Redox subversive substrates of flavoenzymes block malaria parasite development invertebrate hosts & mosquito vectors

Alice-Anne Goetz[1], Liwen Feng[2], Blandine Franke-Fayard[3], Katharina Ehrhardt[*1], Sophie Adjalley[4], Chris Janse[3], Elisabeth Davioud-Charvet[†5], and Stephanie Blandin[‡§1]

[1]Mosquito Immune Responses (Inserm U963 / CNRS UPR9022) – Inserm, CNRS : UPR9022, université de Strasbourg – IBMC, 15 rue Descartes 67084 Strasbourg, France

[2]Laboratoire de Chimie Médicinale (UMR 7509) – Ecole européenne de chimie polymères et matériaux de Strasbourg, université de Strasbourg, CNRS : UMR7509 – 25, rue Becquerel 67087 STRASBOURG CEDEX 2, France

[3]Leiden Malaria Research Group – Leiden University Medical Center Albinusdreef 2 2333 ZA Leiden, Pays-Bas

[4]Sanger Institute – Genome Campus, Hinxton, Cambridge, Royaume-Uni

[5]Laboratoire de Chimie Médicinale – Ecole européenne de chimie polymères et matériaux de Strasbourg, université de Strasbourg, CNRS : UMR7509 – 25, rue Becquerel 67087 STRASBOURG CEDEX 2, France

Résumé

The emergence and spread of drug resistance against most antimalarials on the market raises an urgent need for new therapeutics. Benzylmenadiones (bMDs) are redox subversive substrates of flavoenzymes with potent antiparasitic activity against the blood stages of the human pathogen *Plasmodium falciparum* (Pf). The lead bMD is active against chloroquine and atovaquone-resistant Pf strains and has an IC50 in the nM range. Parasites are exposed to many oxidative stresses during their development, notably upon haemoglobin digestion and key flavoenzymes, such as the glutathione reductase (GR), are essential to maintain their redox homeostasis. The lead bMD is a subversive substrate of recombinant PfGR that was recently validated as an excellent drug target. Indeed, it is not only essential during parasite multiplication in human erythrocytes, but also in mosquitoes, suggesting that subversive redox substrates for GR could be excellent drugs that both treat people and block parasite transmission. Here we report a robust in vivo assay to assess the efficiency of antimalarial compounds as transmission blocking drugs. We show that bMDs are effective against multiple parasite developmental stages and reduce both parasitemia in mice and parasite transmission to mosquitoes. We will further discuss the characterization of the mode of action of benzylMD.

Mots-Clés: antimalarial drug, transmission blocking, menadione, flavoenzymes, redox homeostasis

[*]Auteur correspondant:

[†]Auteur correspondant:

[‡]Intervenant

[§]Auteur correspondant: stephanie.blandin@inserm.fr