evolutionary-conserved, molecular mechanisms can simultaneously influence all causes of death.

## WADDINGTON'S LANDSCAPE OF CELL AGING

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Cellular aging is a complex process that involves many interwoven molecular processes. Studies in model organisms have identified many individual genes and factors that have profound effects on lifespan. However, how these genes and factors interact and function collectively to drive the aging process remains unclear. We investigated single-cell aging dynamics throughout the replicative lifespans of S. cerevisiae, and found that isogenic cells diverge towards two aging paths, with distinct phenotypic changes and death forms. We further identified specific molecular pathways driving each aging fate and revealed that these pathways interact and operate dynamically to enable an early-life switch that governs the aging fate decision and the progression towards death. Our work uncovers the interconnected molecular pathways that drives the aging process and opens up the possibility of designing interventions that simultaneously target multiple network nodes, instead of single genes, to more effectively extend the healthspan.

## DISRUPTION OF CPG ISLAND-MEDIATED CHROMATIN ARCHITECTURE AND TRANSCRIPTIONAL HOMEOSTASIS DURING AGING

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Aging causes the global disorganization of nuclear chromatin architecture. In a normal young nucleus, silent heterochromatin is associated with the nuclear lamina layer underlying nuclear envelope, thus spatially separated from euchromatin at the nuclear center. Notably, aging causes the disruption of nuclear lamina and the decondensation of associated heterochromatin. However, it is not clearly understood how these changes of chromatin architectures contribute to age-related diseases. Through large-scale computational analyses, we present that CpG islands (CGIs) give important clues to answering this question. CGIs are DNA elements with high Cytosine-phosphate-Guanine dinucleotide frequencies. In human, about 60% of total genes contain CGIs at their promoters (CGI+ genes) and are broadly expressed throughout the body. The other 40% of genes that do not have CGIs (CGI- genes) exhibit tissue-restricted expression patterns. Our results demonstrate that, in normal young nuclei, only CGI- genes can reside within lamina-associated heterochromatin when transcriptionally inactive, while CGI+ genes associate with nuclear central euchromatin even when they are repressed. In parallel, we show that age-associated heterochromatin decondensation can specifically de-repress tissue-specific CGI- genes leading to their uncontrolled expressions. Our results further demonstrate that global misregulation of CGI- genes increases the noise in gene transcription that, in turn, causes the loss of cellular identities during aging. Taken together, our study establishes critical implication of CGI-mediated chromatin architecture in age-associated degenerative changes and loss of tissue homeostasis.

## SESSION 1120 (SYMPOSIUM)

### THE LONGEVITY CONSORTIUM: MULTI-OMICS INTEGRATIVE APPROACH TO DISCOVERING HEALTHY AGING AND LONGEVITY DETERMINANTS

Chair: Thomas T. Perls, *Boston University School of Medicine, Boston, Massachusetts, United States*
Co-Chair: Daniel S. Evans, *California Pacific Medical Center Research Institute, San Francisco, California, United States*
Discussant: Evan Hadley, *National Institute on Aging, National Institutes of Health, Bethesda, Maryland, United States*

The Longevity Consortium (LC), a NIA-Cooperative project, is an integrated multi-disciplinary effort with cutting edge bioinformatic, systems biology and chemoinformatics approaches exploiting multiple omics data generated from multiple well-phenotyped aging cohorts, Study of Osteoporotic Fractures, MrOS (fractures in men), Cardiovascular Health Study, the Long Life Family Study and the Centenarian Project to discover pharmacologically targetable protective pathways that promote healthy aging. Omics studies of mice treated with candidate drugs and of multiple species with varying life spans further informs the LC efforts. We describe the integration of the above efforts and the LC goals as well as opportunities for interested investigators to access shared results as well as opportunity funds for pilot projects. Early successes are described in 4 presentations: (1) A genome-wide association study including 1317 centenarians discovered 8 new loci in chromosomes 3, 6, 7, 9, 10, 14 and 15. The list includes new serum pQTLs that suggest a new biological mechanism involved in extreme longevity. (2) Novel, high-throughput discovery-proteomics of serum from 2,473 MrOs participants identified 25 proteins, mostly found in inflammatory pathways, associated with living beyond the 90th percentile birth-cohort survival. (3) A biological age estimation algorithm utilizing multi-omics assays significantly differentiated between 3,558 wellness program participants and controls. (4) Mediation analyses were used to test causal relationships between many candidate aging-modulating drugs and compounds, expression levels of gene and protein variants (eQTLs and pQTLs) and aging and longevity phenotypes. This high throughput method shows promise as a means of discovering candidate drugs for healthy aging.

### THE LONGEVITY CONSORTIUM VISION

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Molecular factors and pathways promoting human longevity and healthy aging can potentially delay or prevent multiple chronic diseases and conditions, but identifying such factors that can be pharmacologically targeted requires an integrated multidisciplinary approach. We describe the design of the five research projects and three cores of the