

Faculty Advisor: Grazyna Nowak, Ph.D.

2009 Voldeng Fellowship Proposal

2009 Pharmaceutical Sciences Research Fellowship Proposal

Title: **Amelioration of Functional Deficits in Ischemic Kidney by Succinate Administration**

Exposure of the kidney to ischemia (a temporary decrease or lack of blood and oxygen supply) results in acute kidney injury. Because pathological conditions due to kidney ischemia are frequent causes of mortality and because organ transplantation becomes increasingly common, identifying treatments that would decrease mortality due to kidney failure is very important. The goal of this project is to determine whether succinate supplementation improves metabolic functions in the kidney injured by ischemia. The kidney function is dependent on energy (ATP), which is generated in mitochondria. Perturbations in mitochondrial functions lead to decreases in ATP production, and result in the decline in kidney function and injury to kidney cells. Effective treatments that protect against these decreases or improve recovery of ATP levels and diminish acute kidney injury are not currently available and dialysis is used as the major therapy to improve renal function. Our preliminary data show that succinate improves survival and cellular functions associated with energy production in renal cells grown in culture<sup>1</sup> and in mitochondria isolated from the kidney in the mouse model of renal ischemia *in vivo*. Succinate improves mitochondrial function and decreases oxidative stress and cell death in injured cells *in vitro*.<sup>1</sup> This project will test whether administration of succinate before or after ischemia improves mitochondrial function and ATP production, and reduces injury to the ischemic kidney. A well established model of mouse renal ischemia followed by reperfusion will be used in this study. We hypothesize that **administration of succinate to the mouse before or after experimental ischemia prevents energy deficits in the kidney and improves kidney repair *in vivo*. The second hypothesis of this project is that succinate reduces oxidative stress and cell death in the kidney injured by ischemia.** We will address these hypotheses by testing whether administration of succinate before and/or after experimental ischemia in mice improves mitochondrial function, renal ATP production, and the function and morphology of the ischemic kidney. The second set of experiments will determine whether succinate administration decreases production of reactive oxygen species and oxidative stress in the ischemic kidney. Completion of these experiments will determine if administration of succinate may serve as a therapy to limit ATP deficits and prevent or decrease kidney injury in conditions that are associated with ischemia in the kidney. This approach might be also beneficial in other organs that are susceptible to the lack of oxygen such as the heart and the brain.

The research fellow will focus on conducting experiments that will measure mitochondrial respiration and activity of several mitochondrial enzyme complexes involved in the production of ATP. In addition, the fellow will measure the levels of creatinine and blood urea nitrogen in serum samples collected from control and experimental mice. The levels of these two metabolites will serve as markers of kidney function in the in vivo experiments. The student will gain hands-on experience with several biochemical procedures (enzyme assays, measurements of respiration, measurements of ATP levels, PCR) and instrumentation (spectrometry, fluorimetry, luminometry, measurement of oxygen levels, PCR thermocycler).

The fellow student will work directly with the faculty and will also learn experimental design, processing of research data, and drawing conclusions from these data.

1. Nowak G., Clifton, G.L., Bakajsova, D. (2008) Succinate ameliorates energy deficits and prevents dysfunction of complex I in injured renal proximal tubular cells. J. Pharmacol. Exp. Ther. 324: 1-8.