Telomeres as Sentinels for Environmental Exposures, Psychosocial Stress, and Disease Susceptibility

September 6-7, 2017

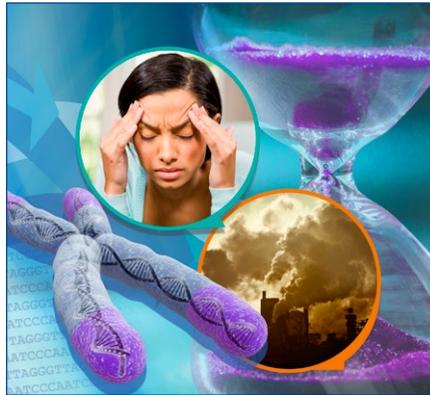**Wednesday, September 6 – 9:00 a.m. – 5:00 p.m.**

Thursday, September 7 – 9:00 a.m. – 2:30 p.m.

NIEHS Building 101, Rodbell Auditorium

111 TW Alexander Drive, Research Triangle Park, N.C.

Co-sponsored by the National Institute of Environmental Health Sciences and National Institute on Aging

National Institutes of Health • U.S. Department of Health and Human Services

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Co-sponsored by National Institute of Environmental Health Sciences and National Institute on Aging

Meeting Framework:

This workshop will bring together experts from relevant research disciplines to explore and discuss how assays of the status of telomeres can best be used, and what research/technology is needed, to advance our understanding of their use in the study of environmental and stress exposures, and disease susceptibility in population-based research. Experts from basic telomere biology, medicine, biopsychology, epidemiology, and related fields will discuss how basic researchers can help epidemiologists/clinicians and vice versa. Discussions will focus on approaches to measurement, factors that need to be measured alongside of telomeres, gene and environment interactions (including both the physical and the social environment), tissue-specific effects, potential for use of surrogate tissues.

Workshop Objectives:

1. To explore current and future possibilities for using the telomere as a potential biomarker of environmental and stress exposure or disease susceptibility by reviewing current knowledge of how the cellular context and biological environment contribute to the observed telomere phenotype/readout (e.g., rates of cellular turnover/concomitant telomere shortening).

2. To discuss the tractability of using telomeres as a proxy/indicator of genomic damage by review of what is known, and what information is needed to understand the extent to which telomeres are damaged from exposures and stress and how their subsequent repair differs compared to the rest of the genome.

3. To consider the themes outlined above in the context of tissue-specific effects, to identify which cells should, or can be used as proxy.

4. Identify how interrogation of telomere status can currently enhance epidemiological studies and the potential for further research.

5. Develop a set of recommendations for moving forward with telomere measurements in population-based studies, and identification of short- and long-term research needs.

Potential Outcomes Include:

– A white paper or comprehensive review article that describes the state of the science, and includes recommendations on how the status of telomeres could currently be used to understand exposures and susceptibility (e.g., as indicators of exposure and/or susceptibility) in population-based research.

– Set of guidelines for telomere length measurement in population studies.

– Articulation of a prioritized research agenda that would bring together basic scientists and epidemiologists or clinicians to address questions related to the workshop**.**

AGENDA

Day One – Wednesday, September 6, 2017

(all times are EDT)

9:00 – 9:15 a.m.   **Welcome Remarks and Charge for the Workshop**

Linda Birnbaum, Ph.D., Director, National Institute of Environmental Health Sciences (NIEHS)

Michelle Heacock, Ph.D., Hazardous Substance Research Branch, NIEHS

Lisbeth Nielsen, Ph.D., Division of Behavioral and Social Research, National Institute on Aging (NIA)

9:15 – 10:15 a.m.   **SESSION ONE: State of the Science**

Goal: Provide an overview of the current research and, where applicable, point out the discrepancies in research findings and possible explanations. Provide a summary of current knowledge related to telomere changes that have been observed in response to stress and environmental exposures drawing from literature in cellular biology, population based studies, and disease-specific research in humans and animal models.

Chair: Michelle Heacock

Presentations:

- *Causality and Association*
  – Mary Armanios, M.D., Johns Hopkins University

- *Environmental Exposures and Telomere Effects*
  – Patricia Opresko, Ph.D., University of Pittsburgh

- *Stress Effects: Differential Lifespan Effects, Pseudo-Lengthening, and Other Complexities*
  – Elissa Epel, Ph.D., University of California, San Francisco

10:15 – 10:30 a.m.   **Break**

10:30 – 11:50 a.m.   **SESSION TWO: Effects of Psychosocial Stress on Telomeres**

Goal: An overview of evidence supporting how stress affects telomere length and telomerase activity and what other markers should be combined with these measurements.

Chairs: Ami Zota, Ph.D., George Washington University, and Max Guo, Ph.D., NIA

Presentations:

- *The Fetal Programming of Telomere Biology Hypothesis*
  – Pathik Wadhwa, M.D., Ph.D., University of California, Irvine

- *Crossing Tissues and Disciplines: Considerations of Tissues and Timing*
  – Stacy Drury, Ph.D., Tulane University

- *Social Status, the Stress Process Model, and Telomere Dynamics*
  – Belinda Needham, Ph.D., University of Michigan

- *Lessons for Development of Biomarkers of Aging From Telomere Research*
  – Idan Shalev, M.D., Ph.D., Pennsylvania State University

Panel Discussion:

Panelists: Pathik Wadhwa, Stacy Drury, Belinda Needham, Idan Shalev, Allison Aiello

Questions to address:

1. How have current studies measured telomere length status and/or changes?

2. Where are there consistencies/inconsistencies in the literature?

3. What is the best way to measure telomere length changes?

4. How do telomere length measures relate to other stress biomarkers and assessments?

5. How do we, should we, parse out other effects for telomere changes?

6. Are stress effects always oxidative, or are other pathways evoked?

7. What other questions are we missing?

11:50 a.m. – 1:00 p.m.   **Lunch**

1:00 – 2:30 p.m.   **SESSION THREE: Critical Considerations of Assessment of Telomere Length Dynamics**

Goal: Provide an understanding of what is being measured in bulk cells versus single cells versus individual telomeres. Discuss the benefits and drawbacks of different approaches of measurement, cell types, and why and when rate of telomere length change (i.e., following length changes over time) should be considered.

Chairs: Alison Bertuch, M.D., Ph.D., Baylor College of Medicine, and Stacy Drury, Ph.D., Tulane University

Presentations:

• *Telomere Length Measurements and Cell Turnover*
  – Peter Lansdorp, Ph.D., British Columbia Cancer Agency

• *Germ Cells Versus Somatic Cells*
  – Shawn Ahmed, Ph.D., University of North Carolina at Chapel Hill

• *Longitudinal Studies of Telomere Length: Assay Considerations and Findings*
  – Jue Lin, Ph.D., University of California, San Francisco

• *The Fate of Dysfunctional Telomeres*
  – Alison Bertuch, M.D., Ph.D., Baylor College of Medicine

• *Germline Genetic Variation in Telomere Biology Genes is Associated With a Spectrum of Phenotypes*
  – Sharon Savage, M.D., National Cancer Institute

Panel Discussion:

Panelists: Peter Lansdorp, Shawn Ahmed, Jue Lin, Alison Bertuch, Sharon Savage, and Sara Hagg, Ph.D. (Karolinska Institutet – remote)

Questions to address:

1. Measuring telomere length in bulk cells versus single cells, bulk telomeres versus individual telomeres, whole cell extracts versus separating leukocytes (mixed cell types) benefits and drawbacks, best approach for measurement and why.

