Editorial

Antimalarial drug discovery and design in the era of resistance

These are interesting times for antimalarial drug research. On the one hand, recent reports from Southeast Asia paint a grim picture of reduced malarial parasite susceptibility to artemisinin combination therapies (ACTs), currently the mainstay of antimalarial treatment in most of the world [1]. History has shown us that the protozoal parasite of malaria (*Plasmodium*), in particular the most lethal human parasite *Plasmodium falciparum*, is adept at acquiring resistance to the antimalarial drugs that we have deployed [2]. The fall from grace of former stalwarts such as chloroquine and sulphadoxine + pyrimethamine has in this respect been spectacular: in some regions the therapeutic lifespan of the latter has been as little as 5 years [3].

On the other hand, progress in understanding parasite biology, antimalarial drug mechanisms of action, drug target identification and validation, and generation of new drug candidates has been advancing at an unprecedented rate [4–9]. In particular, high-throughput screening of vast chemical libraries has identified thousands of drug-like compounds with at least moderate activity on cultured blood-stage parasites, multiplying the number of chemical starting points available for antimalarial lead generation [10]. Methods for cultivation and drug susceptibility testing of liver-stage and pre-sexual (gametocyte) parasites have also improved [11,12]. These advances provide tools for the development of drugs affecting not only the pathogenic forms of malarial parasite but also those responsible for transmission. These latter advances are appropriate to the emerging research agenda for malaria, which emphasizes the development of tools required not just for controlling but for eradicating the disease [13]. Even if these advances translate into new antimalarial drugs in the clinic, it is however likely or perhaps inevitable that they too will fall prey to resistance, and only 'buy us a few years' until yet more drugs can be developed. How can we break out of this vicious cycle?

The purpose of this Special Issue is to address (i) the factors that contribute to the speed of emergence of resistance among different antimalarial drugs, and (ii) strategies for developing therapies less prone to resistance. The aim is to encourage consideration of likely resistance in new antimalarial drug discovery and design projects, and to stimulate thinking about how future therapies might be made more 'resistance-proof'. The current state of antimalarial drug resistance in the field, especially as regards ACTs, and the need for drugs less prone to resistance are first set out by Harald Noedl (University of Vienna) [14]. This is followed by a discussion of our current understanding of antimalarial resistance and how to factor propensity for resistance into antimalarial drug development, by José Garcia-Bustos and Javier Gamo (Glaxo SmithKline, Tres Cantos, Spain) [15]. A number of different approaches to more 'resistance-proof' drugs can be conceived. One, according to David Sullivan (Johns Hopkins School of Public Health, USA) is to develop drugs that target processes outside the genetic control of the parasite, so that resistance cannot easily arise by for example point mutations in the target (e.g. enzyme, receptor) gene [16]. This concept can be taken further, as discussed by Miguel Prudêncio and Maria Mota (Institute of Molecular Medicine, Lisbon), by targetting host factors rather than parasite ones [17]. If these host factors can be inhibited without significant toxicity, this might constitute another form of drug to which resistance could not readily arise. Yet another approach may be to target the pathogenic processes initiated by the parasite, rather than parasite growth and survival *per se*, hence (possibly) avoiding the selective pressure exerted by conventional antimalarial drugs. This idea is considered by Angus

Bell and Daniela Boehm (Trinity College Dublin) [18]. There are other approaches that are being and doubtless will be pursued by the malaria research community. We hope that these articles will stimulate such efforts.

I thank the contributors to this issue for giving generously of their ideas and their scarce time, and Alexis Nzila of the King Fahd University of Petroleum and Minerals, Saudi Arabia for help with editing.

REFERENCES

[1] Ding XC, Beck HP, Raso G. *Plasmodium* sensitivity to artemisinins: magic bullets hit elusive targets. Trends Parasitol 2011; 27: 73-81.
[2] Hyde JE. Drug resistant malaria – an insight. FEBS J 2007; 274: 4688-98.
[3] White NJ, Olliaro PL. Strategies for the prevention of antimalarial drug resistance: rationale for combination chemotherapy for malaria. Parasitol Today 1996; 12: 399-401.
[4] Baker DA. Malaria gametocytogenesis. Mol Biochem Parasitol 2010; 172: 57-65.
[5] Birkholtz L, van Brummelen AC, Clark K, Niemand J, Maréchal E, Llinás M, Louw AI. Exploring functional genomics for drug target and therapeutics discovery in Plasmodia. Acta Trop 2008; 105: 113-23.
[6] Burrows JN, Chibale K, Wells TN. The state of the art in anti-malarial drug discovery and development. Curr Top Med Chem 2011; 11: 1226-54.
[7] Mueller I, Galinski MR, Baird JK, Carlton JM, Kochar DK, Alonso PL, del Portillo HA. Key gaps in the knowledge of *Plasmodium vivax*, a neglected human malaria parasite. Lancet Infect Dis 2009; 9: 555-66.
[8] Prudêncio M, Rodriguez A, Mota MM. The silent path to thousands of merozoites: the *Plasmodium* liver stage. Nat Rev Microbiol 2006; 4: 849-56.
[9] Tilley L, Dixon MW, Kirk K. The *Plasmodium falciparum*-infected red blood cell. Int J Biochem Cell Biol 2011; 43: 839-42.
[10] Guiguemde WA, Shelat AA, Garcia-Bustos JF, Diagana TT, Gamo FJ, Guy RK. Global phenotypic screening for antimalarials. Chem Biol. 2012; 19: 116-29.
[11] Buchholz K, Burke TA, Williamson KC, Wiegand RC, Wirth DF, Marti M. A high-throughput screen targeting malaria transmission stages opens new avenues for drug development. J Infect Dis. 2011; 203: 1445-53.
[12] Derbyshire ER, Prudêncio M, Mota MM, Clardy J. Liver-stage malaria parasites vulnerable to diverse chemical scaffolds. Proc Natl Acad Sci U S A 2012; 109: 8511-6.
[13] malERA Consultative Group on Drugs. A research agenda for malaria eradication: drugs. PLoS Med. 2011; 8: e1000402.
[14] Noedl H. The need for new antimalarial drugs less prone to resistance. Curr Pharm Des 2012; (this issue).
[15] Garcia-Bustos JF, Gamo F-J. Antimalarial drug resistance and early drug discovery. Curr Pharm Des 2012; (this issue).
[16] Sullivan DJ Jr. *Plasmodium* drug targets outside the genetic control of the parasite. Curr Pharm Des 2012; (this issue).
[17] Prudêncio M, Mota MM. Targeting host factors to circumvent anti-malarial drug resistance. Curr Pharm Des 2012; (this issue).
[18] Bell A, Boehm D. Anti-disease therapy for malaria – 'resistance proof'? Curr Pharm Des 2012; (this issue).

Angus Bell

Dept. of Microbiology
School of Genetics & Microbiology
Moyne Institute of Preventive Medicine
Trinity College Dublin
Dublin 2
Ireland
E-mail: abell@tcd.ie