Development of vaccines for parasitic diseases of animals: Challenges and opportunities

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Editorial

Development of vaccines for parasitic diseases of animals: Challenges and opportunities

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Parasitic diseases are a major constraint to efficient livestock production throughout many parts of the world. For the last 50-60 years controlling these diseases has relied, to a large extent, on the use of anti-parasitic agents. However, for some diseases there are no effective anti-parasitic drugs whilst, for others, the relatively late onset of clinical symptoms and diagnosis following infection means that chemotherapy is only partially effective. Conversely, parasites that replicate, re-cycle and transmit rapidly through host populations, such as ticks, mites, enteric nematodes and avian coccidia, require more-or-less continuous mass administration of drugs via food, water or spraying. These latter types of chemoprophylactic control regimes impose enormous selective pressure on the parasite populations, resulting in widespread emergence of drug-resistant organisms.

Vaccination has long been recognised as the most sustainable option for control of parasitic disease in both humans and animals. However, despite decades of research effort, there are only a handful of parasite vaccines available, and all that are licenced are for use against parasites in veterinary species. Until recently all successful vaccines relied on the use of live parasites which are usually attenuated (*Babesia bovis*, *Eimeria* species*, Theileria annulata*, *Toxoplasma gondii*) or partially disabled by irradiation (*Dictyocaulus viviparous*) or concurrent administration of antibiotic (*Theileria parva*). The need to harvest vaccine parasites from animal hosts for the production of most of these live vaccines poses significant challenges for standardisation, quality control, shelf life and cost of manufacture. Although live vaccines have traditionally been considered unacceptable for use in humans the well documented difficulties encountered in developing subunit vaccines for malaria has prompted a recent initiative to explore the use of *Plasmodium falciparum* sporozoites for vaccination.

The biological complexity of parasites, which (unlike viruses and bacteria) progress their lifecycles through several developmental stages that present distinct antigenic profiles to the host, poses unique challenges for vaccine development. A lack of *in vitro* methods for the culture of the relevant stages of many parasites is a significant limitation to progress, and with few exceptions maintenance of parasite populations requires passage through, or establishment of persistent infections in their

specific animal host. Vaccine development is further complicated by the ability of many parasites to modulate host immune responses in order to delay or inhibit parasite clearance. Meanwhile for even the simplest parasites that cause acute infection with no persistence, the critical host-parasite interactions that mediate robust immunity against subsequent parasite challenge are poorly understood. These factors underpin a serious lack of *in vitro* cellular or biochemical assays that can reliably predict the immunoprotective capacity of vaccines. Consequently, with few exceptions, testing and validation of candidate anti-parasitic vaccines continues to rely on costly *in vivo* challenge experiments.

Nevertheless, recovery from the acute phase of parasite infection is often associated with development of immunity to subsequent parasite challenge, encouraging the belief that antigens targeted by the convalescent immune response could be used for vaccination. However, knowledge of the biology of host-parasite interactions and the nature of the immune responses that mediate naturally acquired immunity is required to facilitate focused approaches to identification of candidate antigens for vaccination. The papers in this Special Issue of Parasite Immunology review the current status of research underpinning development of subunit vaccines against 5 important animal parasites, each of which present different challenges for vaccine development. These papers consider advances in understanding the immunobiology of the parasites, as well as strategies adopted to identify candidate vaccine antigens and novel delivery systems used to boost levels of protection.

The coccidian parasite *Neospora caninum* is a leading cause of cattle abortion and reproductive failure for which there are currently no vaccines or antiparasitic drugs. The paper by Horcajo et al, discusses the complex relationship between the parasite and its bovine host, where the outcome of infection depends critically on foetal immunocompetence and the timing during gestation of infection. Live attenuated vaccines show efficacy in reducing transplacental transmission and abortion but suffer from issues related to vaccine preservation and safety. Although killed or subunit vaccines have so far shown limited efficacy, the article highlights recent progress in comparative genomics that has defined a number of virulence factors that are potential novel vaccine targets. Another major issue is the prohibitive cost of evaluating foetal protection in cattle and the article examines the relative merits of current rodent and ruminant challenge models as well as the need for a unified bovine model for testing vaccine formulations.