2. Sample preparation and storage considerations.

3. Telomere measurement techniques (e.g., qPCR versus TRF versus flowFISH), what is being measured, what are the advantages/limitations?

4. Rate of telomere change (shortening or lengthening), and how and when is it crucial to follow over time. Importance of knowing the baseline length (e.g., baseline of shorter or longer telomeres) and addressing the role of cellular context/turnover.

5. Effect of SNPs on TBPs and other telomere maintenance proteins.

6. Calculating effect sizes (e.g., base pairs per year) – can we arrive at a consensus?

7. Do we need, and how do we, account for cells with short telomeres being culled out of population?

8. How can some current assays be adapted to provide more high throughput measurements? Using archived samples?

9. What kind of assays/methods offer greater sensitivity for detection of telomere length?

10. What other questions are we missing?

2:30 – 2:45 p.m.	**Break**

2:45 – 3:00 p.m.	**Recap – Chairs to Give a Recap to Set Up Open Discussion**

3:00 – 5:00 p.m.   **Question and Answer Session/Open Discussion to Consider Overarching Questions**

Chair: Rick Woychik, Ph.D., Deputy Director, NIEHS

Based on presentations and discussion, are there tissue-specific effects? If so, what cells can be used as a reasonable proxy (e.g., can leukocytes, buccal cells be used)? Is there a correlation between cord blood, placenta, and blood spots? Difference in length dynamics in high versus low proliferative capacity cells. If so, can a correction factor be applied so easier cells can be used?

How can epi studies benefit from telomere interrogation? What is the potential of using telomeres to understand exposure and susceptibility, and what is needed to get there (e.g., assays to measure single telomere tracts, knowledge gap as to whether cells, such as leukocytes, can be as reliable proxies)? How best should samples be harvested? Preserved? How to account for plate variability, select reference DNA (qPCR)? How big a telomere change to be seen in an epidemiological study?

How can a basic researcher help epidemiologists/clinicians and vice versa? What can be done right now? What are the possibilities and how do we move forward?

5:00 p.m.   **Remarks from day and adjourn**

Day Two – Thursday, September 7, 2017

(all times are EDT)

9:00 – 10:25 a.m.   **SESSION FOUR: Genetic Susceptibility and the Environment**

Goal: Provide the current research on how mutations in telomere maintenance proteins combined with an environmental factor and/or stress play a role in disease.

Chairs: Patricia Opresko, Ph.D., University of Pittsburgh, and Colter Mitchell, Ph.D., University of Michigan

Presentations:

• *The Biological Meaning of Leukocyte Telomere Length: Is Leukocyte Telomere Length a Biomarker of Human Aging?*
  – Abraham Aviv, M.D., Rutgers University

• *Epidemiological Studies of the Association Between Metal Exposure and Telomere Length*
  – Brandon Pierce, Ph.D., University of Chicago

• *Telomeres as Biomarkers of Psychosocial Stress and Environmental Exposures – on and Off the Planet*
  – Susan Bailey, Ph.D., Colorado State University

• *Genetic and Environmental Influences on Telomere Lengths, Towards Understanding GE Interplay*
  – Chandra Reynolds, Ph.D., University of California, Riverside

Panel Discussion:

Panelists: Abraham Aviv, Brandon Pierce, Susan Bailey, Chandra Reynolds, Yie Liu, Ph.D., NIA, and Sharon Savage (remote)

Questions to address:

1. What other factors contribute to telomere shortening (and in some cases, lengthening) where it is unknown if a gene is involved (e.g., stress)

2. How is the telomere affected? At the telomere nucleotide level? By affecting telomere maintenance via binding Shelterin? Or is it damage to genome where telomeres break off?

3. What role do cell proliferation and/or replication have?

4. DNA repair capacity differences?

5. Effect of SNPs on TBPs and other telomere maintenance proteins?

6. What is the state of current understanding from population-based studies regarding telomeres as a read-out of environmental exposures (physical environment) and stress (psychosocial exposures and stress reactivity)?

7. What is the best way of assessing telomere biomarkers in population based studies (alone, or in relation to other biomarkers of aging)?

8. What are the other possibilities? Are the markers universal or change with different diseases?

9. What do telomere syndromes tell us about maternal effects, paternal effects, transgenerational effects on telomeres? How is this to be used to inform other studies?

10. Effects of secondary/mixed exposures on telomeres – what do we need to think about when we are trying to parse out the effects of mixtures?

11. What other questions are we missing?

10:25 – 10:40 a.m.	**Break**

10:40 a.m. – noon

SESSION FIVE: Combining Telomere Measurements With Other Markers

Goal: An overview of the power of using other biological response markers to improve the integrity of measurements to understand the impact of cumulative exposures.

Chairs: Janine Santos, Ph.D., NIEHS, and Idan Shalev, M.D., Ph.D., Pennsylvania State University

Presentations:

• *Epigenetic Measures and Telomere Length*
  – Colter Mitchell, Ph.D., University of Michigan

• *Mitochondria Are Gatekeepers at the Interface of Genome and the Environment*
  – Martin Picard, Ph.D., University of Pittsburgh

• *Longitudinal Studies of Telomere Length in Hiroshima Atomic Bomb Survivors and in Baltimore Longitudinal Study on Aging Cohort, and the Impact of Telomere Attrition on Immune Function*
  – Nan-Ping Weng, Ph.D., NIA

• *The Impact of Persistent Stress-Related Infections on Telomere Length*
  – Allison Aiello, Ph.D., University of North Carolina at Chapel Hill

Panel Discussion:

Panelists: Colter Mitchell, Martin Picard, Nan-Ping Weng, Allison Aiello, Susan Bailey, and William Copeland, Ph.D., NIEHS

Questions to address:

1. Can the status of telomeres be used to measure cumulative exposures (i.e., stress and environmental exposures)? How can other biological response indicators be used to ground-truth the measurements? Telomerase activity measurements, how/when important?

2. What are the other ways (e.g., biological responses) can be used to measure telomere dysfunction and/or biological aging?

3. SNPs that have been identified and associated with leukocyte telomere length changes are they strong enough to be used as one of the biomarkers, as a proxy for telomere length?

4. How can epigenetics data be used to inform telomere studies?

5. Why telomeres – what advantages do they hold?

6. How are telomeres a unique biomarker in early life and childhood and not in later life?

7. What other questions are we missing?

Noon – 1:10 p.m.   **Lunch**

1:10 – 2:30 p.m.   **Chair Take-Aways**

Lead by Gwen Collman, Ph.D., Director of Extramural Research and Training, NIEHS

Question and Answer Session/Open Discussion to Consider Overarching Questions:

Based on presentations and discussion, are there tissue-specific effects? If so, what cells can be used as a reasonable proxy (e.g., can leukocytes be used)? Difference in length dynamics in high versus low proliferative capacity cells. If so, can a correction factor be applied so easier cells can be used?

