1985 - 2001	Ph.D. in Pharmaceutical and Chemical Sciences - Paris 11 University, France and Senior Scientist - Centre National de la Recherche Scientifique (CNRS), France
2001 - 2002	Visiting Scientist - University of Michigan, USA
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Elisabeth Davioud-Charvet

Drug Development against Disulfide Reductases from Parasites and Cancer Cells

Goal

Design, synthesis and mechanism of disulfide reductase inhibitors and redox-cyclers that affect the redox equilibrium of parasites and cancer cells.

Background

The aim of our interdisciplinary research is to substantiate NADPH-dependent disulfide reductase inhibitors as antiparasitic and cytostatic agents. Such compounds are active per se but, in addition, they can reverse thiol-based resistance against other drugs in parasites and tumour cells. Our strategy is based on the synthesis of subversive substrates or catalytic inhibitors, fluorine-based suicide-substrates, uncompetitive inhibitors, photoreactive inhibitors (as tools for photoaffinity labeling studies) of the selected targets, namely the glutathione reductases (GR) of the malarial parasite *Plasmodium falciparum* and man, the thioredoxin reductases (TrxR) of *P. falciparum* and man, the trypanothione reductase (TR) from *Trypanosoma cruzi*, and the thioredoxin-glutathione reductase (TGR) of *Schistosoma mansoni*.

Research Highlights

Our strategy for inhibitor optimization is based on the design and the synthesis of dual drugs that act as "Trojan horses" drugs consisting of a short chloroquine analogue – active against malaria per se – linked to a GR inhibitor. The strategy was also validated in the current malaria project with new functionalized low-weight 1,4-naphthoquinones derivatives belonging to the 3-benzylmenadione series. The redox-active compounds revealed potent antimalarial effects against chloroquine-sensitive and -resistant strains of *Plasmodium falciparum in vitro* and in mouse malaria models (EP patent). A cascade of redox reactions for antimalarial drug bioactivation involving both heme-

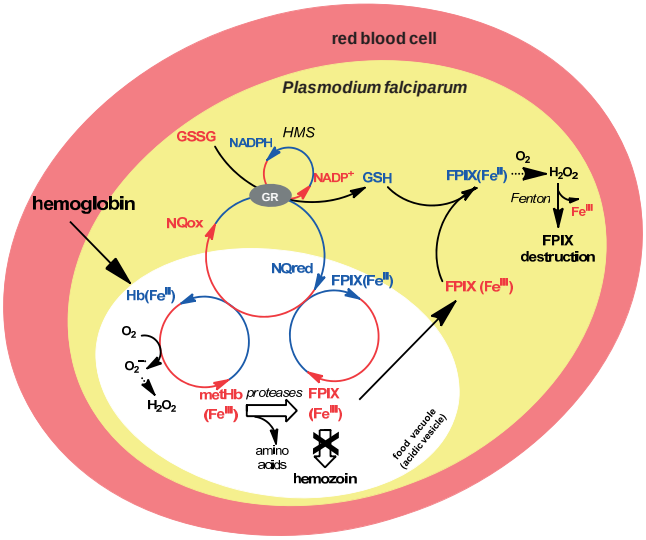

Fig. 1: *"Drowning Plasmodium in Redox" was achieved by 3-benzylmenadione derivatives with potent antimalarial effects both in vitro and in vivo. Compounds with GR redox-cycling activity displaying the ability to reduce iron^{III} to iron^{II} from haemoglobin and heme species.*

