It is a time for us to "Honor the Past, Enrich the Future". Not long ago the study of the biology of aging was exclusively one of description of what happened with age—how do organisms, including humans, change with age at the level of proteins, cells, tissues and physiology. The identification of major genetic factors that substantially increase life span in model organisms ushered in the advent of a highly exploratory period focusing on the molecular, cellular and genetics mechanisms of aging. The convergence of many different streams of basic and clinical research have brought us to today, where we stand on the cusp of new environmental, molecular genetic and pharmacological breakthroughs in the biology of aging that presage new interventions that promise a healthier lifespan. The presentations in this Presidential Symposium will be from four Early Career Investigators presenting their own pioneering research in some of the most important areas of research in the biology of aging.

MECHANISMS OF LIFESPAN EXTENSION BY SIRT6 IN DROSOPHILA MELANOGASTER

Jackson Taylor, Jason Wood, Matthew Finn, Julianna Liu, Evan Mizerak, Sarah Gordon, Corinne Hutfilz, and Stephen Helfand, *Brown University, Providence, Rhode Island, United States*

Sirt6 is a multifunctional enzyme that regulates numerous cellular processes connected to longevity. Overexpressing Sirt6 extends lifespan in mice, but the underlying cellular mechanisms are unclear. Here, we used the powerful genetic tools and short lifespan of Drosophila melanogaster to better understand the precise mechanisms by which Sirt6 regulates longevity. Sirt6 OE in flies produces robust extension of median lifespan in both sexes. Molecular and biochemical analyses reveal that Sirt6 OE reduces expression of genes involved in protein synthesis, including many Myc target genes, via epigenetic regulation. We will further discuss our findings on the connection between Sirt6, Myc, and the molecular regulation of protein synthesis and lifespan, as well as additional Sirt6 longevity mechanisms we identified, including autophagy and silencing of transposable elements.

NEW COMPUTATIONAL APPROACHES TO AGING RESEARCH

Morgan E. Levine, *Yale University School of Medicine, New Haven, Connecticut, United States*

Aging is associated with numerous changes at all levels of biological organization. Harnessing this information to develop measures that accurately and reliably quantify the biological aging process will require systems biology approaches. This talk will illustrate how epigenetic data can be integrated with cellular, physiological, proteomic, and clinical data to model age-related changes that propagate up the levels—finally manifesting as age-related disease or death. I will also describe how network modeling and machine learning approaches (linear and non-linear) can be used to identify causal features in aging from which to generate novel biomarkers. Given the complexity of the biological aging process, modeling of systems dynamics over time will both lead to the development of better biomarkers of aging, and also inform our conceptualization of how alterations at the molecular level propagate up levels of organization to eventually influence morbidity and mortality risk.

EPIGENETICS, HEREDITY, AND AGING

Eric Greer, *Boston Children's Hospital/Harvard Medical School, Boston, Massachusetts, United States*

Longevity has long been shown to be regulated by genetic and environmental factors. We recently showed that longevity in the nematode Caenorhabditis elegans can also be regulated by the transmission of epigenetic information. We have shown that several chromatin modifying enzymes have a transgenerational non-Mendellian effect in worms on the longevity of their descendants. I will discuss some of our recent work attempting to decipher how epigenetic modifications can regulate complex phenotypes, including longevity, and how this non-genetic information can be transmitted across generations.

SEX-DIMORPHISM IN AGING GENE REGULATION: ARE WE MISSING HALF OF THE PICTURE?

Bérénice Benayoun, Ryan Lu, Nirmal Sampathkumar, and Min Hoo Kim, *University of Southern California, Los Angeles, California, United States*

The existence of human supercentenarians reveals a surprising predictor for exceptional longevity: being female. Not only are 33 out of 34 living supercentenarians women, women are also more resistant to most diseases responsible for age-related morbidity in the US. However, because most molecular aging studies generally opt to use only one sex, sex-driven differences in aging remain poorly understood. A key compartment that can actively respond to sex-specific inputs throughout life is the immune system. Indeed, the majority of age-related diseases share common inflammatory mechanisms, a phenomenon described as "inflamm-aging". Macrophages play an important role in the inflammatory response throughout life, and are considered major mediators of this phenomenon. Thus, to unbiasedly dissect sex differences in immune aging, we generated 'omics' data from 4 and 20 months old female and male mice. Intriguingly, we found that transcriptional aging in primary macrophage populations varies strongly between sexes, with up to 20-fold more aging changes in female vs. male cells. Pathways specifically downregulated in females with aging included lysosome, inflammation and phagolysosome. We confirmed experimentally that metabolic preferences of macrophages are indeed directly modulated in this context (e.g. glycolytic preference for male-derived cells). Our results support the notion that there are functional differences in aging trajectories in the immune system of female vs. male mice. Our research could provide new insights into the molecular underpinnings of sex-dimorphism in aging and disease.

SESSION 6505 (SYMPOSIUM)

METABOLISM AND AGING: NEW APPROACHES TO NUTRITION AND DIET IN AGING

Chair: Blanka Rogina

Aging is associated with a functional decline in metabolic, physiological, proliferative, and tissue homeostasis