Antigenic variability is a feature of many parasitic infections, as discussed in the articles on *Theileria* and trypanosomes. The immune responses to the pre-erythrocytic stages of pathogenic *Theileria* species show close similarity to those observed in human malaria, including strain specificity of parasite-specific T cell responses. A live vaccine similar to that currently under investigation for malaria has been available for several decades, but has proved difficult to produce and distribute. The article by Nene and Morrison discusses studies that have provided insight into the cellular immune responses that mediate immunity against *T. parva* and how they determine strain specificity. They discuss how this work has led to the identification of a series of parasite antigens recognised by protective CD8 T cell responses, as well as a sporozoite surface antigen that elicits neutralising antibodies, and summarise results of experimental vaccine studies with these antigens. This paper also includes a comparison of the genomes and known antigens of *T. parva* and *T. annulata*, which reveal a surprisingly high level of antigenic conservation, indicating that progress in vaccine development against one of these parasites will be translatable to the other. .

In the case of African trypanosomes, pursuit of vaccination has been virtually abandoned for the last two decades, because of the lack of obvious strategies to circumvent antigenic variation. In their paper, Black and Mansfield discuss new findings indicating that, in addition to antigenic variation loss of B cells associated with dysregulation of cellular immune responses during infection contributes to failure to control trypanosome infections. They also describe identification of conserved regions in the variable surface glycoproteins that can be used to stimulate helper T cell

responses, which are not normally induced during infection and propose immunisation strategies using these and other antigens that could at least partially circumvent the problem of antigenic variation.

A vaccination approach pursued with some success against metazoan parasites is to identify antigenic targets that do not induce an immune response during the course of natural infection. Notable examples of this 'hidden antigen' approach are licenced commercial vaccines for the one-host cattle tick *Rhipicephalus microplus* (tickGARD®) and the important gastric nematode of sheep and goats *Haemonchus contortus* (Barbervax®). As discussed in the papers from de la Fuente et al, and Matthews et al, the former contains recombinant tick proteins BM86/BM95 whilst the latter uses a mixture of native proteins purified from the lining of the worm gut. Upon injection they induce circulating antibodies in the host which when ingested by the parasites cause gut damage and a reduction in oviposition. A limitation for these vaccines is that levels of circulating anti-parasite antibodies wane rapidly and as the host is not re-exposed to parasite gut material during feeding there is little or no natural boosting. Thus vaccines need to be re-administered regularly.

Gastrointestinal nematodes (GIN) exert a huge burden on global livestock production and anthelminthic resistance is widespread. Currently two vaccines are commercially available: the aforementioned Barbervax®, used to protect sheep against *Haemonchus contortus* in Australia and a recombinant *Echinococcus granulosis* vaccine manufactured by Tecnomax in Argentina. The paper by Matthews et al discusses the immunoprotective vaccine antigens that have been identified to date for several GIN parasites of cattle and sheep, most notably a variety of secretory-excretory proteins from *Ostertagia ostertagi*, *Cooperia oncophora* and *Teladorsagia circumcincta* and a somatic antigen, Hc23 for *H. contortus*. Importantly this paper also considers possible solutions to the most common problems encountered when trying to move from native to recombinant vaccine formulations.

Ticks have evolved a number of complex biological features that enable them to attach to their hosts and feed over a period of several days. The paper by de la Fuente et al discusses research that is beginning to elucidate the molecular basis of different facets of tick-host interactions and outlines how this knowledge, coupled with application of omics technologies, is being exploited to identify candidate antigens for vaccination. Several examples of antigens that induce partial protection are described, but the authors make the valid point that induction of robust immunity may require a vaccine that incorporates a combination of antigens capable of inducing immune responses that target different tick biological functions, and thus have an additive effect on the ability of ticks to attach and feed.

Although each of the papers in this Special Issue addresses parasites that pose different challenges for vaccine development, a common feature is they all highlight advances in understanding the immunobiology of the parasites, which have helped to focus efforts on identification of new candidate antigens for vaccine testing and, in some cases, provided novel concepts on vaccine design.