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A Three-dimensional Hydrogel Cell Culture System for Modeling the Blood-Brain Barrier

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The blood brain barrier is a complex polarized tissue that is formed by the interaction of several cell types including endothelial cells, neurons, astrocytes, and microglia. It has been demonstrated that interactions between these cells are necessary to induce blood brain barrier phenotypes in endothelial cells in vitro. However, no study has yet to produce an in vitro model that accurately represents the permeability and transport properties of brain microvasculature, as measured indirectly by trans-endothelial resistance. We present a novel hydrogel based method for modeling the blood brain barrier. Our system is capable of recapitulating three-dimensional heterogeneous and stratified tissue at cell densities similar to those found in rat cortex. The culture setup consists of a flow chamber constructed above an array of microelectrodes. Three dimensional alginate hydrogel scaffolds containing multiple cell types are crosslinked on top of the electrodes and contained within the flow chamber. This culture setup allows for controlled pulsatile flow while permitting measurement of the electrical properties of endothelial monolayers grown on the surface of the alginate hydrogel. Blood brain barrier integrity is monitored by measurements of trans-endothelial resistance as well as immunohistochemical and microscopically by observation of direct cell interactions and endothelial tight junction formation. We propose that our system is capable of more closely approximating the tissue organization and electrical properties of the intact blood brain barrier.