Schistosomiasis: Basic requirements for the development of a subunit vaccine, using genetic vectors

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Schistosomiasis is a debilitating neglected tropical disease caused by infection with parasitic trematodes of the genus *Schistosoma*. Six species of Schistosoma are the basis of clinical disease in humans, altogether responsible for over 290,000 deaths annually.[1] The clinical manifestations of schistosomiasis are chronic and insidious, including fever, anemia, growth retardation, genital lesions, hepatosplenomegaly and irreversible organ damage.[1] According to recent estimates, schistosomiasis is endemic in 78 countries with over 800 million people at risk for infection.[1] Despite mass drug administration programs with praziquantel, the prevalence of schistosomiasis remains high. A vaccine is urgently needed to control transmission of this disease.[2] Making a vaccine for a multicellular eukaryotic parasite whose genetic machinery is exactly similar to their host, requires more detailed understanding of both host as well as the parasites. An effective schistosome vaccine could offer sustainable reduction in both the prevalence and transmission of the disease.[3–5] The prominent Schistosomiasis vaccines include *S. haematobium* 28-kD Glutathione S-Transferase (rSh28GST), *S. mansoni* 14-kDA Fatty Acid Binding Protein (Sm14), *S. mansoni* Tetraspanin-2 (Sm-TSP-2) and *S. mansoni* Sm-p80/GLA-SE, which are at various stages of human clinical trials.[2] In May 2022, Infectious Diseases Clinical Research Consortium (IDCRC) researchers started conducting a clinical trial of Sm-p80/GLA-SE (SchistoShield). The trial could help pave the way for the world's first vaccine against the disease, offering a safe and cost-effective option to lower its prevalence worldwide.

Currently, adenovirus vectors are being tested as subunit vaccine systems for numerous infectious agents ranging from malaria to HIV to SARS-CoV-2. Several of the presently approved vaccines against SARS-Coronavirus-2 (AstraZeneca/Oxford University, Johnson & Johnson's Janssen COVID-19 Vaccine, and Sputnik V) are based on adenovirus DNA vectors as carriers for the genetic information for the SARS-COV-2 spike glycoprotein.[6] However, the negative aspect of adenoviruses is that it can get integrated into human genome as provirus and lead to serious and even fatal infections such as pneumonia or meningioencephalitis, especially in immunocompromised individuals and children.[7]

In a recent issue of *eBiomedicine*, Perera DJ et al.[8] investigated the performance of a low dose adenovirus vectored vaccine expressing *Schistosoma mansoni* Cathepsin B, to find out if this new putative heterologous prime and boost vaccine with recombinant protein can protect experimental host from infection with schistosomiasis in a murine model. *S. mansoni* Cathepsin B (SmCB) is a parasitic gut peptidase necessary for helminth growth and maturation are essential for the establishment and survival of *Schistosoma mansoni*. This blood fluke expresses a number of gut-associated peptidases that degrade host blood proteins, including hemoglobin, as a means of nutrition.[9] Perera DJ et al.[8] constructed an adenovirus serotype 5 containing *S. mansoni* Cathepsin B (AdSmCB) and delivered it intramuscularly in a heterologous prime and boost vaccine with recombinant protein. The study on AdSmCB vaccine although preliminary in nature, elicited a high T cell cytokine expression and higher protective capacity at very low dose which could preferably avoid the adenovirus vaccine related adverse effects. Higher systemic and cell mediated immune responses, consisting of IgG2c, Th1 effectors, and polyfunctional $CD4^+$ T cells, were detected after the administration of heterologous AdSmCB. The SmCB increased T cell IFNγ production and promoted $CD4^+$ T cell polyfunctionality which was determined by elevated levels of RANTES, a T cell associated chemokine responsible for IFNγ production. Although more of a Th1 favored immune response was elicited, the Th2 response provided by SmCB protein boosts were maintained. This balanced Th1/Th2 immune response in the current findings resulted in a significant protection of experimental mice from *S. mansoni* infection, which are similar to other vaccine formulations that are already in clinical trials.

In a nutshell, this investigation describes a viral vectored vaccine which prophylactically protects from schistosomiasis, at levels comparable to others in pre-

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clinical work and those currently in clinical trials, through a platform which has been widely used in humans and can be easily scaled up for global production. This adenovirus vectored vaccine elicits strong humoral immunity and cellular effectors, balancing Th2 and Th1 arms of immunity to target SmCB-expressing in larvae and adult worms. Additionally, parasite burden reduction by this vaccine led to prevention of pathology caused by *S. mansoni* egg deposition, which is crucial to alleviating chronic morbidities and may significantly aid regions where coinfections make liver pathologies lethal. The main drawback of this study is that it is DNA based and such a vaccine proved to be inefficacious as demonstrated by considerable number of breakthrough infections when used against SARS-CoV-2 or even leading to the death of the vaccinated individuals.

