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REVIEW

Why the radiation-attenuated cercarial immunization studies failed to guide the road for an effective schistosomiasis vaccine: A review

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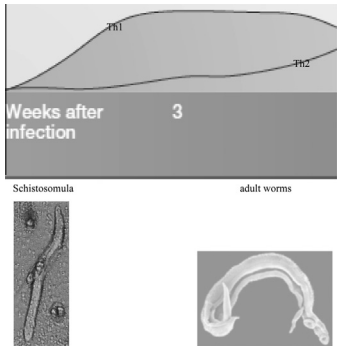
GRAPHICAL ABSTRACT



Schistosomula- and adult worms-derived antigens induce predominant Th1 immune responses. The radiation-attenuated cercariae vaccine efficacy is dependent on induction of Th1 and Th2 immune responses. Accordingly, schistosomula- and adult worms-derived antigens used for effective vaccination must be combined with Th2 immune responses-inducing cytokines or molecules as adjuvant.

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ABSTRACT

Schistosomiasis is a debilitating parasitic disease caused by platyhelminthes of the genus Schistosoma, notably *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*. Pioneer researchers used radiation-attenuated (RA) schistosome larvae to immunize laboratory rodent and non-human primate hosts. Significant and reproducible reduction in challenge worm

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burden varying from 30% to 90% was achieved, providing a sound proof that vaccination against this infection is feasible. Extensive histopathological, tissue mincing and incubation, autoradiographic tracking, parasitological, and immunological studies led to defining conditions and settings for achieving optimal protection and delineating the resistance underlying mechanisms. The present review aims to summarize these findings and draw the lessons that should have guided the development of an effective schistosomiasis vaccine.

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Introduction

Schistosomiasis is a severe parasitic disease caused by members of the genus Schistosoma, notably *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*. More than 200 million persons are infected and up to 800 million, mostly children, are at risk. These statistics may well be underestimated because the stool analysis gold standard technique for diagnosis of the infection is insensitive and unreliable leading the World Health Organization to no longer provide estimates on population infected or at risk. These have been replaced by estimates of population requiring preventive chemotherapy. Egypt is among 51 countries with population requiring chemotherapy despite inaccurate and incomplete information advocating the near eradication of schistosomiasis from Egypt [1]. These hearsays have their foundation on the unreliability of diagnostic techniques and lack of sound and objective epidemiological studies. Failure to assess the prevalence of schistosomiasis leads to people unawareness of its danger. The sequelae are intense reflected in more than 70 million disability-adjusted-life-years (DALYs) and remarkably high rates of years-lived-with disability (YLD) [2]. Praziquantel is the only drug commonly used for treatment. But its efficacy is not proof, and it does not prevent reinfection necessitating its repeated use, thus increasing the threat of development of parasite resistance to the drug [1,2]. Infection and transmission can be prevented if a vaccine is in place. Vaccination studies with radiation-attenuated (RA) schistosome larvae have demonstrated that a schistosomiasis vaccine is a realistic goal [3]. These studies have provided invaluable learning and directions that should have helped developing an effective vaccine composed of purified or recombinant antigens [3]. The present review attempts to outline these lessons and clarify how and where they were disregarded or painstakingly followed.

The radiation-attenuated vaccine model

The life cycle stage used

The infective schistosome stage, the cercariae are commonly used for inducing resistance to challenge infection following radiation attenuation (RA) [4]. Mechanically transformed schistosomula (tailless cercariae) attenuated by X- or gamma irradiation and injected intramuscularly (im) successfully protected mice and cynomolgus monkeys against challenge *S. mansoni* infection [5,6]. However, percutaneously applied RA cercariae were more effective in stimulating resistance (60%) than irradiated, im-administered, schistosomula (40%) [7]. Approximately 500 RA (50 krad of gamma irradiation) 6-day-old lung *S. mansoni* schistosomula, injected im, intraperitoneally (ip), or intravenously (iv) into NIH/Nmri CV and C57BL/6J mice, were also capable of inducing significant ($P < 0.001$) levels of challenge worm reduction (36–56%) that were not very different from approximately 850 RA cercariae as immunizing agents. These findings were construed to indicate that the extravascular stages of development within the skin are not required for the induction of resistance [8]. Conversely, iv-injected RA lung-stage schistosomula derived from optimally RA cercariae failed to confer protection in C57BL/6 mice, suggesting that successful vaccination is not dependent on systemic (vascular), antigen presentation [9,10]. Additionally, irradiated day 21 (# 105) and day 28 (# 58) worms induced much less resistance (reduction in challenge worm burden of 15–27%) than RA cercariae [8].