THE HARTWELL FOUNDATION

2012 Individual Biomedical Research Award

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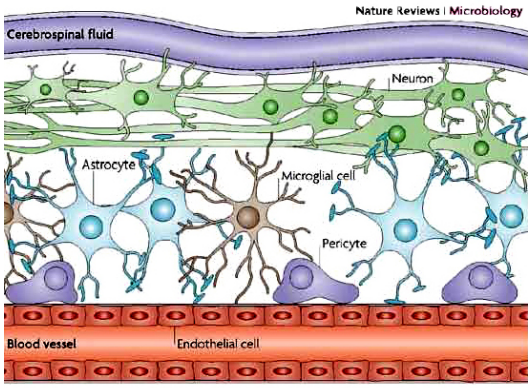
Novel Drug Delivery System Targeting the Blood-Brain Barrier for Treatment of Childhood Brain Tumors

Brain cancer is a devastating and often fatal disease that afflicts children and infants. Even with surgery, radiation and chemotherapy as available therapies, the mortality rates run as high as 80%. This high morbidity associated with surgery and radiation to treat brain tumors is unacceptable. In glioblastoma multiforme, the most common and most aggressive malignant primary brain tumor in children, the inability to deliver chemotherapeutic drugs into the brain is cited as the single most important reason for the high mortality. While chemotherapy is often quite effective against tumor cells in culture, unfortunately virtually all known chemotherapeutic drugs are unable to cross the blood-brain barrier, which acts as a shield to protect our brain from harmful substances and pathogens. Although different approaches for getting chemotherapeutics into the brain have been attempted, most are too invasive and/or toxic; resulting in irreversible damage to surrounding healthy brain tissue and often causing systemic morbidity, as well. However, some pathogens, like the fungal pathogen Cryptococcus neoformans that causes devastating and often fatal meningoencephalitis in immunocompromised patients, have evolved a mechanism to cross the blood-brain barrier in order to invade the central nervous system. In seeking to understand how C. neoformans crosses the blood-brain barrier, Angie recently discovered that it does so by means of a metalloprotease enzyme Mpr1, the presence of which she has also shown to be essential for establishing fungal disease in the central nervous system. The Mpr1 enzyme appears to selectively alter the surface of the blood-brain barrier by making it more permeable. Based on her observations, she proposes that this metalloprotease can be attached to non-toxic nanocarriers of anti-cancer drugs to enable them to cross the blood-brain barrier and effectively target a brain tumor. If she is successful, her approach would revolutionize chemotherapy for glioblastoma and other brain tumors. The current outcome for glioblastoma is so dire that if her proposed technology allowed just a fraction of an anti-cancer drug across the blood-brain barrier the result would have a huge positive impact on the survival of affected children.



Blood-Brain Barrier