How can epi studies benefit from telomere interrogation? What is the potential of using telomeres to understand exposure and susceptibility, and what is needed to get there (e.g., assays to measure single telomere tracts, knowledge gap as to whether cells such as leukocytes can be as reliable proxies)? How best should samples be harvested? Preserved? What are the best model organisms for filling the gaps to move this forward?

How can basic researchers help epidemiologists/clinicians and vice versa? What can be done right now? What are the possibilities and how do we move forward?

2:30 p.m.   **Meeting Wrap-Up**

Lisbeth Nielsen and Michelle Heacock
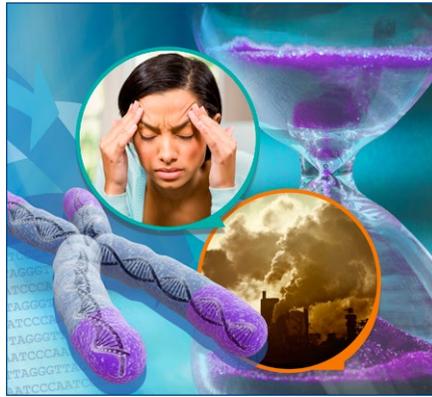
Presentation Abstracts

Session One:
State of the Science

Mary Armanios
Johns Hopkins University
"Causality and Association"

Patricia Opresko
University of Pittsburgh
"Environmental Exposures and Telomere Effects"

Over the last decade interest in measuring leukocyte telomere length (LTL) in human studies of environmental and occupational exposures has grown, based in part on numerous populations studies that reported associations between shorter LTL and various diseases and adverse lifestyle factors. This talk will first summarize published results of LTL measurements from human environmental and occupational exposure studies of air pollution, particulate matter, black carbon, benzene, polycyclic aromatic hydrocarbons, pesticides, persistent organic pollutants, toxic metals, and ionizing radiations. Specific examples of discrepancies in the literature, and approaches to potentially resolve these discrepancies will be discussed, along with possible confounding issues and considerations that pose unique challenges to exposure studies in human populations. The talk will cover proposed mechanisms of environmentally induced changes in telomere length, including damage to telomeric DNA, increased cell proliferation, and alterations in telomerase expression. The most commonly proposed mechanisms are oxidative stress and inflammation, but how oxidative stress alters telomere length homeostasis remains to be fully elucidated. An important consequence of oxidative stress, and genotoxic exposures in general, is damage to the genome. Our lab has been focusing on understanding the consequences of DNA damage at telomeres, and mechanisms for repair. DNA damage and repair at telomeres is uniquely influenced by the ability of telomeres to form alternate structures, coupled with the ability of shelterin proteins to interact with enzymes in every know DNA repair pathway. I will discuss novel systems our laboratory has developed to detect specific types of DNA damage at telomeres, and to selectively induce oxidative base damage at telomeres in cultured cells and in living organisms. As LTL measurements increasing become part of human exposure studies, it will be important to define parameters to ensure high quality data and to address mechanistic questions relate the utility of such measurements. Our laboratory has been focusing on developing approaches to address whether genotoxic exposures directly damage telomeres, and whether damaged telomeres affect cellular function or the health of an organism. Other critical questions include whether LTL can inform about 1) exposure levels or 2) risk of adverse health effects resulting from acute or chronic human exposures on a population and/or individual level. Answering these questions will be challenging but critical for realizing the full potential and utility of LTL measurements in environmental and occupational exposure studies.

Elissa Epel
University of California, San Francisco
""Stress Effects': Differential Lifespan Effects, Pseudo-lengthening, and Other Complexities"

Session Two:
Effects of Psychosocial Stress on Telomeres

Pathik Wadhwa
University of California, Irvine
"The Fetal Programming of Telomere Biology Hypothesis"

Research on mechanisms underlying fetal programming of health and disease risk has focused primarily on processes specific to cell types, organs, or phenotypes of interest. However, the observation that developmental conditions *concurrently* influence a *diverse* set of phenotypes, the majority of which are implicated in *age-related disorders*, raises the possibility that developmental conditions may *additionally* exert effects *via* a *common underlying mechanism* that involves cellular/molecular aging-related processes. In this context, we submit that *telomere biology* represents a process of particular interest because, firstly, this system represents a salient antecedent *cellular* phenotypes for common age-related disorders; secondly, its initial (newborn and early life) setting is a particularly important determinant of its long-term effects; and thirdly, its initial setting appears to be plastic and under developmental regulation. We propose that the effects of suboptimal intrauterine conditions on the initial setting of telomere length and telomerase expression/activity capacity may be mediated, in part, by the "programming" actions of stress-related maternal-placental-fetal oxidative, immune, endocrine, and metabolic pathways in a manner that may ultimately accelerate cellular dysfunction, aging, and disease susceptibility over the lifespan. This presentation will provide an overview of each of the elements underlying this hypothesis, with an emphasis on recent developments, findings, and future directions.

Stacy Drury
Tulane University
"Crossing Tissues and Disciplines: Considerations of Tissues and Timing"

The explosion of studies examining telomere length as both a marker of exposure and a potential predictor of later health outcomes has sparked enthusiasm and a need to establish methodological core considerations that balance practicality, scalability, and accuracy. As with all epigenetic studies, the selection of the tissue for study and the correlation between tissues is an important factor. In addition, both sex differences and developmental changes in the correlation across tissues and the stability of epigenetic marks, including telomere length, add additional layers of complexity. This talk will present published and unpublished data focused on cross tissue correlation of telomere length measured using the MMpQPCR methodology and include placental studies as well as studies in infants, children, and mothers exploring the correlation between tissue (chorion, amnion, villus and umbilical cord), blood (cord blood and peripheral), buccal, and salivary TL measurements. Methodological adaptations for longitudinal studies as well as the selection of reference DNA samples will also be presented.

Belinda Needham
University of Michigan
"Social Status, the Stress Process Model, and Telomere Dynamics"

The stress process model posits that members of socially disadvantaged groups, including those with low socioeconomic status (SES) and racial/ethnic minorities, tend to have worse health outcomes than their higher status peers due to greater exposure and vulnerability to stress. Telomere shortening may provide a link between the stress associated with social disadvantage and premature morbidity and mortality. In this presentation, I will discuss the evidence regarding socioeconomic and racial/ethnic differences in telomere length and telomere attrition across the life course, focusing on results from population-based studies.

