# The *Schistosoma japonicum* Angle on Vaccine Research

Bruno Gryseels[1] has raised important issues in the continuing debate as to whether schistosomiasis vaccines are feasible, indeed whether they are desirable. To my mind, the *Comment* article written in response (Hagan *et al.*, this issue) has attempted to provide a more encouraging and balanced view of the feasibility, and the ethical and safety issues associated with the development of schistosomiasis vaccines for use in humans, including their testing for efficacy in clinical trials. However, the articles by Gryseels and Hagan *et al.* focus on vaccines against schistosomiasis mansoni and schistosomiasis haematobia, where vaccination of human subjects will be necessary to reduce morbidity and as an adjunct to control.

Scientists involved in vaccine development against the Asian or Oriental schistosome, *Schistosoma japonicum*, have embarked on a different approach[2–4]. This is because, unlike the other human forms, schistosomiasis japonica is a true zoonosis; ie. in addition to humans, a large number of mammalian species including buffaloes, cattle, pigs and dogs can harbour the infection naturally. Although this complicates control efforts, it also confers an important advantage over the other human schistosomes, in that, in the search for an effective vaccine against *S. japonicum*, prototype molecules can be tested in large, natural host animals such as buffaloes or pigs. Furthermore, there is extensive epidemiological evidence from China that water-buffalo infection contributes significantly to schistosome infection of the oncomelanid snail intermediate hosts and the maintenance of human transmission in the marshland and lake regions where the majority of clinical schistosomiasis cases occur[5].

Following remarkable protective efficacy trials using irradiated vaccines, a number of defined *S. japonicum* antigens have been shown to confer encouraging levels of protection in buffaloes and other livestock animals[3,4]. The results from these trials have provided cause for optimism for the development of a transmission-blocking vaccine against schistosomiasis japonica to be applied in domestic animals, particularly bovines, to impact directly on human transmission[6]. Development of the vaccine for human use could proceed later if it is deemed necessary. Indeed, a human vaccine may be more of a priority in the Philippines as it is unclear how much involvement reservoir hosts play in *S. japonicum* transmission there. Although additional studies are needed, recent reinfection, epidemiological and laboratory data suggest that some humans naturally acquire immunity to schistosomiasis japonica infection[6], thereby providing some support for the feasibility of developing a human vaccine.

In conclusion, antischistosome vaccines, when available for wide-scale application, should not be considered as the absolute panacea. They represent one component of an integrated schistosomiasis control strategy complementing currently available and effective tools such as chemotherapy, improved sanitation, reticulated water supply, effective sewage draining and health education. I am confident that Gryseels would agree that such an integrated approach is the path to follow.

**References**

1 Gryseels, B. (2000) Schistosomiasis vaccines: a devils' advocate view. *Parasitol. Today* 16, 46–48
2 McManus, D.P. (1999) The search for a vaccine against schistosomiasis – a difficult path but an achievable goal. *Immunol. Reviews* 171, 149–161
3 McManus, D.P. (2000) A vaccine against Asian schistosomiasis: the story unfolds. *Int. J. Parasitol.* 30, 265–271
4 McManus, D.P. (2000) The development of vaccines for schistosomiasis. *Curr. Opin. Invest. Drugs* 2, 24–34
5 Li, Y.S. *et al.* (2000). Epidemiology of *Schistosoma japonicum* in China: morbidity and strategies for control in the Dongting Lake region. *Int. J. Parasitol.* 30, 273–281
6 Ross, A.G.P. *et al.* (2000) Is there immunity to *Schistosoma japonicum*? *Parasitol. Today* 16, 159–164

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# Schistosomiasis Vaccines: The Devils' Advocate's Final Plea

My thoughts on schistosomiasis vaccines are not new to the schistosomiasis research community[1,2]*.

I appreciate J. Bennetts' support (above), but I believe that he takes the argument one step too far. Resources for tropical disease research should not compete with those for tropical disease control: as long as 'research for development', does not become 'development for research', both should be multiplied. There are indeed many other research priorities, but schistosomiasis immunology remains a fascinating and relevant subject, even without a vaccine. Considerable long-term investments may not have yielded a practical vaccine, but the spin-offs have made it worthwhile, and no harm has been done – so far. Premature human trials could change that picture.

