP1 is expressed in the tegmental basal membrane and other tissues of different life stages of the schistosome, whilst SGTP4 is present in the host interactive, apical tegmental membranes (Swain et al. 2011; You et al. 2014). SGTP4 facilitates the import of glucose from the host bloodstream into the tegument. SGTP1 and SGTP4-suppressed parasites are unable to import glucose, providing evidence for the importance of these SGTPs in importing exogenous glucose, and then affecting parasite development in the mammalian host (Krautz-Peterson et al. 2010; Swain et al. 2011; You et al. 2014). Peptide or recombinant form of SGTP4 conjugated with complete (CFA) or incomplete (IFA) Freund’s adjuvant showed no protection against challenge infection with *S. mansoni* in outbred CD-1 mice despite specific cellular and humoral immune responses (Mahana 2007). The reason is due to the explanation mentioned above, namely that no apical membrane antigen is accessible to host antibodies. Limited SM hydrolysis allows nutrient < 400 kDa entry but not host

immune effectors. Another reason lies in GTPs molecule structure (Fig. 1), and poor immunogenicity (Tucker et al. 2018). Such 12 transmembrane domain, hydrophobic molecules, even within EV, are immediately endocytosed by antigen presenting cell (APC), and their conformational epitopes poorly recognized by B cells. Nevertheless, due to its critical importance for schistosomes' survival, SGTP4 is now considered a major target for schistosomiasis chemotherapy (Adekiya et al. 2020).

Glyceraldehyde 3-phosphate dehydrogenase

Glyceraldehyde 3-phosphate dehydrogenase (G3PDH) is a cytosolic antigen. Yet, it was readily detected on the surface of *S. mansoni* 3 h in vitro schistosomula (Goudot-Crozel et al. 1989), lung-stage schistosomula (Tallima and El Ridi 2008; Pirovich et al. 2019, 2020), among adult worms surface membrane-associated molecules, and in larval and adult worms excretory-secretory products (ESP) (Braschi and Wilson 2006; Sotillo et al. 2015). Indeed, schistosome G3PDH (SG3PDH) is considered a prominent moonlighting protein. Moonlighting proteins comprise a subset of multifunctional proteins in which one protein exhibits more than one physiologically critical function (Huberts and Van der klei 2010).

Excretory secretory SG3PDH is considered as one of the major vaccine candidates against schistosomiasis (McManus and Loukas 2008), and plays a role in the prevention of reinfection (El Ridi et al. 2001a, 2004; b). However, due to its high homology (72.5%) to human G3PDH the whole parasite proteins may not be used as a vaccine for fear of inducing autoimmune responses. Therefore, it is better to select SG3PDH derived-peptides sharing the lowest homology to those of human, and the peptides were selected for devising a safe synthetic peptide-based vaccine (El Ridi et al. 2001a). These peptides were examined using serum and lymphocytes from humans resistant to reinfection with *S. mansoni* or *S. haematobium* after treatment

with PZQ of previous infection and from BALB/c and C57BL/6 mice immunized with recombinant rSG3PDH (rSG3PDH). The results revealed that SG3PDH-derived peptides possess human and murine T- and B-cell determinants and immune responses to the peptides correlate with resistance to schistosomiasis infection (El Ridi et al. 2001a).

Linear peptides in MAP or dipeptidic-MAP (D-MAP) constructs induced Th1 and Th2 immune responses in mice but with different protective levels (Tallima et al. 2003; El Ridi et al. 2004; Veprek et al. 2004), supporting the evidence that both Th1 and Th2 immune responses are required for protective immunity against schistosomiasis (McManus 1999; El Ridi 2002; Al-Sherbiny et al. 2003). The failure in developing the SG3PDH vaccine was corrected when SG3PDH was combined with type 2 cytokines or type 2 immunity-inducing cysteine peptidases. The results showed highly significant ($P < 0.0001$) reduction (62–78%) in worm burden, and copious production of IgM, IgG1, and IgA specific antibodies, and IL-4 and IL-5 cytokines in outbred CD-1 mice (El Ridi and Tallima 2013a, b).

Tegument candidate vaccines

Superoxide dismutase

Superoxide dismutase (SOD) antioxidant enzyme is a candidate vaccine against schistosome infection, as it has an important role in schistosome immune evasion (Shalaby et al. 2003). It has a defensive role against tegument attack (lipid peroxidation) in adult worms that result from the release of reactive oxygen species (ROS) by host cells (LoVerde 2004; Chiumiento and Bruschi 2009). Yet, it is expressed with high levels in the adult worms (the least susceptible to immune elimination) and low levels in the larval stages (the most susceptible to immune elimination) (LoVerde et al. 2004). There are two SOD in *S. mansoni*,

