Novel Rational Drug Design Strategies with Potential to Revolutionize Malaria Chemotherapy

F.W. Muregi*[,1,2], P.G. Kirira[3] and A. Ishih[1]

[1]*Department of Infectious Diseases, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashiku, Hamamatsu 431-3192, Japan*

[2]*Centre for Biotechnology Research and Development, Kenya Medical Research Institute (KEMRI), P.O. Box 54840-00200, Nairobi, Kenya*

[3]*Department of Chemistry, Graduate School of Science, Kyoto University, Kitashirakawa Oiwake-cho, Sakyo-ku, Kyoto 6006-8502, Japan*

Abstract: Efforts to develop an effective malaria vaccine are yet to be successful and thus chemotherapy remains the mainstay of malaria control strategy. *Plasmodium falciparum*, the parasite that causes about 90% of all global malaria cases is increasingly becoming resistant to most antimalarial drugs in clinical use. This dire situation is aggravated by reports from Southeast Asia, of the parasite becoming resistant to the "magic bullet" artemisinins, the last line of defense in malaria chemotherapy. Drug development is a laborious and time consuming process, and thus antimalarial drug discovery approaches currently being deployed largely include optimization of therapy with available drugs—including combination therapy and developing analogues of the existing drugs. However, the latter strategy may be hampered by cross-resistance, since agents that are closely related chemically may share similar mechanisms of action and/or targets. This may render new drugs ineffective even before they are brought to clinical use. Evaluation of drug-resistance reversers (chemosensitizers) against quinoline-based drugs such as chloroquine and mefloquine is another approach that is being explored. Recently, evaluation of new chemotherapeutic targets is gaining new impetus as knowledge of malaria parasite biology expands. Also, single but hybrid molecules with dual functionality and/or targets have been developed through rational drug design approach, termed as "covalent bitherapy". Since desperate times call for radical measures, this review aims to explore novel rational drug-design strategies potentially capable of revolutionizing malaria therapy. We thus explore malaria apoptosis machinery as a novel drug target, and also discuss the potential of hybrid molecules as well as prodrugs and double prodrugs in malaria chemotherapy.

Keywords: Antimalarial drugs, apoptosis, hybrid drugs, *Plasmodium falciparum*, prodrugs, topoisomerases.

1. INTRODUCTION

Malaria is the most wide spread parasitic disease caused by protozoal parasite of the genus *Plasmodium*, and approximately half of the world's population is at risk of malaria [1]. Traditionally, four *Plasmodia* species cause human malaria viz. *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae* [2]. Recently, the primate parasite *P. knowlesi* has been established as the fifth causative agent of human malaria [3,4]. *P. falciparum* is the most prevalent and virulent of these parasites, responsible for about 90% of all global malaria-associated deaths each year [5]. In 2008, there were an estimated 243 million global malaria cases with African region accounting for 85% of these cases, followed by the South-East Asia (10%) and Eastern Mediterranean Regions (4%). These afflictions led to an estimated 863 000 deaths, of which 89% were in the African Region, followed by the Eastern Mediterranean (6%) and the South-East Asia Regions (5%) [6]. The goal of eradicating malaria through chemotherapy (eg. chloroquine, CQ, **1,** Fig. **1**) and residual insecticides, thought to be within reach in the 1960s has since been abandoned, and malaria control efforts today are largely geared towards reducing malaria morbidity and mortality [7]. Concerted efforts to develop an effective vaccine have so far been unsuccessful, and thus chemotherapy still remains the mainstay of malaria control strategy [8]. Unfortunately, *P. falciparum* has rendered most of the classical antimalarials including 4-aminoquinolines (eg. CQ and amodiaquine, AMQ) and antifolates (sulfadoxine/pyrimethamine, Fansidar®) ineffective due to increased resistance [9]. Furthermore, most of antimalarials in clinical application are either chemically related and/or share the same putative target, thus may possess similar toxicity and share cross-resistance [10,11]. In order to delay development of resistance, World Health Organization (WHO) currently recommends use of semi-synthetic derivatives of artemisinin (ART, **2**, isolated from Chinese herb *Artemisia annua*) such as artesunate **(3)**, artemether **(4)** and dihydroartemisinin (DHA, **5**) (Fig. **1**) in combination with longer acting drugs as the first-line therapies against drug-resistant falciparum malaria. These combinations are termed as artemisinin-based combination therapies (ACTs), and include artemether-lumefantrine (Coartem®), artesunate-AMQ, artesunate-mefloquine (MFQ), artesunate-sulfadoxine pyrimethamine and DHA-piperaquine [6,12]. However, although there are no confirmed cases of clinical resistance against ART derivatives, hereafter referred to as artemisinins, reports from Southeast Asia (Thai/Cambodia border)—traditionally the 'epicentre' of malaria drug resistance—are alluding to reducing efficacy of this class of drug [13-16], which may be a harbinger of resistance. Resistance to the artemisinins seems inevitable, and thus the urgency for search for novel antimalarial drugs and targets can never be gainsaid. Antimalarial drug discovery approaches currently being deployed largely include optimization of therapy with available drugs including combination therapy and developing analogues of the

*Address correspondence to this author at the Department of Infectious Diseases, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashiku, Hamamatsu 431-3192, Japan; Tel: +81-53-435-2338; Fax: +81-53-435-2337; E-mail: fmuregi@hama-med.ac.jp; fwamakima@yahoo.com

0929-8673/11 $58.00+.00