While we strongly support this investigation, in order for the adenovirus vectored SmCB to enter the first phase of human clinical trial, AdSmCB still has to go a long way. Firstly, all the components of this new vaccine need to be tested for their endotoxin levels. During preclinical development of the next generation vaccines, endotoxin levels should be closely monitored despite the heterogeneity in licensed vaccines. Routine measurement of endotoxin levels is necessary to properly understand preclinical animal study results. The endotoxin levels should also be closely monitored due to the potential of a synergistic effects. A level of <20 EU/mL for recombinant subunit vaccine types is recommended.[10] Secondly, once the authors produce all the components of AdSmCB under good laboratory practice (GLP)/good manufacturing practice (GMP) conditions with desired endotoxin levels as mentioned previously, then the vaccine should be ready to be tested in non-human primates, the results of which would determine if this vaccine is ready for the first phase of human clinical trials. The main reason for this requirement is that while working to develop a molecularly defined vaccine for a multicellular eukaryotic pathogen, most of the time, mice data cannot be replicated in non-human primates. All the subunit anti-schistosomiasis vaccines which are currently undergoing Phase-I or higher human clinical trials have already been extensively tested not only in mice but also in non-human primates. As an example, before the human clinical trials of Sm-p80/GLA-SE (SchistoShield), this investigational vaccine had been extensively tested in more than three hundred baboons in order to qualify for the Phase-I clinical trials.[1]

Contributors

Gul Ahmad wrote and revised this commentary.

Declaration of interests

The author has no conflicts of interest to disclose.

References

1 Zhang W, Le L, Ahmad G, et al. Fifteen years of Sm-p80-based vaccine trials in nonhuman primates: antibodies from vaccinated baboons confer protection *in vivo* and *in vitro* from *Schistosoma mansoni* and identification of putative correlative markers of protection. *Front Immunol*. 2020;11:1246. https://doi.org/10.3389/fimmu.2020.01246. PMID: 32636844; PMCID: PMC7318103.

2 Driciru E, Koopman JPR, Cose S, et al. Immunological considerations for *Schistosoma* vaccine development: transitioning to endemic settings. *Front Immunol*. 2021;12:635985. https://doi.org/10.3389/fimmu.2021.635985. PMID: 33746974; PMCID: PMC7970007.

3 Molehin AJ. Current understanding of immunity against schistosomiasis: impact on vaccine and drug development. *Res Rep Trop Med*. 2020;11:119–128. https://doi.org/10.2147/RRTM.S274518.

4 Siddiqui AA, Zhou Y, Podesta RB, et al. Characterization of Ca(2+)-dependent neutral protease (calpain) from human blood flukes, Schistosoma mansoni. *Biochim Biophys Acta*. 1993;1181:37–44. https://doi.org/10.1016/0925-4439(93)90087-H.

5 Ahmad G, Zhang W, Torben W, et al. Preclinical prophylactic efficacy testing of Sm-p80-based vaccine in a nonhuman primate model of Schistosoma mansoni infection and immunoglobulin G and E responses to Sm-p80 in human serum samples from an area where schistosomiasis is endemic. *J Infect Dis*. 2011;204:1437–1449. https://doi.org/10.1093/infdis/jir545.

6 Tatsis N, Ertl HC. Adenoviruses as vaccine vectors. *Mol Ther*. 2004;10(4):616–629. https://doi.org/10.1016/j.ymthe.2004.07.013. PMID: 15451446; PMCID: PMC7106330.

7 Doerfler W. Adenoviral vector DNA- and SARS-CoV-2 mRNA-based Covid-19 vaccines: possible integration into the human genome - are adenoviral genes expressed in vector-based vaccines? *Virus Res*. 2021;302:198466. https://doi.org/10.1016/j.virusres.2021.198466. Epub 2021 Jun 1. PMID: 34087261; PMCID: PMC8168329.

8 Perera DJ, Hassan AS, Liu SS, et al. A low dose adenovirus vectored vaccine expressing Schistosoma mansoni Cathepsin B protects from intestinal schistosomiasis in mice. *EBioMedicine*. 2022;80:104036. https://doi.org/10.1016/j.ebiom.2022.104036. Epub 2022 Apr 30. PMID: 35500538; PMCID: PMC9065910.

9 Sajid M, McKerrow JH, Hansell E, et al. Functional expression and characterization of Schistosoma mansoni cathepsin B and its trans-activation by an endogenous asparaginyl endopeptidase. *Mol Biochem Parasitol*. 2003;131(1):65–75. https://doi.org/10.1016/s0166-6851(03)00194-4. PMID: 12967713.

10 Brito LA, Singh M. Acceptable levels of endotoxin in vaccine formulations during preclinical research. *J Pharm Sci*. 2011;100(1):34–37. https://doi.org/10.1002/jps.22267. PMID: 20575063.