Optimized In Vitro Model of Blood Brain Permeability

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- Pharmaceuticals

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- animal-free testing
- Blood Brain Barrier
- Drug Development
- Drug Toxicity
- Neuronal cells
- neurovascular unit
- Permeability Testing
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- triculture model

NCS: Purdue University researchers have developed a multicellular blood-brain barrier (BBB) model to assess the permeability of potential drug candidates and xenobiotics. The BBB serves a protective role that can limit the ability of neurotherapeutics to reach the neuronal environment in the brain parenchyma and mitigate disorders. Accurately predicting the permeability of drugs across the BBB remains challenging but is a critical component of guiding successful neurological drug development. Several traditional in vitro BBB permeability assays have been developed; however, they fail to mimic the physiological BBB due to indirect contact of the cellular layers of neuroglia, pericytes and the brain microvessel endothelium found in vivo.

The Purdue researchers developed a direct contact triculture model that mimics the in vivo BBB configuration observed in the neurovascular unit. The Purdue technology incorporates primary human astrocytes (neuroglia), pericytes, and brain microvessel endothelial cells in direct layered contact on a permeable filter support as an accurate model of the BBB to screen for permeability of drugs and other molecules. This in vitro BBB model was optimized by varying several different variables at a time and assessing their influence in the multicomponent BBB model. This technique, known as the design of experiments approach, expedited optimization of this biologically based system and facilitated understanding of the interaction of critical factors in the in vitro BBB model. The model is currently being further developed to assess neurotoxicant permeation rates with an effort to correlate findings with anticipated human in vivo exposure.

Technology Validation: Optimization of the cell culture system was assessed for P-glycoprotein, the transporter protein that can regulate substrate entry across the BBB function, using a substrate and inhibitor along with a set of BBB cellular markers at varying permeation rates. At optimal conditions, the model revealed P-glycoprotein function along with the ability to

differentiate between BBB positive and negative permeants, suggesting an effective BBB screening tool for potential neurological drugs or toxicants.

Advantages:
-Robust, reliable, and reproducible
-Cost Effective
-Time saving
-Animal – free testing

Applications:
-Blood Brain Barrier Permeability Testing
-Neurological Drug Design

Related Publications: Design of Experiment Based Optimization of an in Vitro Direct Contact Triculture Blood Brain Barrier Model for Permeability Screening. Pharmacy & Pharmacology International Journal. Volume 9 Issue 4 - 2021. DOI:10.21203/rs.3.rs-592200/v1

Development of a Direct Contact Astrocyte-hCMEC/D3 Blood-Brain Barrier Coculture Model. Journal of Pharmacy and Pharmacology. Volume 69 Issue 12 – 2017, pages 1684-1696. DOI: 10.1111/jphp.12803

People:

- Knipp, Gregory Thomas (Project leader)
- Lubin, Kelsey Eileen

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Contact OTC:

Purdue Office of Technology Commercialization
The Convergence Center
101 Foundry Drive, Suite 2500
West Lafayette, IN 47906

Phone: (765) 588-3475
Fax: (765) 463-3486
Email: otcip@prf.org