Antigens of Three Medically Important Schistosoma spp

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This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The present study was carried out to review the antigens of three (3) medically important Schistosomes namely: Schistosoma mansoni, S. haematobium, and S. japonicum. The parasites-host relationship, the antigens, the species that produce the antigens, and the functions of the antigens were discussed. Identified antigens include: Sm-24 kDa, Sm108 kDa, Polymorphic mucins, 28/30 kDa Protease, 47 kDa protease, 60 kDa protease, Cercarial Elastase (CE) also called 28/30 kDa, Cathepsin, 22.6 kDa, 23 kDa, 16 kDa/SLP/SPO-1, Prostaglandin E2 (PGE2), SmEnolase, SmCalp1, 28 kDa GST (rSh28GST), 29 kDa, Calpain (Sp80) and SG3PDH. The above mentioned antigens of the parasites were found to be much important since they enable them to compete with body immunity while carrying out their metabolic activities, reproduction, growth, defense, resistance, and so many other things within the host. Therefore, these antigens are very important in immunological studies; hence, it was recommended that, Since some parasite antigens were found to be promising candidates for developing a vaccine to protect against Schistosoma infection, more parasite antigens should be searched for the best planning and development of numerous strategies that aid in the prevention and control of schistosomiasis.

Keywords: Antigens; S. mansoni; S. haematobium; S. japonicum.
1. INTRODUCTION

Schistosomes are dioecious parasitic flukes related to the kingdom Animalia and the phylum Platyhelminthes that infect Schistosomiasis /Bilharziasis, also referred to as Snail fever, in humans and other animals [1]. Schistosomiasis is divided into two types: intestinal and urinary/urogenital schistosomiasis [2].

Infected individuals passed Schistosoma eggs in their feces or urines in a freshwater ecosystem containing snails of the genus Bulinus or Biomphalaria [3]; under perfect circumstances, they lay eggs and discharge miracidia, which swim and enter a specific snail intermediate host [4]; the miracidia inside the snails developed two generations of sporocysts before emerging to infective [5]. The infectious cercariae swim and penetrate the skin of human hosts while carrying out their activities in the polluted water once the cercariae out from snails are released into the water body [6].

As a result of larger growth in schistosomiasis cases, the global health burden of schistosomiasis is increasingly being compared to that of malaria or tuberculosis in certain analyses [1,5]. Due to the parasites’ harboring of numerous resistance antigens, Schistosoma infections can cause lasting damage to different organs, as well as substantial morbidity and disastrous effects on early childhood, adult productivity, and in some cases, death [7].

Because of the sluggish formation of naturally adaptive immunity against pathogens in human bodies, S. haematobium causes varying levels of resistance to re-infection in people [8]. This has been ascribed to the need for the immune system to be exposed to enough parasite antigens, as well as the parasites’ efficient immune avoidance tactics [9].

Because the primary strategy for schistosomiasis control is the treatment of infected individuals with antihelmintic drugs, and praziquantel, which has been widely used, is not 100 percent effective against the three primary Schistosoma species affecting humans (i.e., S. mansoni, S. japonicum, and S. haematobium) [10] it is there for important to review on the antigens of schistosomes with their functions as this might help in designing best research that could help in the development of strong and complementary methods of prevention and control of schistosomiasis globally.

2. ANTIGENS OF SCHISTOSOMES DURING PARASITES-HOST RELATIONSHIP

An antigen is any agent that causes an organism’s body produces antibodies against it; the substance that causes the immune system to produce antibodies (such as chemicals, bacteria, viruses, or pollen) can come from the outside environment of organisms or even from within the organism's body; antigens can activate lymphocytes, which are the body's infection-fighting white blood cells [11]. Foreign antigens (heteroantigens) come from outside the body, and include parts of or substances produced by parasites (such as bacteria, protozoa, and helminths), as well as substances in snake venom, specified protein molecules in foods, and components of serum and red blood cells from other individuals; while, autoantigens, on the other hand, come from within the body [12].

The body can normally distinguish self from non-self, but in people with autoimmune illnesses, normal physiological substances trigger an immunological response, resulting in the production of autoantibodies; thus, any antigen that triggers an immune response is referred to as an immunogen [13].

Antigenic determinants are areas on the surface of antigens that fit and bind to receptor molecules on the surface of antibodies that have a complementary structure [14]. Antibodies multiply and immune responses such as the formation of new antibodies, the activation of cytotoxic cells, or both against the antigen are triggered when lymphocyte receptors bind to the antigens’ surface molecules [15].

Because the immune systems of infected hosts have several life cycle stages of Schistosoma parasites that it must confront [16], schistosomes as helminths internal parasites must rely on and interact with the host for their survival. Cercariae, schistosomula, adult schistosomes, and the eggs generated by adult worms are the life cycle stages that challenge host immunity, and these stages must express various antigens to fit in with the host environment for their metabolic activities [17]. "Many of these antigens may also easily detect and induce cellular, humoral, and immunological responses; some of these responses remain elevated during acute and chronic infection, while others are significantly reduced” [18].
“Even though immunodiagnostics, immunology in *Schistosoma* afflicted people to ascertain resistance to infection or re-infection, immunopathogenesis, and its immunoregulation are the main areas that emerge when looking at human immune responses during schistosomes and host interactions” [19], “such regions mostly focuses on responses to eggs that are either exiting the body via the excreta or are caught in bodily tissues such as the intestine, liver, bladder or blood”, [20].

“The availability of urine experimental infection models has aided much understanding of human immune responses to schistosomes” [21]. “*S. haematobium* infections have been less instructive since adult worms do not migrate to the venous plexus and deposit eggs in the bladders of mice, but the development of an *S. haematobium* egg injection model has begun to yield insights into the pathogenesis of this parasite” [22,23].

“Parasite migrations in humans are unknown, but they are expected to be identical to those in experimental animals, with the same end result: adult worm pairs at certain sites, worms that live in those favored venous settings appear to be immune-resistant, multiple mechanisms are thought to be responsible for their long-term survival in an immunological milieu that is hostile (but ineffective). Some of these could be attributed to the schistosomes’ ability to masquerade through molecular mimicry or the acquisition of host antigens” [24].

Some features of *Schistosoma* species survival, such as isotopic alterations in antigen specificities and immunoregulation, may also include modifications of the host's immunological responses [25]. The protective immune response to schistosome infections has already been extensively studied using mouse models, especially using *S. haematobium* as the infecting species, and it has been discovered that both antibodies and T-cells are required for extra safety [26]. Exposure to reduced cercariae that die before reaching maturation provides excellent protection; single exposure to attenuated cercariae results in limited protection, which is principally connected with the generation of IFN-γ, whereas antibody responses become more essential in the protection of mice that have been treated to attenuated parasites multiple times [27].

“Adult worms generate eggs in their venous sites that are supposed to be taken out of the body via feces or urine and discharged into the environment (from the worms’ perspective). However, venous blood flow transports many of the eggs in the opposite direction or makes it difficult for them to leave; the eggs contain a range of proteases antigens, and other potentially harmful moietyes, which can cause necrosis once lodged in the tissues” [28]. “Granuloma production is the host’s defense against this tissue insult, and it serves to wall off and contain the egg and the proteolytic antigens it releases; immunomodulation of anti-egg antigen responses (granuloma development) develops efficiently in mice and most people during persistent infections to prevent them from overwhelming tissue locations or limiting venous blood flow” [29].