D. McManus (above) reinforces my point that there is still ample potential to exploit non-human models. However, I doubt that an animal vaccine would ever be applicable to the control of human schistosomiasis. There is no veterinary or economic rationale to immunizing cattle and a reduction of egg output in only part of the reservoir will probably have little impact on transmission.

P. Hagan *et al.* (*Comment*, this issue) concede that there are more questions than answers, and, precisely for that reason, feel that human trials are now necessary. I believe, on the contrary, that clinical trials with vaccine candidates that have no reasonable potential of eventual application amount to ill-defined experiments on human 'guinea-pigs', whether conducted under Good Clinical Practice or not.

The Cochrane review and others[3,4], suggest that immunization campaigns do not have, by definition, a high cost:benefit ratio. Neither do all control interventions put a high burden on health services. A vaccine that partially protects against a curable, preventable and mostly mild disease has little public health relevance, even in combination with other tools.

Citing praziquantel resistance to justify the urgency of vaccine development and human trials is misleading. There is no evidence for the emergence of praziquantel resistance, and in an unlikely worst-case scenario, oxamniquine, metrifonate and possibly artesunate still represent adequate substitutes. The real problem for vaccine testing is the ethics of excluding trial sites from routine treatments and control operations.

Equalizing the importance of individual protection to harmful experiments with 'alleviating the plight of the populations', also has dangerous ethical implications. Accordiing to Hagan *et al.*, veterinary

* Gryseels, B., Endpoints in the field evaluation of schistosomiasis vaccines. The SRP International Conference on Schistosomiasis, Cairo (Egypt), March 1995.

Gryseels, B., A schistosomiasis vaccine: can we make it? Can we evaluate it? Can we use it? EMOP Symposium – Vaccines against parasites: if yes, why not? Parma (Italy) September 1996.

Gryseels, B., Schistosomiasis vaccines: a devils' advocate view. TDR/USAID/MOHP Meeting on Progress in Schistosomiasis Vaccinology, Cairo (Egypt), May 1997].

experiences with irradiated cercariae and other parasites provide proof of principle. This may be so, but do they justify human experiments? Results of current vaccine candidates in animal models are variable[5,6] and those from independent testing are frankly disappointing[5]. The 'irrefutable' immunoepidemiological evidence for acquired immunity in adult humans is based on correlations of which the biological causality remains largely speculative. Alternative explanations, such as innate age-related resistance, are as plausible, and are more consistent with observations in several epidemic foci[2]. Also, the evidence for genetic control of susceptibility is so far only a statistical phenomenon that can be easily biased or caused by a small part of the study population. The biological link to immunoregulating genes is no more than a guess[7,8]. Most of all, genetic predisposition cannot be related directly to protective immunity determined by history of exposure.

Hagan *et al.* see no difference between the safety of testing schistosomiasis vaccines compared with testing of drugs. However, the direct toxicity of the antigen is not the issue, but rather its possible interaction with immunopathological pathways in current or future infections. Safety trials in or near endemic areas, certainly in children, carry an incalculable risk, which makes informed consent simply impossible. If creative ways around the ethical and methodological problems of the measurement of vaccine efficacy exist, then they should be identified before embarking on the adventure.

The notion that it would not matter whether worm burdens or worm fecundity are affected remains perplexing. No properly informed patient or physician would accept a vaccine that permits the presence, even increase, of a number of worms, while removing the possibility for diagnosis. The speculation that praziquantel might do the same by soliciting immune responses is irrelevant, at least it removes the existing worms.

I do not share the opinion that scientists should deal with the consequences of social injustice and refer its causes to other fora. The least they should attempt is 'to do no harm'. A schistosomiasis vaccine does not meet a pressing humanitarian need, but will inevitably mask underlying problems and draw scarce resources from overburdened health services facing far more difficult problems.

Unravelling the complex relationship between schistosomes and humans is a great scientific challenge that will eventually advance humankind. It can be done, if Immunologists need to remain focused on Nature's enigmas, rather than on premature vaccine development.

