3.2 PROTECTIVE IMMUNITY—VACCINES

Achim Hoerauf and Cathy Steel**

Summary of Prioritized Research Needs

1) Define the changes to protective immunity among populations undergoing MDA programs (requires longitudinal cohort studies in newborn infants and in adults, identification of markers of protective immunity [sterile and concomitant], and parallel observations in experimental animal models).

2) Assess the impact of MDA-induced alteration of anti-filarial immunity on efficacy of routine vaccines and on co-infections with other helminths, malaria, TB, and HIV/AIDS.

3) Work towards an LF vaccine (as a tool for use post-2010) through
   a) identification and production of protective antigens,
   b) identification of the mechanisms underlying protective immunity,
   c) “piggy-backing” observations on the anti-hookworm vaccine currently under development.

3.2.1 Overview

Why study protective immunity?

The GPELF has thus far been a success story, and because of that success the necessity of still continuing to pursue research on protective immunity or vaccines has been questioned. Valid arguments exist, however, for why such research should continue, or even be accelerated.

Most importantly, it must be remembered that none of the three anti-filarial drugs currently being used is totally curative, and numerous rounds of mass treatment will be necessary to reduce the levels of infection below those necessary to sustain transmission. Indeed, it can be anticipated that such alterations in the levels of infection in communities might have a dramatic impact on the degree of their immunity to LF, resulting in either a higher degree of protection against re-infection with filarial worms (thereby promoting success of the GPELF), or conversely, resulting in less protection (and re-infection with filarial worms (thereby promoting success of the GPELF), or conversely, resulting in less protection (and becoming a potential impediment to elimination). Better understanding of the protective immune mechanisms active in LF-endemic populations is thus important not only to make more precise predictions about the eventual success of elimination efforts, but also to alert the GPELF to potential problems that might arise from altered immunity in treated communities. In addition, the absence of totally curative drugs also argues for sustaining the efforts to generate a vaccine that might still be a cost-effective way both to boost the effectiveness of drugs in eliminating LF and then to help to prevent its recrudescence, particularly as the force of infection (i.e., prevalence/density of infection) progressively decreases towards the end of the Global Program.

The usefulness of a vaccine, especially for the final steps of LF elimination.

A vaccine for LF has long been on the wish list of both the basic research and public health communities. Ironically, and partially because that desire has been around for so long, it has been opined that the arrival of a vaccine would come too late and at too high a cost to be of programmatic value. Clearly, it is not an easy task to generate a vaccine against a multicellular parasite that has used millions of years of co-adaptation to divert the host’s immune system to ensure its long-term survival. However, it is feasible, and several examples exist of successful (i.e., marketed) helminth vaccines for live-stock, as well as one example of a vaccine against human hookworm disease that is currently progressing towards human trials. Furthermore, in the animal filarial infection most closely resembling human onchocerciasis (i.e., cattle onchocerciasis caused by O. ochengi), vaccination with irradiated L3 has resulted in highly significant protection during subsequent field exposure, demonstrating clearly that an epidemiologically relevant protection in the field can be achieved through a vaccine.

From the epidemiologic standpoint of transmission interruption, a vaccine that blocks patency (microfilaraemia) would be equally valuable as one that prevented initial infection. A vaccine that blocks patency in 100% of experimental animals has been available for many years in the form of injected mf in the Litomosoides sigmodontis-infected rat model. This principle could be further developed for LF, and since a vaccine directed against MF would likely increase the proportion of non-patent infections in a population, it would work directly towards GPELF’s overall goal of bringing transmission to a halt.

Finally, the two major microfilaricides DEC and ivermectin both need the host’s immune mechanisms for their maximal effectiveness. A vaccine might therefore provide highly important complementarity, enhancing the effectiveness of the drugs. Such an effect should be most important towards the end of the program when there will be low rates of infection that must be eliminated. A vaccine might also, of course, become the only useful tool, should resistance develop against one of the major drugs now used in the effort to eliminate LF.

Recent advances in understanding the mechanisms of protective immunity.

