

# BLOOD-BRAIN-BARRIER PACKAGE

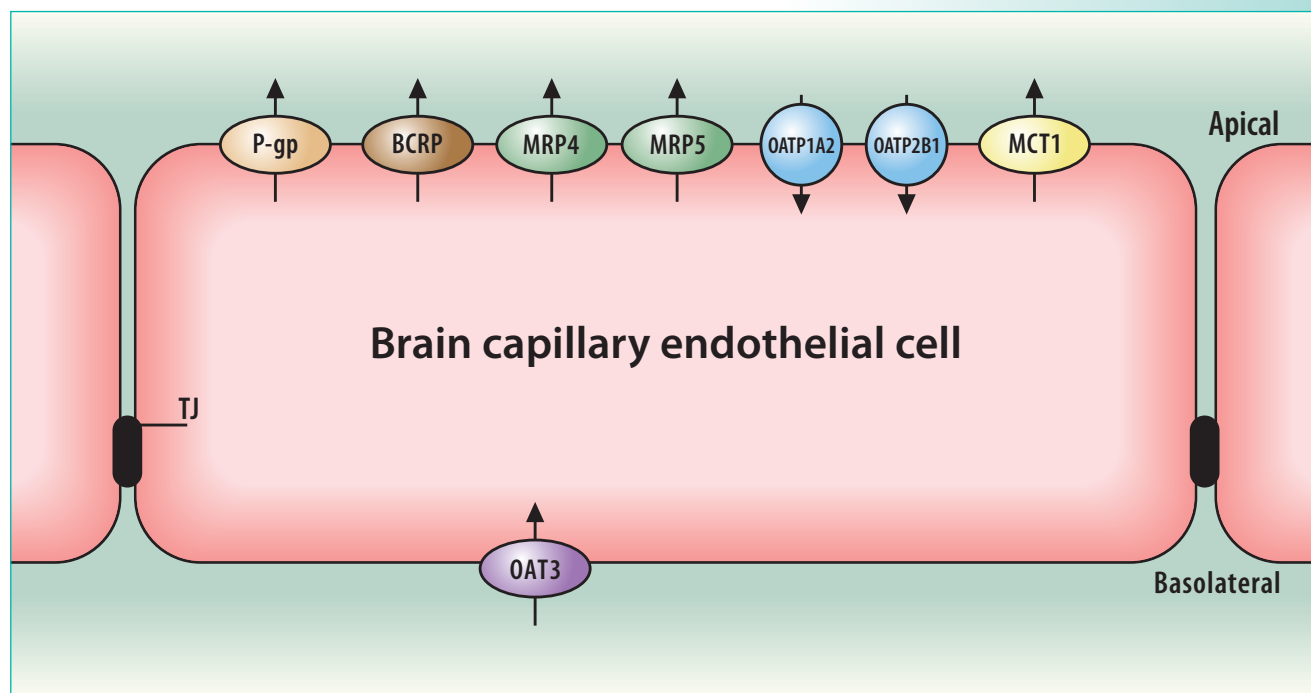
Nowhere in the body is there more need for homeostasis than in the brain. The mechanism for maintaining this barrier function lies in the capillary network supplying blood to the brain.

These capillary endothelial cells in the brain are different to those found in peripheral tissues in various ways:

1. Brain endothelial cells are joined by tight junctions of high electrical resistance providing an effective barrier against paracellular movement of molecules.
2. In peripheral endothelial cells there is good transcellular movement of molecules. There is no such movement in brain endothelial cells.
3. Brain capillaries are in contact with foot processes of astrocytes which essentially separate the capillaries from the neurones.

The blood brain barrier is both a physical barrier and a system of cellular transport mechanisms.

Lipid soluble molecules are able to penetrate through the barrier relatively easily via the lipid membranes of the cells. In contrast, water soluble molecules (e.g. ions) are unable to transverse the barrier without the use of specialized carrier-mediated transport mechanisms. Transporter proteins play an important role in the transport of compounds across the BBB. Substrate specificity, expression levels and activity of the uptake and efflux transporters that are expressed in the BBB differ. Two efflux transporters - MDR1 and BCRP are of main importance in preventing xenobiotics to cross the BBB. Both transporters are expressed on the apical membrane, pumping their substrates from the cell into the bloodstream.



Localization of efflux and uptake transporters in human brain capillary endothelial cell (based on Bronger H et al. (2005) *Cancer Res* 65: 11419-11428).

SOLVO's BBB package consists of an assortment of crossvalidated *in vivo* and *in vitro* tools for studying the drug-transporter and/or drug-drug interactions in this important barrier. The BBB package focuses on two key efflux transporters, MDR1 and BCRP, however assays for other efflux (e.g. MRP4) and uptake (e.g. OATPs and OAT3) transporters present in the BBB are also available.

Membrane based ATPase and vesicular transport assays, the cell based dye efflux assays, and the cellular uptake transporter assays represent HTS assessments that provide transporter specific data to confirm *in vivo* detected interactions. FDA-compliant MDR1-specific monolayer assays (Caco-2, and MDCKII), and the BCRP-MDCKII assay are also available. Living cell based BBB models, like dye efflux transport assays adapted for primary rat brain capillary endothelial cells (RBEC) are also validated with specific interactors and dedicated to explore efflux transporter related inter-species differences. SOLVO's standard and transporter-specific *in vivo* microdialysis services are also integral part of our BBB package.