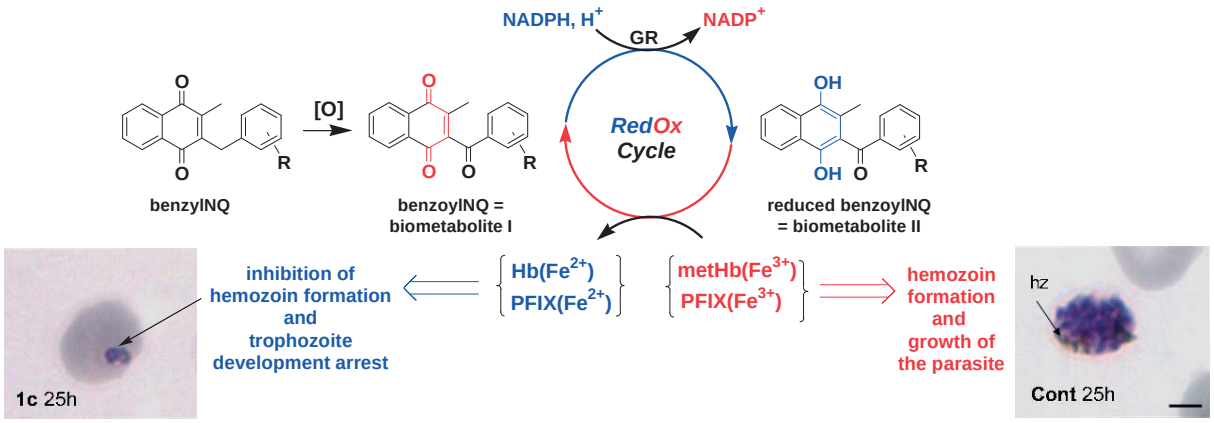

Fig. 2: *Proposed cascade of redox reactions for bioactivation of antimalarial 3-benzyl menadione derivatives (benzylNQ). The reaction cascade in the Plasmodium-infected erythrocyte involves heme-catalyzed oxidations and glutathione reductase-catalyzed reduction leading to inhibition of P. falciparum trophozoite development and of hemozoin formation.*

catalyzed oxidation reactions and the glutathione reductases from the *Plasmodium*-infected erythrocyte was proposed to be involved in the action mechanism of the 3-benzylmenadione series. The biometabolites were shown to act, in oxidized form, as the most efficient subversive substrates of both glutathione reductases of *Plasmodium*-infected erythrocytes described so far, and, in reduced form, to redox-cycle methemoglobin to hemoglobin. Ultimately, the antimalarial naphthoquinones are suggested to affect the redox equilibrium of target cells resulting in trophozoite development arrest, by drowning the parasite in its own metabolic products. For leishmania and trypanosomes various unsaturated ketones derivatives acting as trypanothione-reactive agents were produced and revealed potent trypanocidal effects against pentamidine-sensitive and -resistant strains of *Trypanosoma* and *Leishmania* species *in vitro*. Current efforts include the chemistry of prodrugs of 1,4-naphthoquinones and bis (Michael acceptors) derivatives as antiparasitic drug-candidates (against malaria, trypanosomiasis, and schistosomiasis), biochemical and enzymic studies on the mechanism and the regulation of disulfide reductase *in vivo*.

Selected Publications 2008 - 2010

Davioud-Charvet, E., Lanfranchi, D. A. Subversive substrates of glutathione reductases from P. falciparum-infected red blood cells as antimalarial agents. In K. Becker and P. Selzer (Eds.) Drug Discovery against Apicomplexan parasites – Molecular approaches to targeted drug development, in the series “Drug Discovery in Infectious Diseases”. Wiley, 2010. In press.

Wenzel, N. I., Chavain, N., Wang, Y., Friebolin, W., Maes, L., Pradines, B., Lanzer, M., Yardley, V., Brun, R., Herold-Mende, C., Biot, C., Katalin Tóth, Davioud-Charvet, E. (2010) Antimalarial versus Cytotoxic Properties of Dual Drugs Derived From 4-Aminoquinolines and Mannich Bases: Interaction with DNA. J. Med. Chem. 53, 3214–3226.

Chavain, N., Davioud-Charvet, E., Trivelli, X., Mbeki, L., Rottmann, M., Brun, R., Biot, C. (2009) Antimalarial Antimalarial activities of ferroquine conjugates with either glutathione reductase inhibitors or glutathione depletors via a hydrolyzable amide linker. Bioorg. Med. Chem. 17, 8048–8059.

Wenzel, I. N., Wong, P. E., Maes, L., Müller, T. J. J., Krauth-Siegel, L. R., Barrett, M., Davioud-Charvet, E. (2009) Antitrypanosomal unsaturated Mannich bases active against multidrug-resistant T. brucei brucei strains. ChemMedChem. 4,339-351.

Davioud-Charvet E., Müller, T., Bauer, H., Schirmer, H. 1,4-Naphthoquinones as Inhibitors of Glutathione Reductases and Antimalarial Agents. European Patent EP 08290278.4 (March 26, 2008). PCT/EP2009/053483 (25-03-2009). WO/2009/118327 (01.10.2009).

Viry, E., Battaglia, E., Deborde, V., Müller, T., Réau, R., Davioud-Charvet, E., Bagrel, D. (2008) A sugar-modified phosphole gold complex with antiproliferative properties acting as a thioredoxin reductase inhibitor in MCF-7 cells. ChemMedChem. 3, 1667-1670.

Müller, T., Müller, T.J.J., Davioud-Charvet, E. (2008) Synthesis of photo-reactive naphthoquinones for photoaffinity labeling of glutathione reductases. In Flavins and Flavoproteins 2008, 16, 443–452. Frago, S., Gómez-Moreno, C., Medina, M., Eds. Prensas Universitarias de Zaragoza, Spain, 2008.

Morin, C., Besset, T., Moutet, J.-C., Fayolle, M., Brückner M, Limosin, D., Becker, K., Davioud-Charvet, E. (2008) The Aza-Analogues of 1,4-Naphthoquinones are potent Substrates and Inhibitors of Disulfide Reductases. Org. Biomol. Chem. 6, 2731-2742.

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