

M Northwestern Medicine[®]
Feinberg School of Medicine

Frances Evelyn Feinberg Clinical Neuroscience Research Institute Epilepsy Center





EPILEPSY CENTER AT NORTHWESTERN MEDICINE

At Northwestern Medicine, we have launched our new Epilepsy Center to pursue breakthrough clinical care, research, education, and advocacy for people with seizure disorders of all kinds. We are driven by a commitment to introduce new knowledge and better approaches to diagnose and treat adults and children living with epilepsy.

Our dedicated clinicians and researchers are collaborating to study seizures from the smallest, most molecular level to the scope of the entire human body. Specifically, we are using the latest insights from biology, as well as new high-throughput drug screening techniques, to help develop new drugs and improve the diagnosis of epilepsy. The latest imaging techniques similarly are helping us at Northwestern to define areas of disease and optimize our medical and surgical approaches to patient care. As important, we are conducting therapeutic clinical studies involving patients with epilepsy through our partners at the Ann & Robert H. Lurie Children's Hospital of Chicago and the Northwestern Comprehensive Epilepsy Center at Northwestern Memorial Hospital.

Epilepsy is considered an ancient brain disorder with Hippocrates describing it as a sacred disease around 400 BC. It is a common disease with approximately 1 in 26 people developing it in his or her lifetime. Today, approximately 65 million people across the globe are suffering from some form of epilepsy. It is surprising to learn that epilepsy affects more people than multiple sclerosis, cerebral palsy, muscular dystrophy, and Parkinson's disease combined—yet federal funding for research in epilepsy is disproportionately low.

Uncontrolled seizures are associated with a risk of lasting memory problems, cognitive deficits, personality changes, injury, and death. Currently, medications and/or surgical treatments may eliminate or decrease the number and intensity of seizures, but patients with epilepsy may still be left with unwanted side effects. Side effects include lethargy, hyperactivity, weight gain/loss, dizziness, anemia, and osteoporosis. Some children fortunately outgrow their seizure disorders, but many do not.

A Disease with a Complex Genetic Basis

The genetic basis for epilepsy is complex. Scientists have discovered that some epileptic syndromes arise from a single genetic mutation, whereas other forms of epilepsy are far more complex and suggest the involvement of multiple genes in combination with environmental factors.

At Northwestern, we are seeking a greater understanding of the genetic basis of epilepsy. We recognize that this fundamental knowledge can lead us to the identification of beneficial new targets for therapy. Our investigators are uniquely combining genetics and pharmacology to discover new strategies to treat epilepsy.

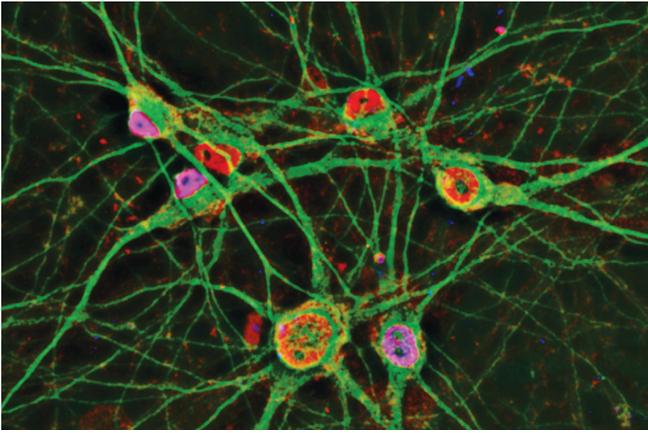
This work is built upon strong partnerships and collaborations among neurologists who care for patients with epilepsy, geneticists with expertise in mapping epilepsy genes, and pharmacologists who study the genes responsible for the molecular basis of epilepsy.

Our studies of ion channels are one powerful example of collaboration among our Northwestern pharmacologists, geneticists, and neurologists. We are focusing on ion channels, which are proteins that endow cells with the ability to move ions across membranes and to generate biological electricity.



“Our new and highly innovative Epilepsy Center at Northwestern Medicine provides opportunities for groundbreaking research at the interface of human genetics, pharmacology, and clinical neuroscience, which will enable discoveries that will translate into better treatments.”

Alfred L. George Jr., MD, Magerstadt Professor and Chair of the Department of Pharmacology



Human neurons-Kiskinis Lab

Why do ion channels matter? Human ion channel genes are the most frequently identified cause of childhood epilepsy, including in Dravet syndrome. Dravet syndrome is a rare neurodevelopmental disorder that begins in infancy and is characterized by severe epilepsy that does not respond well to treatment.

