Why Don’t We Have a Schistosomiasis Vaccine?

R.A. Wilson and P.S. Coulson

Over the past 30 years there has been a concerted effort to understand host immune responses to schistosomes, with the ultimate aim of producing a vaccine for human use. In this issue, Bergquist and Colley, in summarizing recent meetings in Cairo, provide a detailed appraisal of progress towards that goal. It seems an appropriate time to ask why, with reference to Schistosoma mansoni, the development of a vaccine has proved so difficult. This question is explored here by Alan Wilson and Pat Coulson.

Mature schistosomes inhabit the bloodstream, potentially the most hostile immunological environment, yet they are long-lived parasites. They have evolved highly effective mechanisms for evading the consequences of the cellular and humoral immune responses which they provoke. Indeed, they apparently exploit those responses to assist the process of egg excretion from intestinal tissues. Everything points to the evasion mechanisms being deployed by larval schistosomes in the first 24 h after skin penetration which, on the face of it, provides little opportunity for immune attack. In these circumstances, the development of a vaccine was always going to present a challenge.

Do we have the right paradigms?

Research on immunity to schistosomes has thrown up ideas which, at their inception, appeared to provide promising routes to an effective vaccine. In the event they have not proved fruitful and, with the benefit of hindsight, we can offer plausible explanations as to why. The phenomenon of concomitant immunity, first demonstrated in rhesus monkeys and later in mice, dominated schistosome vaccine research from the 1960s to the 1980s. It described the situation where a primary worm burden persisted while the host was resistant to a secondary challenge. It seemed a simple matter to discover how the mature worms induced protection and reproduce this in a vaccine. Concomitant immunity could well hold true in the rhesus monkey, and merits reinvestigation, but in the mouse, it provides little opportunity for immune attack. In these circumstances, the development of a vaccine was always going to present a challenge.

Antibody-dependent cellular cytotoxicity (ADCC) was another major concept which followed on from, and complemented concomitant immunity. Stated succinctly, newly transformed schistosomula are susceptible to killing in vitro by various combinations of antibody isotypes and leukocytes (primarily from humans and rats)1; this vulnerability is lost from 24 h post-transformation. Clearly, a vaccine which replicates this process would be highly effective. Unfortunately, evidence for the efficacy of ADCC in vivo is sparse, and it is plausible that schistosomes have evolved a strategy to reduce their susceptibility to ADCC. New peritoneal parasites remain in peripheral epidermal locations for 48 h (Ref. 8), by which time their immune evasion mechanisms have developed; does this place them beyond the reach of lethal dermal inflammatory responses? Another contributory factor to the failure of ADCC in vivo may be the dominance of antibody isotypes which block rather than mediate the process. In light of the above, there is presently little to suggest that a vaccine based on ADCC mechanisms is going to be feasible.

Leaving aside the question of antigenicity effects, there are two contrasting strategies to develop a vaccine that minimizes worm burden. One is to demonstrate protection in a host which has been exposed to a schistosome infection and then seek to replicate its mechanisms by vaccination; analysis of acquired immunity in humans falls into this category. The second strategy is to invoke by vaccination a novel response not normally encountered by the parasite and against which it has no defence; the radiation-attenuated vaccine may be such an example.

In human schistosomiasis, the decreased prevalence and intensity of infection with age (particularly noticeable around/after puberty), provide the strongest evidence for acquired immunity. Genetic analysis of human populations has also highlighted the presence of a co-dominant major gene controlling the intensity of schistosome infection, which has been localized to a region of chromosome 5 encoding immunological molecules. If we accept that immunity occurs in humans, then the nature of protection remains problematic, with an IgE-mediated mechanism as one of the strongest candidates. This in itself poses dangers since a vaccination regime to promote IgE production may well elicit undesirable side-effects such as exacerbation of allergy. More pertinent is the lack of evidence for immunity in children before puberty. As these are the individuals most in need of protection, it is presently difficult to envisage how a vaccine strategy based on human responses after natural exposure to schistosomes could work for them.

There is one paradigm that has stood the test of time; the radiation-attenuated schistosome vaccine, which protects both rodents and primates. In mice, cell-mediated mechanisms operating against lung-stage parasites appear highly effective and immunity can be augmented to very high levels by co-administration of radiation-attenuated cercariae with interleukin 12 (IL-12) as an adjuvant. Clearly this model is a cause for optimism that a schistosome vaccine is a realistic goal. However, a live attenuated schistosome vaccine is not a practical proposition for use in humans; it can only serve as a precursor for a defined recombinant vaccine.
The Search for a Schistosomiasis Vaccine

Do we have the right antigens?

