Integrating Epigenomics with Life Stress Measurement to Predict Accelerated Aging

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Life stress is known to be a major predictor of morbidity and mortality beyond chronological age (i.e., time since birth). A major hypothesis is that greater life stress leads to accelerated aging, such that an individual's biological age is older than their chronological age, leading to earlier death. However, despite decades of research, identifying suitable biomarkers that can estimate biological age to test this hypothesis has proved difficult.

Fortunately, the past few years have seen the emergence of robust epigenetic clocks, whereby an individual's biological age can be quantified by levels of DNA methylation (DNAm) at key sites in the genome, presenting a unique opportunity for understanding how stress influences biological aging. In this seed grant, we propose to take advantage of access to the NIH-funded ESCAPE dataset that contains state-of-the-art longitudinal stress measurements for ~200 individuals and combine this with genome-wide DNAm data that we will generate for the same individuals. This will allow us, in a cross-sectional framework, to examine the role of stressor type and timing in accelerated biological aging at an unprecedented resolution.

To achieve this goal, we have the 3 following objectives:

Generate genome-wide Single Nucleotide Polymorphism (SNP) and DNAm array data from banked blood samples of 150 individuals from the baseline wave of the ESCAPE study.

Use genome-wide DNAm levels to obtain an estimate of biological age and epigenetic accelerated aging (EAA) of each individual via the DNAm PhenoAge epigenetic clock.

Combine estimates of EAA with existing ESCAPE stress measurements to distinguish between acute vs. chronic and early, cumulative, and current stress in predicting accelerated aging.

The results of this seed grant will then form the basis of a larger project that would examine ~800 individuals (~200 from ESCAPE and ~600 from a new dataset based on a recently funded NIA R01 to Dr. Scott) followed for four years. Critically, we would generate DNAm data from the same individuals from multiple time points, providing an important longitudinal context that is currently absent but much desired in the literature. A longitudinal approach is necessary in order to understand if certain stressors or stressor combinations can change the rate of biological aging, thus altering the trajectory of risk of morbidity and mortality.

Our interdisciplinary team has the necessary subject (i.e., psychosocial stress, biological aging) and methodological expertise (i.e., genomics, longitudinal analysis) and access to the existing samples for this OVPR seed grant proposal. Internal support of the OVPR seed funding for the initial cross sectional

study would establish evidence of our collaboration and demonstrate proof of concept and preliminary data. In the next 18 months, we will target NIA (~$3M direct costs) grant mechanisms that include R01s as well as RFAs specifically seeking analysis of existing longitudinal datasets with psychosocial and genomic data. This new, interdisciplinary research program combining faculty from two departments (Psychology, Ecology & Evolution) fits with NIA's Strategic Directions for Research on Aging6 to better understand (A) the biology of aging and (B) the effects of factors such as stress on aging which are needed to develop effective interventions to maintain health and reduce the burden of age-related diseases and disorders.