**Definition of whole-body transcriptional coordination patterns and their age-related changes**

Aging is a process of functional impairment affected by multiple genetic and environmental causes. Whole-body physiological homeostasis is pivotal for maintaining human health and longevity and is properly maintained by an inter-tissue communication network that coordinates physiological responses among organs and tissues. While gene-to-gene transcriptional co-regulation has been documented in many specific tissues, the global co-regulation of the transcriptome across tissues throughout the body at the system level remains to be studied in detail. With the advent of ultrahigh-throughput sequencing technologies enabling the profiling of gene expression in multiple tissues and even single cells derived from a given donor, we now have the opportunity to conduct high-level analyses of transcriptional coordination among tissues at a large scale and their changes across conditions such as aging.

Our central hypotheses are that (1) gene expression patterns are co-regulated and coordinated between tissues and that (2) the perturbation of this coordination may represent a central mechanism predisposing individuals to disease and the aging process such that studies of shifts in these complex regulatory processes may reveal an important biomarker of aging. Here, we propose to develop a new computational approach and framework to analyze inter-tissue co-expression at the whole-body level so as to decipher global transcriptomic coordination patterns and how they change with aging. We will apply our methodology to multi-tissue and single-cell RNA-sequencing data from both young and aging cohorts. Specifically, we will (1) develop a computational approach to evaluate system-level coordination at the whole-body scale, (2) extend our approach to detect specific whole-body transcriptional coordination patterns, and (3) document age-related changes in such coordination. Our more focused preliminary studies have already demonstrated that metabolic gene expression networks are significantly co-regulated and coordinated across the body and that this coordination changes with age, emphasizing the feasibility and biological relevance of our hypotheses and experimental objectives.

The proposed study employs a pioneering approach to leveraging high-throughput data as a means of elucidating the extent of the global whole-body transcriptional coordination of functionally related genes. In addition, it will define specific coordination patterns to develop a comprehensive model of tissue-axis coordination leading to the establishment of a catalog of crosstalk patterns that will be available to the research community. Finally, this innovative study will advance our understanding of aging and can be used to define a diagnostic tool for evaluating the effects of particular therapeutic drugs and lifestyle changes on the biological age. This work may thus pave the way for new perceptions regarding aging-related treatments, with practical implications that can assist in the development of therapeutic strategies for complex age-related diseases and other interventions that may help to facilitate healthy aging.

# We hypothesize that transcription is co-regulated and coordinated at the whole-body level. Moreover, we propose the existence of global system-dependent transcriptional co-regulation that can be detected through analyses of gene expression data. Our working hypothesis is that whole sets of functionally related genes vary

# prehensive map of these patterns.