The Blood-Brain Barrier in Drug-Resistant Epilepsy (Dr. Ghosh)

Patients with brain and nervous system disorders, like epilepsy, face two major obstacles to therapy: getting medications across the membrane called the blood-brain barrier (BBB) and “drug resistance,” a condition that prevents a patient’s medications from working. A task force of The International League Against Epilepsy estimates that 25-30% epileptic patients are resistant to single or combination therapies. So there is a pressing need to develop more effective treatment strategies. The BBB keeps the brain functioning stably, but it can be difficult to get medicines past it into the brain. The research group of Dr. Chaitali Ghosh focuses on drug metabolizing enzymes (cytochrome P450 and UGT) and transporters (MDR1, MRPs) that affect drugs reaching the brain. The interaction of these enzymes with substances may also determine how well anti-epileptic drugs work and how long treated nerve cells survive in the epileptic brain. The Ghosh lab, working with Cleveland Clinic’s Epilepsy Center, is pioneering studies about how these enzymes and transporters interact in drug-resistant epileptic patients. The lab is comparing studies with (1) patients brain tissue and blood samples (2) parallel studies using a lab-based BBB model system established with patient-specific brain cells that mimics how the BBB works in the body and (3) results from animal models of how seizures affect BBB function. The team is carefully evaluating how regulators (nuclear receptors or transcription factors) work at cellular and molecular levels. With a better understanding of these factors and enzymes in the human epileptic brain, new drugs and approaches to treatment can be precisely designed for individuals who have such brain disorders. With enough support for their continuing advances, the Ghosh lab is poised to help clinicians prevent or treat drug resistance in epileptic patients.

Summary: The Ghosh laboratory is studying how anti-seizure drugs work in the body at the point where brain disorders such as drug-resistant epilepsy or epilepsy in patients who also have other conditions (such as stroke, depression, or cancer) are controlled.

Models of the blood-brain barrier for multiple biomedical uses (Dr. Ghosh)

All the complexities of the living brain cannot be seen, so simplified lab models are needed to simulate how the brain works, in both health and disease. Dr. Chaitali Ghosh is answering this clinical need, leading the way toward precision medicine by creating models of the blood-brain barrier (BBB) that have many potential uses. The BBB is a membrane protecting the brain from foreign substances, but sometimes it can block helpful medications, and it is a great challenge to study. Researchers are aiming for a more complete understanding of the passage across the BBB. The BBB can be damaged by inflammation, infection, traumatic injury, interruption of blood flow (as in stroke), or conditions like epilepsy. Our knowledge of the brain is ever increasing, but we cannot yet “tweak” BBB functions. And although standard laboratory model systems have provided a wealth of knowledge, it is now evident that newer models are needed, ones that more closely mimic how the BBB acts in the body. Dr. Ghosh’s pioneering research is developing user-friendly, “humanized” BBB models that allow her to explore the BBB under normal and disease states. Her new model systems can reproduce a disease condition by using patient-specific brain cells to create a “personalized” model; this step is essential for future drug discovery and development. With these models, investigators could test possible medical compounds at the earliest stages to see if they are likely to work or evaluate the effectiveness of currently prescribed medications that cross the BBB. Dr. Ghosh’s innovative approach to simulating brain and central nervous system disorders has attracted support from the National Institutes of Health and the American Heart Association. With additional much-needed support, Dr. Ghosh could make even more advances in understanding (1) how drugs penetrate the BBB and how they are taken up at a complex of brain/nerve cells and tiny blood vessels called the “neurovascular unit”; (2) how changes in blood flow under stroke-like conditions affect the BBB and drug availability; and (3) how the BBB is involved in cell movement and the targeting of white blood cells to sites of tissue damage in such conditions as multiple sclerosis and epilepsy, to find better treatments.

Summary: The Ghosh laboratory is using dynamic, patient-specific BBB models to understand brain activities and the potentially disruptive changes to the BBB caused by brain disorders. Her goal is to tailor research models to specific patients’ conditions and to improve the availability of medications into the brain for disorders like epilepsy, stroke, and multiple sclerosis.