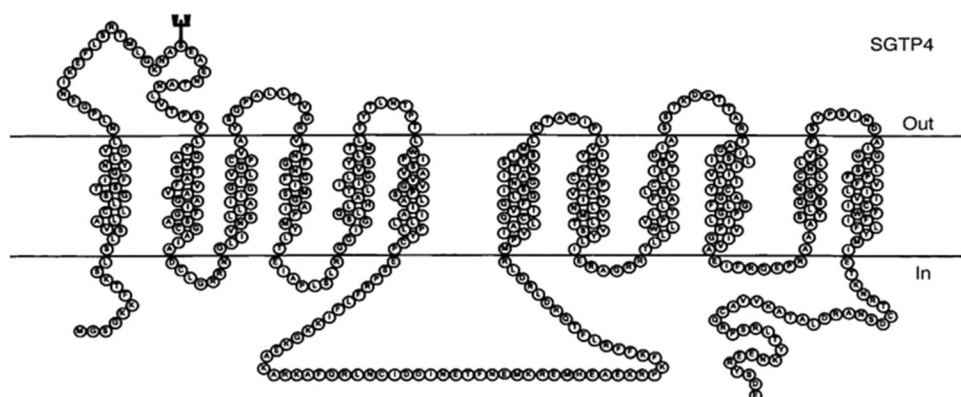


Fig. 1 Schistosome glucose transporter protein 4 structure (Skelly et al. 1998)

one cytosolic Cu/Zn dependent (CT-SOD) and the second extracellular or membrane-associated which contains one peptide signal (SP-SOD) (Mkojii et al. 1988; Nare et al. 1990). Both forms are present in the tegument and the intestinal epithelium of the adult stage, whereas the extracellular form is localized also in the membranes of parenchymatous cells and cellular organelles (Hong et al. 1992; Mei and LoVerde 1997).

Immunization of BALB/c mice with pcCT-SOD led to significantly decreased worm burden (42.8, 35.9 and 38.0%) in three independent experiments, and indicated that pcCT-SOD activates Th1 rather than Th2 immune responses (Cook et al. 2004). Immunization of BALB/c and C57BL/6 mice with DNA based SmCT-SOD and *S. mansoni* glutathione peroxidase (SmGPX) then challenged with *S. mansoni* cercariae resulted in significant reduction in worm burden (44–60% and 23–55%, respectively) in six independent experiments. Additionally, SmCT-SOD and SmGPX DNA-based vaccine was consistently conferring greater than 40% protection, which is the World Health Organization minimum requirement (Shalaby et al. 2003; LoVerde et al. 2004; Tebeje et al. 2016). Similarly, a protective effect of SOD against schistosomiasis in olive baboons was revealed by Carvalho-Queiroz et al. (2015), whereby animals primed with naked DNA of SOD forms and GPX and boosted with the respective recombinant antioxidant proteins encapsulated in polylactic acid (PLA) microspheres, were able to stimulate both humoral and cellular responses (including cytokines and chemokines). This resulted in a reduction in worm numbers, and a pronounced anti-pathology effect compared to control animals (Carvalho-Queiroz et al. 2015; Tebeje et al. 2016).

S. mansoni 29 kDa protein

Sm29 is a glycosylphosphatidylinositol (GPI) integral protein localized in the tegument of mammalian adults and lung-stage schistosomula and absent in cercariae indicating that this antigen plays a role in helping the parasite to adapt to the new environment in mammalian hosts (Braschi et al. 2006; Cardoso et al. 2006a, 2008; Castro-Borges et al. 2011; Sotillo et al. 2015). Sm29 was suggested to play a role in parasite evasion of immune response by interaction with human protein CD59, which inhibits membrane attack complex (MAC) and would help the schistosome to disable immune responses (Bear et al. 2018). As well, it is considered as an immunoregulatory molecule, which regulates inflammatory mucosal diseases (leishmaniasis and asthma) (Oliveira et al. 2016). It was recently identified in 120 k and 15 k EVs of the tegument (Kifle et al. 2020a). Since Coulson and Wilson (1997) have suggested regarding vaccination with irradiated cercariae that the lung is the main site of parasite elimination. Sm29 localization on

schistosomula tegument suggests it as a good target for vaccine development against schistosomiasis. Moreover, Sm29 ortholog is present in ESP of *S. japonicum* with more than 50% homology, suggesting that Sm29 might also be effective against *S. japonicum* (Cardoso et al. 2006b). Immunization of C57BL/6 and TLR4 KO mice with rSm29 induced Th1-Th2 type of immune responses characterized by high levels of IgG1 and IgG2a antibodies and IFN- γ , tumor necrosis factor (TNF)- α , and IL-12 cytokines associated with significant reduction in parasite burden (51%) and pathology (Cardoso et al. 2008). More importantly, rSm29 has shown significant protection (26–48%) in previously *S. mansoni* infected BALB/c mice, treated with PZQ. Protection was characterized by elevated levels of IgG, IgG1, IgG2a, and IgE antibodies, IL-2, IFN- γ , IL-17, IL-4, and CD4 + central memory T cells (Alves et al. 2015). Of note, individuals living in areas endemic for schistosomiasis, the resistance to *S. mansoni* infection and reinfection is associated with the production of IgG1 and IgG3 specific to Sm29 (Cardoso et al. 2006a). Differences observed in antibody titers between the rSm29-immunized group, that did not develop protective immunity and *S. mansoni* infected and PZQ-treated/rSm29 group, which developed a protective immunity, resided in an increased titer of IgG and decreased titer of IgG1. These results suggest that other IgG isotypes may be associated with the protection induced by this vaccine formulation (Alves et al. 2015). Alongside, to improve immunogenicity and safety, rSm29 was linked to gold nanorods carrier directly or by cysteamine functionalization and examined against *S. mansoni* challenge infection in C57BL/6 mice. The results showed a remarkable protection level (34%) characterized by Th1 immune response parameters (Assis et al. 2018). In another study, Sm29 was formulated with alum or monophosphoryl lipid A adjuvant (MPLA) then administered to BALB/c mice reinfected with *S. mansoni*. Sm29-alum induced partial protection against reinfection, reduced worm burden by 29–37% while Sm29-MPLA failed to reduce worm burden, indicating that Sm29-alum can effectively protect against *S. mansoni* reinfection in mice (Alves et al. 2018).

