EDITORIAL

MALARIA GENOMICS AND DISEASE CONTROL

The genesis and assembly of genomic data continues to occur with increasing rapidity. With this process comes the claim and expectation of ability to apply the molecular information concerned to improving disease management, control and prevention. Initially a prime target was the human genome: that database is opening the doors to genetic components of disease as well as to evolutionary considerations. The case by case unraveling of genomics of communicable disease causing organisms now follows in rapid succession. The recent publication of falciparum malaria genome structure is an example with high expectations that require some careful thought.

The AT-rich *Plasmodium falciparum* genome comprises 23 megabases in 14 chromosomes, encoding ~ 5,300 genes (Gardner *et al*, 2002). It is both instructive and perhaps somewhat discouraging to note that genes related to immune system evasion and host-parasite interactions make up a large proportion of the total, so reflecting evolutionary history and presenting a rather tough barrier for drug and vaccine developers to crack. However, inevitably, the catch cry has already gone out widely proclaiming that unraveling the genome DNA sequence will facilitate such developments. Such has been the very optimistic interpretation of most genomics concerned with infectious agents: we live for the moment in a promising, exciting, genomics focused world.

We may well ask how valid is such a connection and to what extent all the efforts to date devoted to drug and vaccine design have been fruitful or in vain when seen against this new information base. This question raises some matters of principle along with the detailed chemical history from molecule to molecule. There is no doubt that having the full genomic catalogue available on-line is a very positive step forward, allowing cross-referencing of existing structural knowledge of both drugs and vaccine candidate molecules and as a take-off point for broader molecular tool design. This is already one successful outcome fully justifying the effort expended, even though there is now a lot more work to be done in selecting the most fruitful roads to take from here, a process that will be accelerated per malaria proteomics (Lasonder *et al*, 2002).

It is, however, of pertinence to note that this scientific effort has emanated almost entirely from well-funded Western academic laboratories, with very limited inputs from scientists in malaria-endemic area institutions, other than as facilitators of access to infected or at-risk populations. This is so despite more than 30 years of somewhat frustrating work focused on attempts at malaria vaccine development to which graduate students and postdocs from malaria-endemic countries have contributed in the context of team efforts in some of the pertinent Western laboratories, often as passing ships in the night, who returned home without adequate facilities or appropriate encouragement to transfer the science to the problem where it is so firmly entrenched. Thus we see a continuing quasi colonial-style approach still well rooted in the new century, instead of the positive option of building the science into the communities where the challenge of the problem is right at hand.

Those with the funds and the power to apply them will argue that it doesn't matter where or by whom the genomic analysis has been done if it leads to effective vaccines or efficacious new drugs, the world needs them as soon as possible. Of course there is a large element of truth in that view, but it evades the point of opportunity missed. Arguably the chance to build-in scientific development is greatest when coupled with intrinsic operational need, in proximity to the disease problem. In the case of malaria the example is particularly cogent.

While many malaria endemic countries still struggle to mount effective disease control programs, some such as Brazil and Thailand have proud records of effective outcomes based on intrinsic field organizational capacity; they also have good intrinsic science. Yet both have seen this capacity used by outsiders from the rich scientific laboratories as convenient, with acknowledgements given in the small print of some ensuing papers. Colonial science, contributing to career paths of the rich, damning the would-be kudos of intrinsic science? This issue, however, goes well beyond

the frustration factor, just as vaccine development goes well beyond the laboratory. Well-heeled travelers aside, malaria vaccines, if and when they do emerge from a dim past, most likely will be simply one set of ingredients in malaria control strategies, which must give priority to integrated sustainability. This means that, initially at least, they must be able to be integrated into control programs that work well and this means programs that are intrinsically driven; there is no place for outsider domination. Thus malaria endemic countries with a proven successful record must come to the fore now in vaccine strategy, as some have over many years with respect to anti-malaria drug trials.

These arguments are not so easily accepted by the vaccine developers, who understandably see the trials as integral to the laboratory process. Initial phase I trials rightfully fall into that category, since failure at that early stage effectively vetoes further work on a given construct. However progress beyond that stage can arguably be better carried out in the context of malaria endemic country science, so that the potential pathway of testing procedures can encompass the flow right through to post phase III integration into proven sustainable disease control programs. Such a strategy necessitates major involvement of endemic country scientists throughout the trial process.

The potential improvement in the application of the genomic information base would be considerable were this approach be taken seriously right now. The ability to select suitable epitopes or epitope combinations as candidate vaccine molecules should be enhanced, especially with respect to minimizing antigenic variation and to monitoring host response to candidate antigens. Carrying out such analyses *in situ* on the verge of defined control areas could provide continuing predictive evaluation in a way that would not be feasible in far-off laboratories. This approach also would facilitate integration of vaccine and drug strategies in a productive manner in the endemic area concerned, so to mould together the several arms of malaria control programs, taking laboratory science into the field and the field data into the laboratory.

The complexity of the problems and thus of potential solution of the problems is aptly exemplified by the situation in the global epicenter of multi-drug resistant falciparum malaria in the Mekong region (Kidson *et al*, 1999). There 6 geographically proximate endemic countries (Cambodia, China/Yunnan, Lao PDR, Myanmar, Thailand, Viet Nam) form a regional continuum with varying economic, cultural, scientific, epidemiological patterns, brought together in a Roll Back Malaria sub-program. Recent establishment of a series of sentinel sites for monitoring anti-malarial drug resistance regularly using a common methodology is paving the way for serious attack on the information base of multi-drug resistance at or near source. The country combination embraces some of the world's best drug monitoring experience and new drug trial capability. Institutional vaccine trial facilities are well established and in the region overall a wide spectrum of disease endemicity and population mobility presents opportunity to carry out a variety of field trials in context with therapeutic strategies. Yet to date little attention has been accorded to the possibilities of this and/or similar opportunities by the drivers of molecular vaccine development programs.

We are thus faced with exciting times in the molecular science of malaria as the result of genome elucidation. We are at the same time faced with opportunity to recast stratagems for more equitable and thus more effective handling of malaria vaccine development and of coupling this with improved management of multi-drug resistance. Genomics can act positively as a stimulus to broader scientific opportunity or negatively as a conduit for laboratory domination.

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