VIEWPOINT

The Mosquito Genome—a Breakthrough for Public Health

Carlos M. Morel, Yeya T. Touré, Boris Dobrokhotov, Ayoade M. J. Oduola

The *Anopheles gambiae* genome sequence will accelerate identification of new insect vector target genes leading to improved strategies for malaria control.

Malaria remains a major killer, particularly in sub-Saharan Africa, with more than 1 million deaths among children every year. Malaria control is based on prompt diagnosis, appropriate drug treatment, protection of high-risk groups, and control of the mosquito vector. Emergence of drug resistance in the *Plasmodium* parasite species that cause malaria and of insecticide resistance (*1*) in the mosquito vectors that transmit the parasite to humans, combined with poor knowledge of mosquito biology and inappropriate vector control strategies, has hindered the many attempts to combat this disease. Publication of the 278-megabase genome sequence of the mosquito *Anopheles gambiae* reported by Holt *et al.* (*2*) on page 129 of this issue, together with the genome sequence of *Plasmodium falciparum*, the most deadly of the malaria parasites, reported by Gardner *et al.* (*3*) in this week's *Nature*, is a major contribution to efforts to combat malaria and other mosquito-borne diseases.

The complex genetics of different anopheline populations and this insect vector's remarkable efficiency are major obstacles to vector control, which must be selective, targeted, and site specific. Designing efficient vector control measures requires an excellent knowledge of mosquito ecology, population biology, and genetics. The limited understanding of mosquito biology, the emergence of insecticide resistance, and the failure of parasite control with drugs prompted the TDR (*4*) and the MacArthur Foundation to convene a meeting in Tucson, Arizona, in 1991 (*5*). Here, a small group of scientists proposed genetically engineering *A. gambiae* so that it could no longer harbor or transmit the *Plasmodium* parasite. This revolutionary idea, accepted by the Joint Coordinating Board of TDR, launched the field of molecular entomology. The 20-year plan had three principal goals: (i) to develop basic tools for the stable transformation of anopheline mosquitoes by the year 2000; (ii) to engineer a mosquito incapable of carrying the malaria parasite by 2005; and (iii) to run controlled experiments to test how to drive the engineered genotype into wild mosquito populations by 2010. The first two goals have already been achieved in *Anopheles* (*6, 7*) and its relative *Aedes* (*8*).

In 1999, a group of experts concluded that sequencing the *Anopheles* genome was both feasible and necessary. The sequencing initiative was launched at the *A. gambiae* Genome Summit convened in Paris by the Institut Pasteur and TDR in 2001. Now, less than 2 years later, the sequencing of the *A. gambiae* genome is complete. The *Anopheles* genome sequence provides us with an architectural scaffold for mapping, identifying, selecting, and exploiting desirable insect vector genes. It will promote our understanding of mosquito biochemistry, physiology, and behavior as well as of malaria epidemiology, and will spur development of new public health interventions. Furthermore, the complete genome sequence will accelerate the engineering of mosquitoes refractory to *Plasmodium* and the development of methods for driving this genotype into wild populations. It will also shed light on the molecular mechanisms of insecticide resistance, spurring development of a new generation of insecticides.

A. gambiae population genetics will be greatly clarified by new genetic markers derived from the genome sequence. This will lead to improved identification of different developmental stages of both sexes, and of blood-meal digestion stages in females. Characterization of the genetic structure of mosquito populations (gene flow, population dynamics, effective population size, dispersal) will establish firm phylogenetic relationships among these populations. The identification of new genes will improve our understanding of vector biology, particularly host-seeking and mating behaviors, biting and resting patterns, and immune responses against *Plasmodium* and other pathogens (*9, 10*). Better knowledge of vector population biology, ecology, and behavior will spur development of improved strategies for planning and implementing targeted vector control measures. For example, information on vector population dynamics and malaria transmission patterns can be used to determine when and where to administer vector control. Screening insecticide activity against specific genomic targets instead of whole insects is now feasible and should accelerate development of new insecticides and repellents.

The *A. gambiae* genome sequence, combined with new molecular tools for transforming mosquitoes, will make a major contribution to malaria control. A "strain" of *A. stephensi* that is unable to transmit malaria in mice has already been engineered (*6, 11*). The next big challenge is to devise strategies to efficiently drive and sustain a stable refractory genotype in wild mosquito populations (*12*). A better understanding of the behavior and evolution of endogenous transposable elements and their interactions with the mosquito genome will be needed for the long-term success of genetic vector control strategies in combatting malaria and other mosquito-borne diseases (*12*). Of course, the use of genetically modified insect vectors (*13*) in the field will require careful consideration of biosafety, ecological, ethical, legal, and social issues to ensure public acceptance (*14*) [see viewpoints by Scott *et al.* (*15*) and Alphey *et al.* (*16*)]. Communication among researchers, decision-makers, and the public is essential, as is the strengthening of collaborations between the developed and the developing world (*17*).

Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland. E-mail: tdr@who.int; www.who.int/tdr

References and Notes

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