

## Essay

# Genomics Research and Malaria Control: Great Expectations

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The protozoan parasite *Plasmodium falciparum* causes falciparum malaria, a fatal parasitic disease in humans, and is transmitted by *Anopheles* mosquito vectors (predominantly the *Anopheles gambiae* complex and *An. funestus* in Africa). There are about 300 million malaria cases and 1–2 million deaths annually, the brunt of which are borne mostly in Africa by children under 5 years of age and by pregnant women. In many African countries, malaria poses a formidable challenge to an overburdened and underfunded

public health system. The current malarial control strategies consist of chemotherapy directed against the malaria parasite and prevention of mosquito vector/human contact using insecticide-impregnated bednets and, to a lesser extent, indoor residual insecticide spraying and environmental control for reducing mosquito breeding sites. There are still no malaria vaccines in clinical practice.

## The Dual Problem of Drug and Insecticide Resistance

Chemotherapy (the use of drugs

to target disease) is used for both treatment and prevention. Drug resistance is increasingly becoming a problem. Some of the antimalarial drugs in current use include quinolines, artemisinins, antifolates, atovaquone/proguanil, and antibiotics. Chloroquine

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(CQ) is a cheap and widely used aminoquinoline, but CQ-resistant parasites have become ubiquitous in endemic countries and other drugs are now used much more frequently (Ridley 2002). Fansidar, a combination of sulphadoxine and pyrimethamine (SP), is a first-line treatment in several African countries, but resistance to SP is spreading rapidly. Targeting the mosquito vector with pyrethroid-impregnated bednets, in addition to chemotherapy, is an effective method of controlling malaria transmission. However, pyrethroid resistance has been reported in *An. gambiae* s.s. in West Africa, and there is concern about its emergence in East Africa (Chandre et al. 1999). Thus, the public health problem due to malaria is exacerbated by the emergence of drug-resistant parasites and insecticide-resistant mosquitoes. The clinical application of efficacious intervention tools is therefore an urgent imperative for malarial control. This brings into sharp focus the importance of genomics research for drugs, vaccines, diagnostics, and insecticides. The unraveling of the genomes of humans, *P. falciparum*, and *An. gambiae* has ushered in a new era of hope that genomics research will result in the development of new and better tools for malaria control.

### Early Pickings from the Malaria Genome

The *P. falciparum* genome of 22.8 megabases (Mbp) distributed among 14 chromosomes consists of 5,300 protein-coding genes (Gardner et al. 2002). *P. falciparum* possesses a relict plastid, the apicoplast, homologous to the chloroplasts of plants and algae. The apicoplast is essential for parasite survival and functions in the anabolic synthesis of fatty acids, isoprenoids, and heme (Seeber 2003). These essential metabolic pathways are not present in humans and are therefore ideal targets for the development of safe antimalarial drugs. Inhibitors of type II fatty acid biosynthesis (triclosan and thiolactomycin) and mevalonate-independent isoprenoid biosynthesis (fosmidomycin and FR900098) with potent antimalarial activities have been identified by computational mining of the genome data. The fact that fosmidomycin has rapidly entered into clinical trials underscores the great utility of genomics research in the control of malaria (Lell et al. 2003).

### Malaria Functional Genomics

About 3,200 proteins (60%) in *P. falciparum* have no known functions (Gardner et al. 2002). The greatest challenge of malarial functional

genomics (the elucidation of the functions of genes encoded by an organism's genome) is to assign functions to these proteins, thus comprehensively identifying the proteins that function at various lifecycle stages and that function together to carry out particular cellular processes, e.g., red blood cell invasion, signal transduction, growth, vesicular trafficking, etc. The application of functional genomics approaches allows the properties of many genes and proteins to be assessed in parallel on a large scale. These approaches are being used to address specific questions about the biology of *P. falciparum*. Gene profiling (determining which genes are expressed) by microarray technology allows a rapid, parallel analysis of genome-wide changes in gene expression over a variety of experimental conditions (e.g., chloroquine versus saline control), tissues, and cell types; these genes can be clustered (ordered by expression pattern) to identify those that function in the same process. One of the most promising applications of microarrays is the study of differential gene expression during the complex *P. falciparum* lifecycle, specifically the formidable and challenging task of determining which subset of the 5,300 genes is represented in the transcriptome of each stage (Bozdech et al. 2003; Le Roch et al. 2003). These approaches are beginning to yield invaluable insights about new vaccine candidates, novel drug targets, and the molecular basis of drug resistance.

Proteomics is the study of all the proteins expressed in an organism. Global protein analysis offers a unique means of determining not only protein expression, but also interacting partners, subcellular localizations, and post-translational modifications of proteins of whole proteomes. Analyses of the proteomes of parasites that have been exposed to distinct environmental stimuli (e.g., chloroquine versus saline control) or that manifest distinct phenotypes (drug resistant versus drug sensitive) might also facilitate the identification of biochemical drug targets and of the specific proteins involved in drug resistance. Comparative genomics (the comparison of genomes of related species), on the other hand, will yield invaluable insights about the biology of and the pathogenesis of disease associated with different parasites, i.e., *P. falciparum*



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**Figure 1.** Patients at Apac Hospital  
Of the patients waiting at the Out-Patient Department of Apac Hospital in Northern Uganda, the majority are mothers of children under 5 years old with malaria. (Photograph by Toshihiro Horii, Department of Molecular Protozoology, Research Institute for Microbial Diseases, University of Osaka, Osaka, Japan.)