“Soluble worm antigen (SWA) of *S. mansoni* was utilized as a good control; experimental *S. mansoni* infections in T cell defective mice revealed key roles for the immune response in worm maturation and granuloma formation” [30]. Mice have a balanced or Th1 immune response to parasite antigens during the early stages of infection; however, once egg deposition begins around 6 weeks after infection, a dramatic shift to a Th2-type response occurs, this immunologic shift is caused in part by specific schistosome egg antigens interacting with dendritic cells, and in part by the action of certain carbohydrate epitopes [31]. “In humans, uncontrolled production of the Th2 cytokine IL-13 leads to extensive liver fibrosis, which is the functional cause of hepatosplenic disease” [32].

However, “because depletion of Th2 responses, particularly IL-4, leads to internal necrosis and host mortality as a consequence of increased pro-inflammatory Th1-type responses, Th2 reactions also serve as a host protective role, and their proper control reduces overall host pathology. Activated macrophages and IL-10, on the other hand, are part of the Th2-type regulatory feedback that limits the initial granulomatous inflammation, which peaks in size and severity at 8 weeks after *S. mansoni* infection” [33]. “As the infection progresses, these and other immunomodulatory mechanisms further limit granuloma formation, resulting in smaller granulomas and less fibrosis in newly deposited eggs after 12 weeks of infection” [34].

“Initial reports on schistosome molecular mimicry in host species was presented in 1965, when it
was discovered that *B. glabrata* had antigens that were similar to those identified in maturing *S. mansoni* larvae" [35]. Polyclonal antibodies to hemolymph from *S. mansoni* resistant (10-R2) and susceptible (M-line) *B. glabrata* strains later proved this, with both interacting extensively with the surface of *S. mansoni* miracidia and sporocysts" [32]. "This relationship lasted for at least 48 hours after the larvae were changed from miracidia to sporocyst, implying that the working to develop larvae share at least certain surface antigens during the first 48 hours of infection, when they are most likely to be targeted by the snail immune response; cross-reactive immunoglobulin tests also suggest some form of molecular mimicry, but such studies lack the specificity required to examine shared antigens" [36].

Glycan mimicry is thought to be aided by larval transformation proteins (LTPs) generated by the Schistosoma parasite during miracidium-to-sporocyst transformation, however, host hemolymph proteins and systemic hemocytes can react with LTPs because far-western blotting revealed a distinct binding pattern between LTPs and hemolymph proteins isolated from *B. glabrata* strains with varied compatibility with *S. mansoni*. This shows that *S. mansoni* uses various glycan epitopes antigens during larval metamorphosis [37].

When Cercaria intends to penetrate an individual’s skin, the process of penetration may be aided by both mechanical movement and antigen that breaks down cell-to-cell adhesions [38]. The head gland, sub-regimental cell bodies, and acetabular glands are all potential sources of antigen [39]. While each of these sources may play a role in parasite penetration, the acetabular glands, which contain lengthy duct-like cytoplasmic extensions extending to the parasite anterior and are filled with proteases, are the most plausible suspect. Acetabular gland secretions are produced during migration through the skin’s collagen-rich basement membrane and have been confirmed to secrete for up to three days after infection [16].

Proteolytic factors responsible for skin penetration have been discovered to use a wide range of serine protease antigens to degrade host structural components [40]. During penetration, *S. mansoni* creates many serine proteases, which are discharged from its acetabular glands [41].

3. *SCHISTOSOMA ANTIGENS AND THEIR FUNCTIONS*

Antigens from schistosomes are thought to play a role in the pathological physiology of schistosomiasis. Numerous schistosomes antigens have been studied, with the majority of them derived from *S. mansoni, S. haematobium*, and *S. japonicum*; categorization of schistosome antigens recognized by monoclonal antibodies (MoAbs) could improve schistosomiasis influence for two main reasons [42]. Initially, those very antigens may contain specific markers that serve as targets for immune attack, making them possible future candidates for vaccine development; second, where the antigen has the diagnostic possibility, it can be investigated to improve diagnosis and provide useful information on schistosome evolution and classification [43].

When *S. mansoni* enters the snail, it releases venom allergen like protein 9 named SmVAL9, which causes the up-regulation of *B. glabrata* matrix metalloprotease: this is an important metalloprotease in remodeling tissue, and it is maybe hypothesized that this facilitates parasite entry and penetration into host tissue [44]. A study of excretory/secretory (E/S) product synthesis by sporocysts in vitro identified two more immune modulators. The first is a polypeptide of around 24 kDa that was found to be capable of inhibiting protein synthesis by snail hemocytes in vulnerable M-line snails, but not in the more resistant 10-R2 strain [45]. The existence of a Sperm-coating protein/TPx-1/Ag5/PR-1/Sc7 (SCP/TAPS) domain in the *S. mansoni* genome was demonstrated to feature 29 of these proteins, which are characterized by the presence of a venom allergen-like protein family [46].

Using mass spectrometry, the SmVALS 4, SmVAL 10, and SmVAL 18 were discovered in the E/S components of cercaria, accounting for around 3% of the normalized proteins detected there [47]. SmVAL24 has been found in the acetabular glands using whole-mount in situ hybridization, although only two of the SmVAL proteins have been functionally described to date [48]. SmVAL4 has the ability to bind lipids and cholesterol, albeit it has yet to be determined how this can affect the host immune response [49].

SmVAL18, on the other hand, has been demonstrated to bind plasminogen and aid in its breakdown into plasmin, a protein involved in
complements element degradation, extracellular protein denaturation, and fibrinolysis. As a result, SmVAL18 could potentially aid parasite migration through the epidermis and prevent blood clotting after venule penetration [50]. Only one VAL, SjVAL-1, has been studied in S. japonicum, and it has been found to localize to cercariae penetration and head glands, suggesting a probable role in migration into host venules (Chen et al., 2018).

108 kDa is protein that was demonstrated to be able to scavenge superoxide anions produced by phagocytosis-stimulated M-line of B. glabrata hemocytes, thus shielding the parasite from this harmful oxygen species [51].

S. mansoni up-regulated an invadopysin 33.2-fold in B. glabrata hemocytes 12 hours post infection, and this invadopysin, identified as SmLeish, was revealed to be capable of reducing the velocity of susceptible M-line B. glabrata hemocytes. This function is important for reducing the frequency with which sporocysts are encapsulated by hemocytes in vitro, and it was also discovered to be important for B. glabrata survival [52]. S. mansoni’s mimicry goes beyond surface epitopes, since sporocysts can create host-like adrenocorticotropic hormone, which is converted by host hemocytes into melanocysteitimating hormone, causing hemocytes to circle up towards the sporocyst [53].

Polymorphic mucins (SmPoMucs) of S. mansoni are also group of antigens that were discovered as part of a proteomics screen to find preferentially abundant proteins produced by B. glabrata-compatible and incompatible strains of S. mansoni, and have since become one of the most intensively studied constituents of resistance polymorphism in the S. mansoni system; these antigens have variability that should be considered as a key mechanism [54].

A 28/30 kDa protease capable of cleaving casein, gelatin, C3, C3b laminin, fibronectin, keratin, and collagens IV and VIII; a 47 kDa protease capable of cleaving gelatin, casein, collagen type VI, and elastin; and a 60 kDa protease capable of cleaving casein and gelatin are among these proteases [55].

SmCE (Schistosoma mansoni Cercarial Elastase) which is also called 28/30 kDa variant antigen, is the most important, accounting for around 36% of the total volume of acetalubar gland contents [56]. The presence of SmCE throughout the intra-mammalian section of the S. mansoni life cycle emphasizes its relevance. Cercariae, lung stage schistosomulae, and adult worms all have a membrane-bound version of the protein [57]. Although S. haematobium has a protease similar to SmCE antigen that fulfills the same role as S. mansoni, it was long assumed that S. japonicum did not produce any serine protease during first penetration events because SmCE antibodies did not react with S. japonicum cercarial extracts [58].

