Benz Lab



As a physician-scientist and medical oncologist for over 40 years, Dr. Benz continues to focus his lab's efforts on cancer research, focusing on experimental therapeutics. As summarized below, three independent lab projects currently in progress await participation by a talented Postbacc candidate looking to make a difference in human health research. Two of these have become interdisciplinary projects with promising clinical applications for not only cancer patients but also individuals at risk for developing cardiovascular or neurodegenerative diseases.

1. Working with our Buck's Mass Spec/Proteomics group who helped us identify a pivotal role for variably acetylated p300/CBP complexes in regulating the half-life of a cancer-driving oncogenic (HER2/ERBB2) transcript, we are now post-transcriptionally targeting the amplified oncogenic receptor's mechanism using a new class of oral and well tolerated epigenetic drugs that selectively target this complex, accelerate the rapid decay of HER2/ERBB2 mRNA, and cause cancer cell death in our various model systems representing the 20% of newly diagnosed patients with this most aggressive form of breast cancer. Further mechanistic studies are needed to preclinically advance this most promising new anti-cancer treatment approach.

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 low nutrient stress conditions. Surprisingly, our orally bioavailable PRODH suicide inhibitor (*N*-PPG) also turned out to penetrate and beneficially impact normal host (mouse) tissues, including the brain, by inducing mitohormesis and the mitochondrial unfolded protein response (UPR^{mt}). We've just reported on biochemical, behavioral, transcriptomic, and metabolomic mouse studies in collaboration with the Ellerby Lab, demonstrating the promise of *N*-PPG in preventing neurodegeneration; so future studies are now planned using genetically engineered mice to assess its effectiveness in preventing Alzheimer's Disease. Serendipitously, we also found that our *N*-PPG drug inhibits another homologous mitochondrial enzyme that selectively catabolizes hydroxyproline (PRODH2), opening up the possibility of using *N*-PPG as a long sought treatment for a rare inborn error of metabolism known as primary hyperoxaluria.

3. During a series of population-based molecular-genetic studies we've reported on in USA and UK women, we've identified a commonly occurring genetic variant in the well known growth factor axis, IGF1/IGF1R, intimately linked to human aging and disease. Inheritance of this IGF1R single nucleotide polymorphism (SNP) variant confers protective benefit 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 via an unknown 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.

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