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Malaria genomes 'completed'

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With another highly coordinated series of press releases, embargoes and precision-timed conferences, Nature and Science announced that the genomes behind malaria are as good as finished. *Nature* concentrates on the infective agent Plasmodium falciparum and its rat equivalent *P. yoelii yoelii*, while *Science* sheds light on the mosquito vector, Anopheles gambiae.

Ever since French pathologist Charles-Louis Laveron's late 18th century discovery of the link between *Plasmodium sp*, mosquitoes, and malaria, the fight has been on to rid the world of this scourge. Currently, however, the disease has the upper hand. More people are infected than ever before, with three children dying of the disease each minute.

The question now is how to make best use of this heroic piece of sequencing? Opinions are divided.

As co-author of the key *P. falciparum* genome paper, and leader of the effort at The Sanger Centre, Cambridge, UK, Neil Hall is understandably upbeat, seeing great scope for identifying potential drug targets. "One candidate is a microbial lactate dehydrogenase pathway that does exist in humans but is only used in anaerobic conditions," he told *The Scientist*, "but the most interesting area is the apicoplast." This microbial organelle has the same evolutionary origin as chloroplasts in green plants, and being non-mammalian it is an obvious target for drugs. Around 10% of genes in the genome code for proteins within this organelle, all of which are potential drug targets.

In fact, there seems almost no end of targets. Around 60% of *P. falciparum* genes have no previously identified function and 50% have not been seen in any other species. Any of these could be candidates.

But drugs are a poor route to solving the health crisis; they tackle disease, but don't stop people getting ill and are often too expensive for the majority of victims. A better solution is a vaccine, but here the genome may be of less use. "Most people agree that the genome will have more value for drug discovery than vaccines," says Oxford University's Adrian Hill, whose research unit now has a DNA-based viral vaccine for malaria in phase-2 clinical trials in Gambia.

But Neil Hall believes the genome will help scientists study antigenic variation. "That will obviously help people who want to understand the interaction with the host immune system. It would also give people who are looking for vaccines, the tools needed to apply high-throughput technologies to identify good vaccine targets."

In addition, proteomic analysis is revealing the stage in the life cycle of the microbe that each protein is expressed in. Only proteins expressed while the microbe is in a human are candidates. "It's not a matter of what's there, but when it is happening," explains Neil Hall.

The question on everyone's lips is, how long will it take? Neil Hall points out that drugs and vaccines take a minimum of a decade to move from concept to delivery, but adds that some sequences have been available for six years, so a few people have already got a head start. "One shouldn't overestimate the short-term value," adds Adrian Hill. "I don't think there will be people jumping up and down in Tanzania saying 'fantastic, they have the genome'."

"The real point is that there is not enough money going into product development. If you want something in five or 10 years' time, you put your money today into medium- or short-term projects. You don't put it into fundamental research in the genome," says Hall. "Someone needs to invest a lot of money in product development and small scale field trials now."

But the economics is simple. The potential market for a malaria vaccine in the developed world is $200 million per year and probably another $200–300 million in the developing world. This, says Hill, is too small for multinational pharmaceutical companies that are looking for multi-billion dollar returns from low-risk products - malaria vaccines are high risk. The consequence, he says, is a huge gap between the funding for malaria and for any other disease which causes comparable morbidity and mortality. "Of course, the recent reports of malaria showing up on the East coast of America could change all that," he comments.

Currently the funding gap is partially filled by public money and charitable funding, and the world's two biggest charities; The Wellcome Trust and the Gates Foundation are making important contributions to vaccine development. "The biggest funder remains the Pentagon and NIH, because of its interest in protecting US military," Adrian Hill points out.

Some people worry that vested interests in rich Northern countries have too much say, with the results imposed on the countries that bear the brunt of the illness. Director of the South African National Bioinformatics Institute in Bellville, Winston Hide is disappointed that no one had enabled countries where malaria is endemic to join in with the sequencing effort. "The bottle necks are the usual ones - lack of expertise, capital equipment and funding," he says. He also complains that proposals from endemic countries are often "ignored as they are not made in developed countries."

"Increased funding for malaria has been evolving recently. Unfortunately it goes mainly to the developed North, and has not been implemented in disease endemic countries," he says, but adds that the South African government has earmarked the equivalent of $40 million for a national Bioinformatics Network aimed at tackling not only malaria, but HIV and TB as well.

"Not being included in genome projects of *Plasmodium* and *Anopheles* has had a dramatic impact on the availability of using the data," he complains, adding that as a consequence important discoveries that could be made by these sidelined scientists may have been delayed.

While people in uninfected countries chase drugs and vaccines, Hide introduces a more immediate concern. He hopes that the genome may speed up production of antigen-based diagnostic tests. "Accurate diagnosis has a major impact," he says.

Hopefully, there will be more dialogue between all those involved in the search for ways of combating malaria during the next phase.

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