Proteomic analysis of the host/parasite molecular interface during S. japonicum penetration into mouse skin revealed a single S. japonicum cercarial elastase (SjCE2b) produced in cercaria and localized to the acetalubar glands, though levels of this protein are low compared to those found in S. mansoni and S. haematobium [59].

Sm16/SmSLP/SmSPO-1 antigens is an anti-inflammatory protein discovered in S. mansoni, it makes up around 3–4% of the protein released by cercariae within the first 3 hours after infection, implying a role in parasite survival [57]. Sm16.8 kDa was shown to change cytokine profiles by inhibiting IL-1a production in keratinocytes, lowering ICAM-1 expression in endothelial cells, preventing LPS-induced neutrophil migration into the dermis, and decreasing LPS-mediated IL-6, TNF-a, and IL-1b production [60]. It reduces the ability of mouse bone marrow derived macrophages to produce IL-12p40, IL-10, and IFN-ginduced NO 2, as well as decreasing antigen processing by phagocytic cells in mice [61].

Sj16 is the Sm16.8 kDa counterpart found in S. japonicum that has also been shown to have immunomodulatory properties, including a reduction in macrophage maturation and modulation of cytokine production in thioglycollate-induced peritoneal mouse cells by upregulating IL-10 and IL-1RA while downregulating MIP-2, IL-1b, and IL-12p35 [62]. Sj16.8 kDa has the ability to increase the number of CD4+ CD25+ Foxp3+ regulatory T cells, implying that it can not only suppress inflammatory responses but also help to generate a regulatory response [63].

It was discovered that Schistosome E/S fractions containing a 23 kDa antigen have been shown to specifically target T lymphocytes for apoptosis, a process thought to be mediated by causing an up-regulation of both the Fas Ligand and Fas receptor on CD3+ cells [64]. The inability of
vaccinated mouse lymphocytes to recognize the E/S products of invading parasites may be partly due to the loss of T lymphocytes during early penetration, as a functional T cell driven response would be significantly impeded [65].

*S. mansoni* can produce prostaglandin E2 (PGE2), as well as an E/S product of less than 30 kDa in size that can up-regulate the production of PGE2 and IL-10 from human keratinocytes; this appears to be important for infection kinetics, as IL-10 deficient mice are able to slow schistosomula travel through the skin and into the lungs [66]. The 23 kDa and 30 kDa immunomodulatory antigens were discovered through filtration of schistosome E/S products, although their specific molecular identities have yet to be determined. Yet, the usage of prostaglandins is not restricted to PGE2, as PGD2 produced by the parasite prevents epidermal Langerhan cells from migrating to neighboring lymph nodes. Given that the generation of PGD2 by *S. mansoni* requires a 28 kDa Glutathione S-transferase, the possibility of using such a factor as a vaccine candidate was investigated in the early 1990s. Sadly, recent phase 3 clinical trials of the *S. haematobium*-derived rSh28GST (Bilhavax) vaccine have shown that it is ineffectual in providing considerable immunity [67].

SmKK7, a protein with considerable resemblance to K+ channel blockers in scorpion venom, is another possible immunomodulator that has yet to be functionally defined. This might potentially work in limiting the activation of surrounding lymphocytes [48]. While mechanical movement throughout the epidermis aids in the loss of the glycocalyx, the close interaction of SmCE has been indicated as a possible assistance during this process [64]. While the glycocalyx is shed, schistosomulae go through a complex remodeling of their outer membrane, transitioning from a trilaminate to a heptalaminate form that lasts until adulthood [68]. This freshly created heptalaminate membrane then begins to exhibit a number of surface-bound components aimed at preventing complement and immunoglobulin-based attacks. Paramyosin, a chemical found in both schistosomula and adult worms, is one of these molecules. On schistosomulae exposed to human serum, paramyosin has been demonstrated to bind complement components C1, C8, and C9, preventing the membrane assault complex from polymerizing and depositing [69].

Two antigens found in *S. mansoni* namely, SmEnolase and SmCalp1, are thought to aid in tissue disintegration at least in part. Their presence in the eggs is thought to aid in fibrinolysis [70]. Furthermore, the egg is thought to aid its own survival by producing SmKI-1 as a means of surviving neutrophil elastase-mediated death, as well as a chemokine binding protein (SmCKBP) that reduces inflammation and inflammatory cell recruitment via the binding of CXCL8 and CCL3; these immune modulating and immune evading tactics allow the egg to migrate through the host intestine/bladder, eventually being excreted in order to begin the [71].

Cathepsin B is one of the schistosomes’ portentous antigens that relates to the cysteine proteases, a group of lysosomal cysteine proteases that has been discovered to play a significant role during intracellular proteolysis [72]. A heavy chain ranging from 25 to 26 kDa and a light chain of 5 kDa are found in mature cathepsin B, and these chains are linked by disulfide dimers [73].

Cathepsin B is involved in the control of IL-12 production as well as the expression of antigen-presenting MHC class II molecules [74]. It also boosts the activity of other proteases such matrix metalloproteinase, urokinase (serine protease urokinase plasminogen activator), and cathepsin D, therefore it’s crucial for extracellular matrix proteolysis, intercellular communication disruption, and reduced protease inhibitor expression [75]. It is also engaged in autophagy and catabolism, both of which are beneficial in tumor malignancy. It was recently discovered to have minimal ligase activity, allowing it to bind peptide fragments via an amide bond, and it may be implicated in particular immunological resistance [76].

*S. mansoni* cathepsin B1 (SmCB1), one of substantial worm extract peptides and also Excretion Secretion Proteins (ESPs), has been recognized as a critical anti-schistosome vaccine candidate with the ability to initiate Th17 responses in addition to Th1 and Th2 responses in various studies conducted on Schistosomes [77, 78]. Major hemoglobin-digesting enzymes found in *S. haematobium* include SmCB1 and *S. mansoni* cathepsin L1 (SmCL1, CL) [79] (Wendt et al., 2020). SmCB1 is mainly expressed in cercariae’s caecum and protonephridia, whereas SmCL1 is found in the gastrodermis and
tegument of mature worms [80]. SmCB1 and SmCL1 are both important ESPs [81].

Recent research has found that vinyl sulfone inhibitors enzymes of the SmCB1 target may have the ability to affect parasite growth, as well as that interfering RNA of SmCB1 inhibited parasite development both in culture and in an animal study of transmission [79,82].

In CD-1 mice and Syrian hamsters, adjuvant-free, enzyme active SmCB1 or FhCL1 in recombinant version alone or in combination with another vaccine candidate SG3PDH/PRX-MAP were seen to stimulate greater protection with an increase in IgG1 isotype titers (no IgE was detected) and Th2 cytokines against S. mansoni and S. haematobium infection [79,80]. Immunization of CD-1 mice and Syrian hamsters with active rSmCB1 and SmCL3 alone or in combination with rSG3PDH resulted in significant protection against S. mansoni and S. haematobium challenge infection, indicating that the efficacious trivalent vaccine should now be tested in nonhuman primates for evaluation as a potential vaccine to control human schistosomiasis [79].

Despite producing less protein upon change to schistosomulae than S. mansoni, cathepsins have emerged as an alternate facilitator of penetration in S. japonicum cercaria, which have up to 40-fold higher cathepsin-B-like activity than their S. mansoni counterparts [58,59].

Cathepsins are still produced by S. mansoni, and two of them (Cathepsin L1 and Cathepsin B) are found in the parasite’s post-acetabular glands. Given the significance of post-acetabular glands in creating mucous-like secretions to aid adhesion to host skin, these cysteine proteases could play a role in breaking down the skin’s immunological barrier. Alternatively, the fact that cathepsin activity is involved in the adult schistosome gut suggests that the presence of cathepsins in cercariae could simply be evidence of the development of digestion-related elements in later life cycle stages [83].

