

## SOLVO introduces a screening toolbox to investigate interactions of small molecules with ABCB1 (P-gp, MDR1)

ABCB1 (P-Glycoprotein – P-gp, Multidrug Resistance Protein 1 – MDR1) is an ABC transporter protein capable of extruding xenobiotics from the cells into the intercellular space and exerts a cytoprotective function (Ambudkar SV et al., 2006). Historically, it was the first protein described to confer drug resistance to tumor cells thus rendering chemotherapy ineffective (Juranka PF et al., 1989).

ABCB1 transports a wide range of structurally not related compounds (van Helvoort A et al., 1996). ABCB1 is densely expressed at a number of important pharmacokinetic barriers, such as intestinal epithelium, blood-brain barrier, hepatocytes or proximal tubules (Sugawara I, 1990). These properties make ABCB1 a key player in pharmacokinetics and its involvement in systemic distribution of drugs has been proved in many cases (Shitara Y et al., 2006).

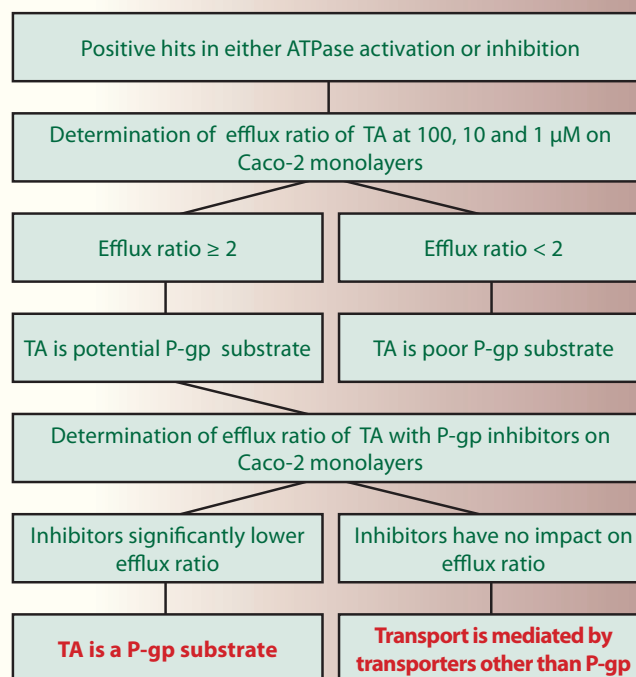
As several widely used drugs are ABCB1 substrates, which limits their concentration in protected organs (e.g., brain), coadministration of other substrates or inhibitors (other drugs or dietary) may cause severe drug-drug or food-drug interactions (Marchetti S et al., 2007).

Due to these factors, screening for ABCB1 interactions has become an industry and standard is also being introduced in regulatory guidance documents.

### The SOLVO P-gp Toolbox:

1. SOLVO applies ATPase and Calcein assays for the identification of molecules interacting with ABCB1 on a large set of early leads. These two assays are optimized for high throughput and detect both substrates and inhibitors of ABCB1 with high sensitivity.
2. Based on the results in either series of experiments, SOLVO designs and performs Caco-2 monolayers as the ultimate proof for ABCB1 interactions on a smaller set of test articles.
3. For late development ABCB1 interaction studies based solely on Caco-2 monolayers are also available as a separate package in compliance with the FDA draft guidance (<http://www.fda.gov/cber/gdlns/interactstud.pdf>, Appendix D).

For the **determination whether the test article is an ABCB1 substrate**, the following procedure and decision making is applied (based on the FDA's decision trees):



For the **determination whether the test article is an ABCB1 inhibitor**, the following procedures and decision making are applied:

