POLICY FORUM: INFECTIOUS DISEASE

# Research (Genomics) Is Crucial to Attacking Malaria

Stephen L. Hoffman

In the past 30 years, we have witnessed vaccines eliminate smallpox from the planet, polio from the Western hemisphere, and serious disease caused by *Haemophilus influenzae* in the developed world. During that same period, we have seen the number of cases and deaths from malaria increase in many parts of the world. There are 300 to 500 million new infections, 1 to 3 million new deaths, and a 1 to 4% loss of gross domestic product (at least $12 billion) loss annually in Africa caused by malaria (*1*). The main causes are that our best drug, chloroquine, has been rendered useless by drug resistance in much of the world; *Anopheles* mosquitoes have become resistant to some of our insecticides; and we have not had the funds and will to optimally attack the problem using existing tools.

**POINT COUNTERPOINT**

Knowing the sequence of the *Plasmodium falciparum* genome and the genomes of other parasites that cause malaria, as well as the specifics of gene and protein expression at different stages in the life cycle and under pressure from different drugs, will increase our chances of developing new and better drugs, and vaccines. Having genomic information for *A. gambiae*, the major vector in Africa, will make possible new approaches to development of insecticides. Investment in *Plasmodium* and *Anopheles* genomics will facilitate development of new ways to prevent development of infectious sporozoites in *Anopheles* mosquitoes and for reducing contact between infectious mosquitoes and humans. Finally, knowledge of the human genome offers unprecedented potential for understanding who is and is not susceptible to dying from malaria, and who might benefit most from a particular type of vaccine.

Scientists recently looked at the unpublished sequence of chromosome 14 of *P. falciparum* and found two genes encoding putative enzymes involved in isoprenoid biosynthesis (*2*). They found that the recombinant protein expressed by one of these genes was inhibited by two drugs that suppressed the in vitro growth of multidrug-resistant *P. falciparum* and cleared parasitemia in mice infected with a rodent malaria parasites. If these findings lead to drug licensure, the entire $25M international investment in sequencing the *P. falciparum* genome will have been justified.

In the case of vaccine development, we know that we can entirely prevent susceptibility to *P. falciparum* infection in volunteers for 9 months by immunizing with radiation-attenuated sporozoites (*3*) and that children who live to 3 to 10 years of age in areas highly endemic for malaria rarely, if ever, develop severe malaria and die. In both cases the protected individuals are exposed to the entire parasite and to the proteins encoded by its 5000 to 6000 genes. It is possible that induction of immune responses against a few, key proteins will be adequate for duplicating this whole-organism immunity. If protective immunity requires induction of immune responses against 100 or even 500 different target proteins, then the genome project offers us the most immediate way to identify those targets and to begin the process of developing vaccines based on them.

It is also possible, albeit unlikely, that acquired immunity has nothing to do with the fact that children stop dying after a certain age in highly endemic areas. Perhaps, some of these children have a genetic resistance to dying and would survive regardless of intervention. Having the human and parasite blueprint, and the computational biology capacity that goes with it, may allow us to develop a simple diagnostic that would identify at birth who is most at risk of dying of malaria. This would allow us to target those individuals. A single nucleotide polymporphism in the gene encoding the β chain of human hemoglobin, responsible for the sickle cell trait, is associated with a 90% decrease in the chance of dying from a *P. falciparum* infection. What other SNPs or SNP complexes will we find in the human, *Anopheles*, and parasite genomes, and how will they help us develop better approaches to the infection and the disease?

Detractors of the genomics approach state that we already have the tools we require to control malaria. For reducing contact between infected mosquitoes and humans, we have these means: filling in breeding sites, larviciding, spraying houses with insecticides, insecticide-impregnated bed nets, and house screening. Effective application of these measures would lead to reduced morbidity and mortality from malaria. However, given the extremely high transmission rate of *P. falciparum*, especially where *A. gambiae* mosquitoes predominate, the capacity of the mosquitoes to develop resistance and the requirement for maintenance of the interventions for many years, we cannot be confident that they will do as good a job as we desire, or continue to be effective in the future.

For reducing morbidity and mortality in infected individuals, we have early case detection and treatment. However, optimal tools for early diagnosis do not exist, even if we had a perfect health-care delivery system. Work in Senegal has clearly shown how rapidly mortality increases when drug resistance appears (*4*), and there is no certainty that resistance will not develop to all of the new combination drug regimens.

Even if our current, poorly applied control measures were optimal, it is necessary to examine what is meant by the term "control." Common use of the word in reference to malaria emerged with the end of the malaria eradication campaign of the 1950s and 1960s. It represents our recognition of our inability to eradicate malaria. "Control" implies that we will be happy with a 30% reduction in malaria-associated morbidity and mortality. The use of the word control means that we are willing to accept several febrile illnesses per year, modestly reduced hemoglobins, modest numbers of school absences, and perhaps decreased cognitive functioning in children as long as those children do not die of malaria. This is a reasonable interim solution, but it is totally unacceptable as a vision. Our vision must be to eradicate malaria, and we do not have the drugs, vaccines, antimosquito measures, and knowledge of the disease to be confident that we can do this and sustain our advances. We must invest heavily in international efforts like Roll Back Malaria to increase our application of current tools to the control of malaria. However, we would be foolish and irresponsible not to invest in research, if we are serious about improving and sustaining current control interventions and eventually eradicating malaria. Genomics is a critical component of 21st century biomedical research. It provides an incredible opportunity for increased insight into the biology of *Plasmodium* spp. parasites, and their *Anopheles* spp. vectors, and the pathogenesis of malaria in humans.

The author is at the Naval Medical Research Center, Silver Spring, MD 20910–7500, USA. E-mail: hoffmans@nmrc.navy.mil

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