The fusion of Sm29 with Sm14, designated as Sm14/29 alone or combined with polyinosinic-poly cytidylic acid [poly (I:C)] adjuvant elicited significant reduction of adult worm burden by 48.4% and 44.7%, liver egg burden by 82.8% and 73.5, intestinal egg count by 72.8% and 76.6%, respectively, in Swiss albino mice (Mossallam et al. 2015; Eyayu et al. 2020). Similarly, Sm29 fused with Sm-TSP-2 resulted in reduction (22–35%) of worm burden, with an elevated level of IgG1 and IgG2 antibodies, IFN- γ and TNF- α in C57BL/6 mice (Pinheiro et al. 2014). These results suggest the multi-antigens fusion proteins might be potential vaccine candidates. More recently, a multi

epitope-based vaccine containing predicted epitopes from Sm14, Sm21.7, Sm23, Sm29, Smp80, Sm-CB, and SM-TSP-2 antigens was developed. Immunoinformatic analysis demonstrated that the vaccine has a high potential to stimulate T and B-cell mediated immune responses, and indicated that a multi epitope-based vaccine can be utilized for prophylactic or therapeutic aims in response to the infection caused by *S. mansoni* (Rahmani et al. 2019).

Insulin receptors

Schistosomes are unable to synthesize insulin (Affholter et al. 1988); instead, they depend on host insulin for fecundity and growth. Insulin (5808 Da) regulates glucose uptake, improves the viability of schistosomes, and promotes the metabolism and development of adult worms (Vicogne et al. 2004; Saule et al. 2005; Ahier et al. 2008; You et al. 2009). Two types of insulin receptors (IRs) have been isolated from *S. mansoni* (SmIR1 and SmIR2) (Khayath et al. 2007), and *S. japonicum* (SjIR1 and SjIR2) (You et al. 2010). IR-1 is located on the tegument basal membrane and the internal epithelium of adult worms and plays a role in utilizing host insulin, while SjIR-2 is located in the parenchyma of males and the vitelline tissue of females and has a role in controlling worm growth and development (Khayath et al. 2007; You et al. 2010).

Insulin receptors are suggested as transmission blocking vaccine candidates. Administration of mice with anti-SjIRs antibodies or SjIRs knocking down evoked reduction in glucose uptake, starvation and stunting of adult worms, and reduction in egg output (You et al. 2010, 2015). The development of a vaccine based on the ligand domains of SjIR1 and 2 using peptides derived from their primary sequences, may be feasible due to their low homology to human IR (HIR) and are highly antigenic with the ability to bind human insulin (You et al. 2014). Thus, immunization of CBA mice with the L1 subdomain of the SjIR2 (SjLD2) fusion protein expressed in *Escherichia coli* resulted in highly significant reductions in numbers of adult worms (40–50%), mature intestinal eggs (75%), fecal eggs (56–67%), and hepatic granuloma density (45–55%). However, due to the poor immune response generated, it was hard to obtain consistent results using rSjLD2 protein, which had a tendency to degrade during the processes of expression and purification. Nevertheless, further work improving the expression/purification of rSjLD2 is currently underway in order to prevent its degradation (You et al. 2012). Additionally, peptide analogues derived from SjIR1 and SjIR2 have shown high binding affinities to host insulin. These peptide analogues were shown to have more than 10 times higher binding affinity for human insulin than peptides derived from the human IR in the same sequence positions (Stephenson et al. 2016).

Cytosolic vaccines

Paramyosin

Paramyosin, a 97-kDa myofibrillar protein with a coiled-coil structure, was exclusively found in invertebrates. It is expressed in the penetration glands of cercariae, the tegument of schistosomula, and the contents of membrane-bound elongate bodies within the tegument and sub tegmental cell bodies of adult worms. It protects worms from complement-mediated damage by binding human C8 and C9 proteins, preventing complement activation at the terminal stage, in vitro and in vivo. Paramyosin protein either native or in a recombinant form was considered a vaccine candidate for protection against schistosomiasis (Gobert and McManus 2005; Deng et al. 2007; McManus and Loukas 2008; Jiz et al. 2015; Eyayu et al. 2020). Additionally, paramyosin peptides were recognized by T cells of humans resistant to schistosomiasis infection and reinfection (Fonseca et al. 2005; Eyayu et al. 2020).