Idan Shalev
Pennsylvania State University
"Lessons for Development of Biomarkers of Aging From Telomere Research"

Accumulating evidence from aging interventions in animals suggests molecular changes underlying age-related disease and disability can be slowed or reversed. A barrier to translation of these therapies to humans is the development of biomarkers that effectively capture differences in the rate of aging over short periods of time. Recent advances in algorithm-based approaches show promise, but require further investigation before their use in interventions to slow aging and extend health span. Lessons learned from telomere length, a candidate aging biomarker for which there has been substantial research, reveals four emerging themes which can inform the design of new studies to evaluate biomarkers of aging: (*i*) the biomarker functions as a biological clock and is mechanistically linked to the aging process, (*ii*) the biomarker is correlated with chronological age and predicts morbidity and early mortality, (*iii*) the biomarker is responsive to exposures known to increase risk for age-related disease, (*iv*) the biomarker can be measured in a precise and reproducible manner. Mitigating measurement limitations may be possible with algorithm-based approaches that correlate multiple measures using standardized clinical parameters. Algorithm-based biomarkers have also been shown to change across the life course and predict mortality and disease processes, but trade precision for lack of specificity with respect to mechanism. Until cellular-level processes governing age-related variation in composite measures are better understood, algorithmic measures can be used in tandem with more established aging biomarkers like telomere length. This practice can potentially inform the next generation of mechanistic research into aging by targeting those measures which were responsive to a promising intervention, but were not the direct target of the intervention.

Session Three:
Critical Considerations of Assessment of Telomere Length Dynamics

Peter Lansdorp
The University of British Columbia
"Telomere Length Measurements and Cell Turnover"

By including an internal control (bovine thymocytes) in flow FISH telomere-length measurement of human leukocytes, it is possible to obtain accurate data that can serve to help diagnose genetic telomere problems and evaluate other techniques. Telomere length at any given age shows marked variation, but differences in telomere length between males and females at birth are maintained over a lifetime. Longitudinal studies in baboons suggest that leukocyte telomere length reflects the rate of stem cell divisions. Stress and injury to stem cells may be reflected in leukocyte telomere length, but limited studies into the dynamics of such responses suggest that short-term effects should be distinguished from long-term effects with dynamics that are currently poorly understood.

Shawn Ahmed
University of North Carolina at Chapel Hill
"Germ Cells Versus Somatic Cells"

Telomere disorders in humans often display genetic anticipation such that telomerase deficiency in germ cells results in progressive deterioration of telomere length over successive generations, accompanied by earlier and earlier onset of lethal somatic diseases such as aplastic anemia or pulmonary fibrosis. Telomerase deficiency in these disorders persists in somatic stem cell populations. It is also possible for individuals to inherit telomeres of wildtype lengths, but to display telomere instability in somatic cells when telomerase is suppressed. This may lead to a several seemingly unrelated disorders. To conclude, possible effects of environmental or social factors on telomere length should consider including analysis of telomerase-positive and telomerase-negative cell types.

Jue Lin
University of California, San Francisco
"Longitudinal Studies of Telomere Length: Assay Considerations and Findings"

Compared to cross-sectional studies, there are only a limited number of studies that provide longitudinal measurements of telomere length (TL). While these studies have confirmed findings from cross-sectional studies, a few unique features stand out with longitudinal analysis: the rate of TL change is reported to be inversely associated with baseline TL and a fraction of the participants have telomere lengthening over time. I will discuss whether these observations reflect measurement variability and/or true biological phenomenon as they are the subject of rigorous debates. I will also discuss practical assay considerations to minimize telomere length assay variability. Applying these considerations, we have discovered interesting associations with

longitudinal telomere length (LTL) change. I will discuss two of these studies. In a cohort of overweight and obese pregnant women, telomere length was measured at three timepoints early pregnancy (⩽ 16 weeks gestation), and 3- and 9-months postpartum. Telomere length (LTL) at all three timepoints from the same participant are highly correlated (Pearson correlation r > 0.89). No cross-sectional associations were found between sugar-sweetened beverage (SSB) intake and LTL, adjusting for sociodemographic and health characteristics. However, we found in the longitudinal analysis, that decreased SSB consumption from baseline to 9 months postpartum was associated with greater concurrent LTL lengthening (β = − 0.102, 95% confidence interval (CI) − 0.192, −0.013). In a cohort of premenopausal women, half of whom are mothers of autistic children, we measured TL in CD4+, CD8+CD28+, and CD8+CD28− T cells; B cells; and peripheral blood mononuclear cells (PBMC) at baseline and 18 months later. TL changes over 18 months were correlated among three T cell types within the same participant. Additionally, PBMC TL change was also correlated with those of all three T cell types, and B cells. The rate of shortening was significantly greater for B cells than for the three T cell types. CD8+CD28− cells, despite having the shortest TL, showed significantly more rapid attrition when compared to CD8+CD28+ T cells. These results suggest systematically coordinated, yet cell type-specific responses to factors and pathways contribute to telomere length regulation.

Allison Bertuch
Baylor University
"The Fate of Dysfunctional Telomeres"

Sharon Savage
National Cancer Institute
"Germline Genetic Variation in Telomere Biology Genes is Associated With a Spectrum of Phenotypes"

The widespread use of genomics has led to numerous discoveries of rare and common genetic variants in telomere biology genes associated with human disease. Rare pathogenic variants (i.e., mutations) cause dyskeratosis congenita (DC) and related telomere biology disorders (TBDs). Common genetic variants (i.e., single nucleotide polymorphisms, SNPs) associated with cancer risk in telomere biology genes have been uncovered through cancer genome-wide association studies (GWAS).

DC is the prototypic TBD characterized by the mucocutaneous triad of abnormal skin pigmentation, nail dystrophy, and oral leukoplakia as well as a very high risk of bone marrow failure, hematologic and solid malignancies, pulmonary fibrosis, and many other medical problems. Telomeres less than the first percentile for age, measured by flow cytometry with in situ hybridization (flow FISH) in lymphocyte subsets, is diagnostic of DC. The development of the diagnostic test and discovery of the genetic causes has led to a growing appreciation of a wide range of TBD phenotypes with variable genetic penetrance and expressivity. The most profoundly affected individuals present in childhood and may have features of DC, very short telomeres, and a constellation of other features such as cerebellar hypoplasia, intrauterine growth restriction (IUGR), and immunodeficiency in Hoyeraal-Hreidarsson syndrome (HH), bilateral exudative retinopathy and intracranial calcifications in

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Revesz syndrome, bone abnormalities, gastrointestinal bleeding, and intracranial calcifications in Coats plus. At the other end of the clinical spectrum are middle-aged or older adults with just one feature of a TBD, such as apparently isolated aplastic anemia or pulmonary fibrosis.

DC and its related TBDs are caused by X-linked recessive (XLR), autosomal dominant (AD), autosomal recessive (AR), or de novo pathogenic germline variants in at least 14 genes critical in key components of telomere biology. These genes can be divided by their function in telomere biology as follows: 1) telomerase components: *DKC1* (XLR inheritance), *TERC* (AD), *TERT* (AD, AR), *NOP10* (AR) *NHP2* (AR), *NAF1* (AD), *WRAP53* (AR), *PARN* (AD, AR); 2) the shelterin telomere protection complex: *TINF2* (AD, *de novo*), *ACD* (AD, AR), *POT1* (AR); 3) telomere capping: *CTC1* (AR), *STN1* (AR); and 4) others: *RTEL1* (AD, AR). Notably, rare germline pathogenic variants in other components of telomere biology have also been associated with familial melanoma (*POT1, ACD*), familial chronic lymphocytic leukemia (*RAP1, POT1),* familial glioma (*POT1*), and angiosarcoma in a Li-Fraumeni syndrome-like family (*POT1*).

