

James & Esther King Biomedical Research Program

Martynyuk, Anatoly

*Anesthesiology
University of Florida*

*2008 Program
Bridge (1-year project)*

Project Title: Balanced, Polyvalent Antiglutamatergic Action as a Novel Approach to Efficacious and Safe Neuroprotection

Project Summary: Stroke continues to be a major cause of death, disability, and economic expense in the world. Tobacco consumption, both active and passive, is an important risk factor for stroke. The only therapy currently available for a limited number of patients is an intravenous administration of tissue plasminogen activator shortly after symptom onset to re-establish cerebral blood flow in case of vessel occlusion. The pathophysiology of stroke is a complex process with overactivated glutamate signaling as one of the primary events that initiates numerous and diverse intracellular processes leading to cell death. For this reason, the glutamatergic system has been a promising target for potential neuroprotective therapy. However, glutamate is a major excitatory neurotransmitter that plays a critical role in normal brain physiology. Therefore, it is not surprising that many previous highly selective and potent glutamate receptor antagonists failed clinical trials, primarily because of side effects they produced. This study tests the novel concept that antiglutamatergic agents with polyvalent actions and moderate potency have the potential to overcome these limitations by producing efficacious neuroprotection and still enabling a level of balanced glutamate receptor activity required for physiological brain functions and thus avoiding significant side effects. During investigation of the mechanisms whereby high concentrations of the aromatic amino acid phenylalanine (Phe) affect the brain in phenylketonuria (PKU) patients, we found that this aromatic amino acid depresses the glutamate system in a way that may form a basis for the development of such drugs. This grant aims at investigating neuroprotective effects of the aromatic amino acid derivative, 3, 5-dibromo-D-tyrosine. It may become a novel, much-needed drug, or a prototype of drugs, not only against stroke, but also against a variety of other pathologies involving similar etiology, such as epilepsy, Alzheimer, and Parkinson.