Sm23, SG3PDH, calpain, Sm-TSP-2, saponin B domain-containing proteins, GST, Sm29, cathepsin domain-containing proteins namely cathepsin B and cathepsin L, proteases, and oxidants were previously announced to also be developed in worm generated 15 k (286 proteins) and 120 k (716 proteins) membrane proteins (EVs) [81,84,85].

Distinctive ESPs antigens were obtained from cercariae, lung-stage schistosomula, and adult worms from several schistosome species [86]; Tetraspanin, Sm/Sh22.6, Sm29, Sm200, and phosphadiesterase are Cathepsin B antigen family that are extensively expressed throughout the schistosomula phase (Gobert et al., 2010). Furthermore, research that used the RNAi approach to silence genes revealed the relevance of these certain proteins for parasite proliferation and survival [87]. Using mass spectrometry (MS)-based proteomics and information from the genome, transcriptome, and genetic maps, similar membrane protein was found in adult worm tegument preparations [88].

Previously, a proteomic findings show that Sm29 and Sm200 are linked to the parasite cell surfaces via a GPI-anchor, while aquaporin, dysferlin, TSP-2, and ATP diphosphohydrolase are the most abundant proteins in adult worm tegument, among some of the investigated molecules. All of these proteins express a catalog of protein expressed in the schistosome tegument, and some of them have been evaluated as vaccine antigen in Castro-Borges et al., [89].

Sm22.6 is a tegumental protein that has a counterpart in S. japonicum (Sj22.6) and in endemic situations, S. haematobium (Sh22.6) is involved in re-infection resistance (Dunne et al., 2017; Santiago et al., 2018) with Freund adjuvant had a 34.5 percent reduction in worm burden, whereas Sm22.6 formulated with alum did not induce protection against schistosomiasis but did induce a regulatory response that modulated allergic asthma in mice [90].

In both Ghanaian and Egyptian parasite strains, a 29 kDa S. haematobium species-specific antigen (ShSSA) was discovered. Despite the efficacy of a monoclonal antibody (MAb) to ShSSA in a field dipstick for the diagnosis of urinary schistosomiasis, SHSSA has not been completely described [91].

S. haematobium 28-kD GST (rSh28GST); S. mansoni 14-kDa (Sm14); S. mansoni tetranspin; 9-kDa surface antigen; Sm-TSP-2; and S. mansoni calpain (Sm-p80) are among the recombinant antigens (Aya et al. 2021). Many of the above-mentioned antigen candidates, such as TSP-2, Sm23, GST, Sm29, and calpain, have recently been discovered in extracellular vehicles (EVs) of schistosome adult worms [81]; extracellular vesicles are membrane-enclosed
vesicles that are constantly secreted by different types of cells and play an important role in removing unnecessary cell components [92].

The 28 kDa glutathione S-transferase of *S. haematobium* vaccine, commonly known as the 28 kDa glutathione S-transferase (Sh28GST) vaccine, is a major ESP expressed in the tegument and sub-tegument of adult and larval schistosomes [80]. It plays a key function in fatty acid metabolism and prostaglandin D2 synthesis, and it may help parasites evade the immune system [93].

In chimpanzees and patas monkeys, recombinant *S. haematobium* glutathione S-transferase (rShGST) vaccine mediated high levels of protection associated with intense specific IgG and IgA antibody responses; phase 1 trial was done to examine the safety and tolerability of two or three intramuscular injection of 100 lg rSh28GST antigen with Alum as adjuvant in young, healthy, Caucasian male [67]. The vaccine’s safety, tolerability, and immunogenicity were also demonstrated in adults and children living in endemic areas [94].

The only antigen for Bilharziasis that has reached Phase 3 clinical trials is rShGST; in Phase 3, 250 Senegalese children aged 6–9 years old were cured of schistosome infection and randomized to receive three subcutaneous injections of either rSh28GST/Alhydrogel (Bilhva group) or Alhydrogel alone (control group) at four-week intervals, followed by a booster one year after the first injection. In addition, students who receive the rSh28GST vaccine had higher levels of essential IgG1, IgG2, and IgG4 antibodies, but no IgG3 or IgA isotypes. Acquired immunity to Sh28GST is associated to IgG3 and IgA antibodies in human groups. The failure to achieve protection against urinary schistosomiasis could be due to an issue with antibody isotypes or the distorting effect of PZQ treatment prior to the first and last immunizations [47,95].

The vaccination against *S. haematobium* 28 kDa glutathione S-transferase (Sh28GST) is exhibited in the tegument and sub-tegument of adult and larval schistosomes, and is the most common Excretion Secretion Proteins [80]. It plays a key function in fatty acid metabolism and prostaglandin D2 synthesis, and it may help parasites evade the immune system [93]. Some many studies in rodents, primates, and cattle using the recombinant protein (expressed in Saccharomyces cerevisiae) revealed a partial protective effect against schistosome infection, a significant reduction in worm burden (40–60 percent), and a substantial decrease in female worm reproductive capacity and eggs viability [96].

In rats and baboons, the Sm-p80 ortholog expressed in the tegument of *S. japonicum* and *S. haematobium* adult worms offered considerable cross-species resistance against *S. mansoni*, *S. japonicum*, and *S. haematobium* illnesses [97]. Recombinant Sm23 and other TSPs extracted from adult *S. haematobium* worms were shown to induce significant protection against challenge infection with *S. mansoni*, as measured by reductions in liver (47 percent, 38 percent, and 41 percent) and intestinal (47 percent, 45 percent, and 41 percent) egg burdens. These findings suggest that EV surface proteins could be exploited to develop anti-schistosome vaccines (Mekonnen, 2020)

The SG3PDH antigen is one of the most promising vaccine candidates for schistosomiasis, and it helps to prevent re-infection [98]. However, because of its high homology (72.5%) with human G3PDH, the whole parasite proteins cannot be used as a vaccine for fear of inducing autoimmune responses. As a result, it is preferable to choose SG3PDH derived-peptides with the least resemblance to human peptides, and the peptides were chosen for the development of a safe synthetic peptide-based vaccination; These peptides were studied in serum and lymphocytes from humans resistant to re-infection with *S. mansoni* or *S. haematobium* after treatment with PZQ for previous infection, as well as BALB/c and C57BL/6 mice immunized with recombinant rSG3PDH (rSG3PDH); the findings revealed that SG3PDH-derived peptides contain human and murine T- and B-cell determinants, and immune responses to EL Ridi et al., [80].

The 29 kDa protein is a glycosylphosphatidylinositol (GPI) integral protein found in the tegument of mammalian adults and lung-stage schistosomula, but not in cercariae, suggesting that this antigen aids the parasite in adjusting to its new environment in mammalian hosts [99]. Sm29 may potentially assist the schistosome evade immunological responses by interacting with the human protein CD59, which suppresses the Membrane Attack Complex
### Table 1. Summary of some schistosomes' antigens, Species that produced them, Importance and References

