There are currently no FDA-approved therapeutics that can slow, halt, or prevent Alzheimer’s disease (AD) and only five approved drugs that treat the cognitive symptoms associated with AD. One of the key challenges with treating neurological diseases such as AD is delivery of systemically-administered therapeutics in the blood across the blood-brain barrier (BBB) into the brain. The BBB, composed of the endothelial cells that line cerebral capillaries, tightly regulates transport of molecules between the blood and the brain parenchyma and in doing so, severely limits the transport of therapeutics for neurological disease. Immunotherapies are an attractive class of therapeutic for AD due to their high target specificity and affinity however they generally exhibit notoriously low brain transport. Furthermore, while many immunotherapy drug candidates have shown efficacy in preclinical animal models, none have demonstrated disease-modifying effects in human clinical trials; studying transport of therapeutics in vivo in humans is challenging. Therefore, the goal of this research is to develop a human cell-based in vitro BBB model and to apply the model to study transport of therapeutics in AD.

An ideal BBB model is made from human brain microvascular endothelial cells (BMECs), forms a tight barrier with in vivo-like transport restriction, and can be modified to mimic normal or pathological states. In this work, we differentiate human induced pluripotent stem cells into BMECs as the basis for the in vitro model which are capable of physiologically-relevant barrier performance. The model was characterized by measuring transendothelial electrical resistance (TEER), small molecule permeability, expression of BMEC-specific proteins and directional transport of a known substrate. We evaluated the permeabilities of several known small molecule drugs that can serve as benchmarks for the evaluation of new therapeutics, and validated the benchmarking system with the FDA approved AD drugs. We established a relationship between TEER and brain permeability of two different classes of drugs, suggesting fundamental differences between how small and large molecule therapeutics are transported.

While studying transport of therapeutics, it is also important to consider the effects of pathological states on the BBB. AD is often accompanied by increases in plasma-derived proteins found in the brain and changes to expression or activity of transport proteins. Furthermore, molecular transport can be affected by secondary insults such as inflammation. The effects of pathological states on specific features of the BBB as well as the molecular mechanisms of immunotherapeutic transport are poorly understood. We employed a neuroinflammation model and observed impaired barrier function as measured by a decrease in barrier tightness and an increase in antibody transport. This response is partially mitigated by the
presence of astrocytes. These results suggest that a breakdown in trancellular transport precedes any increase in paracellular permeability in disease and provide a link neuroinflammation and specific aspects of BBB breakdown. The model was lastly used to gain fundamental insights into the transport behavior of immunotherapies through the use of inhibitors and probes of different endocytic routes in normal, neuroinflammation and AD models. IgG transport is a saturable process and different endocytic pathways are likely responsible for IgG uptake in normal and pathological conditions.

Models of the cells that comprise and surround the BBB can facilitate a more thorough understanding of disease progression, help identify new therapeutic targets, and can advance the development of new therapeutics for neurodegenerative diseases capable of reaching targets in the brain. These findings offer critical insights into the direct effects of pathological states on barrier function and demonstrate that this in vitro model can be applied to study the transport of different classes of therapeutics from the blood to the brain. Furthermore, these efforts provide a basis for future studies of transport of therapeutics at the BBB in disease, and this approach can be extended to the study of other neurological diseases and classes of therapeutics.