

DEVELOPMENT OF AN IN VITRO BLOOD-BRAIN BARRIER MODEL FOR BRAIN DISPOSITION SCREENING OF PHARMACEUTICALSG. Stolper¹; M. Klausner¹; J. Sheasgreen¹; P. Hayden¹

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Solute distribution between blood and brain is strictly regulated by the blood-brain barrier (BBB). While the BBB performs an important function in keeping unnecessary or harmful molecules from the brain, it poses a challenging problem in delivering therapeutics, including anticancer, antibiotic or antipsychotic drugs into the brain. Conversely, preventing potentially damaging molecules from overcoming the BBB is also an increasing problem, especially when combinations of therapeutics are encountered. Medical and pharmaceutical scientists therefore have a growing need for rapid, reliable in vitro models of the BBB for preclinical screening of pharmaceutical BBB transport properties. The current presentation describes initial results in development of an in vitro BBB model derived from bovine brain capillary endothelial cells (BCEC). Capillary vessels were first isolated from bovine brains. Individual BCECs were then released by further enzymatic digestion of the capillaries. BCEC thus obtained were cryopreserved. The isolation procedure produced a highly pure population of BCECs, as demonstrated by immunocytochemical staining for the endothelial cell marker von Willebrand factor. After recovery from cryopreservation, BCECs were cultured on microporous membrane culture inserts to produce the BBB model. Transmission electron microscopy and H&E stained light microscopy of the cultures show uniform endothelial cell monolayers with evidence of tight junction formation. Immunocytochemical staining also demonstrated uniform expression of the tight junction protein ZO-1 localized along the BCEC borders. Permeation of Lucifer yellow across the BBB culture was low, further demonstrating development of barrier function. Finally, Western blotting experiments were conducted to reveal the presence of the important BBB efflux transporter p-glycoprotein. These results show significant progress in development of a reliable in vitro BBB model that will be useful for preclinical screening of candidate pharmaceutical compounds. This work was supported by NCI Grant # R43 CA101703-02.

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