2023 IMPACT CIRCLE

Project Title: **Identifying novel therapeutic targets for rejuvenation potential that influence psychosocial and biological aging hallmarks using Mendelian randomization-based precision medicine approach.**

Investigator(s) and collaborations: Principal Investigator: **Dr. Pankaj Kapahi, Ph.D.** (Professor): Biogerontology;

Unmet Need/Primary Question: The process of human aging is complex and individualized One cause of individual variability could be the responses to social factors which influence the physical and cognitive outcomes and multimorbidity[1,2]. Recent findings strongly suggest that psychosocial determinants of health have deep genetic and biological roots[3,4], however, the discovery of genetic variants associated with psycho-social hallmarks of aging had proven elusive[5,6]. Genetic variants that modulate the rejuvenation pathways in humans can be utilized to assess the efficacy of therapeutic interventions. The overall goal of this proposal is to develop genetic and pharmacological interventions relating to molecular and physiologic factors rooted in human genetic association studies that will reverse age-related decline and rejuvenate health.

Background: 23% of the total global burden of disease is attributable to disorders in aged individuals. As the process of human aging shows large inter-individual variation, the translation of preclinical findings to clinical scenarios becomes challenging. It has been shown by earlier findings that psychosocial determinants of health are likely to impact fundamental mechanisms of *aging* and/or senescence. Therapeutic stasis is mainly attributable to the unknown pathophysiology caused by these psychosocial and biological factors. For example, depression and telomere length[7] are found to be negatively associated. On the other hand, major depressive disorder is associated with accelerated cellular aging characterized by an insufficiency of protective or restorative mediators[8]. Thus, the likelihood of poor health span and of accelerated aging is increased by the interaction between these psychosocial and biological factors at cellular level. While there are numerous phenome- and genome-wide association studies available, there is no convincing evidence that the presence of psychosocial and biological factors is a causal risk factor for health span traits in humans. We will pioneer the use of Mendelian Randomization (MR) to test for causal associations between biological and social hallmarks of aging collectively using human phenome- and genome-wide association studies and use these to develop individualized therapeutic interventions. MR studies are often described as naturally occurring randomized trials in which germline genetic variants are randomly assigned by nature (Figure 1). MR studies would help identify drug targets that could save millions of dollars and time and prevent unnecessary exposure to adverse drug effects[9]. We have previously applied this approach to Alzheimer's Disease (AD) and successfully identified novel causal associations and candidate gene-to-drug targets[10,11] (Figure 2).

Novel Hypothesis: Using the Mendelian Randomization inference method to test the novel hypothesis that different psychosocial and biological factors are causally associated with the risk of mortality and healthspan based on publicly available summary data of GWAS on different psychosocial exposures and summary data of large-scale GWAS on longevity. Here, we are focusing on identifying rejuvenating interventions for social and biological hallmarks of aging using a combination of Mendelian Randomization based precision medicine approach in humans and appropriate human cell culture models of aging.

Project Proposal: We will test our hypothesis through the following two specific aims:
1) To identify candidate genetic variants using mendelian randomization from Phenome (PheWAS) and Genome-wide association studies (GWAS) of longevity and age-related traits. We will determine the role of lifestyle and psychosocial factors like depression, positivity, physical activity and diet on mediating mortality and healthspan traits in humans. Genetic variants associated with conserved mechanisms of healthy longevity as potential rejuvenation targets, for drug discovery will be identified using Mendelian Randomization analyses for causality analysis [16-18] controlling for population stratification, confounding due to environmental causes, and potential heterogeneity in genetic effects. Genes that confer a protective effect are of particular interest as they may serve as a potential treatment avenue for rejuvenation. One example of such a gene we have already identified is prostacyclin synthase in mediating a causal link between depression in neurodegenerative diseases. 2) To discover drugs as leads that could be used for rejuvenating human lifespan by targeting either variants occurring in the identified candidate genetic modifiers or their pathways. Based on therapeutic hypotheses relating genetic function to healthy aging, we will identify small molecules that can mediate gene expression change in human cells and tissue from signatures extracted from but not limited to the LINCS L1000 dataset[12], the original Connectivity Map (CMap) dataset[10], and the Gene Expression Omnibus (GEO)[11]. The screen will identify promising lead *compounds* ready for advancement down the drug development pathway as well as new targets for future drug development efforts.[2]

Description of Potential Impact: Using human omics data driven hypotheses to discover new drugs makes our approach faster and more cost-effective, providing new insights into disease mechanisms and targets. Importantly, this gene-to-drugs collaborative project will be the first to use the genetics of individuals with social hallmarks of aging as a guide for the development of therapeutic approaches for rejuvenation itself rather than composite diseases for preventing, delaying onset and progression, and possibly even reverting many multiple age-related diseases. The resulting optimized system also serves as a potential high-throughput drug screening system, which is of human origin and will have the advantage of being controlled for potential confounding factors. We highlight that the proposed study can be applied in a broad range of ways to generate previously undocumented insights. For example, if depression and cellular senescence share genetic determinants this would uncover genetic factors mediating susceptibility to disease in both healthy and diseased individuals with unprecedented power. Collectively, these investigations will result in the optimization of the entire workflow process for the application of a precision medicine approach to develop individualized diagnostics and treatment for aging and age-related diseases.