| S/N | Antigen(S) | Species that Possess the Antigens | Function of the Antigens | Reference(s) |
|-----|------------|----------------------------------|--------------------------|--------------|
| 1.  | Venom Allergen-like (VAL) antigen family | *S. mansoni*  
* S. japonicum | They promote the parasites access and entry into host tissue; they possess the capacity to combine lipids and cholesterol; they have ability to prevents blood clotting following penetration. | Fernandes et al., [48]; Yoshino et al., [44]; Fernandes et al., 2019 |
| 2.  | Sm-24 kDa | *S. mansoni* | Blocking snail hemocytes' ability to make protein | Connors et al., [45] |
| 3.  | Sm108 kDa | *S. mansoni* | The antigen has the capacity to scavenge superoxide anions produced by *B. glabrata* hemocytes' M-line driven phagocytosis; it protect the parasite from these damaging oxygen. | Dinguirard et al., [51] |
| 4.  | Polymorphic mucins (SmPoMucs) | *S. mansoni* | It provide with resistance polymorphism components in the *S. mansoni* system | Roger et al., [54] |
| 5.  | 28/30 kDa Protease | *S. mansoni* | Ability to break casein, gelatin, collagens IV and VIII, C3 and C3b, fibronectin, and laminin | McKerrow and Salter, [55] |
| 6.  | 47 kDa protease | *S. mansoni* | Gelatin, casein, collagen type VI, and elastin all can be broken down by it. | McKerrow and Salter, [55] |
| 7.  | 60 kDa protease | *S. mansoni* | These proteases include those that can cleave casein and gelatin. | McKerrow and Salter, [55] |
| 8.  | Cercarial Elastase (CE) also called 28/30 kDa | *S. mansoni*  
* S. haematobium*  
* S. japonicum* | roughly 36% of acetabular proteins are elastase antigens | Roger et al., [54] |
| 9.  | Cathepsin | *S. mansoni*  
* S. haematobium*  
* S. japonicum* | Enhancing cercarial adherence to the host skin; Weakening the skin's immune system; growth of digestive components in later life cycle stages; drug-resistant in parasites; They were tested as potential vaccination candidates. | Liu et al., [59]; Dalton et al., [83]; Dvorá et al., [58] |
| 10. | 22.6 kDa | *S. mansoni*  
* S. haematobium*  
* S. japonicum* | Re-infection resistance; Vaccine candidates | Dunne et al., 2017; Santiago et al., 2018; Pacífico et al., 2016 |
| 11. | 23 kDa | *S. mansoni*  
* S. haematobium*  
* S. japonicum* | Selectively induce apoptosis in T lymphocytes | Kumar and Ramaswamy, [65] |
| 12. | 16 kDa/SLP/SPO-1 | *S. japonicum*  
* S. mansoni* | It influences cytokine profiles and decreases the capacity of mouse bone marrow-derived macrophages to generate IL-12p40, IL-10, and IFN-ginduced NO2; It also has a function in enhancing parasite survival. | un et al., 2012; Curwen et al., [56]; Crosnier et al., [61] Sailer et al., [60]; Hu et al., [62] |
| 13. | Prostaglandin E2 (PGE2) | *S. haematobium*  
* S. mansoni*  
* S. japonicum* | It stops the migration of epidermal Langerhan cells to nearby lymph nodes. | Hervé et al., 2013; Riveau et al., [47] |
| 14. | SmEnolase and SmCalp1 | *S. mansoni* | Aid in tissue deterioration; it is believed that their presence in eggs facilitates fibrinolysis | Figueiredo et al., [70] |
| 15. | 28-kD GST (rSh28GST); | *S. haematobium* | Removal of superfluous cell components; Use as a source for vaccines, and potential aid to parasites in evading the immune | Teboje et al., [93]; Pluchino and Smith [92]; Aya et al. 2021; |
(MAC) and hence aids the parasite in evading immune responses [100].

Sm29 kDa was prepared with alum or monophosphoryl lipid adjuvant (MPLA) and given to BALB/c mice re-infected with *S. mansoni* in another investigation. Sm29-alum produced protective effects against superinfection and decreased worm load by 29–37%, whereas Sm29-MPLA did not, demonstrating that Sm29-alum can successfully prevent mice from *S. mansoni* re-infection [101].

In Swiss albino mice, the mixture of Sm29 and Sm14, identified as Sm14/29 alone or in conjunction with polyinosinic-poly cytidylic acid adjuvant, resulted in significant reductions of adult worm burden by 48.4 percent and 44.7 percent, liver egg burden by 82.8 percent and 73.5, and intestinal egg count by 72.8 percent and 76.6 percent, respectively; similarly, Sm29 [102-106]. The above mention antigens and their functions as well as the spp that produce them were summarized in Table 1.

### Table 1

| S/N | Antigen(S) | Species that Posses the Antigens | Function of the Antigens | Reference(s) |
|-----|------------|---------------------------------|--------------------------|---------------|
| 16  | 29-kDa     | *S. mansoni*                    | It is believed to be an immunoregulatory molecule that regulates inflammatory mucosal illnesses; Plays a significant role in the removal of extracellular components; Aids parasite adaptation to mammalian hosts. | Sotillo et al., [99]; Bear et al., [100]; Oliveira et al., 2016. |
| 17  | Calpain (Sp80) | *S. mansoni* | Act as a source of vaccination and play a significant function in eliminating extraneous cell components. | Molehin et al., [97]; Mekonnen et al., 2020 |
| 18  | SG3PDH | *S. mansoni* | One of the most promising schistosomiasis vaccine options, and it aids in preventing re-infection | McManus and Loukas [98]; EL Ridi et al., [80]; |

### 4. CONCLUSION AND RECOMMENDATIONS

During the course of interaction between schistosomes and their hosts (definitive and intermediate hosts), the parasites produce many antigens which enable them to reproduce and survive within the hosts environment, the antigens performing particular importance in both the parasites and the hosts, some of the identified importance include: resistant, tissue damage, serve as a vaccine candidate, escape to the immune responses, mimicry, and many others. Therefore, we recommended that, many more antigens produced by parasite should be investigated because of their function in planning and creating many ways that help in prevention and control of schistosomiasis since some were observed to be good candidates for recovery of vaccine against Schistosoma infections.

### COMPETING INTERESTS

Authors have declared that no competing interests exist.

### REFERENCES

1. King CH. Toward the elimination of schistosomiasis. England Journal of Medicinal research. 2009;360(2):106-9. DOI: 10.1056/NEJMp0808041, PMID 19129524.
2. Colley DG, Secor WE. Immunology of human schistosomiasis. Parasite Immunol. 2014;36(8):347-57. DOI: 10.1111/pim.12087.
3. Greenberg RM. New approaches for understanding mechanisms of drug resistance in schistosomes. Parasitology. 2013;140(12):1534-46. DOI:10.1017/S0031182013000231, PMID 23552512.
4. Kasinathan RS, Morgan WM, Greenberg RM. Genetic knockdown and pharmacological inhibition of parasite multidrug resistance transporters disrupts egg production in Schistosoma
mansoni. PLOS Negl Trop Dis. 2011;5(12):1425.
DOI: 10.1371/journal.pntd.0001425.

5. Hotez PJ, Kamath A. Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden. PLOS Negl Trop Dis. 2009;3(8): e412.
DOI: 10.1371/journal.pntd.0000412, PMID 19707588.

6. Müller JT, Coulibaly T, Fürst I. Effect of schistosomiasis and soil-transmitted helminth infections on physical fitness of school children in Côte d’Ivoire. PLOS Negl Tropical Dis. 2011;5:12-39.

7. Butterworth P, Demeure CE, Bourgois A, Prata A, Dessein AJ. Evidence for an association between human resistance to Schistosoma mansoni and high anti-larval IgE levels. European J Immunol. 2016;21:2679-86.

8. Smithers DW, Gammage TJ. The isolation of a 22 kDa band after SDS-PAGE of Schistosoma mansoni adult worms and its use to demonstrate that IgE responses against the antigen(s) it contains are associated with human resistance to reinfection. Parasite Immunol. 2010;19:79-89.

9. Terry KC. Genetic diversity of a population of Schistosoma haematobium derived from schoolchildren in east central Zimbabwe. J Parasitol. 2014;87(4):762-9.

10. Hamburger J, Lustigman S, Siangok TK, Ouma JH, Mahmoud AA. Characterization of a purified glycoprotein from Schistosoma mansoni eggs: specificity, stability, and the involvement of carbohydrate and peptide moieties in its serologic activity. J Immunol. 1982;128(4):1864-9. PMID 6174618.