GWAS have identified SNPs in telomere biology genes associated with cancer risk in the general population. In contrast to the rare, highly penetrant pathogenic variants described above, many of the SNPs identified in GWAS have a minor allele frequency of more than 5% in the population of interest. SNPs in the *TERT-CLPTM1L* locus on chromosome 5p15.33 have been associated with risk of at least 11 cancer types, including bladder, breast, glioma, lung, melanoma, non-melanoma skin cancer, ovarian, pancreas, prostate, testicular germ cell cancer, and chronic lymphocytic leukemia. Fine-mapping studies of this region have identified specific genetic loci associated with both increased and decreased risk of at least 12 different cancers. Similarly, other GWAS have identified SNPs in *RTEL1* associated with glioma, lung, and prostate cancer. SNPs in or near *TERC, DLCRE1B,* and *POT1* have also been associated with cancer risk to varying degrees.

Rare and common genetic variants in telomere biology genes are associated with a variety of human illnesses that share a common biology. The spectrum of DC/TBD phenotypes is due to incomplete penetrance and yet-to-be identified genotype-phenotype associations; longitudinal studies are required to fully understand the clinical consequences in these individuals. GWAS suggest that common genetic variants in telomere biology genes also play a role in cancer etiology. Moving forward, it will be important for researchers to identify commonalities in biology and clinical phenotypes to gain a full understanding of the role of telomere biology genes variants and human disease.

Session Four:
Genetic Susceptibility and the Environment

Abraham Aviv
Rutgers University
"The Biological Meaning of Leukocyte Telomere Length:
is Leukocyte Telomere Length a Biomarker of Human Aging?"

The notion that leukocyte telomere length (LTL) is a passive biomarker — a 'telomeric clock' of human aging — has dominated telomere epidemiology over the last decade. However, the 'telomeric clock' concept, extrapolated from research in cultured cells, may not apply in vivo. New evidence from population genetic studies suggests that a dynamic interplay between selective forces and telomere length results in trade-offs for specific health outcomes. From a biological perspective, this could occur because short telomeres might increase the risk to a category of diseases related to restricted cell proliferation and tissue degeneration, including cardiovascular disease, whereas long telomeres increase the risk to another category of diseases related to proliferative growth, including major cancers. Support for this idea comes from: a) the concept of precedence, i.e., telomere length being largely determined during early life, decades before disease onset; b) evolutionary/genetic considerations; and c) mechanistic insight explaining association between LTL and adult-onset human diseases.

Brandon Pierce
The University of Chicago
"Epidemiological Studies of the Association Between Metal Exposure and Telomere Length"

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, and 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 >15 epidemiological studies to date. Most of these studies utilized biomarkers of exposure measured in urine, blood, or saliva. Some studies leverage a well-defined primary exposure source (such as contaminated drinking water or occupational exposure) while other studies may have multiple exposure sources that contribute to the population's exposure. The most commonly studied metals are arsenic, cadmium, and lead (>5 studies each). While no metals show consistent evidence of association across all studies, evidence suggests that arsenic exposure is positively associated with TL (potentially through upregulation of *TERT* and telomerase) whereas 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 level (in terms of both the mean and variance), statistical power (e.g., sample size), exposures occurring in the context of complex mixtures (e.g., cigarettes), and biases due to flaws in study design. Major challenges for future studies of environmental exposures and TL include obtaining measures of TL in disease- and toxicant-relevant tissues, inferring causality for associations observed in the presence of complex mixtures, and assessing the role of TL as a potential mediator between the effects of exposure and disease.

Susan Bailey
Colorado State University
"Telomeres as Biomarkers of Psychosocial Stress and Environmental Exposures – on and off the Planet"

Consistent with the premise that psychosocial stress contributes to telomere shortening, we demonstrated that displacement/relocation of villagers in central India resulted in significantly shorter telomeres compared to those of villagers who remained in the more isolated village [*PNAS*, 2015]. Importantly, significant associations between shortened telomere length and each of three key indicators of stress – less healthy cortisol and ⍺-amylase profiles (salivary analytes), and greater psychosomatic suffering (Bradford Somatic Index) – were also found in this highly distressed non-Western population.

In a rural Honduras feasibility study, and consistent with environmental exposures contributing to telomere shortening, telomeres were found to be an informative biomarker of exposure to indoor air pollution (woodstove smoke). Interestingly, frequencies of short telomeres – rather than average telomere length – correlated with micronuclei, a well-established biomarker of air pollution, and particulate matter exposure.

Fukushima, Japan provides an extraordinary research opportunity for examining the impacts of environmental ionizing radiation exposures (IR) on free-ranging wildlife in highly contaminated exclusion zones. In a pilot field study using wild boar as a sentinel species, and together with accurate quantification of external and absorbed dose, telomere length and cortisol were evaluated as a function of terrestrial IR dose, and as companion biomarkers of exposure; a trend toward shorter telomeres with increasing dose was observed.

The goal of our NASA Twins Study investigation was to evaluate telomere dynamics (i.e., changes with time before, during, and after the one-year mission) as a relevant biomarker of aging and health risk for astronauts during long-duration missions. Telomere dynamics captures and combines the unique stresses and exposures encountered during spaceflight (e.g., galactic cosmic rays and microgravity). Somewhat surprisingly, rapid and transient telomere *lengthening* was specifically associated with spaceflight. Results are currently being correlated with the other Twins Study "genomics"-based investigations (e.g., epigenomics, transcriptomics) to gain mechanistic insight into these intriguing results.

Together, these studies, as well as many others, support telomere length maintenance as a general, pancultural biomarker of health, in that it represents a key integrating component for the cumulative effects of genetic (individual susceptibilities), lifestyle (e.g., nutritional, psychological, physical), and environmental (e.g., air pollution, ionizing radiations) factors, on aging and age related degenerative diseases (e.g., cardiovascular disease and cancer).

Chandra Reynolds
University of California, Riverside
"Genetic and Environmental Influences on Telomere Lengths,
Towards Understanding GE Interplay"

Telomere length (TL) is a biomarker of aging where shortening, or different degrees of shortening, may occur due to environmental exposures as well as genetic influences. A large meta-analysis of quantitative genetic studies [1] suggests strong heritable influences on cross-sectional TL differences ranging from 62 to 86%. The latest genome-wide association analysis of TL has identified less than ten genetic variants, which is far from what would be expected [2]; however, these results may soon be updated by larger ongoing studies. Longitudinal studies in aging twin samples likewise suggest genetic influences on individual differences in TL across time, although extant genetic risk scores may contribute to overall TL but not to differential change [3] leaving open whether additional specific genetic factors may predict TL dynamics. Other efforts using Mendelian Randomization techniques have provided support for a direct causal association of longer TL and better cognitive performance [4] and shorter TL and Alzheimer's disease risk [5], for example. We consider the extent to which environmental and genetic influences may be dynamic over late life and present twin-pair methods that may enhance understandings of GE interplay.