Due to its location, paramyosin is presumably unavailable for interaction with the immune response (youPearce et al. 1986). Yet, C57BL/6 mice vaccination with native or partial recombinant paramyosin fragment with BCG conferred protection (26–39%) by stimulating T cells to produce IFN- γ that induces macrophages to kill schistosomula. However, specific epitopes in the immunogen are required because a heterologous paramyosin and myosin from a different invertebrate genus was not protective. These data suggested that paramyosin protective action is cell-mediated and not antibody-dependent (Pearce et al. 1988; McManus and Loukas 2008). On the other hand, mice vaccinated intradermally with *S. mansoni* or schistosomula extracts with *Mycobacterium Bovis* BCG adjuvant were significantly protected against subsequent infection, and antibodies predominantly recognized paramyosin (Lanar et al. 1986; Sher et al. 1986). In addition, a BALB c/C3H HFl mouse monoclonal IgE antibody recognized *S. japonicum* paramyosin (Nara et al. 1997), and showed protection (19–58%) against cercarial infection following passive transfer (Kojima et al. 1987a; b). Conversely, paramyosin immunogen failed to confer the same level of protection in multi-antigen DNA-based form (Tang et al. 2008). Furthermore, immunization of Swiss albino mice three times with purified Sm97 induced 44.1%, 59.1%, and 61% reduction in worm burden, intestinal egg loads, and granuloma size, respectively. The protective immunity was associated with high levels of specific anti-Sm97 IgG1 and IgG2 antibodies (Diab and Aly 2011; Eyayu et al. 2020).

Immunization of C57BL/6 mice with Sm14 peptides alone or mixed with paramyosin peptides reduced worm burden (26–36.7% or 28–29.2%), intestinal eggs (67% or

46%), and also liver pathology (54–61% or 43–52%), respectively. Protection was related to a Th1 type immune response provoked by Sm14 peptide immunization. Thus, vaccination with paramyosin peptide did not mediate protective immunity or reduce pathology and immunization was associated with a Th2 immune response (Garcia et al. 2008).

In contrast, in a large-scale treatment-reinfection study, Th2 cytokine response and IgE antibody to Sj97 were shown to be highly associated with resistance to reinfection with *S. japonicum* (Leenstra et al. 2006; Jiz et al. 2009; Wu et al. 2017). In rodents, its protective potential without adjuvant against *S. mansoni* was 24–53% and 62–86% against *S. japonicum* (Jiz et al. 2015; El Ridi and Tallima 2013a). Due to its high immunogenicity against *S. japonicum*, plans are made to move it toward phase I clinical trials.

Thus, the 97 kDa protein is recommended as a promising vaccine candidate for *S. japonicum* (McManus and Loukas 2008; Kurtis et al. 2015; Luna and Campos 2020), principally in sheep, pigs, and water buffaloes. Chinese Sj-97 has shown significant partial protection (32–45%) in sheep (Taylor et al. 1998), pigs (Chen et al. 2000) and water buffaloes (McManus et al. 2001). Moreover, rSj-97 vaccine formulated with Montanide ISA 206 was strongly immunogenic among water buffaloes resident in an area endemic for schistosomiasis *japonicum* (Jiz et al. 2016; You et al. 2018). In addition, three independent studies (in 2008, 2013, and 2016) with full-length rSj-97 vaccine formulated with Montanide ISA 206 showed reduction (51.5–60.9%) in worm burden, and elevated levels of IgG1 and IgG2 antibodies after challenge infection with *S. japonicum* (Wu et al. 2017; You et al. 2018).

Gastrointestinal tract vaccine candidates

One of the most important requirements for *S. mansoni* survival is the processing of ingested blood in the gut by different peptidases, and nutrients uptake. Impairment of these processes represents an important strategy for vaccine development because the worms will not survive inside the host and will die from starvation. Many digestive tract proteins, which are not recognized by host immune responses during normal infection and are essential for parasite survival, have been tested (Figueiredo et al. 2015).

Schistosoma mansoni lysosome-associated membrane protein (Sm-LAMP) is highly enriched in the digestive tract of *S. mansoni*, located in the gastrodermis. Sm-LAMP in soluble and insoluble form was shown to provide limited protection against *S. mansoni* infection in CBA mice but might be used in combination with other vaccine candidates to provide more protection (Nawaratna et al. 2015).

Another protein possesses a dynein light chain family (DLC/LC8) domain, which is evolutionarily conserved in schistosome and different organisms, and is located in distal gut and in the tegument of schistosomes (Diniz et al. 2014). Recombinant *S. mansoni* DLC12 and DLC13 combined with alhydrogel adjuvant induced high antibody titers (IgG) and decreased worm burden of 43% and 51%, respectively, and decrease in granuloma size of 70% in BALB/c mice, reflecting the protein Immunoprotection potential (Diniz et al. 2014).

Sm10 protein (also called micro exon gene-4.1) is located on the surface and lumen of the esophageal and intestinal tract of adult worms and lung-stage schistosomula. It was shown to induce a mixed Th1/Th2-type response with reduction in the worm (25–32%) and liver egg (43.6%) burden as well as a reduction in the number of granulomas (23.8%) in C57BL/6 mice, suggesting Sm10.3 as a potential vaccine candidate (Martins et al. 2014).

