

Speaker Abstracts

Single cell analytical techniques in aging research—Murat Acar

Aging is a leading cause of human morbidity and mortality, but efforts to slow or reverse its effects has been hampered by an incomplete understanding of aging at the single-cell level. With recently developed techniques for performing genetic and phenotypic characterizations at single-cell resolution, comprehensive monitoring of time-dependent changes occurring in individual aging cells is now possible. Single-cell-level experimentation can elucidate key biological insights about cellular aging that are masked in population-level studies. In this talk, I will outline innovative single-cell level techniques that have opened new avenues of investigation to the aging research community. I will describe how microfluidic devices can automate the microscopic monitoring of yeast cells throughout their replicative lifespan. I will also talk about how large-scale RNA sequencing techniques can be applied to age-enriched pools of single cells in order to comparatively study transcriptomic changes in young vs. old cells.

Contributions of Toxicants to the Development of Age-Related Diseases—Julie Andersen

Recent estimates place the heritability of human lifespan as low as 7% (Ruby et al., 2018). In agreement with this, replicate lifespan analysis of genetically identical invertebrates show extraordinary plasticity, suggesting that environmental factors likely play a dominant role in lifespan as well as healthspan. Relevant environmental factors including dietary and other lifestyle factors, environmental exposure to pollutants, metals, and man-made chemicals, and factors such as psycho-social stress are all likely to play some role. In addition to their actions during aging, the action of environmental agents at critical periods of development are also likely to affect age-related phenomena later in life.

Research in the field of age-related diseases often focuses primarily on genetic factors. Genetic mutations however may account for only a small percentage of overall disease cases. A better understanding the impact of the environment and the mechanisms underlying its effects on age-related diseases will be an essential component towards developing more refined therapeutics for these disorders. This includes how toxins act to exacerbate aging processes as well as the potential for their increased toxicity in older individuals. The development of “gerotoxicology” databases documenting the role of toxins in aging and age-related diseases would greatly increase our understanding of the interconnection between the two. Screens for novel agents would additionally allow us to build on what is known about environmental contributions to aging and age-associated diseases. Such studies would undoubtedly increase the quality of life in old age and possibly lifespan.

The epigenetic impact of prenatal heavy metal exposure—Andres Cardenas

Prenatal and early life exposure to metal contaminants that easily cross the placenta and blood brain barrier is ubiquitous. Exposure to heavy metals during critical windows of development is associated with multiple organ system toxicity including adverse developmental outcomes. The fetal epigenome is established early during development and shown to be sensitive to environmental exposures providing a

prime target to influence health throughout the life course. Results from epidemiological cohorts on maternal exposure to arsenic, mercury and lead suggest disruption of the newborn's epigenome. Data on the evaluation of tissue specific DNA methylation signatures, persistence of perturbations and involvement in adverse early life outcomes is presented. The role of these epigenetic perturbations on the development of disease markers is evaluated. Overall, emerging data suggests that early life exposure to heavy metals disrupts DNA methylation marks, some but not all are malleable and associated with known metal toxicity. Reducing and eliminating early life exposure to metals and other contaminants can provide a key prevention strategy to optimize healthy aging and development.

Integration of the Science of Aging with Environmental Health Research Through the Perspective of Biomarkers: A conceptual view of the aging process. — Luigi Ferrucci

Aging is a complex of stereotypical changes that every living individual undergo from the time of their conception/birth to their death. The aging process can be conceptualized as a progressively changing equilibrium between entropic forces that produce damage accumulation and resilience mechanisms that repair or compensate such damage. When the damage accumulation overloads the capacity for repair, organisms undergo progressive decline in function. It is important to underline that aging occur a different interconnected level, from the most basic biological mechanisms, the phenotypic consequences to their functional manifestations, and each one of these levels should be assessed by specific metrics. However, while the phenotypic manifestations and their functional consequences have been studied, the intrinsic mechanisms of aging biology remain hypothetical and have been mostly studied in animal models. The chain of events that leads from the derangement of biological levels, to phenotypes and to their functional consequences is characterized by temporal gaps due to strong compensatory capacity and, therefore, can only be studied longitudinally.

Air Pollution, Cigarette smoke, and brain health across the lifespan. — Caleb E. Finch

Air Pollution (AirPoll) and Cigarette smoke (CigS) are gerogens that increase risk of accelerated cognitive decline aging and Alzheimer disease in human populations. Mechanisms defined in animal models include increased amyloidogenesis, enhanced by ApoE4, neurite atrophy, and attenuated adult neurogenesis. Candidate gerogens shared by AirPoll and CigS include polycyclic aromatic hydrocarbons (PAH), lead (Pb), and transition metals. A broader approach is needed for these and other environmental factors in aging of the brain and other body systems.