Although many hurdles, including the lack of an in vitro culture system for filariae and the absence of tools for easy genetic manipulation, initially led to slower progress toward a vaccine for LF than with vaccines for other infectious organisms, over the past decade there has been dramatic improvement in our understanding of the mechanisms that lead to protective immunity against filarial L3 and MF. Several factors account for this, but most important are advances in the development of animal models. While naturally occurring im-
munity in endemic populations has been described for both humans and cattle (and likely dependent on the age of the host), experimental models have also now demonstrated that protection can be induced in animals by irradiated L3s. Indeed, many of these models have suggested that the Th2 response, most importantly working through interleukin-5 (IL-5), is essential for protection both in vaccine-induced and in primary resistance to infection. Other Th2-related responses (IL-4, eosinophils, and/or IgE) have also been shown to be necessary for protection to either the L3 or mf stage of the filarial parasites. Work with this model confirms that a Th2 response, including immune mechanisms in filariasis is the recently developed mouse L. sigmodontis model that allows development of the full filarial life cycle in inbred BALB/c mice. Work with this model confirms that a Th2 response, including IL-5-dependent mechanisms involving eosinophil degranulation in the skin, is needed for L3-induced immunity, while mf patency appears also to be controlled by Th2 dependent mechanisms sometimes working synergistically with Th1 responses to limit filarial infection.

In addition to these newly extended models, dramatic advances in molecular biology, including a now fully sequenced filarial genome (for B. malayi) currently being annotated, along with the advent of new technologies such as RNA interference (RNAi), protein three-dimensional imaging, novel methods of gene delivery, etc., have all led to what promises to be “a golden age for filariasis research” that provides unprecedented opportunities to build on earlier work to identify protective immune mechanisms and to develop new vaccine candidates.

3.2.2 Research Needs

Effect of MDA on anti-filarial immunity in populations.

The reduction of LF transmission (with its lowered parasite exposure in individuals) will likely reduce populations’ naturally acquired immunity to filariasis. This change could have unintended consequences for global elimination efforts, such as increased susceptibility to infection or to patency (microfilariaemia), increased disease burden in children, or increased morbidity in both filariasis and other concurrent infections. Research that is urgently needed should focus on

- studies of birth cohorts in areas with ongoing MDAs, since tolerance to filarial parasites may be acquired through prenatal antigen exposure (that would diminish as infection loads in mothers decrease, with a consequent change in immunoreactivity to filariae that might result in desirable protection or in unwanted immunopathology),
- research using the available animal models to address these same issues in a manner complementary to the studies in humans.

Impact of MDA-induced alteration of anti-filarial immunity on co-infections.

In areas endemic for LF other infections (including malaria, HIV, TB, and other helminths) are usually abundant and likely to stimulate host responses that may alter the clinical expression and state of immune protection to these infections. For example, epidemiologic studies in Thailand suggest that elimination of helminth co-infections might increase the frequency of cerebral malaria, while in Africa elimination of helminth co-infections actually reduced the frequency of acute malaria attacks. The limited success in treating and preventing TB may in part be influenced by immune downregulation by chronic helminth infection, and similar factors may also account for the finding of reduced success of vaccination programs in the face of chronic helminth infection. There is, therefore, a clear need for studies

- to define the influence of chronic helminth infections (treated as part of the GPELF MDA) on the clinical expression of acute or severe malaria syndromes,
- to evaluate the impact of the GPELF (and consequent reduction of helminth infections) on the efficacy of all routine vaccinations,
- to develop animal models for co-infections that allow immunologic parameters and disease manifestations to be studied, and
- to permit assessment of potential causal relationships between an immune mechanism induced by one infection and its impact on a concurrent infection.

Development of animal models.

While the need for animal models to move from correlations to mechanisms is well recognized, a major problem is that no fully suitable model for LF (particularly for Bancroftian filariasis) exists in animal species that can be easily maintained in the laboratory. Therefore, data must be obtained from multiple surrogate models with experiments being designed such that complementary results will be generated, ideally by a consortium of those working with the different models. Therefore, studies should be expanded on

- models for B. malayi and B. pahangi infections that have been incompletely explored with the most recently developed immunology tools (e.g., in cats, rats, and ferrets) to address issues of immunity and re-infection,
- a model to study W. bancrofti in mice by adapting the chamber model already used successfully for onchocerciasis,
- the murine model of infection with L. sigmodontis to define more fully the components of the immune system relevant to immunity against L3, to vaccination using modern gene delivery systems, and to MF clearance and patency.
“Piggy-back” studies on hookworm vaccine development.

A hookworm vaccine, currently entering safety trials in humans, is based on recombinant antigens. Given the homology of recombinant proteins used in this vaccine to key filarial molecules that have already been tested successfully for immunogenicity in animal models (e.g., Ancylostoma-secreted protein 2, ASP-2), a cross-over effect between hookworm and filarial infection might be expected. While synergistic effects would be welcomed, an antagonistic effect (enhancement of filarial infection due to the development of tolerance induced by the vaccine) would also be a potential concern to be evaluated. Therefore, a potentially unique opportunity (and an important research need) should be pursued

- to develop trials for LF that “piggy-back” on the current studies to develop a vaccine for human hookworm infection.

3.2.3 References