Sm32 is an asparaginyl peptidase (SmAE) member of the legumain family; it is released as an ESP that hydrolyzes pro-enzymes involved in the degradation of hemoglobin (Dalton and Brindley 1996; Chlichlia et al. 2002). It was shown to induce humoral response against the native protein and *S. mansoni* homogenate when used in DNA formulation but it failed to reduce the challenge worm burden (Chlichlia et al. 2002). Additionally, hydrophilic regions of the molecule with Freund's adjuvant showed limited immunogenicity in rabbits and mice (Noya et al. 2003a; Chacon et al. 2003).

A PDZ (PSD-95/Dlg/ZO-1) domain-containing schistosome protein, syntenin (SmSynt), is localized in the gastrodermis of *S. mansoni*, in spite of none of the proteomic and transcriptional studies identified this protein at this location (Figueiredo et al. 2014). C57BL/6 mice vaccinated with the rSmSynt showed reduction (30–37%) in worm burden and production of IgG antibodies and Th1-cytokines (Figueiredo et al. 2014).

Four proteins possessing the characteristic saposin domain were identified in schistosome vomit (Hall et al. 2011). A gut saposin-like protein (SmSLP-1) binds sphingolipids, facilitating their degradation by ceramidases and also binds other lipids, sequestering them in the gut lumen for transport and uptake into the cells (Don et al. 2008; Hall et al. 2011). SmSLP-1 has proven to be immunogenic when recombinant form of this protein elicited high antibody titer, but the number of adult worms and eggs recovered from vaccinated CBA/CaH mice did not decrease (Don et al. 2008), suggesting that not all gut proteins tested as vaccine were protective.

Indeed, the efficacy of these vaccines remains dependent on the ability of antibodies to bind to these enzymes and inhibit their function. The reason why not all of digestive tract antigens induced protection is because the parasite gut

pH is low and seems to be an unsuitable environment for antibodies. Despite that, many digestive tract antigens elicited some protection (Figueiredo et al. 2014).

Additionally, many other antigens like Sm22.6 (Pacífico et al. 2006a; b), ECL or Sm200 (Nascimento et al. 2007; Martins et al. 2012), and Sm21.7 (Ahmed and Romeih 2001; Ahmed et al. 2006) and others also showed ability to provoke significant immune responses, but were not progressed further.

Excretory/secretory proteins

It was recently documented that actually all *S. mansoni* and *S. haematobium* surface membrane, tegumental and digestive tract candidate vaccine antigens are ESPs, readily detectable in worm derived 15 k (286 proteins) and 120 k (716 proteins) EVs. Sm23, SG3PDH, calpain, Sm-TSP-2, saponin B domain-containing proteins, GST, Sm29, cathepsin domain-containing proteins namely cathepsin B and cathepsin L, proteases, oxidants were identified (Sotillo et al. 2016; Samoil et al. 2018; Kifle et al. 2020a; Mekonnen et al. 2020). El Ridi and Tallima (2009, 2013a) and El Ridi et al. (2015) were the first to advocate that vaccine candidates should only be sought among the developing and migrating larvae ESPs because ESPs are able to induce innate and adaptive immunity and are accessible targets to host immune elements.

Different ESPs molecules have been derived from cercariae, lung-stage schistosomula, and adult worms of several schistosome species (Harrop et al. 1999; Knudsen et al. 2005; Curwen et al. 2006; El Ridi and Tallima 2009; Liao et al. 2011; Young et al. 2012). Most of the schistosome antigens candidates induced type 1 response, except radiation-attenuated cercariae induced Th1-/Th2-immune responses. So, type 1 and 2 immune responses have an essential role in significant parasite elimination and more associated with resistance to reinfection (He and Geha 2010; Price et al. 2010; Siracusa et al. 2011; Badr et al. 2015; El Ridi et al. 2015; Tallima et al. 2015).

Recombinant antigens

Since ESP such as calpain, SG3PDH, 14–3–3-like protein, thioredoxin peroxidase (TPX) etc. in a recombinant form, predominantly elicit poorly protective type 1 immune responses, it was necessary to direct the immune response toward the type 2 arm. Cysteine peptidases derived from such diverse sources as papaya (papain; Sokol et al. 2008), house dust mite, Derp1 (Roche et al. 1997; Kikuchi et al. 2006), *Leishmania mexicana* (Pollock et al. 2003), and many fungal allergens (Shen et al. 1998; Kheradmand et al. 2002) were used (El Ridi and Tallima 2013a). Furthermore, they have the ability to act as adjuvants in the absence of

other adjuvants (Chapman et al. 2007; Cunningham et al. 2012). CD-1 mice vaccinated with a combination of the larval ESP, rSG3PDH, and TPX peptide, in conjunction with papain or cytokines, i.e., TSLP (thymic stromal lymphopoietin), IL-25 or IL-33, exhibited predominant Th2 responses, which correlated with highly significant ($P < 0.0001$) reduction of 62–78% in challenge worm burden (El Ridi and Tallima 2013a).

