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EDITORIAL

Malaria Vaccines: Overview and Perspective for Developing Countries

During the 1980s there were remarkable advances made towards development of a malaria vaccine.[1] Efforts were primarily focused on the sporozoite or infective stage of the malaria parasite's complex life-cycle. A series of sporozoite peptide vaccines were made against *P. falciparum* (PF) using the techniques of modern biotechnology. The rationale for these vaccines was that antibodies directed against a dominant repeated epitope of the circumsporozoite (CS) surface protein appeared to neutralize sporozoite infectivity - at least *in vitro* and in animal studies. It was also known that individuals protected by experimental immunization with irradiated sporozoites as well as naturally infected individuals had serum CS antibodies. There was, however, no evidence that CS antibodies were protective in natural infections.

Both a recombinant and a synthetic CS peptide vaccine were tested in human volunteers in the USA. Both vaccines were safe but not very immunogenic. Challenge of immunized volunteers with infected mosquitoes revealed poor efficacy. The failure of these first sporozoite peptide vaccines can be attributed-at least in part-to their poor immunogenicity and apparent lack of boosting potential. There was also concern that the experimental challenge model was defective in that the numbers of infective sporozoites introduced possibly overwhelmed the induced immune response.

Following the disappointment over the initial sporozoite vaccine trials the strategy for further vaccine development focused on trying to improve the carrier component-particularly for recombinant constructs based on the CS repeat region. Efforts were also directed at improved adjuvants and at the production of a liposome vaccine. Currently a variety of CS peptide constructs involving carrier components thought to be rich in T cell epitopes have been produced and tested for safety and immunogenicity in volunteers. All have been safe but only one showed impressive immunogenicity. This improved CS sporozoite vaccine is now undergoing further clinical testing in the USA.

Efforts to develop vaccines against other stages of the malaria parasite have been slow. Except for a multicomponent synthetic vaccine containing sequences from both the PF sporozoite and asexual blood-stages there have been no other reported vaccine studies in man.[2] Various laboratories are working on the identification of protective antigens from asexual blood stages, sexual stages (both in man and in the mosquito) and pre-erythrocytic liver stages. Over the next few years these efforts will certainly produce recombinant and synthetic candidate vaccines for testing in man.

Almost all the efforts to develop a recombinant or synthetic malaria vaccine have been in industrialized countries with the WHO playing an important coordinating role. So far, however, developing countries -those countries that most need a malaria vaccine-have had very little direct involvement in malaria vaccine design and development. Up to now this situation can be rationalized on the basis of the tremendous costs for biotechnology based research and particularly, prototype vaccine manufacturing on a scale to support human volunteer testing in compliance with strict regulatory practices. It can further be argued that this scenario is the best possible and that developing countries with malaria problems should stand-by to receive safe and

potentially effective vaccine products for local evaluation and advanced or large-scale field testing.

Despite the appeal of this approach there is a potentially counterproductive flaw. It is a flaw that developing countries can, however, have a direct role in correcting. The problem is at the roots of vaccine design which are currently deeply planted in modern industry-linked laboratories. Our ability to culture the PF parasite has led, I believe, to a preoccupation with *in vitro* phenomena. In addition we have come to rely on murine and primate animal malaria models that may poorly predict-if not mislead-actual immunological events in man. This focus has de-emphasized our study of human malaria in the natural host - man. How then can we expect to identify protective parasite antigens when we do not know what protective immune responses actually operate in the human host? Put another way, rational vaccine development requires that we know enough human malaria immunology to identify protective vaccine targets. In order to accomplish this goal we need to systematically study malaria infection and disease in the human host. We need to examine how the immune response develops and to determine those adaptive effector mechanisms that kill or limit parasite growth. We need to try and understand how in a stable ecosystem the human host achieves an equilibrium with the malaria parasite in which the host is asymptomatic with a low parasitemia-yet sterilizing immunity does not occur.

Given this overview and comments on the current situation in malaria vaccine research what then are the implications for developing countries? Formost I believe that developing countries must take a more active role in the overall process of malaria vaccine design and development. Most importantly this role can be focused on the conditions and resources that are uniquely the developing countries' - malaria disease, national interests and expertise in malaria control and critically a core of enthusiastic and dedicated scientists and clinicians. By combining these resources with the already established research capabilities of industrialized countries a collaborative venture can be launched that focuses on understanding the immunology of human malaria as a driving force for rational vaccine design and development. In practical terms there are two basic approaches for organizing vaccine related research in the developing countries: 1) Establishing programs for basic clinical research on malaria infection and disease using the available products of biotechnology as tools to probe and dissect the human immune response and, 2) Pursuing direct involvement in early testing of vaccine candidates-particularly emphasizing clinical immunology research in conjunction with Phase I (safety and immunogenicity) and Phase II (efficacy) studies in malaria experienced (semi-immune) volunteers.

There are hopefully many creative ways to implement these approaches. Establishing the interface between technology and human malaria is, however, essential. One way to achieve this interface is through the establishment of research centers. First in the more advanced developing countries then the others as a function of acceptance and potential. Industrial institutions and the WHO have the role of helping to build and support these research centers through technology transfer, training and funding. The developing countries have the task of providing the core investigators and experience and access to human disease.

Success then depends on collaboration that takes full advantage of the special talents and resources that both the industrialized and developing countries have to offer. This collaboration is in essence sharing. But it is sharing in new locations. Being so to speak where the action is-face to face with malaria as a human problem.

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