2023 IMPACT CIRCLE

Project Title: **To test the impact of glycation lowering intervention with multimodal effects on longevity mechanisms on reducing body weight, improving glucose metabolism, and slowing aging.**

Investigator(s) and collaborations: **Dr. Pankaj Kapahi (PI); Dr. John Newman (Co-PI)**

Unmet Need/Primary Question: Aging is the largest risk factor for late-life chronic diseases and constitutes a significant healthcare burden. Aging and several age-related diseases do not have a single cause but rather involve multiple biological pathways. A major gap in our knowledge remains in understanding the different mechanisms regulating the process of aging that leads to age-related health decline. The primary objective of this proposal is to identify a robust intervention to target the drivers of aging to enhance human healthspan. If successful this proposal will help to develop a low-cost, highly accessible solution to slow aging and age-related decline in function.

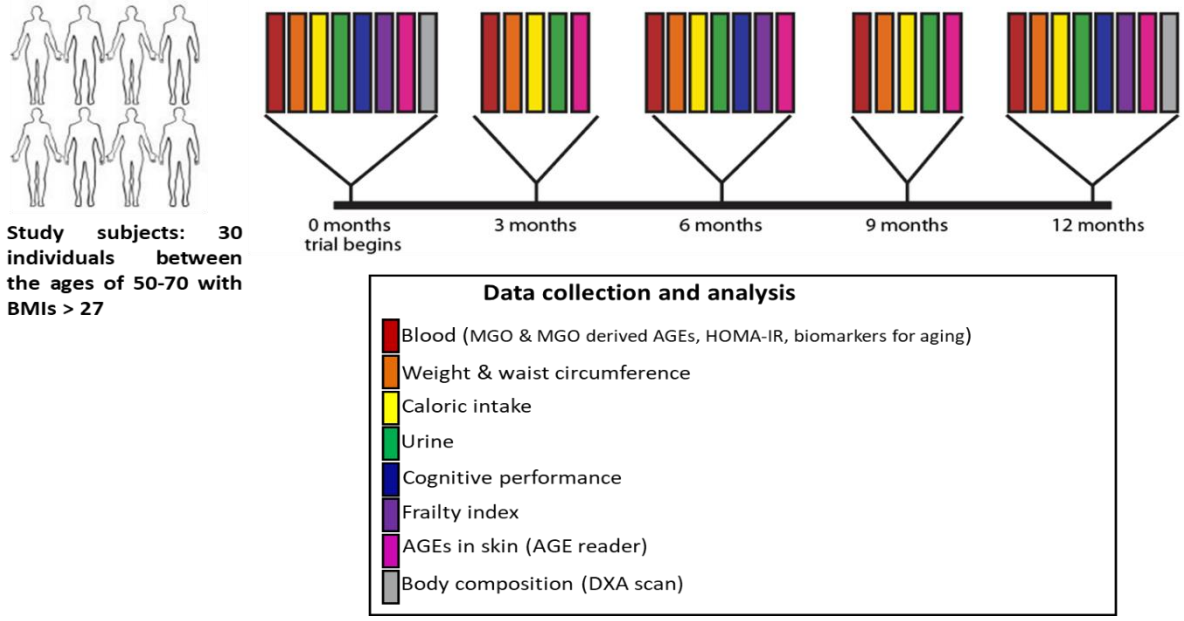
Background: Since the cause of aging and several age-related diseases is multifactorial, shaped by both genetics and the environment, developing therapeutics that can engage multiple pathways involved in aging is likely to be a much more effective approach. Our overall goal is to discover mechanisms and identify effective therapeutics that slow aging and enhance human healthspan. Advanced glycation endproducts (AGEs), generated as part of a normal metabolic process, mediate the toxicity of sugar in aging and age-related diseases. AGEs formation is accelerated under hyperglycemia and during aging enhancing the risk of diseases such as diabetes and Alzheimer's disease. We screened a combination of glycation-lowering compounds (Gly-Low) that are Generally Regarded As Safe (GRAS), that act synergistically to detoxify AGEs. Gly-Low combination consists of lipoic acid, nicotinamide, pyridoxine, thiamine, and piperine, which have previously been shown to slow aging and neurodegeneration when administered individually. In our preclinical studies, we have earlier demonstrated that the combination displayed a synergistic effect from glycation and aging-related stress.

Novel Hypothesis: Our central hypothesis is that treatment with Gly-Low will slow aging by targeting multiple known longevity pathways to improve human healthspan.

Project Proposal: We will conduct a Phase 1, placebo-controlled clinical trial to evaluate the efficacy of 12-month oral Gly-Low treatment in 30 aged individuals with BMIs > 27 to (Figure 1) in the following two aims. Aim 1) Determine the impact of a Gly-Low on body weight and metabolic markers. Aim 2) Determine the effect of a Gly-Low on age-related functional decline and biomarkers. Each participant will take this supplement or placebo in a pill form orally once in the morning. Aim 1 primary endpoint will be reduced body weight and secondary endpoints will include measurement of caloric intake, waist

circumference, glucose metabolism (HOMA-IR), and reduced MGO and MGO-derived AGEs in sera. Aim 2 primary endpoints will be frailty, based on cognitive performance (e.g. memory), physical performance, and a clinical frailty index. The secondary endpoint will determine whether Gly-low reduces blood biomarkers for aging. The trial will determine whether Gly-Low supplementation induces the benefits of caloric restriction, which would have relevance for aging and diseases with overnutrition as a risk factor. Furthermore, we expect that by targeting multiple longevity pathways Gly-Low can serve as a safe and robust intervention to slow age-related functional decline in humans. Successful completion of this innovative project will result in combination therapy that can complement ongoing treatments to enhance health and slow a range of age-related diseases including diabetes and dementia.

Description of Potential Impact: Our proposed idea is translational because we propose to test a method to slow aging through multimodal effects including glycation reduction, calorie restriction, reduced inflammation, increased fat burning, and enhanced neuroprotection using a combination of supplements that have been designated GRAS by the FDA. Successful completion of this proposal would yield clinical evidence for Gly-Low's ability to engage multiple pathways that enhance longevity using a combination of compounds that function synergistically to promote metabolic health, calorie restriction, enhance neuroprotection, and thus slow aging. Due to these beneficial effects, Gly-Low as a dietary supplement would positively impact the healthspan of all individuals including donors. The results from this pilot study would yield promising data to secure additional



funding to conduct large-scale clinical trials to test the efficacy of Gly-low compounds in selected human subjects. Our proposal has the potential to help develop a low-cost highly accessible treatment that can complement existing therapeutics to slow aging and age-related diseases.

Figure 1. Overview of the study design to measure the effects of Gly-low. Participants will be screened for up to 30 days before entering the 12-month trial and followed up for another 30 days following the trial's completion.