A synthetic vaccine against the parasitic worm *Schistosoma mansoni.*

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ABSTRACT

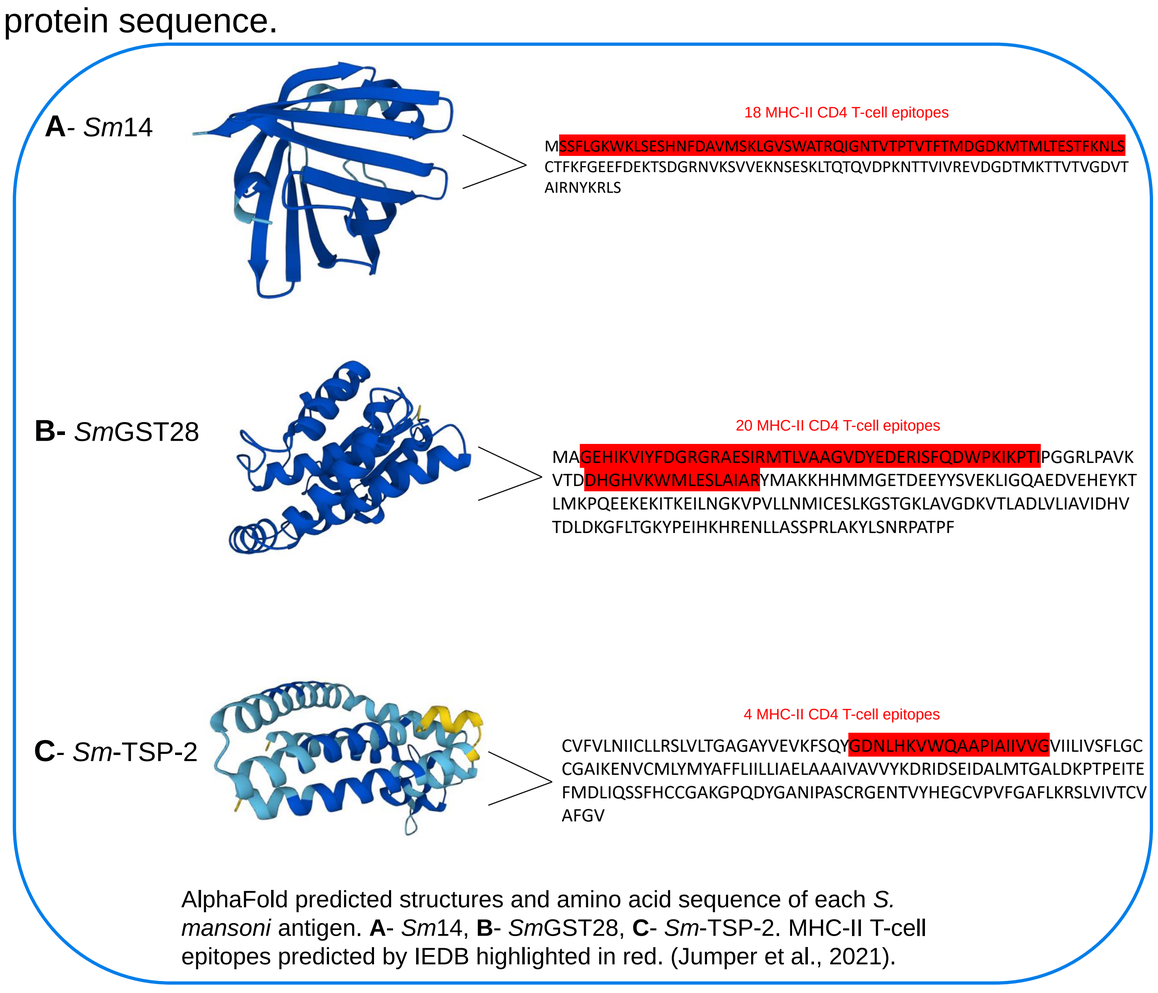
Schistosomiasis is a parasitic disease that affects over 200 million people worldwide resulting from infection with trematode blood flukes of the genus *Schistosoma*, including *S. mansoni*, the causative agent of intestinal schistosomiasis. The current treatment strategies against schistosomiasis involves mass drug administration (MDA) campaigns with Praziquantel and prevention methods including the reduction of snail hosts. However, the limited effectiveness of these approaches due to the high likelihood of reinfection and the potential for development of drug resistance has driven the search for alternative approaches, including the production of an effective vaccine. Anti-*Schistosoma* vaccines have the potential to induce long term immunity, as evidence exists of natural resistance in individuals within schistosome endemic areas, linked to a T-helper 2 cell-associated response. There is currently no effective vaccine against schistosomiasis in widespread clinical use. We are investigating the potential of a Virus-like particle (VLP) antigen assembly platform for development of an effective vaccine against schistosomiasis, through designed assembly of *S. mansoni* antigens based around a Hepatitis-B core VLP. Three previously validated *S. mansoni* antigens, *Sm*14, *Sm*GST28 and *Sm*-TSP-2, have been chosen using MHC class II T cell epitope prediction (IEDB), which identified several immunogenic T cell epitopes. Through in vivo testing of this multi-component vaccine in a murine schistosomiasis infection model, we aim to interrogate whether VLP-based delivery of these epitopes is successful in generating effective protection against *S. mansoni*.

