Antimalarial Drug Discovery: *In Silico* Structural Biology and Rational Drug Design

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Abstract: Malaria remains one of the most burdensome human infectious diseases, with a high rate of resistance outbreaks and a constant need for the discovery of novel antimalarials and drug targets. For several reasons, Plasmodial proteins are difficult to characterise structurally using traditional physical approaches. However, these problems can be partially overcome using a number of *in silico* approaches. This review describes the peculiarities of malaria proteins and then details various *in silico* strategies to select and allow descriptions of the molecular structures of drug target candidates as well as subsequent rational approaches for drug design. Chiefly, homology modelling with specific focus on unique aspects of malaria proteins including low homology, large protein size and the presence of parasite-specific inserts is addressed and alternative strategies including multiple sequence and structure-based prediction methods, sampling-based approaches that aim to reveal likely global or shared features of a Plasmodial structure and the value of molecular dynamics understanding of unique features of Plasmodial proteins are discussed. Once a detailed description of the drug target is available, *in silico* approaches to the specific design of an inhibitory drug thereof becomes invaluable as an economic and rational alternative to chemical library screening.

Keywords: Malaria, antimalarials, pharmacophore, structure-based drug discovery, *in silico.*

1. BACKGROUND

More than 2 billion people are at risk of malaria and current clinical episodes are estimated to be as high as 500 million cases and nearly 3 million deaths per year, mainly children and pregnant women in resource-poor environments [1]. The scale of the malaria problem emphasises the fragile nature of prevailing control programmes and the importance of developing more effective methods for the prevention, treatment and ultimately, the eradication of malaria [2]. Combating malaria (caused by *Plasmodium* species) requires significant financial and organizational resources, yet malaria itself restrains economic development, creating a vicious cycle in developing countries [3-5].The devastating socio-economic and public health impact of malaria is mostly experienced in sub-Saharan Africa and is galvanized by the emergence and rapid spread of drug-resistant parasites and the lack of a licensed vaccine. Even if and when effective vaccines do become available, chemotherapy will still be required. The discovery of new and robust anti-malarial drugs, preferably acting on new targets that have not mutated yet into resistant forms, is therefore urgently needed. However, because malaria is considered a disease of poverty, there is very little incentive for pharmaceutical companies to partake in a global antimalarial effort except for provision of funds for selected projects and research institutes [6]. The onus therefore falls predominantly on publicly funded research groups, academic institutions and public-private partnerships established since 2000, to identify and develop novel antimalarial strategies [7].

In general, there has been a steady decline in the number of new molecular entities entering clinical development and reaching the market over the past 10-15 years due to high levels of drug attrition mainly attributed to unanticipated efficacy and toxicity problems [8]. Part of the blame seems to reside in the extensive use of High-Throughput Screening (HTS) against ambiguous or single targets which in effect reduces the biological context by separating the target from other cellular proteins and processes that might impact its function [9] and lack of diversity in existing chemical libraries [10]. The phenotypic robustness of biological systems often reduces the effectiveness of a single-target compound [11]. One compound-one target strategies therefore need to be adapted and it is suggested that the focus should be on promiscuous compounds that modulate multiple target proteins to achieve the desired results [12]. Cell-based high content screening (HCS) circumvents this problem, since it allows the detection of small molecules acting in the cellular context [13], but it leaves the question of the actual target unresolved. HTS technology is often limited to big pharmaceutical companies due to the high cost involved in screening of targets but is also limited by high attrition, with a hit-rate of between 0.01-1% of compounds screened [14]. The process is sequential, with ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicology) properties determined later on in the discovery

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