Preclinical modeling of drug delivery for glioblastoma therapy

Lawler S.

Legoretta Cancer Center Brown University, Providence, USA

Efficient drug delivery to GBM is a major obstacle as the blood-brain barrier (BBB) prevents passage of the majority of cancer drugs into the brain. It is also recognized that the blood-brain tumor barrier (BTB) in the growing tumor represents a challenge. We have identified a BTB gene signature, with functions related to vasculature development, morphogenesis and cell migration. We identified cadherin 5 (VE-cadherin) as a core molecule in this set and confirmed its overexpression in GBM vasculature using spatial transcriptomics of GBM patient specimens. We found that the indirubin-derivative, 6-bromoindirubin acetoxime (BIA), could downregulate CDH5 and other BTB signature genes, causing endothelial barrier disruption in endothelial monolayers and BBB 3D spheroids *in vitro* and *in vivo,* where it improved survival in murine models. Overall, our work reveals potential targets at the BTB for improved chemotherapy delivery and the bifunctional properties of BIA as a BTB modulator and potentiator of chemotherapy, supporting its further development.