It is axiomatic that a schistosome vaccine will com-
prise one or more abundant antigens in an appro-
 priate formulation or live vector. The selection of six
candidate vaccine antigens by WHO for independent
evaluation (see Bergquist and Colley, this issue) was
something of a mixed blessing. On the one hand it
raised expectations that a vaccine was within reach.
On the other, the existence of the WHO programme,
together with reported successes by the antigen donors,
inhibited the search for new vaccine candidates. For
a variety of reasons, none of the six candidates performed
to the required standard in trials with mice. The human
situation is not as clear-cut. It is possible that the
intensity of responses to these candidates, resulting from
preceding exposure to schistosomes, correlates with re-
sistance status. What is surprising about the vaccine can-
didates is that five of them are intracellular, and only
one a membrane protein. The five intracellular antigens
are abundant constituents of adult worms and turn up
frequently when cDNA libraries are screened with anti-
schistosome serum. Intuitively, they are not the kind
of molecules one would expect a parasite to release into
e its environment unless it was first damaged by some
non-immune process, and so they would not be avail-
able to the immune system under normal circumstances.
Exceptions are the holocrine secretion of cercarial acet-
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shedding of the cercarial tegument plasmamembrane
during transformation, where natural release might oc-
cur; these early events would implicate the newly pen-
tetrated parasite as a target for protective mechanisms.
In this context, Gobert (this issue) attempts to ration-
alize, in terms of schistosome biology, the choice of
5-glycoprotein paramyosin as a vaccine candidate.

Latest estimates suggest that the schistosome gen-
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Do we need a schistosomiasis vaccine?

In view of the manifold obstacles, it is worth asking
‘Why develop a vaccine?’ particularly when the efficacy
of chemotherapy apparently makes one unnecessary.
There appear to be two potent arguments. The first is
that the clinical course of disease is insidious30, in the
minority of individuals with a high worm burden
transitions to severe and irreversible pathology is usually
diagnosed at too late a stage for chemotherapy to affect
the outcome. In those individuals who acquire low to
moderate worm burdens, the rationale for vaccination
or chemotherapy appears to be similar, provided that
the two therapies are equally effective. Arguably, in that
situation a vaccine would be welcome because of its
capacity to limit worm accumulation whereas chemo-
therapy removes worms after they have accumulated.
The second reason is that with continuing chemo-
therapy it seems almost inevitable that drug resistance
will appear. Indeed, seven laboratory passages of the
life cycle with subcurative chemotherapy were suffi-
cient to select for resistance to praziquantel39. Fur-
thermore, there are already reports of low efficacy of
the drug in Egypt30 and Senegal32. The multiple drug
resistance acquired by helminth parasites of livestock,
which has compromised control measures30, provides
a salutary warning in this respect.

In summary, we suggest that a schistosomiasis vaccine
is both desirable and feasible. However, not only are
new protective antigens needed, but they must be devel-
oped in the context of defined effector responses. Only
then can we address the complex question of antigen
formulation to manipulate immunity in a specific
direction which will maximize parasite elimination.
In this article, Robert Bergquist and Dan Colley deal with the consolidated, international efforts to generate a schistosomiasis vaccine; in particular, they summarize the deliberations of a series of meetings, held in Cairo, Egypt, 21–25 May 1997, with the aim of reviewing the current status of affairs in this respect in order to make recommendations for the future course of schistosomiasis vaccine development.

More than 600 million people in the tropics are at risk of schistosomiasis and the number of infected individuals worldwide is near 200 million. Contributing to its security and spread is the inadequate attention paid to this snail-borne infection in the construction of man-made lakes, irrigation projects, etc. Chemo-therapy remains the cornerstone of intervention but rapid reinfection demands frequent retreatment and emphasizes the need for a more long-term approach.

The existence of at least partially protective immunity in exposed humans would make a vaccine a logical complement to drug therapy. Studies in experimental models have been highly productive and are still much needed but may not adequately represent the human situation. Preliminary results from coordinated in vitro laboratory and field epidemiological research regarding the protective potential of a set of well-researched, defined schistosome antigens (Table 1) support the initiation of clinical trials. After the selection of suitable vaccine candidates the logical next step would be to scale up antigen production accordingly to good manufacturing practice (GMP) and plan for Phase I/II trials, first in adults and then in children. Since the slow maturation of natural resistance does not temper reinfection in time either to stop serious morbidity from developing or to hinder transmission, younger age groups are the prime target for vaccination.

The efforts to develop a schistosomiasis vaccine described here deal exclusively with Schistosoma mansoni, a bias reflecting the fact that the S. mansoni life cycle is the easiest to maintain in the laboratory, away from endemic areas, and most antigens were first identified in this species. In reality, there is now a genuine interest in developing vaccines against the other common causes of human schistosomiasis (S. japonicum and S. haematobium).

Although somewhat further down the road of vaccine development, it should be appreciated that the ultimate vaccine for each of these might have to be a combination of two or more antigens. The possibility of synergistic action would increase by incorporating antigens from different developmental stages of the parasite and the progress of research on the larval stage therefore needs complementary work on antigens emanating from other stages, for example, cercarial proteases. In addition, the design of a successful vaccine will not be based solely on the most effective way of inducing immunity but must also consider the technical feasibility of vaccine production, the prospects of passage through existing regulatory bodies, and the ease of incorporation into immunization delivery programmes.

**On mice and men**

Based on the need for an assessment of potentially protective immune responses, which might also be of importance in human immunity, the antigens depicted in Table 1 were subjected to independent testing in mice. In parallel, determination of cell-mediated and humoral responses against the same antigens in humans living in endemic areas was carried out with the aim of perhaps narrowing down the range of potentially protective antigens.

The path towards clinical trials was initiated by contracting two laboratories with recognized expertise in experimental schistosomiasis to undertake independent mouse studies in parallel, using both

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**Schistosomiasis Vaccines: Research to Development**

N.R. Bergquist and D.G. Colley