Epilepsy is a chronic debilitating neurological disorder of humans and animals worldwide. The lifetime prevalence of epilepsy is ~2% (>65 million people). According to the Centers for Disease Control and Prevention (CDC) report, about 10% of Americans experience a seizure during their lifetime, and ~3% of those experienced the first seizure would develop epilepsy during their lifetime. Despite a significant progress in epilepsy research, the precise mechanism of epileptogenesis that follows an insult such as trauma, exposure to neurotoxic chemicals, infection, or gene mutation, are still largely unknown. Traditionally, neuronal hyperexcitability attributed as the major cause or consequence of epileptogenesis. Antiepileptic drugs (AEDs) development was focused on ion channels that excite neurons (antagonists) or promote inhibitory neurons function (agonists) to dampen hyperexcitability. However, the current AEDs are ineffective in about 1/3 of patients with acquired temporal lobe epilepsy (TLE), the most common type of all epilepsies. There is a need for the development of drugs that target alternative pathways to cure/modify epilepsy. TLE precedes neuroinflammation (reactive gliosis and proinflammatory cytokine/chemokines production), nitrooxidative stress, neurodegeneration, and increased epileptiform spiking ("disease promoters"), which persist even after the disease is established. In this seminar, novel therapeutic drugs that target the disease promoters and the mechanistic pathways will be discussed.