Session Five:
Combining Telomere Measurements with Other Markers

Colter Mitchell
University of Michigan
"Epigenetic Measures and Telomere Length"

This talk will briefly cover three aspects linking telomere length (TL) and change in telomere length (ΔT) and epigenetics. First, TL and ΔT are often conceived of as measuring a latent biological aging. More recently epigenetics is similarly being discussed as a method for examining "biological aging." In particular, several epigenetic clocks (at least 4 prominent versions) now exist. A comparison of the different clocks, TL, and ΔT will be discussed. Second, epigenetic data can be used to examine cell distribution — a potential confounder of TL and ΔT comparison between people. This paper will provide some examination of the effect of cell distribution on TL and ΔTin whole blood and saliva only. Third, I provide some evidence of epigenetic loci associated with TL in saliva.

Martin Picard
Columbia University
"Mitochondria are Gatekeepers at the Interface of Genome and the Environment"

In addition to producing energy, mitochondria perform several biochemical and signaling functions. Recent evidence suggests that, like sentinels in a dynamic environment, mitochondria i) sense, ii) integrate, and iii) signal information. Mitochondria thereby transmit information about external stressors, translating stress mediators into molecular signals and biological responses. To understand how this influences events within the cell nucleus, including gene expression and telomere dynamics, we have genetically manipulated different aspects of mitochondrial functions in cells and mice, and combined stress paradigms with systems biology. This work has shown that mitochondria regulate the nature and magnitude of cellular and systemic responses to psychological stressors. Using novel methods to profile mitochondrial health in human blood, we have also found that acute and chronic exposure to psychological stress may influence mitochondrial energy production capacity and mitochondrial DNA distribution. Together, these studies provide converging evidence for a role of mitochondrial stress signaling at the genomic-environment interface.

Nan-Ping Weng
National Institute o Aging
"Longitudinal Studies of Telomere Length in Hiroshima Atomic Bomb Survivors and in Baltimore Longitudinal Study on Aging Cohort, and the Impact of Telomere Attrition on Immune Function"

We are examining the role of telomere length with age and its impact on lymphocyte functions using longitudinal samples. To determine the long-term impact of ionizing radiation (IR) on cell function and aging, we measured telomere length and other biomarkers in survivors of the atomic bombing at Hiroshima during World War II, 50 to 68 years post-exposure (two timepoints per person). We found that telomere length of leukocytes was inversely correlated with the dose of IR, and this effect was primarily found in survivors who were exposed at younger ages, specifically those <12 years old. In addition, IR diminished the associations between telomere length and selected aging biomarkers that were observed in survivors with no dose. We also measured telomere length change in PBMCs and isolated T and B cells of BLSA cohorts over an average 13 years and observed loss of telomere length in a highly individualized manner. To assess the impact of telomere attrition on immune function in the old population, we selected healthy older adults who have relatively short or long telomere lengths to compare their immune response to influenza vaccine. We found that B cells from individuals with a robust antibody response to the influenza vaccine had significantly longer telomeres than those with a poor antibody response. Furthermore, IAV M1-specific CD8+ T cells from the long telomere group exhibited significantly better expansion in vitro compared to those from the short telomere group. Together, our findings show that telomere length change with age is highly individualized, and IR has long lasting detrimental effect on telomere length, and telomere length is positively associated with a robust lymphocyte response to influenza vaccine.

Allison Aiello
University of North Carolina at Chapel Hill
"The Impact of Persistent Stress-Related Infections on Telomere Length"

Numerous persistent pathogens, including cytomegalovirus and other herpesviruses, have been implicated in chronic disease and associated mortality. These same viruses have been shown to be acutely reactive to stressful exposures. Some research suggests that multiple herpesviruses may synergistically cause damage to various tissues and organs of the body via direct and indirect immunological pathways. Our earlier research has suggested that cumulative damage resulting from exposure to multiple persistent pathogens may play a larger role in mortality than the contribution of any single pathogen. At the same time, our work supports a role for psychosocial stressors in altered immune response to some herpesviruses. We hypothesized that leukocyte telomere shortening may be one pathway by which herpesvirus pathogen burden may synergistically influence longevity. This presentation will first describe the state of the literature on pathogen burden, stressors, and survival. Next, we will present novel data linking multiple persistent herpesviruses to shorter telomere length and telomerase using data from multiple large-scale studies. Our findings provide key insights on the role of multiple persistent infections and biological aging as measured by telomeres.

Biographies

Shawn Ahmed
University of North Carolina at Chapel Hill

Shawn Ahmed received his Ph.D. from Iowa State University, primarily working on biochemical structures of telomeric oligonucleotides with Eric Henderson. He went on to the Laboratory of Molecular Biology in Cambridge, England, where he studied the genetics of telomerase and germ cell immortality in Caenorhabditis elegans (C. elegans), under the guidance of Jonathan Hodgkin. In 2001, Ahmed took a position at the University of North Carolina at Chapel Hill, where he is currently professor of genetics and biology.

Ahmed's group has performed large-scale genetic screens to study telomerase and germ cell immortality in C. elegans. From the perspective of telomere biology, the group has defined genes required for telomerase activity, and has also characterized genes that repress telomerase and the telomerase-independent telomere maintenance mechanism termed Alternative Lengthening of Telomeres. The Ahmed group has also studied a small RNA-mediated genome silencing pathway that promotes germ cell immortality, which implies that epigenetic silencing defects could be a cause of senescence.

Allison Aiello
University of North Carolina at Chapel Hill

Allison Aiello, Ph.D., is professor of epidemiology at the University of North Carolina at Chapel Hill (UNC) Gillings School of Global Public Health, where she leads the Social Epidemiology Program, is a Fellow at the Carolina Population Center, and on the advisory board of the Center for Health Equity Research. Prior to joining UNC, Aiello spent 10 years on faculty at the University of Michigan in the Center for Social Epidemiology and Population Health, after completing the Robert Wood Johnson Foundation Health and Society Scholars Program. Aiello's research integrates concepts from both sociological and biological sciences to develop unifying research approaches for addressing complex health questions across the life course. She has a long-standing interest in health equity research and the integration of biomarkers in social science research. Aiello has published over 150 journal articles and has written several book chapters.

Mary Armanios
Johns Hopkins University

Mary Armanios, M.D., is professor of oncology and genetic medicine at the Johns Hopkins University School of Medicine. Her research interests have focused on understanding the role of telomeres and telomerase in disease. Armanios earned her medical degree at the Ohio State University, where she went on to complete a combined internal medicine and pediatrics residency. She then moved to Johns Hopkins University to complete fellowships in oncology and molecular biology and genetics. She is currently the clinical director of the Telomere Center at Johns Hopkins University and overseas the telomere diagnostics lab in Johns Hopkins Hospital. Armanios is a member of the American Society for Clinical Investigation and serves as Associate Editor of the *Journal of Clinical Investigation*.

Abraham Aviv
Rutgers University

Abraham Aviv, M.D., was trained as a pediatrician, but his interests have covered a wide range of topics relating to cardiovascular disease. Aviv has been director of the Hypertension Research Center and later the director of the Center of Human Development and Aging at the New Jersey Medical School, at Rutgers University for 30 years. Throughout this period, his research has been funded continuously by the National Institutes of Health and other agencies in the United States and abroad.