Since papain, IL-25, IL-33, or TSLP may not be used for human vaccination, they were replaced by a parasite-derived cysteine peptidase (El Ridi et al. 2015; Tallima et al. 2015). One of the major worm extract proteins and ESPs is *S. mansoni* cathepsin B1 (SmCB1), a novel critical anti-schistosome vaccine candidate with a capacity to initiate Th17 besides Th1 and Th2 responses (El Ridi et al. 2014a; Ricciardi et al. 2016; Soloviova et al. 2019). SmCB1 and *S. mansoni* cathepsin L1 (SmCL1, CL) are major hemoglobin-digesting enzymes (Day et al. 1995; Brady et al. 1999a, 1999b, 2000; Bogitsh et al. 2001; Caffrey et al. 2018; Wendt et al. 2020). SmCB1 is expressed at high levels on the caecum and protonephridia of cercariae while SmCL1 is localized to the gastrodermis and the tegument of adult worms (El Ridi et al. 2014b). Both are prominent ESPs, particularly enriched in EVs (Kifle et al. 2020a; b). Recent studies revealed that vinyl sulfone inhibitors of the SmCB1 target will impact the parasite's ability to grow (Jílková et al. 2011, 2020); as well, RNA interference of SmCB1 slowed the growth of the parasite both in culture and in an animal model of infection (Correnti et al. 2005).

Adjuvant-free, enzymatically active SmCB1 or FhCL1 in recombinant form alone or in combination with another vaccine candidate SG3PDH/PRX-MAP were shown to induce high levels of protection with an increase in IgG1 isotype titers (no IgE was detected), and Th2 cytokines against *S. mansoni* and *S. haematobium* infection, in CD-1 mice and Syrian hamsters, respectively. It was suggested that peptidases can boost early adaptive immune responses, and have in-built immune enhancing properties that are protective on their own, besides having the ability to enhance the protective responses to other molecules (El Ridi et al. 2014a, b; Tallima et al. 2015, 2017a, b). *Schistosoma mansoni* cathepsin L3 (SmCL3) is another cysteine peptidase that is also expressed in digestive tract of *S. mansoni* worm (Dvořák et al. 2009). CD-1 mice and Syrian hamsters immunized with enzymatically active rSmCB1 and SmCL3 alone or combined with rSG3PDH induced a significant ($P < 0.002$) protection of (up to 60 and 70%, respectively) against *S. mansoni* and *S. haematobium* challenge infection. This indicated that the efficacious trivalent vaccine should now be used as trials in non-human primates for assessment as a potential vaccine to control human schistosomiasis (Tallima et al. 2017a; b).

Adjuvants were shown to enhance the immunogenicity and protective efficacy of *S. mansoni* cathepsin B (SmCB, CB) formulated with CpG elicited significant protection in C57BL/6 mice characterized by elevated levels of Th1 cytokines (IFN- γ and TNF- α). SmCB formulated with Montanide ISA 720 VG induced significant protection with elevation of both Th1 and Th2 cytokine immune responses (Ricciardi et al. 2015, 2016). A two-dose, starting with oral gavage of attenuated *Salmonella enterica* Typhimurium strain (YS1646) bearing the nirB_SspH1_CB plasmid followed by intramuscular recombinant enzyme (rCB), or immunization with rCB combined with sulfated lactosyl archaeol archaeosomes or addavaxTM was able to reduce both worm and tissue egg burdens by 80–90%, which is the best result recorded among *S. mansoni* vaccine candidates in murine model (Hassan et al. 2019; Perera et al. 2020).

Of note, enzymatically inactive SmCB1, *Fasciola hepatica* cathepsin L1 (FhCL1) (El Ridi et al. 2014a; b), *S. haematobium* cathepsin L (Abdel Aziz et al. 2019), and papain (Tallima et al. 2019) displayed reduced, yet significant, protective capacity against *S. mansoni* and/or *S. haematobium* challenge infection independently of their proteolytic activity. Furthermore, Tallima and colleagues have found that active and chemically-inactivated non helminth cysteine peptidase, papain induced highly significant reduction (> 65 and 40%, respectively) in worm burden associated with 85% decrease in intestinal egg viability in mice. These results suggested that one or more papain structural motifs might be responsible for induction of the significant protection (Tallima et al. 2019).

All vaccine candidates are now known to be via their transport in EVs available to both elicit immune responses and be accessed by immune effectors, namely antibodies able to hunt and chase the developing schistosomula, forcing their extravasation especially at the lung and liver stage (El Ridi et al. 2017; Sotillo et al. 2016; Samoil et al. 2018; Kifle et al. 2020a; Mekonnen et al. 2020). The reproducible and highly significant reduction in worm burden and worm egg attrition elicited by cysteine peptidases was recently explained. These molecules do not only induce type 2 antibodies, they also result in accumulation of uric acid and arachidonic acid (ARA). It was recently proposed that specific antibodies and the schistosomicide ARA combine towards parasite worm and egg attrition. (Tallima et al. 2019, 2020a; b). Curiously, EV derived from adult *S. mansoni* were found to be internalized by vascular endothelial cells and monocytes and to powerfully up regulate ARA metabolism (Kifle et al. 2020b).

The cysteine peptidase vaccine protection was recently found to be associated with high levels of serum antibodies and an increase in the levels of uric acid and ARA in blood and tissues around 17 days post infection (Tallima et al. 2019, 2020a). Uric acid directed the immune responses

towards the type 2 axis, increased the antibody response, and elicited an increase in free ARA, responsible for worm and egg attrition. The powerful oxidant stress-inducing properties of ARA are responsible for its schistosomicidal action, but are counteracted by the anti-oxidant properties of uric acid. It was thus sought to avoid the uric acid-inducing capacity of ARA, via use of an enzyme-inactive peptide construct (Tallima et al. 2019, 2020a; b).

