

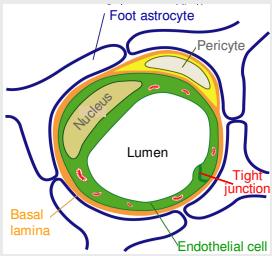
# In vitro Blood-Brain Barrier model

Pharmaceutical R&D

## A primary rat *in vitro* blood-brain barrier model to predict drug candidate entrance to the brain

nicolas.perriere@vigicell.fr

### Blood-Brain Barrier: Complex and active interface between blood and brain

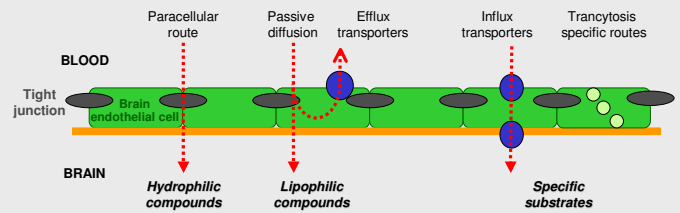


The Blood-Brain Barrier:

- Maintains brain homeostasis
- Controls all flux between blood and brain
- Protects from xenobiotics

Particular properties of BBB's endothelial cells are conferred by the cerebral microenvironment:

- Expression of tight junctions
- Only specific passage
- Expression of polarized transporters



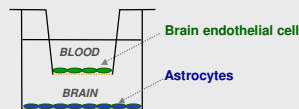
Properties of BBB are a combination of passive diffusion, active and facilitated transport (efflux and influx).

### VigiCell offers a physiological *in vitro* model that maintains these specific properties

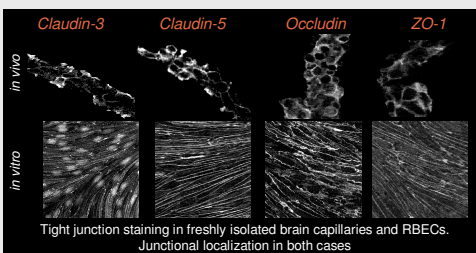
#### 1 | Similar to *in vivo*

*In vivo* characteristics preserved using our *in vitro* standardized model

- Primary culture
- Rat syngenic coculture (endothelial cells [RBECs] + glial cells)
- Freshly isolated cells



Tight junction expression, localization and functionality

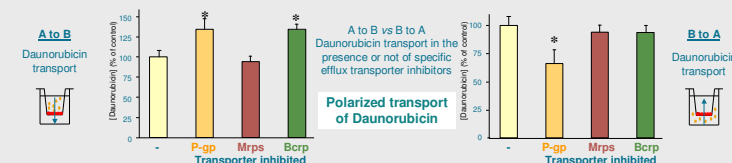
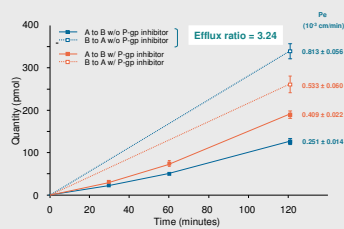
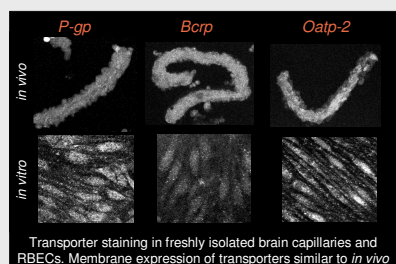


Paracellular permeability (Pe : 10<sup>-3</sup> cm/min)

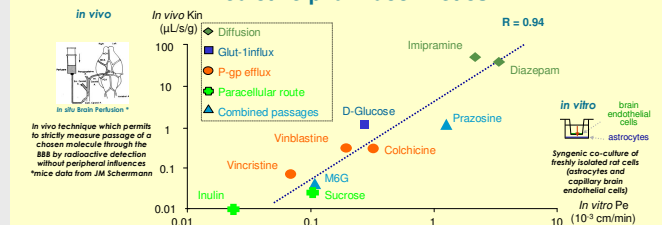
substance	inulin	fluorescein	FD4	FD40	FD70	
Pe	0.10	0.05	0.12	0.05	0.015	0.01

Low permeability values similar to *in vivo*

Transporter expression, polarization and functionality



#### Predictive pharmacokinetics



Strong correlation between *in vitro* and *in vivo* permeabilities, independent of the passage mechanisms

#### 2 | Quality & Reproducibility

Standard animal

- Strain: CrI:OFA(SD) rat, male, 2 weeks old
- Fresh primary cells

Protocol strategy

Preservation of brain endothelium properties

- Soft enzymatic digestions
- Short amplification
- Reduced culture time to avoid dedifferentiation

Standardized protocol

Minimization of cell culture intra- and inter-variability

- Positive selection of brain endothelial cells with BBB phenotype
- Seeding on inserts at D4 with a defined cellular density
- Permeability study realized at D10

Internal control

- A fluorescent dye is coadministered with the drug candidate in each BBB insert

$$\text{Perm}_{(\text{Fluorescein})\text{AtoB}} = 0.12 \pm 0.02 \cdot 10^{-3} \text{ cm/min (n=40)}$$

#### 3 | Services : screening & customized studies

CELL CULTURE

- Production of 2 cultures per week (up to 96 inserts)

ADAPTABILITY

- Shipment and protocol adapted to your needs (concentrations, controls, reproducibility, mechanistic studies...)
- Access to mass spectrometry facility

VALIDATION

- Control of membrane integrity for each culture insert
- Control of P-gp functionality for each culture

OUR COMMITMENT

- Permeability experiments within 8 days after reception of the drug candidate
- Your analysis within 24h after assay results are received

#### 4 | Publications

- Perrière N et al. Puromycin-based purification of rat brain capillary endothelial cell cultures. Effect on the expression of blood-brain barrier-specific properties. *J Neurochem.* 2005 Apr;93(2):279-89.
- Perrière N et al. A functional *in vitro* model of rat blood-brain barrier for molecular analysis of efflux transporters. *Brain Res.* 2007 May 30;1150:1-13.
- Adenot M et al. Applications of a blood-brain barrier technology platform to predict CNS penetration of various chemotherapeutic agents. 1. Anti-infective drugs. *Chemotherapy.* 2007;53(1):70-2.
- Pifferi E et al. n-3 Fatty acids modulate brain glucose transport in endothelial cells of the blood-brain barrier. *Prostaglandins Leukot Essent Fatty Acids.* 2007 Nov-Dec;77(5-6):279-86.

nicolas.perriere@vigicell.fr  
Tel. : +33 1 49 58 34 79  
7 rue Guy Moquet 94800 Villejuif FRANCE

**vigicell**  
health & environment