THE HARTWELL FOUNDATION

2008 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **Michael R. Taylor, Ph.D.**
Assistant Member
Department of Chemical Biology and Therapeutics

Institution: **St. Jude Children's Research Hospital**

Proposal: **Genetic and Chemical Dissection of the Blood-Brain Barrier**

In groundbreaking studies with zebrafish, Dr. Taylor was able to demonstrate that this well-established model organism for the study of vertebrate development possesses the structural properties of a blood-brain barrier (BBB) — the unique physical barrier created by the cells of the smallest blood vessels (capillaries) that supply blood to the brain in mammals, including mice and humans. This observation is important because the BBB remains the single most important obstacle to the successful delivery of new and better antibiotics, antivirals, anesthetics and chemotherapeutics, as well as the emerging class of gene and protein target drugs. In mammals, the BBB maintains the local environment necessary for proper neuronal function by controlling the selective permeability of surrounding tissues to the constituents of blood. Acting as the brain's gatekeeper, the BBB protects against wide fluctuations of water, oxygen, carbon dioxide, and many other nutrient and waste chemical substances, while restricting the entrance of proteins and potentially harmful blood-borne agents. Disruptions of the BBB have been associated with disease. Today, the clinical significance and restrictive properties of the BBB present a very challenging problem for target drug therapy of central nervous system disorders. The molecular mechanisms responsible for BBB development, maintenance and selectivity remain ambiguous and no consistent strategy exists for molecular design of desired chemotherapeutic agents that will cross the intact barrier. Existing models for the BBB are unsuitable because of their poor capacity for high-throughput genetic and small-molecule screens. To increase the therapeutic effectiveness of important drugs, Dr. Taylor proposes that it may be possible to identify specific chemical signals to induce capillary cells of the BBB to adopt characteristics that will result in increased selectivity toward desired molecules. Using a transgenic zebrafish that will “report” on the presence or absence of the BBB will enable for the first time high-throughput genetic and chemical screens to identify genes involved in the complex control of BBB selectivity. If successful, Dr Taylor will make a transformative contribution to rational drug design, delivery and discovery.