Aviv has focused on telomere biology, epidemiology, and genetics for the last 16 years. During this time, he has led large-scale collaborative investigations with the Framingham Heart Study, the Cardiovascular Health Study, the Family Heart Study, the Women's Health Initiative, the Jackson Heart Study, the Bogalusa Heart Study, TwinsUK, the Danish Twin Registry, including the Longitudinal Study of Aging Danish Twins, and others. His recent and ongoing collaborations include several projects with the Norwegian Institute of Public Health, which oversees the Norwegian Mother and Child Cohort Study (MoBa); a study comprising more than 100,000 newborns and their parents. These projects reflect his view that telomere length dynamics, (telomere length at birth and its age-dependent shortening thereafter), during early life is the principal determinant of telomere length throughout the life course. Thus, learning about the factors, genetic and environmental, that define telomere length during this critical time, (which includes intra-uterine growth and development), is essential for understanding the role of telomere biology in human health and disease.

Susan Bailey
Colorado State University

Susan Bailey, Ph.D., is a professor of Radiation Cancer Biology in the Department of Environmental & Radiological Health Sciences at Colorado State University (CSU) in Fort Collins, Colorado. Bailey is currently vice president elect of the international Radiation Research Society. In addition to training and mentoring of graduate students, she also serves as director of CSU's Program of Research and Scholarly Excellence (PRSE) in Cancer Biology & Comparative Oncology (CBCO), and of CSU's Telomeres & Telomerase Laboratory.

A native of Los Alamos, New Mexico, she received her master's and doctorate degree in biomedical sciences from the University of New Mexico School of Medicine. As a radiation cytogeneticist with a particular interest in telomeres, her research efforts have provided novel insights into basic mammalian telomere biology. Most recently, her research has demonstrated the value of assessing telomere dynamics as an informative biomarker of life stress, (e.g., in a non-Western, central India, context), and of exposures in extreme environments, (e.g., the International Space Station), as one of the NASA Twins Study investigators.

Allison Bertuch
Baylor College of Medicine

Alison Bertuch, M.D., Ph.D., is an associate professor in the Departments of Pediatrics and Molecular & Human Genetics at Baylor College of Medicine. She is also the director of the Bone Marrow Failure Program at Texas Children's Hospital in Houston. Her research interests are in the areas of telomere biology and bone marrow failure. Her laboratory conducts basic research into the mechanisms governing the structure, maintenance, and function of telomeres. She has made key contributions to the understanding of the functions the DNA repair factor Ku at telomeres in both the genetically tractable yeast model and human cells. She also conducts translational research in the area of dyskeratosis congenita, a bone marrow failure and cancer predisposition syndrome that results from a defect in telomere biology. Her work has focused on uncovering the molecular effects of germline mutations in telomere biology genes that result in severely short telomeres in children and the development of early-onset and severe manifestations of dyskeratosis congenita.

Linda Birnbaum
National Institute of Environmental Health Sciences

A board certified toxicologist, Linda Birnbaum, Ph.D., has served as a federal scientist for over 37 years. She has received many awards and recognitions, including the North Carolina Award in Science, the Women in Toxicology Elsevier Mentoring Award, the Society of Toxicology Public Communications Award, EPA's Health Science Achievement Award and Diversity Leadership Award, the National Center for Women's 2012 Health Policy Hero Award, the Breast Cancer Fund Heroes Award, and 14 Science and Technology Achievement Awards, which reflect the recommendations of EPA's external Science Advisory Board, for specific publications. Birnbaum was also elected to the Institute of Medicine of the National Academies, and received an honorary degree from Ben-Gurion University in Israel.

Birnbaum is a former president of the Society of Toxicology, the largest professional organization of toxicologists in the world; former chair of the Division of Toxicology at the American Society of Pharmacology and Therapeutics; and former vice president of the American Aging Association. She is the author of more than 800 peer-reviewed publications, book chapters, and reports. She is also an adjunct professor at several universities, including the University of North Carolina at Chapel Hill and Duke University.

A native of New Jersey, Birnbaum received her master's and doctoral degrees in microbiology from the University of Illinois at Urbana-Champaign.

Gwen Collman
National Institute of Environmental Health Sciences

Gwen Collman, Ph.D., is director of the NIEHS Division of Extramural Research and Training where she leads approximately 60 professional staff in areas of scientific program administration, peer review, and the management and administration of about 1,500 active grants each year. She directs scientific activities across the field of environmental health sciences including basic sciences (i.e.,

DNA repair, epigenetics, environmental genomics), organ-specific toxicology (i.e., reproductive, neurotoxicology, respiratory), public health related programs (i.e., environmental epidemiology, environmental public health), and training and career development. She also oversees the implementation of the Superfund Research Program and the Worker Education and Training Program.

Prior to her current role, Collman served in program development and management, beginning in 1992 as a member, then as Chief of the Susceptibility and Population Health Branch. During this time, she directed research on the role of genetic and environmental factors on the development of human disease, from animal models of genetic susceptibility to population studies focusing on etiology and intervention. She was responsible for building the NIEHS grant portfolio in environmental and molecular epidemiology, and developed several complex multidisciplinary research programs. These include the NIEHS Breast Cancer and the Environment Research Centers Program, the NIEHS/EPA Centers for Children's Environmental Health and Disease Prevention, and the Genes, Environment and Health Initiative. Also, under her guidance, a team created a vision for the Partnerships for Environmental Public Health programs for the next decade.

In recognition of her achievements, she is the recipient of numerous NIEHS Merit Awards, two NIH Director's Awards, and the DHHS Secretary's Award for Distinguished Service. Collman received a Ph.D. in Environmental Epidemiology from the University of North Carolina School of Public Health where she was awarded the 2009 H.A. Tyroler Distinguished Alumni Award.

William Copeland
National Institute of Environmental Health Sciences

William Copeland, Ph.D., is chief of the Genome Integrity and Structural Biology Laboratory (GISBL) at the National Institute of Environmental Health Sciences (NIEHS). Copeland was trained in biochemistry with Jon Robertus at the University of Texas at Austin in the Department of Chemistry. He conducted his postdoctoral work with Teresa Wang in the Department of Pathology at Stanford University School of Medicine, where he studied the human DNA polymerase alpha – primase complex. He joined the NIEHS in 1993 in the Laboratory of Molecular Genetics and received tenure in 2001. As an independent investigator, his work has concentrated on mitochondrial DNA replication, diseases from POLG mutations, and mitochondrial toxicity from antiviral nucleoside analogs. Copeland has been recognized internationally for his work on the mitochondrial DNA polymerase and served as the president of the Mitochondrial Research Society, chair of the United Mitochondrial Disease Foundation (UMDF), twice chair of the annual UMDF scientific meeting. At NIEHS, Copeland was awarded Mentor of the Year (2005) and received the National Institutes of Health (NIH) Mentor of the Year award in 2006. He is currently the chair of COP1, chair of the space and renovation committee, institute liaison to the NIH Office of AIDS Research, Rare disease network, and mitochondrial interest group, as well as serves on the Radiation Safety Committee and the Distinguished Lecture Series, and Conference Selection Committee. He was appointed Chief of the Laboratory of Molecular Genetics in 2010 and assumed the role of Chief of GISBL upon its inauguration in 2014.

