Table 1 *S. mansoni* Recombinant Proteins That Have Shown Vaccine Efficacy in Animal Models or Human Studies

Protein or cDNA	Location in adult worm	Identity	Protective vaccine in mice[a]	Protective role in humans[b]	Reference
Sm-TSP-2[c] (tetraspanin D)	Tegument apical membrane[c]	Tetraspanin integral membrane protein	++ worms (recombinant protein) ++ eggs (recombinant protein)	Yes—PR IgG1/G3	74 56
Sm-TSP-1	Tegument apical membrane	Tetraspanin integral membrane protein	+ worms (recombinant protein) ++ eggs (recombinant protein)	No	56
Sm29[c]	Tegument apical membrane	Unknown but has C-terminal transmembrane domain	++ worms (recombinant protein)[d]	Yes—PR IgG1/G3	61
Sm23[e]	Tegument apical membrane	Tetraspanin integral membrane protein	+ worms (multiantigenic peptide – [MAP]) + worms (plasmid DNA)	Yes—DIR IgG3 to MAP3	75, 76 77
Sm-p80	Associated with tegument inner membrane	Calpain—neutral cysteine protease	+ worms (plasmid DNA) ++ worms (plasmid DNA including cytokines)	ND	78 71
Sm14[e]	Whole body, cytosolic	Fatty acid binding protein	++ (recombinant protein)	Yes—DIR	79 80, 81, 82 77
Sm28-GST[e]	Whole body	Glutathione-*S*-transferase	+ worms (recombinant protein) eggs	Yes—DIR	83 77
Sm28-TPI[e]	Unknown in adult but tegument of newly transformed somula	Triose phosphate isomerase	+ worms (transfer of anti-TPI mAb)	Yes—DIR IL-5 to MAP-4 IgG2 to MAP-4	84 76 77
Sm97 paramyosin[e]	Tegument of schistosomula and musculature of adults	Paramyosin	+ worms (recombinant and native proteins)	Yes—PR IgG DIR IgE	85 86 57 77
CT-SOD	Tegument and gut epithelia	Cytosolic Cu–Zn superoxide dismutase	++ worms (plasmid DNA)	ND	87 88

[a]Data as reported in initial publications from inventor's laboratories; + = 30% to 50% reduction in worm/liver egg burdens; ++ = >50% reduction in worm/liver egg burdens.
[b]PR—protective role from studies with *P*utatively *R*esistant subjects; DIR—protective role from studies with *D*rug *I*nduced *R*esistant subjects.
[c]Identified in tegument outer membrane from biotinylated worms using proteomics (71).
[d]Sergio Costa Oliveira, personal communication.
[e]Vaccine efficacy tested independently (68) and adult worm reductions did not exceed 40%.

water buffaloes, the major reservoir for transmission of *S. japonica* in China, and only a small (but significant) reduction in worm numbers was evident in vaccinated animals (93).

The clinical efficacy of BILHVAX has not yet been determined, so there is a desperate need to bring new antigens forward to clinical trials, establishing a pipeline for production and clinical assessment. Below, we highlight the most recent and pertinent data on the major vaccine antigens for schistosomiasis—some have been the focus of attention for many years, while others are newly described but show particular promise.

Tetraspanins

Tetraspanins are four transmembrane domain proteins containing two extracellular loops—a short loop 1 (EC-1) with little tertiary structure and a larger 70– to 90–amino acid loop 2 (EC-2), which has four or six cysteines that form disulfide bonds. In general, the extracellular loops mediate specific protein-protein interactions with laterally associated proteins, or in some cases, known ligands (reviewed in Ref. 94). The four transmembrane domains provide stability during biosynthesis, and are crucial for assembly and maintenance of the tetraspanin web, a scaffold by which many membrane proteins are laterally organized (95). Although their functions are unknown, it is now apparent from proteomic studies that a family of tetraspanins is expressed in the schistosome tegument (70,71,96), and at least three of these show promise as vaccines (Table 1). Sm23 was the first schistosome tetraspanin identified (97). Sm23 is expressed in the tegument of *S. mansoni*, and is one of the independently tested WHO/TDR vaccine candidates (68). Sm23 is most efficacious when delivered as a DNA vaccine (98), and does not confer protection as a recombinant protein when formulated with alum. *S. japonicum* Chinese strain SjC23 administered as a DNA vaccine in mice has provided modest reductions in worm burdens and liver eggs in some studies (99) but no protection in other labs (100). The protective effect of the SjC23 plasmid DNA vaccine was enhanced with IL-12 in pigs (101) and mice (90,99), and by CpG immunostimulatory sequence in mice (102). By combining Sj23 and Sj14 (see below section on Sm14/Sj14) as fusions or coadministered DNA vaccines, significant reductions in adult worms and reductions in granuloma sizes were achieved (103). As with the other *S. japonicum* candidate vaccines, extensive large animal field trials are now required to determine the precise protective potency of SjC23 with or without immunostimulatory cytokines and adjuvants.

A reporter-based signal sequence capture technique was used to identify two new *S. mansoni* tetraspanins (*Sm*-TSP-1 and