Therapeutic approaches for neuronal network disruption in limbic epileptogenesis

Temporal lobe epilepsy (TLE), or limbic epilepsy, the most common form of epilepsy in adults, has no cure. The current medical treatments are not effective to control some limbic seizures. Patients with TLE are still at risk for early mortality and comorbidities such as cognitive dysfunctions, depression and anxiety disorders. They also have higher prevalence of systemic disorders that exacerbate adverse effects from anti-epileptic drugs. TLE also carries a social stigma and increases the costs of health care and community. TLE is characterized by spontaneous recurrent complex partial seizures (limbic seizures) that arise in the hippocampus, spread within limbic circuitry and to other brain regions. LE is a product of complex biological events denominated limbic epileptogenesis (LE). LE is associated with brain injuries that alter neuronal network connectivity, which is leading to hyper-excitability and limbic seizure susceptibility. Brief hippocampal spontaneous epileptiform activity, or microseizures observed in LE reflect small epileptogenic generators related to strong depolarization from pyramidal layers associated with an increased hyper-excitability, thus reflecting a complex pathological microcircuit activity. Microseizures are related to spontaneous bursts of certain groups of neuronal networks that lead to robust neuronal reorganization in epilepsy (i.e., chronic epilepsy), contributed, in some way, by an impairment of altered GABAergic perisomatic interneurons suggesting a dynamic and complex pathophysiology for the neuronal network involved in LE. Also, pathological high frequency oscillations (pHFOs) might precede microseizures and it could contribute to the propagation of MEA. pHFOs may recruit and synchronize other aberrant neuronal networks, which then trigger spontaneous recurrent seizures. Those aberrant networks are related to modification of dendritic spines (DS), subcellular site of the formation of aberrant neuronal network in LE. DS, morphological signature of postsynaptic sites and excitatory synaptic transmission, play a critical role in neuronal network assemblies during epileptogenesis. Modulation of activated inflammatory pathways, voltage-gated sodium channels, and the mTOR pathway are proposed for anti-aberrant neuro-network plasticity in LE. Continued clinical and experimental research in LE is critical for the discovery of new therapies to prevent TLE and to reduce adverse effects and pharmaco-resistance. Overall, the challenge in epilepsy research is to evaluate promised interventions for epileptogenesis and at the same time to identify biological mechanisms that can prevent aberrant neural network dysfunction.

Biography
Alberto E Musto, MD, PhD is a Physician-Scientist and Medical Educator of the Department of Pathology and Anatomy of the Eastern Virginia Medical School, Virginia, USA. His scientific goal is to identify a potential biomarker and preventive therapies for epilepsy. Currently, his research is focusing in the cellular and molecular mechanisms of immune-inflammatory process that contribute to the development of aberrant neuronal networks after brain injuries. He has been studied the role of pro-inflammatory mediators in experimental models of epilepsy using in vivo recordings of neural activities from chronically implanted microelectrodes in the brain and its correlations with neural damage, microglia cells and dendritic spine modifications using histological and biochemical approaches. He has been involved actively in medical education and neuroscience research in Universidad de Buenos Aires, and Universidad Austral, Argentina and Louisiana State University Health Sciences Center, USA supported by CONICET, Argentina and NIH, USA. He received board certifications in both Neurology and Radiology, completed Post-graduate studies in medical education, and management in health systems in Argentina. He completed a doctoral thesis in Neurobiology in Argentina and a Post-doctoral fellowship in neuroprotection in USA.

mustoae@evms.edu