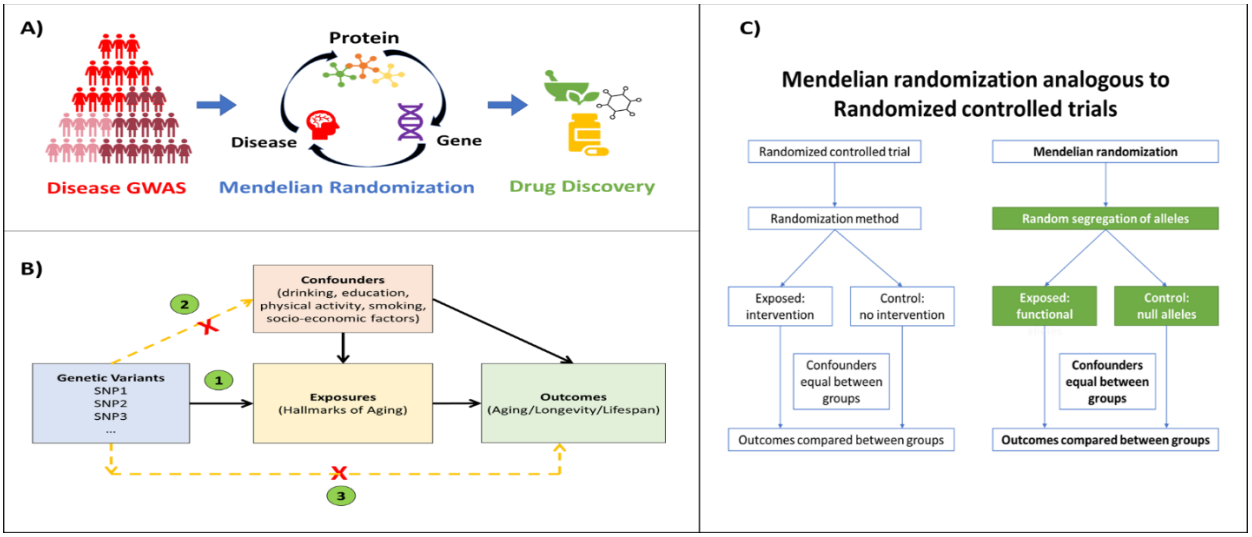

Figure 1. (A) Overall schematic of the proposal to use Mendelian Randomization with omics data to identify potential new drug targets. (B) A directed acyclic graph representing the MR framework. 1: the instruments must be associated with the exposure; 2: the instruments must influence the outcome only through the exposure; 3: the instruments must not associate with measured or unmeasured confounders. (C) Diagram illustrating the analogy between Mendelian randomization (MR) and a randomized controlled trial.

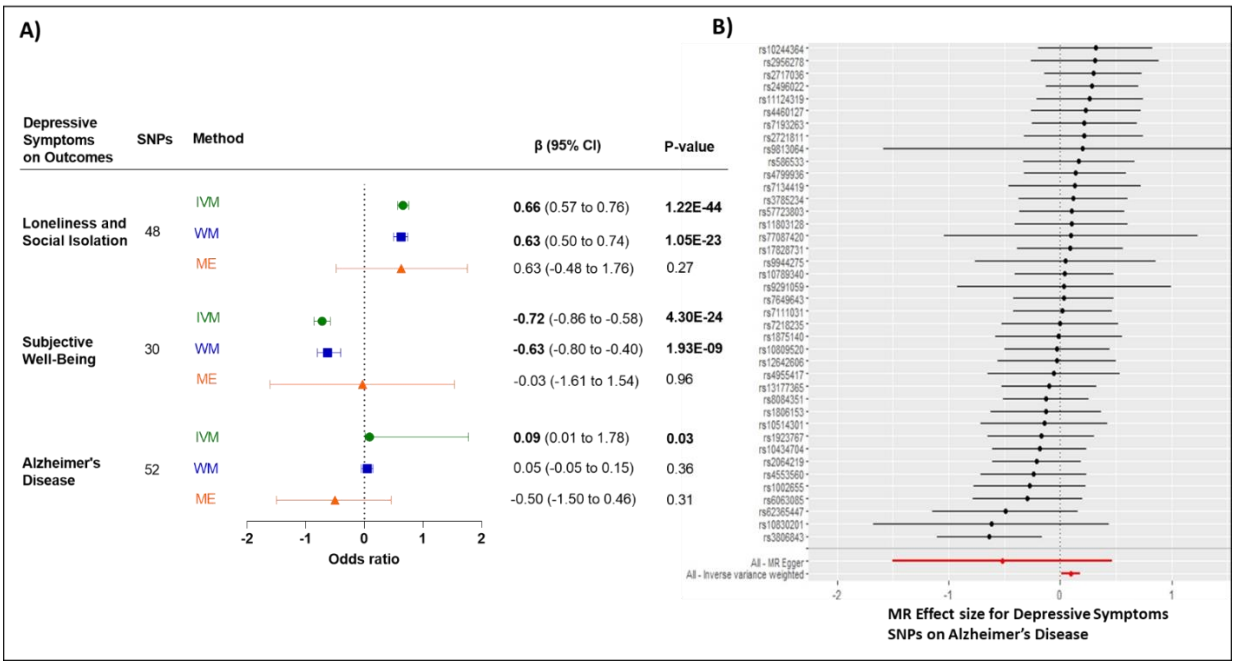

Figure 2. (A) Mendelian randomization (MR) estimates the risk of loneliness, subjective well-being, and Alzheimer's disease associated with depressive symptoms using instrumental single-nucleotide polymorphisms (SNPs). MR estimates were calculated using the inverse-variance weighted (IVM), weighted median (WM), and MR-Egger (ME) method to summarize the effect of each individual SNP. Beta (β) represents the risk of the disease per genetically determined 1-unit increase in depressive symptoms. (B) Forest plot of the Depressive Symptoms SNPs associated with risk of AD. The x-axis shows the MR effect size for the Depressive Symptoms GWAS dataset on AD from the AD GWAS dataset. The y-axis shows the analysis for each of the SNPs and the SNPs in total using the MR-egger and inverse variance weighted (multiplicative random effects) methods.