Antigenic peptides

Peptide vaccine might be more useful than whole protein and live-attenuated formulations, because peptide vaccine decreases the possibility of using immunosuppressive epitopes and epitopes that elicit an autoimmune response. However, peptide vaccine presents limitations in terms of obtaining an effective immune response in a population with high genetic variability. The choice of epitopes to form a peptide vaccine depends on their ability to elicit the desirable immune response and to be presented by a wide range of HLA molecules (Purcell et al. 2007). Nevertheless, the efficacy of synthetic peptide vaccine has been evaluated against many microorganisms, and has shown to confer a partial protection in vivo against parasite diseases (Patarroyo et al. 1987; de Oliveira et al. 1994; Noya et al. 2003b). Additionally, synthetic peptides that contain epitopes of infectious agents' protein have been used in the diagnosis of various human diseases (Gómara and Haro 2007).

Regarding schistosomiasis, different vaccine candidates in a peptide construct have been tested. One of those candidates was a peptide containing B and T cell epitopes derived from protease inhibitor, kunitz protein of *S. mansoni*, resulted in significant reduction (89–91%) in female worm burden in BALB/c mice (Hernández-Goenaga et al. 2019). In addition, peptides derived from Sm14, paramyosin, and Sj28GST antigens have shown that Sm14 and Sj28GST induced Th1 immune response against *S. mansoni* and *S. japonicum* infection in C57BL/6 mice (Li et al. 2005; Garcia et al. 2008). Another two peptides derived from SmA263K protein were synthesized as lipid core peptides (LCPs), with or without adjuvant. Antibodies released against LCPs recognized native enzyme in the esophagus and anterior regions of the gastrodermis of adult worms (Dougall et al. 2014).

Actually, most peptides are not immunogenic and they can be easily removed by the body, and hence, must be conjugated to a carrier protein to elicit the required immune responses. The chemical composition of the carrier drawbacks, notably its immune dominance and low ratio of an antigen to a carrier, limit their use (Tam 1995). Instead peptides were conjugated to protein (bovine serum albumin (BSA), keyhole limpet hemocyanine) or artificial

carriers (MAPs, sequential oligopeptide carriers, etc.) (Tam 1988; Tsikaris et al. 1996a, b; Mezo et al. 1997).

The MAP formulation allows many peptides to be associated in a single construct, and it can be immunogenic with or without inbuilt adjuvant. It was first developed by Tam (1988), when he replaced the protein carrier with a small score matrix comprising oligomeric lysine, providing a very high density of peptide epitopes at the surface of the construct with a small non-protein core matrix as a scaffold (Fig. 2) (Tam 1988). Synthesizing peptides as MAP and peptide dendrimers can induce higher immune response and recently were used as a vaccine model against *Plasmodium falciparum* (Mahajan et al. 2010), *Yersinia pestis* (Shreewastav et al. 2012), filarial nematodes (Immanuel et al. 2017), and human immunodeficiency viruses (HIV) (Sahay et al. 2019). Besides, all required protective B and T cell epitopes can be included in one single MAP molecule (Fig. 2) (Joshi et al. 2013). Additionally, MAP vaccine systems have been developed to avoid the adverse effects associated with conventional vaccines (i.e., live-attenuated, killed, or inactivated pathogens), carrier proteins, and cytotoxic adjuvants (Fujita and Taguchi 2011).

Schistosoma mansoni SG3PDH mono-epitopic and bis-diepitopic MAP immunogens elicited in C57BL/6 mice considerable cellular and humoral immune responses (Veprek et al. 2004). Thus, six peptides bearing B and T cell epitopes derived from the primary sequence of *S.*

mansoni SG3PDH and synthesized in a dipeptide MAP induced both Th 1 (IgG2a and IgG2b isotypes) and Th2 (IgG1 isotype) immune responses, and elicited the release of IL-2, IL-4, and IFN- γ (El Ridi et al. 2004), while the whole molecule containing these peptides could not elicit the release of IL 4 in BALB/c mice and human (El Ridi et al. 1998, 2001a; Tallima et al. 2003). SG3PDH derived MAP construct administered to BALB/c mice appeared to induce both Th1 (IgG2a and IgG2b) and Th2 (IgG1 or IgE) immune responses. This is in line with protective immunity in schistosomiasis requiring both Th1 and Th2 immune responses (Butterworth 1994; Coulson 1997; McManus 1999; Dunne and Mountford 2001; El Ridi 2002; Al-Sherbiny et al. 2003).