**References**

1 Gryseels, B. (2000) Schistosomiasis vaccines: a devils' advocate view. *Parasitol. Today* 16, 46–48

2 Gryseels, B. (1994). Human resistance to schistosomes: age or experience? *Parasitol Today* 10: 380–384

3 Jefferson, T. *et al.* (1998) Evidence-based vaccinology: the work of the Cochrane Vaccines Field. *J. Epidemiol. Community Health* 52, 207–208

4 King, M. (1990) Health is a sustainable state. *Lancet* 336, 664–667

5 Bergquist, N.R. and Colley D.G. (1998) Schistosomiasis vaccines: research and development. *Parasitol. Today* 14, 99–104

6 McManus, D.P. (1999) The search for a vaccine against schistosomiasis – a difficult path but an achievable goal. *Immunol. Rev.* 171, 149–161

7 Abel, L. *et al.* (1991) Evidence for the segregation of a major gene in human susceptibility/resistance to infection by *Schistosoma mansoni*. *Am. J. Hum. Genet.* 48, 959–970

8 Muller-Myshok, B. *et al.* (1997) Further evidence suggesting the presence of a locus on human chromosome 5q31-q33, influencing the intensity of infection with *Schistosoma mansoni*. *Am. J. Hum. Genet.* 61, 452–454

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# Naturally Acquired Versus Vaccine-induced Immunity to Malaria: A Dual Role for TGF-β and IL-12?

In their recent review in *Parasitology Today*[1], Omer *et al.* gave an authoritative perspective on the immunoregulatory role of transforming growth factor (TGF)-β in the immune response to parasitic infections. This cytokine has been known to mainstream immunology for many years, but has hitherto been peculiarly neglected by malaria immunologists. Until the publication by Omer and Riley of their seminal work on rodent *Plasmodium* species[2], little was known about the role of TGF-β in malaria, the principal disease with which the authors deal, a stark contrast to that known about the more recently identified interleukins (IL). The review does an excellent job in postulating the Jekyll-and-Hyde character of TGF-β in performing concentration-dependent pro- and anti-inflammatory functions. These upregulate and downregulate T-helper type 1 (Th1)-mediated immune responses, respectively, thereby initially promoting antibody-independent mechanisms that control acute parasitaemia, but later suppressing their activity in order to reduce inflammation-associated pathology. If this is correct, severe malaria in humans may be linked to a reduced capacity of an individual to produce TGF-β. As TGF-β upregulates IL-10 production without downregulating interferon (IFN)-γ in murine malaria infections[2], this may also explain the raised levels of these crossregulatory cytokines in acute bouts of *P. falciparum* in humans[3].

The kinetics of TGF-β activity appear to be crucial for effective control of parasite density: too much TGF-β, too early, would prevent cell-mediated immunity (CMI) through IFN-γ and tumour-necrosis factor (TNF)-α from curbing a rapid escalation of parasitaemia; too little TGF-β, too late, would enable exacerbation of disease through pathology associated with excess production of these Th1-type cytokines. This is reminiscent of the dynamic balance between the immunosuppressive and antiparasitic roles of nitric oxide (NO) during acute blood-stage malaria, which also varies dramatically depending on the exact time of infection[4]. However, the dual role of TGF-β in temporally promoting pro- and anti-inflammatory cytokines presents a practical difficulty to identifying if and how modulating levels of TGF-β could be used to potentiate immunity, while avoiding immunopathology. Such concerns apply less to cytokines that promote a polarized response for which their presence or absence has a more predictable effect. This is the case for IL-12, a key regulator of Th1-type functions in the natural immune response, but which is proposed as a cytokine adjuvant of candidate malaria vaccines[5]. A diminished acute-phase IL-12 response may expedite a lethal outcome of blood-stage infection regardless of the host–parasite match[6]. Thus, potentiating IL-12 secretion may form the basis of a protective immune response capable of reducing parasite density to sub-clinical levels.

Moreover, prophylactic recombinant IL-12 reduces acute parasitaemia and significantly increases survival of inbred mice to primary infection with virulent strains of *P. chabaudi* and *P. yoelii*[6,7]. While this suggests the potential therapeutic value of treatment with IL-12, the degree of protection (but not the nature of the immune response) conferred by inoculation of this cytokine does vary with the dose and timing of delivery. This stresses the importance of determining the appropriate regimen to avoid toxicity associated with the induction of high levels of TNF-α[8] Clearly, the ability of TGF-β