MHC-II CD4 T-CELL EPITOPE PREDICTION

Three *S. mansoni* antigens were selected, all of which have previously demonstrated protection in mouse models and have been the subject of recent clinical trials. These include:

- Tetraspanin (TSP) integral membrane protein TSP-2 (*Sm*-TSP-2) (Tran et al., 2006).
- Fatty acid binding protein (*Sm*14) (Santini-Oliveira et al., 2016; Tendler et al., 1996).
- Glutathione S-transferase class-mu 28 kDa isozyme (*Sm*GST28) (Riveau et al., 2012; Riveau et al., 2018).

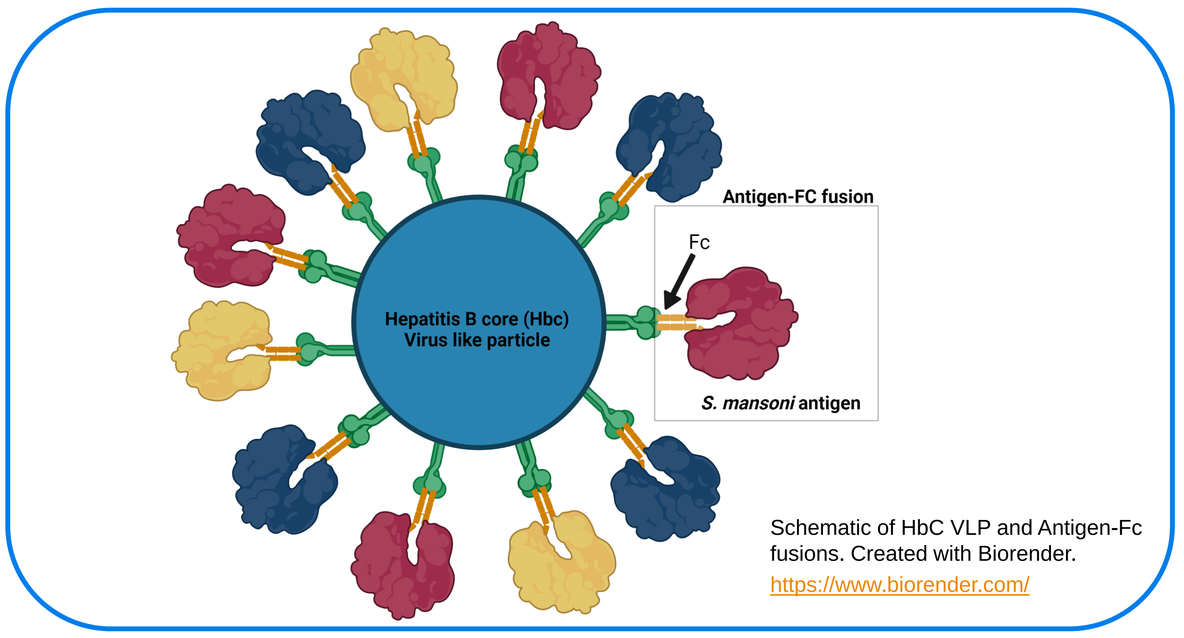
The IEDB database was used to predict MHC-II CD4 T-cell epitopes on these proteins. Using the MHC class II binding affinity, CD4 T cell immunogenicity and MHCII-NP processing tools, the top 10% of epitopes predicted by all three of these tools were identified and mapped onto each protein sequence.