11. Delves PJ, Martin SJ, Burton DR, Roitt IM. Roitt's essential immunology. 13th ed. John Wiley & Sons, Ltd.; 2017.58. 201-17.

12. Kotsias F, Cebrian I, Alioatti A. Antigen processing and presentation. Int Rev Cell Mol Biol. 2019;348:69-121.
DOI: 10.1016/bs ircmb.2019.07.005, PMID 31810556.

13. Kapingidza AB, Kowal K, Chruszcz M. Antigen-antibody complexes. Subcell Biochem. 2020;94:465-97.
DOI: 10.1007/978-3-030-41769-7_19, PMID 32189312.

14. Laura S, Berendam Stella J, Engelhard Victor H. The antigen processing and presentation machinery in lymphatic endothelial cells. Front Immunol. 2019;10(17):225-7.

15. Saylor K, Gillam F, Lohnes T, Zhang C. Designs of antigen structure and composition for improved protein-based vaccine efficacy. Front Immunol. 2020;10(6):279-83.

16. Hambrook JR, Hanington PC. Immune evasion strategies of schistosomes. Front Immunol. 2020;11:624178. DOI: 10.3389/fimmu.2020.624178, PMID 33613562.

17. Liu F, Lu J, Hu W. New perspectives on host-parasite interplay by comparative transcriptomic and proteomic analyses of Schistosoma japonicum. PLOS Pathol. 2016;2:29-36.

18. Hokke CH, Fitzpatrick JM, Hoffmann KF. Integrating transcriptome, proteome and glycome analyses of Schistosoma biology. Trends Parasitol. 2007;23(4):165-74.
DOI: 10.1016/j.pt.2007.02.007, PMID 17336161.

19. Chiotsulo L, LoVerde P, Engels D. Schistosomiasis. National review in. Microbiology. 2014;2:12-3.

20. Wilkins HA, Goll PH, Marshall TF, Moore PJ. Dynamics of Schistosoma haematobium infection in a Gambian community. III. Acquisition and loss of infection. Transm Res Soc Trop Med Hyg. 2014;78:227-32.

21. Knopp S, Amé SM, Person B, Hattendorf J, Rabone M, Juma S et al. A 5-year intervention study on elimination of urogenital schistosomiasis in Zanzibar: parasitological results of annual cross-sectional surveys. PLOS Negl Trop Dis. 2019;13(5):e0007268.
DOI: 10.1371/journal.pntd.0007268, PMID 31059495.

22. Pennington LF, Alouffi A, Mbanefo EC, Ray D, Heery DM, Jardetzky TS et al. H-IPSE is a pathogen-secreted host nucleus-infiltrating protein (Infiltrin) expressed exclusively by the Schistosoma haematobium egg stage. Infect Immun. 2017;85(12):e00301-317.
DOI: 10.1128/IAI.00301-17, PMID 28923894.

23. Pearson MS, Pickering DA, McSorley HJ. Enhanced protective efficacy of a chimeric form of the schistosomiasis
vaccine antigen Sm-TSP-2. PLOS Negl Trop Dis. 2018;6:55-64.

24. Tanigawa C, Fujiy Y, Miura M, Nzou SM, Mwangi AW, Nagi S et al. Species-specific serological detection for schistosomiasis by serine protease inhibitor (SERPIN) in multiplex assay. PLOS Negl Trop Dis. 2015;9(8):e0004021. DOI: 10.1371/journal.pntd.0004021, PMID 26291988.

25. Gaze S, Driguez P, Pearson MS, Mendes T, Doolan DL, Trieu A et al. An immunomics approach to schistosome antigen discovery: antibody signatures of naturally resistant and chronically infected individuals from endemic areas. PLoS Pathog. 2014;10(3):e1004033. DOI: 10.1371/journal.ppat.1004033, PMID 24675823.

26. Chen Q, Zhang J, Zheng T, Chen H, Nie H, Zheng B et al. The role of microRNAs in the pathogenesis, grading and treatment of hepatic fibrosis in schistosomiasis. Parasit Vectors. 2019;12(1):611. DOI: 10.1186/s13071-019-3866-0, PMID 31888743.

27. Cook RM, Carvalho-Queiroz C, Wilding G, LoVerde PT. Nucleic acid vaccination with Schistosoma mansoni antioxidant enzyme cytosolic superoxide dismutase and the structural protein filamin confers protection against the adult worm stage. Infect Immun. 2004;72(10):6112-24. DOI: 10.1128/IAI.72.10.6112-6124.2004, PMID 15385516.

28. Colley DG, Cook JA, Freeman GL, Jr, Bartholomew RK, Jordan P. Immune responses during human schistosomiasis mansoni. I. In vitro lymphocyte blastogenic responses to heterogeneous antigenic preparations from schistosome eggs, worms and cercariae. Int Allergy Appl Immunol. 2017;53:420-33.

29. Dresden MH, Sung CK, Deelder AM. A monoclonal antibody from infected mice to a Schistosoma mansoni egg proteinase. J Immunol. 1983;130(1):1-3. PMID 6336621.

30. Perrin C, Lepesant JMJ, Roger E, Duval D, Fneich S, Thuillier V. Schistosoma mansoni mucin gene (SmPoMuc) expression: epigenetic control to shape adaptation to a new. Host PLOS Pathol. 2018;9(8):135-71.

31. Yoshino TP, Brown M, Wu XJ, Jackson CJ, Ocacidz-Ruiz R, Chalmers IW et al. Excreted/secreted Schistosoma mansoni venom allergen-like 9 (SmVAL9) modulates host extracellular matrix remodelling gene expression. Int J Parasitol. 2014;44(8):551-63. DOI: 10.1016/j.ijpara.2014.04.002, PMID 24859313.

32. Taft AS, Vermeire JJ, Bernier J, Birkeland SR, Cipriano MJ, Papa AR et al. Transcriptome analysis of Schistosoma mansoni larval development using serial analysis of gene expression (SAGE). Parasitology. 2009;136(5):469-85. DOI: 10.1017/S0031182009005733, PMID 19265565.

33. Zahoor Z, Davies AJ, Kirk RS, Rollinson D, Walker AJ. Larval excretory-secretory products from the parasite Schistosoma mansoni modulate HSP70 protein expression in defence cells of its snail host, Biomphalaria glabrata. Cell Stress Chaperones. 2020;15(5):639-50.

34. Capron A, Biguet J, Rose F, Vernes A. The antigens of Schistosoma mansoni. II. Comparative immunoelectrophoretic study on various larval stages and of adults of both sexes. Immunological aspects of the host-parasite relationships of S. mansoni cercaria and adults. Ann Inst Pasteur. 2015;109(5):798-810.

35. Yoshino TP, Cheng TC. Snail Host-Like Antigens Associated with the Surface Membranes of Schistosoma mansoni Miracidia. J Parasitol. 2018;64(4):752-4.

36. Lehr T, Frank S, Natsuka S, Geyer H, Beuerlein K, Doenhoff MJ. NGlycosylation patterns of hemolymph glycoproteins from Biomphalaria glabrata strains expressing different susceptibility to Schistosoma mansoni infection. Exp Parasitol. 2018;126(4):592-602.

37. Mitchell KM, Mutapi F, Savill NJ, Woolhouse MEJ. Protective immunity to Schistosoma haematobium infection is primarily an anti-fecundity response stimulated by the death of adult worms. Proc Natl Acad Sci U S A. 2012;109(33):13347-52.
39. Yousef H, Sharma S. Anatomy, skin ( integument), epidermis. State pearls: state pearls publishing. 2018;177:225-7.