Blood DNA Methylation Age and Environmental Exposures: Fine Particle Air Pollution and Urine Metal Findings in the VA Normative Aging Study—Jamaji C. Nwanaji-Enwerem

Harmful environmental exposures and aging have been implicated in multiple shared diseases; hence, studying their relationship is a promising strategy to further understand the adverse impact of environmental exposures on human health. Measures of DNA methylation age (DNAm-age) are novel biological aging metrics that have been strongly associated with human morbidity and mortality. In participants enrolled in the VA Normative Aging Study, we examined the relationships of ambient PM_{2.5} – total mass and its major component species – and metal exposures with novel DNA methylation-based markers of blood DNAm-age. We estimated 1-year PM_{2.5} levels at participants' addresses using satellite-based models. Metals were measured in participants' urine samples. Our results support a positive association of long-term (1-year) ambient particle levels with Horvath DNAm-age and demonstrate that

sulfate and ammonium were the PM_{2.5} component species most associated with Horvath DNAm-age. Further analyses demonstrated significant effect modification of the PM_{2.5} and DNAm-age relationship by endothelial function, mitochondrial genome, and microRNA processing gene variants. DNAm-age was also significantly associated with a number of serum measures related to these effect modifiers including mitochondrial DNA copy number, intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM). Manganese was significantly associated with DNAm PhenoAge. Our results add novel evidence that environmental exposures are associated with increases in methylation-based biological aging and suggest that these DNA methylation-based measures may be useful for identifying individuals at-risk for diseases related to toxic exposures. Further research is necessary to confirm these findings more broadly.

The influence of chemical exposures on development—John Meeker

Exposure to exogenous chemicals can affect human health and development through numerous modes of action. Widespread human exposure to known or suspected reproductive and developmental toxicants has been documented in the United States and worldwide, as have trends for increased rates of developmental diseases and disorders among children. While a still relatively new area of research, a growing body of human evidence shows that exposure to a number of chemicals commonly found in consumer goods, personal care products, food, drinking water, and other sources may adversely affect child development through altered endocrine function or other mechanisms. This presentation will give a brief background on trends in exposure to environmental chemicals and altered child development, and specific examples of recent human evidence for adverse effects of select environmental chemicals on child development at important aging landmarks will be presented. Finally, recommendations for future research in these areas will be discussed.

The role of race, racism and social vulnerabilities in disparities in cardiometabolic risk and health aging—Uchechi Mitchell

This talk will explore pathways leading to disparities in various indicators of physiological functioning and implications for healthy aging among racial and ethnic minorities. The talk will specifically review evidence of racial/ethnic differences in accelerated aging and various biomarkers, explain how social factors—including poverty, racism and discrimination—increase vulnerability to poor health and physiological dysregulation, and highlight the joint impact of these social vulnerabilities and environmental exposures on health inequities.

The association of exposure to metals with telomere length and aging-related health outcomes—Brandon Pierce

Numerous investigators have hypothesized that occupational or environmental exposure to metals may impact telomere length (TL) or other aspects of telomere biology (e.g., integrity, protection, maintenance); representing a potential mechanism of metal toxicity. Metals are hypothesized to affect TL via exposure-induced oxidative stress, inflammation, DNA damage, and impaired DNA damage repair; however, the mechanisms of toxicity for most metals are not fully understood. Associations between exposure to metals and leukocyte TL have been examined in >20 epidemiological studies to date. Most of these studies utilized biomarkers of exposure measured in urine, blood, or saliva. The most commonly studied metals are arsenic, cadmium, and lead. While no metals show consistent evidence of association

across all studies, evidence suggests that arsenic exposure is positively associated with TL while lead and cadmium exposure are negatively associated with TL. The lack of consistency across the results is potentially due to differences in study population exposure levels, statistical power, timing of exposure assessment (early vs. later life), exposures occurring in the context of mixtures, and biases due to flaws in study design. More recent studies focus on the impact of pre-natal or early-life exposure to metals and TL, in part because TL shortens at a much faster rate in early life than in adulthood. Major challenges for studies of environmental exposures and TL include obtaining measures of TL in disease- and toxicant-relevant tissues, inferring causality for observed associations, and assessing the role of TL as a potential mediator between the effects of exposure and disease.

Maternal stress, particle matter exposure, and development—Rosalind Wright

Progressive DNA damage and mitochondrial decline are both considered to be prime instigators of natural ageing. These two pathways have largely been viewed separately. Recent studies reveal a molecular circuit that directly links DNA damage to compromised mitochondrial biogenesis and function. Telomere dynamics during early development largely determinative of relative TL for life. Newborn TL is a potential biomarker of effects of maternal-fetal processes shaped by environmental exposures during gestation on child long-term health. Mitochondrial biomarkers are also increasingly explored as novel sensors and mediators of environmental effects. These two interrelated phenomena have not been widely studied in early life. Longitudinal pregnancy cohort studies link maternal smoking, increased maternal BMI, lower SES, heightened stress, depression in pregnancy, ambient pollution exposures, and chemical exposures (e.g., metals) with shorter newborn TL. More recent data underscore the need to also consider exposures occurring cumulatively over the mother's life course as well as race/ethnicity- and sex-specific effects.