Our team at Northwestern is ready to launch large-scale studies of the mutant human ion channels involved in epilepsy. We also will work to find new targets for therapy by maximizing the new information that is emerging regarding the genetic basis of epilepsy. We recently installed an automated electrophysiology platform, which is the first of its kind in North America. This technology will enable our experts to conduct high-throughput drug screening of ion channels at a speed and scale never possible before. The goal is to find new lead compounds that can serve as the starting points for drug development. Once novel therapeutic compounds are identified, we are well-equipped to evaluate them in our animal models of epilepsy, including the Dravet syndrome model.

Our colleagues at the Epilepsy Center at the Ann & Robert H. Lurie Hospital of Chicago are in a unique position to make fundamental contributions to our molecular understanding of epilepsy, and therefore, the treatment of childhood epilepsy. Through initial genome-wide studies, it has been demonstrated that the intergenic regions of our genome (the 98% of the genome that does not code for protein coding genes) consist of *cis*-regulatory elements known as “enhancers” that are critical in development. The malfunction of these enhancers results in disease development, including epilepsy. Experts in pediatric neurology at the Lurie Children’s Epilepsy Center and collaborators in biochemistry and molecular genetics are taking



advantage of the wealth of samples that have been collected from patients at the Lurie Children’s Epilepsy Center over the past 15 years. This team is analyzing these samples by using full-genome sequencing to search for evidence of enhancer malfunction. These samples also will be studied to determine the genomic/epigenomic signature of epilepsy.

Studies that Center on Treatment-Resistant Epilepsy

While clinical symptoms can be managed effectively with currently available medication in approximately two-thirds of patients with epilepsy, the disease is resistant to treatment, or refractory, in more than one-third of cases. At Northwestern, our neurology group is investigating disease mechanisms in treatment-resistant epilepsy and screening for more effective therapeutics.

A lack of easy access to brain cells from patients with epilepsy has hampered the field’s progress toward the discovery of more effective treatments. Scientists are finding that human cell-based assays are a promising tool for drug discovery, particularly in complex diseases of the nervous system such as epilepsy. Our experts are using exciting new tools to create cell-based models of epilepsy that can serve as platforms for the discovery of improved therapies. To begin to explore cell-based models of epilepsy, the neurology team is focusing on Dravet syndrome.

The groundbreaking technology of reprogramming, which allows for the generation of patient-specific induced pluripotent stem cells, has created an unprecedented opportunity for a new approach toward more personalized preclinical drug development. For example, it will be possible to generate stem cells from an individual patient and use these cells in culture to test the effectiveness of a new drug for that patient. Specifically, recent breakthroughs have allowed for the robust differentiation of neurons and interneurons, which are both directly implicated in various types of epilepsy. Recent advances in genome editing, which allows for the repair or introduction of particular disease-causing DNA mutations, enable the creation of cell-based disease models with fully characterized genetic backgrounds.



Given that epileptic seizures ultimately result from an imbalance in the electrical activity of neuronal cells, it is crucial to be able to study the electrophysiological properties of diseased and healthy neurons. Recent technological advancements complete the “puzzle” that allows for effective stem cell-based modeling and drug discovery for epileptic syndromes. These specific advances include the development of multi-electrode array chips that allow for population recordings of large quantities of neurons, as well as the Optopatch, which allows for targeted recordings of neuronal subtypes of choice in a high-throughput format and in an all-optical fashion.

Mapping the Brain to Treat Epilepsy with Surgical Precision

At Northwestern Medicine, we also are spearheading innovative ways to map the brain during epilepsy surgery. Using the most advanced techniques, such as awake brain mapping, we can identify brain tissue that is causing seizures. In the operating room, surgeons can remove this brain tissue, leaving the patient neurologically intact and without the burden of epilepsy. Other recent advances include stereo EEG. This is an exciting new technology that allows surgeons to localize a seizure with great precision by using minimally invasive approaches. Northwestern is one of the very few centers in the country that is performing this procedure as a collaboration between our academic neurologists and neurosurgeons.

THROUGH NORTHWESTERN MEDICINE, WE ARE CREATING A NATIONAL EPICENTER FOR HEALTHCARE, EDUCATION, RESEARCH, COMMUNITY SERVICE, AND ADVOCACY.

Northwestern Medicine

Northwestern Memorial HealthCare and Northwestern University Feinberg School of Medicine are seeking to impact the health of humankind through Northwestern Medicine. Our commitment to transform healthcare and to be among the nation’s top academic medical centers will be accomplished through innovation and excellence.

We recognize that every positive contribution we have made to neuroscience care, research, and education has been made possible by donors who have entrusted us with their philanthropic support.

We invite loyal donors and interested friends to join us in advancing our new Epilepsy Center within the Frances Evelyn Feinberg Clinical Neuroscience Research Institute. Your gifts of outright support and endowment will provide the resources we need to introduce breakthroughs that will improve the diagnosis and treatment of people with epilepsy today and in the future.