# *Trauma-Induced Changes in Cortical Circuit Function: Posttraumatic Epileptogenesis and its Prevention by Early Drug Intervention*

**Douglas S. F. Ling, Ph.D.**
Department of Physiology and Pharmacology
SUNY Downstate Health Sciences University

**Study Team Members:** Lie Yang, M.D., Ph.D., Jeffrey H. Goodman, Ph.D., Ana Mejia-Bautista, M.S., Sonia Afroz, Ph.D., Anika Sanjana, B.S., Patrick Quan, Hillary B. Michelson, Ph.D., Helen A. Valsamis, M.D., Robert Colbourn, Ph.D., Anthony Fringuello, B.S., Sabina Hrabetova, M.D., Ph.D., Roseanna Zanca, Ph.D., Peter A. Serrano, Ph.D.

Our laboratory is investigating the changes in cortical circuit function caused by traumatic brain injury (TBI) that lead to posttraumatic epilepsy (PTE), and evaluating early, post-injury drug interventions to prevent PTE. We use both *in vitro* and *in vivo* rat-based models of severe cortical neurotrauma. Our *in vitro* studies using rat neocortical slices have shown that a purely mechanical insult (i.e., lateral cut) which ablates the superficial cortical layers induces a persistent hyperexcitability, as exhibited by stimulus-evoked epileptiform discharges. This hyperexcitability appears to stem from two distinct sources: (1) a reduction in GABAergic inhibition; and (2) an increase in glutamatergic excitation consequent to the enhancement of AMPAR conductance. Using this model, we have screened candidate agents for neuroprotective potential, including levetiracetam (LEV), an FDA-approved, SV2A-ligand antiseizure drug. We found that LEV reduced epileptogenesis when delivered to slices within 1 h after injury. Our *in vivo* studies using the CCI model have shown that within 2 – 3 weeks after severe cortical TBI, there is a progressive development of evoked and spontaneous epileptiform activity, including prolonged, ictal-like discharges, as measured *ex vivo* in acute slices of somatosensory cortex. We have found that early, post-injury administration of a single dose (IP) of LEV or its newer, FDA-approved, congener brivaracetam (BRV) prevents the development of spontaneous epileptiform activity, even when dosing is delayed by 1 hour after trauma. To further assess the antiepileptogenic efficacy of LEV and BRV, we have recently added chronic EEG recordings for continuous monitoring of posttraumatic epileptic seizures *in vivo*.