40. Ittiprasert W, Mann VH, Karinshak SE, Coghlan A, Rinaldi G, Sankaranarayanan G. Programmed genome editing of the omega-1 ribonuclease of the blood fluke, Schistosoma mansoni. E-life. 2019;8:e41337.

41. Castro-Borges W, Dowle A, Curwen RS, Thomas-Oates J, Wilson RA. Enzymatic shaving of the tegument surface of live schistosomes for proteomic analysis: A rational approach to select vaccine candidates. PLOS Negl Trop Dis. 2011;5(3):e993. DOI: 10.1371/journal.pntd.0000993, PMID 21468311.

42. Berhe N, Medhin G, Erko B, Smith T, Gedamu S, Bereded D et al. Variations in helminth faecal egg counts in Kato-Katz thick smears and their implications in assessing infection status with Schistosoma mansoni. Acta Trop. 2004;92(3):205-12. DOI: 10.1016/j.actatropica.2004.06.011, PMID 15533288.

43. Yoshino TP, Brown M, Wu XJ, Jackson CJ, Ocadiz-Ruiz R, Chalmers IW et al. Excreted/secreted Schistosoma mansoni venom allergen-like 9 (SmVAL9) modulates host extracellular matrix remodelling gene expression. Int J Parasitol. 2014;44(8):551-63. DOI: 10.1016/j.ijpara.2014.04.002, PMID 24859313.

44. Connors VA, Lodes MJ, Yoshino TP. Identification of a Schistosoma mansoni sporocyst excretory-secretory antioxidant molecule and its effect on superoxide production by Biomphalaria glabrata hemocytes. J Invertebr Pathol. 1991;58(3):387-95. DOI: 10.1016/0022-1201(91)90185-s, PMID 1664845.

46. Berriman M, Haas BJ, Loverde PT, Wilson RA, Dillon GP, Cerqueira GC et al. The genome of the blood fluke Schistosoma mansoni. Nature. 2009;460(7253):352-8. DOI: 10.1038/nature08160, PMID 19606141.

50. Fernandes RS, Barbosa TC, Barbosa MMF, Miyasato PA, Nakano E, Leite LCC et al. Stage and tissue expression patterns of Schistosoma mansoni venom allergen-like proteins SmVAL 4, 13, 16 and 24. Parasit Vectors. 2017;10(1):223. DOI: 10.1186/s13071-017-2144-2, PMID 28482920.

51. Dinguirard N, Cavalcanti MGS, Wu XJ, Bickham-Wright U, Sabat G, Yoshino TP. Proteomic analysis of Biomphalaria glabrata hemocytes during in vitro encapsulation of Schistosoma mansoni sporocysts. Front Immunol. 2018;9:2773. DOI: 10.3389/fimmu.2018.02773, PMID 30554666.

52. Hambrook JR, Kaboré AL, Pila EA, Hanington PC. A metalloprotease produced by larval Schistosoma mansoni facilitates infection establishment and maintenance in the snail host by interfering with immune cell function.
53. Lodes MJ, Yoshino TP. J Invertebr Pathol. The Effect of Schistosome Excretory-Secretory Products on Biomphalaria glabrata Hemocyte Motility. 2019;56(1):75-85.

54. Roger E, Gourbal B, Grunau C, Pierce RJ, Galinier R, Mitta G. Expression analysis of highly polymorphic mucin proteins (Sm PoMuc) from the parasite Schistosoma mansoni. Mol Biochem Parasitol. 2008;157(2):217-27. DOI: 10.1016/j.molbiopara.2007.11.015, PMID 18187213.

55. McKerrow JH, Salter J. Invasion of skin by Schistosoma cercariae. Trends Parasitol. 2002;18(5):193-5. DOI: 10.1016/s1471-4922(02)02309-7, PMID 11983589.

56. Curwen RS, Ashton PD, Sundaralingam S, Wilson RA. Identification of novel proteases and immunomodulators in the secretions of schistosome cercariae that facilitate Host Entry. Mol Cell Proteomics. 2006;5(5):835-44. DOI: 10.1074/mcp.M500313-MCP200.

57. Ghendler Y, Parizade M, Arnon R, McKerrow JH, Fishelson Z. Schistosoma mansoni: evidence for a 28-kDa membrane-anchored protease on schistosomula. Exp Parasitol. 1996;83(1):73-82. DOI: 10.1006/expr.1996.0051, PMID 8654554.

58. Mashiyama ST, Braschi S, Sajid M, Knudsen GM, Hansell E, Dvorák J, J. J, Biochem. 2019. Differential use of protease families for invasion by schistosome cercariae:90(2):345-58.

59. Liu M, Ju C, Du XF, Shen HM, Wang JP, Li J et al. Proteomic analysis on cercariae and schistosomula in reference to potential proteases involved in host invasion of Schistosoma japonicum larvae. J Proteome Res. 2015;14(11):4623-34. DOI: 10.1021/acs.jproteome.5b00465, PMID 26370134.

60. Salter JP, Lim KC, Hansell E, Hsieh I, McKerrow JH. Schistosome invasion of human skin and degradation of dermal elastin are mediated by a single serine protease. J Biol Chem. 2000;275(49):38667-73.
development from cercaria to adult worm. Int J Parasitol. 1973;3(1):13-25. DOI: 10.1016/0020-7519(73)90004-0, PMID 4687430.

69. Deng J, Gold D, LoVerde PT, Fishelson Z. Inhibition of the complement membrane attack complex by Schistosoma mansoni Paramyosin. Infection immunology. 2016;71(11):6402-10. DOI: 10.1016/j.infeimm.2016.08.006, PMID 27375570.

70. Figueiredo BC, Da’dara AA, Oliveira SC, Skelly PJ. Schistosomes enhance plasminogen activation: the role of tegumental enolase. PLoS Pathog. 2015;11(12):e1005335. DOI: 10.1371/journal.ppat.1005335, PMID 26658895.

71. Everts B, Hussaarts L, Driessen NN, Meevissen MHJ, Schramm G, van der Ham AJ et al. Schistosome-derived omega-1 drives Th2 polarization by suppressing protein synthesis following internalization by the mannose receptor. J Exp Med. 2012;209(10):1753-67. DOI: 10.1084/jem.20111381, PMID 22966004.

72. Lambeth TR, Dai Z, Zhang Y, Julian RR. A two-trick pony: lysosomal protease cathepsin B possesses surprising ligase activity. Royal Society of chemical Biology. 2021;2(2):606-11. DOI: 10.1038/s43593-021-00063-9, PMID 33830432.

73. Vigneswaran N, Zhao W, Dassanayake A, Muller S, Miller DM, Zacharias W. Variable expression of cathepsin B and D correlates with highly invasive and metastatic phenotype of oral cancer. Hum Pathol. 2018;39(8):931-7. DOI: 10.1016/j.humpath.2018.04.024, PMID 29636030.

74. Alapati K, Kesana K duri, Rao JS, Dasari VR. uPAR and cathepsin B-mediated compartmentalization of JNK regulates the migration of glioma-initiating cells. Stem Cell Res. 2014;13(2):71-26. DOI: 10.1016/j.scr.2014.02.008, PMID 24699410.

75. Mort JS, Burtle DJ, Cathepsin B. Int J Biochem Cell Biol. 1997;29(5):715-20. DOI: 10.1016/s1357-2725(96)00152-5, PMID 9251238.

76. Kirschke H, Barrett AJ, Rawlings ND. Proteinases 1: lysosomal cysteine proteinases [journal]. Protein Profile. 1995;2(14):1581-643. PMID 8771190.

77. Ricciardi A, Dalton JP, Ndao M. Evaluation of the immune response and protective efficacy of Schistosoma mansoni cathepsin B in mice using CpG dinucleotides as adjuvant. Vaccine. 2015;33(2):346-53. DOI: 10.1016/j.vaccine.2014.11.016, PMID 25448114.

