New findings could lead to treatments for epilepsy, behavioral disorders

October 11 2012

Three studies conducted as part of Wayne State University's Systems Biology of Epilepsy Project (SBEP) could result in new types of treatment for the disease and, as a bonus, for behavioral disorders as well.

The SBEP started out with funds from the President's Research Enhancement Fund and spanned neurology, neuroscience, genetics and computational biology. It since has been supported by multiple National Institutes of Health-funded grants aimed at identifying the underlying causes of epilepsy, and it is uniquely integrated within the Comprehensive Epilepsy Program at the Wayne State School of Medicine and the Detroit Medical Center.

Under the guidance of Jeffrey Loeb, M.D., Ph.D., associate director of the Center for Molecular Medicine and Genetics (CMMG) and professor of neurology, the project brings together researchers from different fields to create an interdisciplinary research program that targets the complex disease. The multifaceted program at Wayne State is like no other in the world, officials say, with two primary goals: improving clinical care and creating novel strategies for diagnosis and treatment of patients with epilepsy.

The three studies were published in high-impact journals and use human brain tissue research to identify new targets for drug development, generate a new animal model and identify a new class of drugs to treat the disease. In the first study, "Layer-Specific CREB Target Gene

Induction in Human Neocortical Epilepsy," published recently in the *Journal of Neuroscience*, donated human brain samples were probed to identify 137 genes strongly associated with epileptic seizures.

Researchers then showed that the most common pathway is activated in very specific layers of the cortex, and that it's associated with increased numbers of synapses in those areas. Because epilepsy is a disease of abnormal neuronal synchrony, the finding could explain why some brain regions produce clinical seizures.

"Higher density of synapses may explain how abnormal epileptic discharges, or spikes, are formed, and in what layer," Loeb said, adding that localizing the exact layer of the brain in which that process occurs is useful both for understanding the mechanism and for developing therapeutics.

The first study, which identified a new drug target for epilepsy, precipitated a second study that has found such a drug.

In the second study, "Electrical, Molecular and Behavioral Effects of Interictal Spiking in the Rat," published recently in Neurobiology of Disease, SBEP researchers found that the same brain layers in the rat are activated as in the human tissues and searched for a drug to target those layers. In fact, the first drug they tried, a compound called SL327 that has been used in nonhuman subjects to understand how memory works, "worked like a dream," Loeb said. "SL327 prevented spiking in rat brains," he said, "which not only prevented seizures, but led to more normal behaviors as well."

That finding led to collaborations between Loeb's lab and Nash Boutros, M.D., professor of psychiatry and behavioral neurosciences, and the Belgian drug company UCB.

"Whereas animals that developed epileptic spiking became hyperactive, those treated with the drug and had less spiking in their brains were more like normal animals," Loeb said. "Now whenever we screen for drugs for epilepsy, we look at behavior as well as epileptic activity."

Noting that many seizure medicines currently are used to treat various psychiatric disorders, Loeb said the SBEP team's latest round of work marks a "nice crossover" between psychiatry and neurology in the field of drugs related to epilepsy.

In the third study, just published in *Genetics*, researchers say they have found "fascinating interrelationships" between "junk" long noncoding RNA and normal RNA that are regulated by human brain activity. That work has the potential to be translated into new genetic treatments for epilepsy.

"This study shows how the human brain deals with half of the human genome in its most important function, electrical activity, using human brain tissue from patients with epilepsy to understand the basic molecular processes of how the brain works, and what's unique about human brains compared to the brains of less-developed species," Loeb said.

The third study, titled "Activity-Dependent Human Brain Coding/Noncoding Gene Regulatory Networks," is a collaborative effort between Loeb's lab and Leonard Lipovich, Ph.D., assistant professor of neurology and molecular medicine and genetics. It found that certain genes and their noncoding counterparts (which some researchers have called "junk") are co-regulated, or turned on at the same time, with brain activity.

"This tells us that some of these noncoding genes may actually have functions in brain activity," Loeb said. "In some, turning one on turns

another one off. Some are regulatory and can be used to control plasticity genes—which are involved in memory, learning and behavior—with one of these novel, noncoding RNA genes."

The synergy exhibited by the three studies, Loeb said, is testimony to the multidisciplinary nature of Wayne State's systems biology platform, partly developed with a remarkable three-dimensional database created in cooperation with Farshad Fotouhi, Ph.D., dean of the College of Engineering, and Jing Hua, Ph.D., associate professor of computer science.

"SBEP is a cross-campus endeavor," Loeb said. "These studies are the fruits of the labor of this consortium and only exist at WSU. The next steps will be translating these exciting findings into new treatments to prevent or even cure patients with epilepsy and other psychiatric disorders."

Provided by Wayne State University