In vitro Pharmacology: Drug Interaction with ABC Transporters

In addition to metabolic enzymes, interaction of drugs with ABC transporters is an important potential source of drug-drug interactions. P-glycoprotein (ABCB1, MDR1) remains the main ABC transporter in limiting absorption of drugs from the intestine as well as in limiting drug passing across the blood-brain barrier. Concomitant administration of drugs that both interact with the same transporter can lead to serious changes in their pharmacokinetic properties and may lead to toxicity.

Apart from the role of ABC transporters in drug ADME properties, ABC transporters are important and well studied mediators of multidrug resistance of various tumours. Inhibition of ABC transporter function in cancer could, thus, lead to improvement of chemotherapy results.

Being aware of the pitfalls of various methods addressing interactions with ABC transporters Fidelta offers expertise in several functional assays for ABC transporters:

- Rhodamine-123 exclusion in P-glycoprotein (ABCB1, MDR1) overexpressing cells (Figure 1)
- Calcein accumulation in P-glycoprotein (ABCB1, MDR1) overexpressing cells
- Fluorescent dye exclusion in membrane vesicles overexpressing ABC transporters (MDR1, MRP1, MRP2, MRP3, MRP5) (Figure 2)
- ATP-ase activity of ABC transporters (MDR1, MRP1, MRP2, MRP3, BCRP) (Figure 3)

Fidelta's cellular assays are performed on the validated cell line MES-SA/Dx5 with overexpression of MDR1, and their parent cell line MES-SA. The cells were characterized by mRNA and protein expression of eight ABC transporters reported capable of drug transport (Litman et al. 2001, Munić et al. 2010)

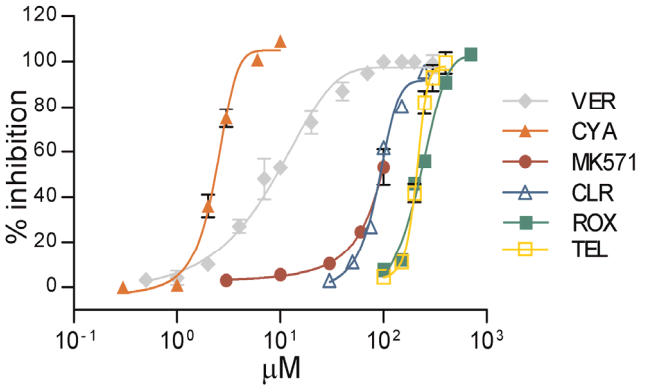

Figure 1. Effect of drugs on rhodamine-123 exclusion from MES-SA/Dx5 cells via P-glycoprotein (ABCB1, MDR1) (Munić et al. 2010)

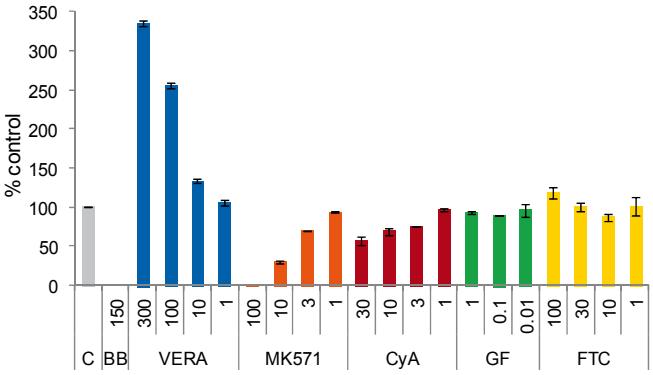

Figure 2. Interaction of drugs with CDCF transport via MRP2 on membrane vesicles (Munić et al. 2011)

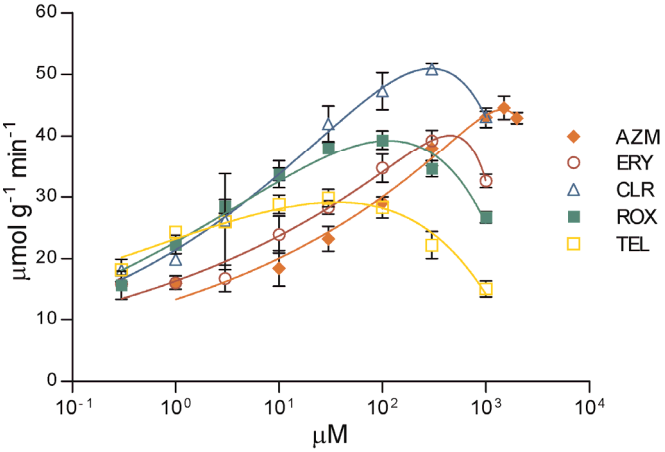

Figure 3. Effect of 5 drugs on ATPase activity of P-glycoprotein (ABCB1, MDR1) on membranes overexpressing the transporter (Munić et al. 2010)

References
Munić et al. 2010, Eur J Pharm Sci 41, 86;
Munić et al. 2011, Eur J Pharm Sci 43, 359;
Litman et al. 2001, Cell Mol Life Sci 58, 931

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