AlphaFold predicted structures and amino acid sequence of each *S. mansoni* antigen. **A**- *Sm*14, **B**- *Sm*GST28, **C**- *Sm*-TSP-2. MHC-II T-cell epitopes predicted by IEDB highlighted in red. (Jumper et al., 2021).

CONSTRUCT DESIGN and CLONING

- The function of the modified VLPs is linked to the ability of the constructs to display multiple *S. mansoni* antigens on the surface. This will be achieved by incorporating antibody binding domains into the major immuno-dominant region (MIR) of the VLP spikes (in green). These domains can strongly bind Fc, allowing binding of a range of *S. mansoni* antigens by Fc fusions (highlighted by the box).
- To do this recombinant TOPO plasmids will be expressed in an HEK cell system for the production of recombinant proteins and subsequent protein purification.



Schematic of HbC VLP and Antigen-Fc fusions. Created with Biorender.
https://www.biorender.com/

- The amino acid sequences of the three *S. mansoni* antigens were codon optimised to *Homo sapiens* using the 'GeneArt' tool (Thermo Fisher Scientific). These sequences were then inputted into the construct template for generation of antigen-Fc fusions and insertion into the pcDNA 3.4 TOPO vector for the production of recombinant proteins and the combination with the VLP.
- Commercial plasmids containing the *S. mansoni* antigen ORFs were transformed into XLI-Blue competent *E. coli* cells (Agilent) for plasmid amplification.
- *S. mansoni* antigen insert fragments were then subsequently ligated into pcDNA 3.4 TOPO vector.
- Recombinant plasmids were transformed into XL-10 Gold ultra-competent *E.coli* cells (Agilent) for plasmid amplification and confirmed as wildtype through sanger sequencing (Azenta GENWIZ).

FUTURE WORK

- In vivo testing in a murine schistosomiasis infection model will be used to compare the immune response to the *S. mansoni* antigen-VLP complex compared to the antigens alone and antigens with previously tested adjuvants.
- The effect on adult worm number and egg burden will also be compared, aiming to see a reduction of 75% in both, as suggested by the Preferred Product Characteristics (PPC).

REFERENCES

Jumper J et al. (2021) Highly accurate protein structure prediction with AlphaFold. Nature, 596: 583–589.

Riveau G et al. (2012) Safety and immunogenicity of rSh28GST antigen in humans: phase 1 randomized clinical study of a vaccine candidate against urinary schistosomiasis. Plos Neglected Tropical Diseases, 6: e1704.

Riveau G et al. (2018) Safety and efficacy of the rSh28GST urinary schistosomiasis vaccine: A phase 3 randomized, controlled trial in Senegalese children. PLoS Negl Trop Dis, 12: e0006968.

Santini-Oliveira M et al. (2016) Schistosomiasis vaccine candidate Sm14/GLA-SE: Phase 1 safety and immunogenicity clinical trial in healthy, male adults. Vaccine, 34: 586-594.

Tendler M et al. (1996) A Schistosoma mansoni fatty acid-binding protein, Sml4, is the potential basis of a dual-purpose anti-helminth vaccine. Proc. Natl. Acad. Sci, 93: 269-273.

Tran M. H. et al. (2006) Tetraspanins on the surface of Schistosoma mansoni are protective antigens against schistosomiasis. Nature Medicine, 12: 835-840.