ARISTEA S. GALANOPOULOU MD PhD

ROLE OF $GABA_A$ SIGNALING IN EPILEPTOGENESIS AND BRAIN DEVELOPMENT, EFFECTS OF EARLY LIFE EPILEPSY ON BRAIN DEVELOPMENT, MODELS OF INFANTILE SPASMS AND EARLY LIFE EPILEPSY, PATHOPHYSIOLOGY OF RETT SYNDROME

The maturation of $GABA_A$ receptor-mediated signaling from excitatory to inhibitory is an age-related process controlled by cation chloride cotransporters, such as KCC2. As a result, GABA exerts dual functions, being an important neurotrophic factor during early development and the principal inhibitory neurotransmitter of the mature central nervous system. In our laboratory we have been investigating the age and gender specific mechanisms through which early life stressors and seizures may disrupt the normal patterns of brain development, by disrupting the neurotrophic effects of GABA. We are also studying methods to reverse these adverse processes. Furthermore, we are very interested in understanding how epileptogenesis proceeds in the developing brain and what is the specific role of $GABA_A$ receptors in this process.

To better understand the pathophysiology and design better methods to treat catastrophic early life epilepsies, we are developing and studying new models of early life epilepsy. These include models of symptomatic infantile spasms that recapitulate most of the features of the human condition. Several projects are under way to elucidate the pathophysiology of infantile spasms. Furthermore, we are conducting preclinical trials to find better treatments. Our studies have provided preclinical evidence for new potential treatments with disease modifying properties for these early life epileptic encephalopathies.

Rett syndrome is one of the major causes of mental retardation and epilepsy. Most of these patients have mutations in the MeCP2 gene and also manifest abnormal stereotypic movements and autonomic dysfunction. Despite the devastating course of the disease, two independent laboratories have recently demonstrated that, in mice, phenotypic reversal can be achieved by restoring the normal function of MeCP2. We are using a mouse model of Rett syndrome to determine how pathogenic mutations of MeCP2 may interfere with the function and physiology of structures involved in the control of motor system and seizures, like the substantia nigra and how these processes may be reversed by appropriate therapeutic interventions.

Students interested in these projects will gain exposure to a variety of *in vivo* and *in vitro* techniques that combine molecular biology, *in vivo* and *in vitro* electrophysiology, histological, and behavioral studies and will be involved in projects with direct translational relevance to the clinical practice, i.e. identification of novel therapies.

Selected References:

Galanopoulou AS, Gorter JA, Cepeda C; Finding a better drug for epilepsy: the mTOR pathway as an antiepileptogenic target. Epilepsia 2012; (in press)

Galanopoulou AS, Buckmaster PS, Staley KJ, Moshé SL, Perucca E, Engel J Jr, Löscher W, Noebels JL, Pitkänen A, Stables J, White HS, O'Brien TJ, Simonato M; American Epilepsy Society Basic Science Committee And The International League Against Epilepsy Working Group On Recommendations For Preclinical Epilepsy Drug Discovery: Identification of new epilepsy treatments: issues in preclinical methodology. Epilepsia 2012; 53(3): 571-82.

Ono T, Moshé SL, **Galanopoulou AS**.: Carisbamate acutely suppresses spasms in a rat model of symptomatic infantile spasms. Epilepsia 2011; 52(9): 1678-84.

Raffo E, Coppola A, Ono T, Briggs SW, **Galanopoulou AS**: A pulse rapamycin therapy for infantile spasms and associated cognitive decline. Neurobiol. Dis. 2011; 43(2): 322-9.

Chudomelova L., Scantlebury MH, Raffo E, Coppola A, Betancourth D, **Galanopoulou AS**. Modeling new therapies for infantile spasms. Epilepsia: 2010; 51(Suppl. 3):27-33.

Chudomel O, Herman H, Nair K, Moshé SL, **Galanopoulou AS.** Age- and gender-related differences in GABA(A) receptor-mediated postsynaptic currents in GABAergic neurons of the substantia nigra reticulata in the rat. Neuroscience: 2009; 163(1): 155-67.

Galanopoulou AS. Dissociated gender-specific effects of recurrent seizures on GABA signaling in CA1 pyramidal neurons: role of $GABA_A$ receptors. J Neurosci. 2008; vol 28 (7): 1557-67.

Galanopoulou AS: Sexually Dimorphic expression of KCC2 and GABA function. Epilepsy Res. 2008; 80(2-3):99-113.