Benz and Ellerby Labs

Background. As a physician-scientist and medical oncologist for nearly 40 years, Dr. Benz continues to focus his lab's efforts on translational cancer research focusing primarily on experimental therapeutics. Working on a large Buck Institute interdisciplinary geroscience project along with Buck neuroscientists and mitochondrial experts, the Benz lab synthesized and reported in 2019 on the anti-cancer potential of a unique suicide inhibitor of the mitochondrial enzyme proline dehydrogenase (PRODH) needed for the survival, growth and metastasis of various cancer cells under hypoxic and low nutrient stress conditions. Surprisingly, our orally bioavailable PRODH suicide inhibitor, *N*-propargylglycine (*N*-PPG), also turned out to penetrate and beneficially impact normal host tissues including the brain by inducing mitohormesis and the mitochondrial unfolded protein response (UPR^{mt}). Collaborating on mouse studies with the Buck neuroscience lab of Dr. Lisa Ellerby, we performed and then reported on the comparative biochemical, behavioral, transcriptomic, and metabolomic measurements that confirmed the beneficial brain mitohormetic and neuroprotective effects of *N*-PPG in both wildtype (B6/CBA) mice and a short-lived genetically engineered (R6/2) mouse model expressing the mutated Huntington's protein. Over the past 4 years two Buck Institute postbaccalaureate students, co-sponsored by both the Benz and Ellerby labs, serendipitously discovered that *N*-PPG also inhibits another homologous mitochondrial enzyme expressed only in liver and kidneys that catabolizes hydroxyproline (PRODH2, also referred to as HYPDH). This surprising finding led to our most recent report predicting that use of *N*-PPG to irreversibly inhibit PRODH2 would meet a long sought clinical need to find a life-saving drug treatment for the rare and often fatal inborn error of metabolism causing Primary Hyperoxaluria associated with severe and recurrent formation of calcium oxalate kidney stones in infants.

Proposed Project (jointly sponsored by Benz & Ellerby labs). *Catalytic inactivation of mitochondrial PRODH2/HYPDG to treat Primary Hyperoxaluria and prevent Ca-oxalate kidney stone formation*. Ca-oxalate nephrolithiasis is the most common cause of age-associated recurrently kidney stone formation, sporadically afflicting ~10% of all adults while also causing early renal failure in ~5,000 US children born with one of three different genetic types of Primary Hyperoxaluria (PH). Using a mouse model of type-2 PH bearing genetic knockout (KO) of the enzyme converting glyoxylate to glycolate (Grhpr), we have now confirmed that these mice develop hyperoxaluria and severe Ca-oxalate nephrolithiasis associated with early death. We have also shown that daily oral gavage of *N*-PPG normalizes their urine oxalate secretion, prevents their kidney stone formation, and extends the survival of Grhpr KO mice to that of normal controls. Future project aims include delineating the specific cellular and molecular mechanisms by which *N*-PPG protects against renal tubule damage and kidney stone formation in these Grhpr KO mice, and determining if this novel drug candidate can also prevent kidney stone formation in a mouse model of sporadic Ca-oxalate nephrolithiasis.

Desired Skills or Experience: Background and strong interest in pursuing biological sciences by independent and creative problem solvers. Prior molecular/cellular lab experience preferred.