On the other hand, vaccination of C57BL/6 mice with single-epitope-peptide-DNA dual vaccines (PDDV) elicited either T cytotoxic, T helper, or B cell responses. The multicomponents (3 PDDV components) formulation could trigger different immune responses in immunized mice, yet, was less immunoprotective than a single-epitope PDDV formulation. Results suggested that combination of many antigens did not increase the protective potential of the vaccine when compared to the protection of each antigen separately mediated (Wang et al. 2010). However, a bivalent MAP construct containing peptide sequences containing B and T cells determinants derived from Sm28GST and SmTPI proteins was shown to induce B-

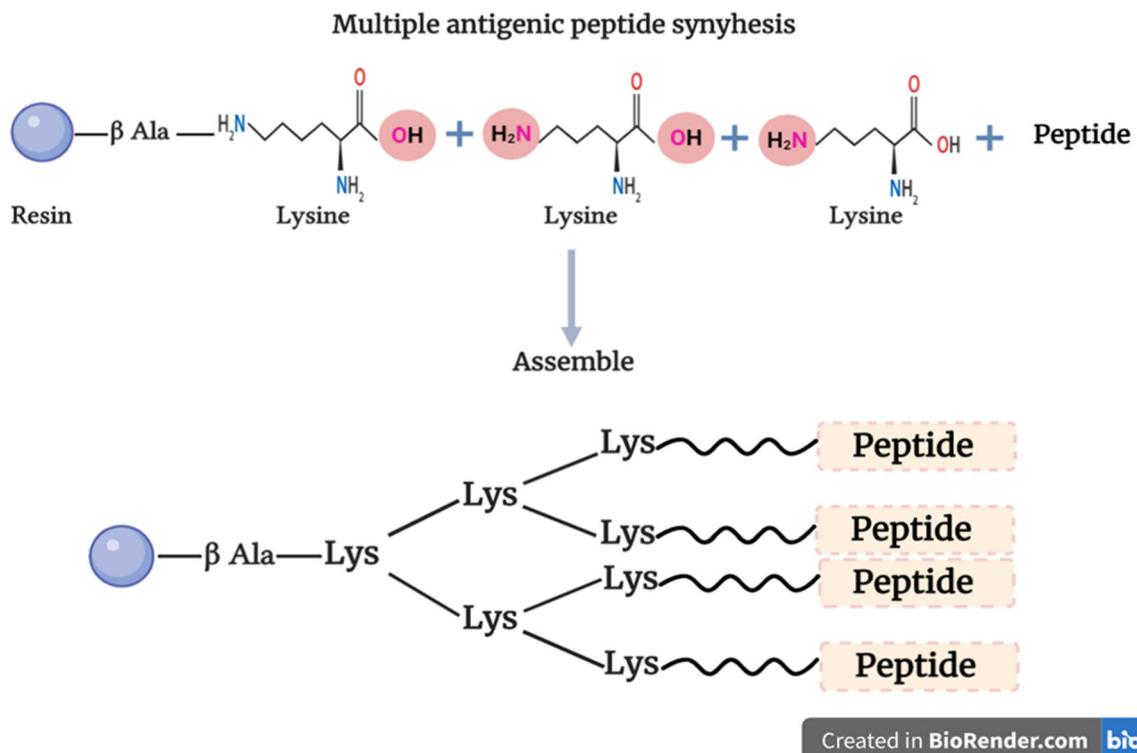


Fig. 2 Multiple antigenic peptide structure

and T-cell responses and the antibodies were mainly directed not only against the peptide derived from the Sm28GST but also against the whole Sm28GST protein when administered to BALB/c, CBA/N, and C57BL/6 mice (Ferru et al. 1997). MAP construct containing B- and T-cell epitopes derived from SmTPI was used to prime human and murine spleen cells in vitro driving Th1 immune response, and stimulating the release of IFN- γ which play an important role in both *S. mansoni* protective immunity and pathology (La Flamme et al. 2001; Henri et al. 2002; Reis et al. 2008).

Similarly, Sm28GST derived peptides synthesized in two tetravalent mono-epitopic MAPs displayed high antigenicity, indicating that MAPs were stronger agents than monomeric peptides in both specificity and immunogenic activity against schistosome infection in patients and rabbits (Huang et al. 2005).

Otherwise, MAP constructs have elicited significant protection against other parasites, *Toxoplasma gondii* (Darcy et al. 1992), *Fasciola gigantica*, (Jezek et al. 2007), *Trichinella spiralis* (Gu et al. 2020), and microorganisms, *Streptococcus mutans* OMZ 175 and a mannan from *Saccharomyces cerevisiae* (Lett et al. 1995).

Concluding remarks

Schistosomiasis is one of the important helminthic diseases closely linked to poverty and affecting the health. *S. mansoni* infection causes intestinal diseases and affects the liver and spleen. Several countries including Egypt depend on PZQ as chemotherapy against schistosomiasis; however, the appearance of drug resistant strains limits its use. Additionally, mass drug administration alone will not eliminate schistosomiasis. The need for developing vaccine is of great important for public health. Proteins that are specific to schistosomes and show limited similarity with any other proteins are considered as effective and protective vaccine antigens. One of the main clinical endpoints for vaccine efficacy is reduction of schistosomiasis morbidity. Therapeutic potential of vaccine should be tested first in rodents, non-human primates and bovines before using in human clinical trials. Several vaccine candidates have been discovered and showed different protection levels. Protective capacity of vaccines was achieved by induction of either Th1 or Th2 or both responses. Also, protection levels of candidate vaccines are improved after antigen formulation or combining of either different genes or antigens. However, most research groups had no financial and logistic ability to access trials in baboons or pre-clinical human trials, resulting in neglect of vaccines that potentially might save millions of lives.

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Conflict of interest No conflict of interest are declared by all authors.

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