

A rapid *in vitro* model for Blood-Brain Barrier screening of neurotoxic chemicals.

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The Blood Brain Barrier (BBB) can be considered as the main interface between blood and brain that regulates the homeostasis of the brain interstitial fluid. The brain capillary endothelial cells, forming the BBB, are distinct from the other vascular bed cells by: the presence of continuous tight junctions, a very low transcellular vesicular transport that implies the presence, at the cell surface, of specific transporters and receptors implicated in blood/brain exchanges. These properties of brain endothelial cells are mainly enhanced by the surrounding glial cells environment.

To provide an *in vitro* system for studying brain capillary functions a process of coculture has been developed, that closely mimics the *in vivo* situation, by culturing brain capillary endothelial cells (EC) on one side of a filter and glial cells on the other (Dehouck et al., 1995). This model has shown a good correlation coefficient between *in vitro* and *in vivo* analysis of a wide range of molecules tested (Cecchelli et al., 1999).

Only 3-28% of all chemicals have effects on the CNS (Pietro et al., ATLA, 32, 37-50,2004). However, even if only a small amount of compounds passes the BBB, the effect on the CNS can be severe if the compound binds with high affinity to the target. Although it is not clear whether neurotoxicity tests should be carried out before or after testing the passage across the BBB, for those substances which there is enough evidence to suggest that there are likely neurotoxic, they should be tested for neurotoxicity.

To reduce time necessary to the establishment of the BBB model (6 weeks), which is the bottleneck in limiting the efficiency of the drug discovery process, we have developed a new *in vitro* BBB model in 24 well-plates which can be used after only 4 days culture for primary screening (HTS). To recreate the interactions between endothelial and glial cells, we set up a "conditioned medium" adapted among other things from the culture medium of the coculture glial and endothelial cells. The development of this specific BBB inducing medium made possible to induce all the properties of the BBB at the level of endothelial cells, without requires the presence of glial cells, after only 4 days culture.

The advantages of this 24 well-system built in only 4 days are a model specifically adapted for early screening of a large amount of compounds and a decrease in resources need to grow and sustain the cells. This new *in vitro* BBB model will significantly accelerate the screening of potential neurotoxic chemicals.