

## Editorial

# Bioinformatics and drug target selection for malaria control

The use of antimalarial drugs is an important component of malaria control programmes. These drugs class broadly into quinolines, artemisinin, antifolates, atovaquone/proguanil and antibiotics. The effectiveness of drugs is increasingly compromised by resistance. The development of new antimalarials and improvement of existing ones is therefore crucial to reduction of the increasing disease burden and economic loss due to malaria. Publication of the genome sequences of the most virulent human malaria parasite, *Plasmodium falciparum* and a rodent parasite, *P. yoelii yoelii* open new opportunities for intensive research to identify critical parasite determinants encoded in the genomes that can serve as drug targets and candidates for drug discovery programmes. The future availability of genome sequences of primate and other human and rodent malaria parasites will permit comparative analysis and open the ability to test the efficacy of drugs in robust model systems prior to clinical trials.

The challenge of identifying good drug targets will rely on integration of disparate data from high-throughput technologies such as genome and cDNA sequencing, microarrays, proteomics, structural genomics and metabolic networks. This integration requires mining databases using bioinformatics tools to detect patterns that make parasite determinants stand out as candidates for drug discovery. According to Yuthavong<sup>1</sup> the characteristics of a good malaria drug target are (i) essential feature of the parasite life cycle, must differ significantly from any analogous process in the host (ii) lack of alternative pathways which circumvent the target (iii) preferred accessibility to the parasite or accumulation within the parasite of lead compounds (iv) low potential for development of drug resistance (v) involvement in a rate limiting biochemical process (vi) ability to readily test effects of inhibitors on the target (to validate the target) (vii) presence of a straightforward test system for high-throughput screening and (viii) different specificity for inhibition from the host enzyme/receptor, existence of known specific inhibitors.

Comprehensive study of the function and interactions of candidates in the context of a host-parasite relationship is crucial before committing them to the complete discovery process. Some bioinformatics approaches that exploit the biological data include gene expression analysis, search for acquisition of foreign genetic material and scanning for genes under positive selection.

Knowledge of how malaria parasite genes are regulated is key to exploiting them as targets; the differences in levels, time and stage/tissue of expression as well as in comparison to that of the host. Little is known about the mechanisms of transcription and translation in malaria

parasites when compared to organisms such as yeast or their apicomplexan relative *Toxoplasma gondii*. For example, the role of alternative splicing needs to be intensively studied. Early studies on alternative transcripts in *P. falciparum* speculated that multiple protein isoforms could be a means of diverting host immune response from the major functional isoform. Temporal and spatial data on protein diversity can be used to design inhibitors that are specific to the major isoform.

Malaria parasites have an indispensable organelle called the apicoplast that is thought to be of bacterial and algal origins by secondary endosymbiosis. Genome analysis has identified about 500 nuclear-encoded genes that are targeted to the apicoplast. Horizontal transfer of genetic material from this organelle to the nuclear genome can now be intensively studied using bioinformatics to reveal biological processes unique to the parasite, which take place in the apicoplast and/or the parasite cytoplasm. Such processes can be target of antibiotics and herbicides.

Bioinformatics tools for high-throughput positive selection scanning of inter- and intraspecies orthologous DNA sequences has the potential to yield important mutations that confer a selective advantage to malaria parasites. Combining data from sequence alignment such as type, location and effect of such mutations with protein structure data such as substrate binding and cleavage sites can improve design of selective inhibitors. This type of integrated view has been used to explain host specificity among blood-feeding parasites.

It is important to re-emphasise the need to develop bioinformatics capacity in disease endemic countries<sup>2</sup>. A better understanding of the parasite biology and excellent capacity to use bioinformatics tools will accelerate the control of malaria.

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#### **References**

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