INVESTIGATION OF TRANSPORTER INTERACTIONS OF ANTIMALARIALS USING IN VITRO ASSAYS

Lívia Marton[1,3], Péter Szerémy[1,2], Szilvia Gedey[1], Gerda Szakonyi[3], János Márki-Zay[1,2]

[1]Solvo Biotechnology, University of Szeged, [2]Faculty of Pharmacy, Institute of Pharmaceutical Analysis, [3]Faculty of Medicine, Department of Biochemistry,
E-mail: mliviuniversitas@gmail.com

Options to control spread of malaria are increasingly limited due to emergence of parasites resistant to widely used antimalarials, therefore discovery of novel antimalarials appears crucial as ever. However, animal experiments are too expensive and laborous for the pharmacokinetic characterization of large number of compounds. The fate of administered drugs may largely depend on their interactions with transporter proteins, which are present in all major pharmacologically relevant barriers. Furthermore, transporters are key determinants of antimalarial drug resistance of plasmodiums as well. The aim of this study was to examine whether the high-throughput (HTS) membrane-based transporter assays can be applied to characterize the transporter interactions of candidate antimalarials.

Reference antimalarials, such as artemisinin, chloroquine, mefloquine, quinine, etc, have been tested for their interaction with the ABC-transporters MDR1, MRP1 and BCRP using the Solvo PredEasy ATPase kits and the interaction with the SLC family members OCT1 and OCT2 uptake transporters in cell-based assay. Measured IC_{50} and EC_{50} values were correlated with the clinical observations on the tested antimalarials.

In case of Amodiaquine, Hydroxychloroquine, Primaquine, Pyrimethamine, Proguanil, Artemisinin, Artesunate, Atovaquone, Clindamycin, Halofantrine, our data are the first proof for transporter interaction of these clinically important drugs. Artemisinin is a substrate for MDR1, chloroquine is inhibitor of the MDR1 and substrate for the MRP1 and BCRP, mefloquine is substrate for the MDR1 but at higher concentrations is a not specific inhibitor of all the transporters and quinine is substrate for the MDR1. These results corresponded exactly to the clinical data on the antimalarials tested.

We conclude that the membrane- and cell-based HTS in vitro assays can be applied to facilitate the ADME characterization of candidate antimalarials.