

James & Esther King Biomedical Research Program

Hu, Bingren

*Department of Neurology
University of Miami*

*2007 Program
Bridge (1-year project)*

Project Title: Irreparable Ribosomal Damage After Focal Brain Ischemia (Stroke)

Project Summary: Stroke (or focal brain ischemia) is a serious clinical problem. On average, every 45 seconds someone in the United States has a stroke, totaling more than 700,000 incidents each year. A substantial number of these stroke incidents can be associated with tobacco use. Tobacco exposure increases stroke severity and the incidence of stroke death by 2- to 3-fold. However, the molecular mechanisms of stroke-induced neuronal damage are still poorly understood, and there are few effective clinical treatments available for stroke patients. Therefore, study of molecular mechanisms of stroke is essential to understand how tobacco use increases stroke incidence and how to develop new therapeutics for treatment of this devastating tobacco-related disease. Tobacco smoking generates numerous reactive intermediates that interact with proteins to form toxic protein adducts in our body. These protein adducts are highly toxic in neurons because they are highly likely to deposit into vital cellular organelles such as mitochondria and the endoplasmic reticulum (ER). We have recently found large quantities of toxic proteins in the proteasomes, and on mitochondrial and ER membranes. Deposition of toxic proteins in these vital organelles leads to functional failure of these organelles after focal brain ischemia (stroke). Therefore, tobacco use is likely to increase incidence of stroke and stroke severity by aggravating the functional failure of multiple cellular organelles. The objective of this project is to investigate molecular mechanisms underlying the functional failure of vital cellular organelles and to explore treatment measures that rescue damaged vital organelles after stroke. Our studies strongly suggest that toxic deposition of abnormal proteins in vital cellular machinery is a consequence of malfunction of protein quality control systems. This grant employs state-of-the-art molecular gene transfection technologies to rescue the failure of protein quality control systems in neurons after stroke. Therefore, this grant will provide new avenues for treatment of stroke.