Benz Lab

As a physician-scientist and medical oncologist for over 40 years, Dr. Benz continues his lab's focused efforts on cancer research, in particular, experimental therapeutics. As summarized below, three independent lab projects currently in progress await participation by a talented Postbacc/RA candidate looking to make a difference in human health research. Two of these are now interdisciplinary projects with promising clinical applications for not only cancer patients but also healthy individuals at risk for developing neurodegeneration or kidney stones.

1. Working with our Buck's Mass Spec/Proteomics group who helped us identify a pivotal role for acetylated p300/CBP chromatin complexes in regulating the half-life of cancer-driving oncogenic transcripts like HER2/ERBB2 mRNA, we are now therapeutically inhibiting the amplified *HER2/ERBB2* oncogene's post-transcriptional mechanism using a new class of oral and well tolerated epigenetic drugs that induce accelerated decay of HER2/ERBB2 mRNA and cause cancer cell death in our experimental systems modeling the 20% of patients newly diagnosed with this most aggressive form of breast cancer. Further mechanistic studies are needed to preclinically advance this most promising new anti-cancer treatment strategy.

2. Our lab synthesized and first reported on the anti-cancer potential of a unique suicide inhibitor of the mitochondrial enzyme proline dehydrogenase (PRODH), necessary for cancer growth and metastasis under hypoxic and nutrient stress conditions. Surprisingly, our orally bioavailable PRODH suicide inhibitor (*N*-PPG) also turns out to penetrate the brain as well as beneficially impact normal host tissues by inducing mitohormesis and the mitochondrial unfolded protein response (UPR^{mt}). In close collaboration with the Ellerby lab, we've reported biochemical, behavioral, transcriptomic, and metabolomic mouse data demonstrating the promise of *N*-PPG in preventing neurodegeneration. Serendipitously, we've also recently discovered that *N*-PPG specifically inhibits another structurally related mitochondrial enzyme, PRODH2, that selectively catabolizes hydroxyproline in liver and kidney organs. This PRODH2 inhibition metabolically impairs liver and kidney synthesis of oxalate, dramatically reducing oxalate secretion and oxalate kidney stone formation. To better understand the latter effect, we are now using experimental systems to demonstrate that *N*-PPG exposure reduces oxalate-induced cell stress and senescence in cultured renal tubule cells.

3. Using several population-based molecular-genetic studies involving USA and UK women, we've shown the health benefit of a commonly inherited genetic variant in the growth factor receptor axis, IGF1/IGF1R, associated with human aging and disease. Inheritance of this IGF1R single nucleotide polymorphism (SNP) variant protects against future development of breast and other cancers, as well as cardiovascular disease. Our current lab studies are now trying to determine exactly how this normal SNP variant within the 3'UTR of the *IGF1R* gene functionally reduces its mRNA expression level via a putative RNA binding protein, producing its lifelong beneficial reduction in *IGF1R* tissue expression.

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