78. Soloviya K, Fox EC, Dalton JP, Caffrey CR, Davies SJ. A secreted schistosome cathepsin B1 cysteine protease and acute schistosomiasis induce a transient T helper 17 response. PLOS Negl Trop Dis. 2019;13(1):e0007070. DOI: 10.1371/journal.pntd.0007070, PMID 30653492.

79. Tallima H, Abou El Dahab M, Kareem S, Dalton JP, El Ridi R. Protection against Schistosoma haematobium infection in hamsters by immunization with Schistosoma mansoni-derivered cysteine peptidases, SmCB1 and SmCL3. Vaccine. 2017;35(50):6977-83. DOI: 10.1016/j.vaccine.2017.10.069, PMID 29122387.
84. Sotillo J, Pearson M, Potriquet J, Becker L, Pickering D, Mulvenna J et al. Extracellular vesicles secreted by Schistosoma mansoni contain protein vaccine candidates. Int J Parasitol. 2016;46(1):1-5. DOI: 10.1016/j.ijpara.2015.09.002, PMID 26460238.

85. Samoil V, Dagenais M, Ganapathy V, Aldridge J, Glebov A, Jardim A et al. Vesicle-based secretion in schistosomes: analysis of protein and microRNA (miRNA) content of 650 exosome-like vesicles derived from Schistosoma mansoni. Sci Republications. 2018;8(7):25-7.

86. Young ND, Jex AR, Li B, Liu S, Yang L, Xiong Z et al. Whole genome sequence of Schistosoma haematobium. Nat Genet. 2012;44(2):221-5. DOI: 10.1038/ng.1065, PMID 22246508.

87. Morales ME, Rinaldi G, Gobert GN, Kines KJ, Tort JF, Brandley PJ. RNA interference of Schistosoma mansoni cathepsin D, the apical enzyme of the hemoglobin proteolysis cascade. Mol Biochem Parasitol. 2008;157(2):160-8. DOI: 10.1016/j.molbiopara.2007.10.009, PMID 18067980.

88. Criscione CV, Hirai LL, LoVerde H, Anderson TJC. Genomic linkage map of the human blood fluke Schistosoma mansoni. Genome Biol. 2019;10(6):134-41.

89. Castro-Borges W, Dowle A, Curwen RS, Thomas-Oates J, Wilson RA. Enzymatic shaving of the tegument surface of live schistosomes for proteomic analysis: a rational approach to select vaccine candidates. PLOS Negl Trop Dis. 2011;5(3):e993. DOI: 10.1371/journal.pntd.0000993, PMID 21468311.

90. Pacifico LGG, Fonseca CT, Barsante MM, Cardoso LS, Araujo MI, Oliveira SC. Aluminum hydroxide asso-ciated to Schistosoma mansoni 22.6-kDa protein abrogates partial protection against experimental infection but not alter interleukin-10 production’. Mem Inst Oswaldo Cruz. 2016;101(3):365-8.

91. Markakpo US, Armah GE, Fobil JN, Asmah RH, Anim-Baidoo I, Dodoo AK et al. Immunolocalization of the 29 kDa Schistosoma haematobium species-specific antigen: a potential diagnostic marker for urinary schistosomiasis. BMC Infect Dis. 2015;15:198. DOI: 10.1186/s12879-015-0931-y, PMID 25927905.

92. Pluchino S, Smith JA. Explicating exosomes: reclassifying the rising stars of intercellular communication. Cell. 2019;177(2):225-7. DOI: 10.1016/j.cell.2019.03.020, PMID 30951665.

93. Tebeje BM, Harvie M, You H, Loukas A, McManus DP. Schistosomiasis vaccines: where do we stand? Parasit Vectors. 2016;9(1):528. DOI: 10.1186/s13071-016-1799-4, PMID 27716365.

94. Mo AX, Agosti JM, Watson JL, Hall BF, Gordon L. Schistosomiasis elimination strategies and potential role of a vaccine in achieving global health goals. Am J Trop Med Hyg. 2014;90(1):54-60. DOI: 10.4269/ajtmh.13-0467, PMID 24402703.

95. Alsallaq RA, Gurarie D, Ndeffo Mbah M, Galvani A, King C. Quantitative assessment of the impact of partially protective anti-schistosomiasis vaccines. PLOS Negl Trop Dis. 2017;11(4):e0005544. DOI: 10.1371/journal.pntd.0005544, PMID 28410369.

96. Capron A, Riveau G, Capron M, Trottein F. Schistosomes: the road from host-parasite interactions to vaccines in clinical trials. Trends Parasitol. 2005;21(3):143-9. DOI: 10.1016/j.pt.2005.01.003, PMID 15734662.

97. Le L, Molehin AJ, Nash S, Sennoune SR, Ahmad G, Torben W et al. Schistosoma egg-induced liver pathology resolution by Sm-p80-basedschistosomiasis vaccine in baboons. Pathology. 2018;50(4):442-9. DOI: 10.1016/j.pathol.2018.01.004, PMID 29739616.

98. McManus DP, Loukas A. Current status of vaccines for schistosomiasis. Clin Microbiol Rev. 2008;21(1):225-42. DOI: 10.1128/CMR.00046-07, PMID 18202444.

99. Sotillo J, Pearson M, Becker L, Mulvenna J, Loukas A. A quantitative proteomic analysis of the tegumental proteins from Schistosoma mansoni...
schistosomula reveals novel potential therapeutic targets. Int J Parasitol. 2015;45(8):505-16. DOI: 10.1016/j.ijpara.2015.03.004, PMID 25910674.

100. Bear JW, Long T, Skinner D, McKerrow JH. Predictions of novel Schistosoma mansoni- human protein interactions consistent with experimental data. Sci Reproduction. 2018;8:1-14.

101. Alves CC, Araujo N, Bernardes WPdOS, Mendes MM, Oliveira SC, Fonseca CT. A strong humoral immune response induced 570 Journal of Parasites and Diseases (April-June 2021) 45(2): 557-580 123 by a vaccine formulation containing rSm29 adsorbed to alum is associated with protection against Schistosoma mansoni reinfection in mice. Front Immunol. 2018;9: 2488. DOI: 10.3389/fimmu.2018.02488.

102. Eyayu T, Zeleke AJ, Worku L. Current status and future prospects of protein vaccine candidates against Schistosoma mansoni infection. Parasite Epidemiol Control. 2020;11:e00176. DOI:10.1016/j.parepi.2020.e00176, PMID 32923703.

103. Badr AM, Al-Halbosiy MMF, El Ridi R. Differential immune responses to excretory–secretory antigens of lung-stage larvae of Schistosoma mansoni in mice and rats. J Basic Appl Zool. 2015;69:26-33. DOI: 10.1016/j.jobaz.2014.12.002.

104. Chen L, Rao KVN, He YX, Ramaswamy K. Skin-stage schistosomula of Schistosoma mansoni produce an apoptosis-inducing factor that can cause apoptosis of T cells. J Biol Chem. 2002;277(37):34329-35. DOI: 10.1074/jbc.M201344200, PMID 12107158.

105. Montresor A. Arithmetic or geometric means of eggs per gram are not appropriate indicators to estimate the impact of control measures in helminth infections. Transitional R Soc Trop Med Hyg. 2019;101:773-6.

106. Di Bella S, Riccardi N, Giacobbe DR, Luzzati R. HiStory of schistosomiasis (bilharziasis) in humans: from Egyptian medical papyri to molecular biology on mummies. Pathog Glob Health. 2018;112(5):268-73. DOI:10.1080/20477724.2018.1495357, PMID 30016215.