

Dr. Kathryn Todd

Title: Investigations of novel strategies to improve cellular and behavioral outcomes after focal embolic cerebral ischemia

a) Statement of the health problem or issue:

Stroke is the leading cause of chronic disability and the third most common cause of death in North America. Yet, we still do not have effective strategies to protect brain cells from the devastating effects of stroke. This grant proposal seeks to increase our understanding of the cascade of events that occurs in the brain after a stroke and how we can more effectively save brain cells after a stroke.

b) Objective of your project:

The brain's immune system is relatively separate from the peripheral immune system because of the blood-brain barrier. The cells that primarily make up the brain's immune system are the microglial cells. In the event of any injury to the brain, microglial cells can become "too much of a good thing". This occurs because once activated (by a stroke, traumatic brain injury or neurological disease such as Alzheimer's Disease), microglial cells release a wide variety of substances including pro-inflammatory cytokines and matrix metalloproteinases; both of these substances can cause nerve cells to die and both can break down the blood-brain barrier, a situation which is toxic to the brain. I am using drugs that block the activation of microglial cells and investigating the effects of these drugs on the release pro-inflammatory cytokines, on the expression of proteins that initiate cell death processes, and on the microvasculature of the brain (the blood-brain barrier). I am trying to tip the balance away from signaling brain cells to die and toward increasing cell survival signals.

c) How will you undertake your work:

I use animal models of stroke. If you ask someone who has had a stroke if they remember any pain, most will tell you that they do not. For ethical reasons, the animals used in my studies are completely anesthetized before undergoing a stroke. At various time points after the onset of the stroke (1 hour, 3 hours, 6 hours) I begin treatment with one of the two drugs that act as anti-inflammatory agents and block the inflammatory response. I am then evaluating the effects of the drugs alone or in combination with thrombolysis (the only treatment used clinically for stroke) on cell death signaling molecules and the blood-brain barrier.

d) What is unique/innovative about your project:

The fact that I am conducting a comprehensive study of the effects of the neuroinflammatory response on cell death signaling factors and cerebral microvasculature is unique. Additionally, I am using a model that is relevant to stroke in humans. I anticipate that the data gained from these studies will significantly enhance our knowledge of the pathogenesis of stroke and perhaps identify an effective treatment strategy.

e) Relevance to mission statement of the Heart and Stroke Foundation:

The outcomes of my research project will increase our understanding of two important and fundamental brain responses to stroke and elucidate effective strategies to increase brain cell survival after a stroke.