

Editorial from Guest Editor

Malaria continues to kill at an alarming rate of about 1-2 million deaths annually. Early predictors have health officials extremely concerned because it is estimated that this death rate will increase due to the high level of malaria drug resistance and the lack of effective and inexpensive chemotherapy options. Decades of malaria drug development have resulted in structurally similar classes of compounds that do little to circumvent established drug resistance mechanisms in the parasite. In addition to drug resistance, the mechanisms of antimalarial activity of several of these drugs are unknown or not very well understood which complicates efforts to design effective derivatives of these drugs. Knowledge-based drug design is needed more than ever in the fight against malaria to introduce new drugs with known mechanisms of actions. Structure-based approaches to malaria drug discovery to include high throughput screening, virtual and computer-aided design, and synthesis of chemical libraries, are currently being applied to develop the next generation of effective antimalarials. In this age of significant drug resistance, these approaches provide an opportunity to introduce novel chemical entities into the malaria drug development pipeline.

In this issue of *Combinatorial Chemistry & High Throughput Screening*, we have assembled a collection of articles on the discovery of new antimalarial agents. This issue will focus on strategies of knowledge-based drug design to identify new chemical entities, in addition to topics on target screens and library design.

We begin the theme with an article by C. Mehlin on the efforts to gain structural information on malarial proteins. This review focuses on several malarial enzyme targets for which there are crystal structures available. The difficulty associated with the expression and purification of malarial proteins is a major stumbling block in rational drug design and these setbacks are discussed. For those enzymes that are amenable to structural determination, co-crystallization of inhibitors with enzymes provides a wealth of information required to guide antimalarial drug discovery.

Although rational drug design methodologies are being applied to several malaria enzymes, we chose to review efforts on two recently developed malaria drug target programs. Zhiqiang and coworkers compare fatty acid synthesis between bacteria and malaria and describe recent efforts to target these unique enzymes in *Plasmodium falciparum*. In particular, targeting β -ketoacyl-ACP synthase III (KASIII) to identify potent antimalarial agents is presented. Continuing with this theme, Keenan and coworkers describe an iterative process that includes high throughput screens and computer aided inhibitor design to select potent, yet specific inhibitors of the malarial cyclin dependent protein kinases (CDKs). Unlike fatty acid biosynthesis, CDKs are highly conserved throughout eukaryotes and this article provides an overview of the approaches used to target conserved enzymes that are essential for malaria growth and development.

Targeting malarial enzymes or metabolic pathways for chemotherapeutic development requires synthesis of specific chemical libraries. Initial drug discovery leads may arise from the screening of chemical databases; however, refinement towards specificity and potency must be supported by synthetic efforts. Deprez-Poulain and Melnyk describe the synthesis of piperazine libraries with potent antimalarial activity. They then describe how these libraries were used to elicit a possible mechanism of action similar to that of chloroquine and expand on the approach with the identification of the aminopeptidase Pfa-M1 as a potential target of these compounds.

In addition to specific targets, metabolic pathways can be targeted to kill the malaria parasite. Three articles in this series present evidence that compounds can be designed to inhibit the metabolic processes within the parasite. Salom-Roig and coworkers describe the synthesis of compounds that appear to have dual functions associated with antimalarial activity. Three generations of compounds, (bis-quaternary salts, bis-amidines, and bis-thiazolium salts), were synthesized to target

phosphatidylcholine biosynthesis and heme detoxification pathways in the parasite. These compounds have potent activity against malaria parasites in culture and in animal models. Tekwani and Walker continue the theme of targeting heme detoxification and discuss several *in vitro* -hemin formation assays. The development of these assays has made it possible to screen for inhibitors of hemozoin synthesis in high throughput formats. Several chemical classes have been screened in this system to include quinolines, xanthenes, azoles, and natural products. The last article on targeting systems rather than individual targets is from Staines and coworkers. They describe exploitation of the new permeability pathways (NPP) in the parasite using two novel approaches. In the first, they describe several chemical classes that are effective inhibitors this permeability pathway which is lethal in the parasite. Second, they describe the use of this pathway to deliver drugs or inhibitory compounds into the parasite. Finding novel ways of introducing antimalarial agents into the parasite is a challenge, since malaria is an intracellular parasite enveloped within several biological membranes. The NPP may provide a way of ensuring that particular compounds are delivered to the specified target within the parasite.

We conclude with a topic that many investigators do not like to think about because it can mean the end to any potential lead compound from their respective drug discovery programs: pharmacokinetics and toxicity. Shearer and coworkers describe the role of metabolic studies in the development of new antimalarial agents. In particular, they describe ADME (absorption, distribution, metabolism, and excretion) assays that if used properly within the drug discovery pipeline, can effectively guide antimalarial drug design and prevent many setbacks that cost a significant amount of time and money.

In summary, we have collected several articles that discuss approaches to antimalarial drug discovery using rational drug design methodologies. Although there are multiple efforts in malaria drug discovery, these articles deal with new areas that have the potential of introducing new chemical entities into the malaria drug development pipeline. It is hoped that this volume will provide insight into the rational drug design paradigm and how it can be applied for the discovery of novel antimalarial agents. For scientist working outside the realm of tropical diseases, this issue may serve as a reminder that malaria remains a significant problem in the world and that every effort is essential to keep the malaria drug development pipeline full with the next generation of potential malaria chemotherapeutics.

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