Stacy Drury
Tulane University

Stacy S Drury, M.D., PhD., is currently the associate director of the Tulane Brain Institute, vice chair of research in the Department of Pediatrics and holds the Remigio Gonzalez, MD Professorship of Child Psychiatry. She completed her undergraduate degree at the University of Virginia and her master's in human genetics at the University of Michigan. She then completed her M.D. and Ph.D. (Genetics) at Louisiana State University, New Orleans and her adult and child psychiatry residencies at Tulane. She currently directs the Behavioral and Neurodevelopmental Genetics Laboratory (http://www2.tulane.edu/som/bangl/) and is co-director of the Stress Environment Research Collaborative for Health Disparities and a member of the Executive Committee for the recently formed Violence Prevention Institute at Tulane. Both her clinical work and research focus on the intersection between early life adversity, epigenetic and genetic factors and child neurodevelopmental and health trajectories. Her highly transdisciplinary lab, coupled with her integrated clinical practice directly linked to public health and policy efforts, provides an opportunity to translate the science of early life adversity into language understandable across disciplines with the long-term goal of both improving child health trajectories and training the next generation of clinicians, scientists, and policy makers.

Elissa Epel
University of California, San Francisco

Elissa Epel, Ph.D., is a professor in the Department of Psychiatry, at University of California, San Francisco. Her research aims to elucidate mechanisms of healthy aging, and to apply this basic science to scalable interventions that can reach vulnerable populations. She is the director of the Aging, Metabolism, and Emotions Lab, and the Center for Obesity Assessment, Study, & Treatment, (COAST), and associate director of the Center for Health and Community. She studies psychological, social, and behavioral pathways underlying chronic psychological stress and stress resilience that impact cellular aging. She also studies the interconnections between stress, addiction, eating, and metabolic health. With her collaborators, she is conducting clinical trials to examine the effect of self-regulation and mindfulness training programs on cellular aging, weight, diet, and glucose control. She leads or co-leads studies funded by NIH (NIA, NCCIH, NICHD, and NHLBI) including a Stress Network, and a multi-campus center on obesity. She is involved in NIH initiatives on role of stress in aging, and on reversibility of early life adversity, and Science of Behavior Change. She is also on the Steering Council for Mind & Life Institute. Epel studied psychology and psychobiology at Stanford University (BA), and clinical and health psychology at Yale University (Ph.D.). She completed a clinical internship at the Palo Alto Veterans Healthcare System. Epel has received several awards including the APA Early Career Award, the Academy of Behavioral Medicine Research Neal Miller Young Investigator Award, and is a member of the National Academy of Medicine.

Max Guo
National Institute on Aging

Max Guo, Ph.D., is the Chief of the Genetics and Cell Biology Branch, Division of Aging Biology at the National Institute on Aging (NIA), NIH. Trained as a molecular biologist and geneticist, he obtained a Ph.D. in Biochemistry on study of RNA splicing with Alan Lambowitz from the Ohio State University in 1992. He did his postdoctoral training on oncogenes with J. Michael Bishop at University of California at San Francisco. Before joining NIH as a Program Officer in 2002, he was an assistant professor of Cancer Biology at the Sidney Kimmel Comprehensive Cancer Center of Johns Hopkins Medical School. He was a program officer of Genetics and Genomics at National Institute on Alcohol Abuse and Alcoholism (NIAAA) and National Heart, Lung, and Blood Institute (NHLBI) from 2002 to 2007. From 2008-2011, he was the deputy director of the Division of Metabolism and Health Effects, NIAAA. He joined NIA in 2011 and is responsible for the genetics and chromatin portfolio.

Sara Hägg
Karolinska Institutet

Sara Hägg, Ph.D., is currently assistant professor at the Department of Medical Epidemiology and Biostatistics at Karolinska Institutet (KI) in Stockholm, Sweden. She also holds a Docent title in Molecular Epidemiology (an academic appointment translated as associate professor). She did her undergraduate training at Stockholm University majoring in Molecular Biology (M.Sc.) and Computer Science (B.Sc.) and completed her thesis in Computational Biology (Ph.D.) at Linköping University, Sweden, in 2009. She held postdoctoral fellowships at KI (2011-2014) in Genetic Epidemiology and at Uppsala University (2013-2014) in Molecular Epidemiology. After that, Hägg has run her own research group at KI focusing on molecular epidemiological studies of aging. In 2016, she did a short sabbatical at the Department of Medicine at Stanford University School of Medicine.

The main topics of her research involve: 1) leukocyte telomere length and causality using Mendelian Randomization studies for age-related diseases, as well as longitudinal telomere shortening across old age; 2) longitudinal epigenetic influences on aging in twins using genome-wide DNA methylation data and the epigenetic clock; and 3) development of biological age predictors using samples from prospective cohorts of aging and omics data. The data used in her research comes from different sources, such as the Swedish Twin Registry where several longitudinal cohorts of aging are used (SATSA, GENDER, HARMONY, OCTO-Twin, TwinGene), the Health and Retirement Study (HRS), the Mayo Clinic Study of Aging, the UK Biobank, and the Genomic Aggregation Project in Sweden (GAPS).

Michelle Heacock
National Institute of Environmental Health Sciences

Michelle Heacock, Ph.D., received her doctorate from Texas A & M University in College Station, Texas for her work on the interplay between DNA repair proteins and telomeres. Her postdoctoral

work was conducted at NIEHS where she studied the DNA repair pathway, base excision repair. Her research focused on understanding the causes of cellular toxicity caused by DNA damaging agents. Michelle is currently a program administrator for the Hazardous Substance Research Branch in the Division of Extramural Research, at the NIEHS. Her current grant portfolio includes research that ranges from telomeres, DNA repair, and Superfund Research Program Center grants.

Peter Lansdorp
British Columbia Cancer Agency

Peter Lansdorp, M.D., Ph.D., has made numerous contributions to studies of blood-forming stem cells and telomere biolology. For most of his career, he worked at the Terry Fox Laboratory in Vancouver, Canada, where he maintains a laboratory. In 2011, he became the founding Scientific Director of the European Institute for the Biology of Ageing (ERIBA) at the University of Groningen in the Netherlands. He returned to Vancouver in 2016. His current research interest is focused on applications of Strand-seq, a single cell sequencing technique developed in his laboratory.

Jue Lin
University of California, San Francisco

Jue Lin, Ph.D., is a research biochemist at University of California in San Francisco. She received her B.S. from Fudan University (Shanghai, China) in 1992 and Ph.D. from Cornell University in 1999. She joined Elizabeth Blackburn's lab for her postdoctoral training in 1999, working on various aspects of yeast telomerase regulation, including the template region of the RNA component of telomerase, discovery of a universal RNA core structure for telomerase RNA, and a novel mechanism for how the protein PinX1p inhibits telomerase activity. She, together with Elizabeth Blackburn and Elissa Epel, pioneered the work on psychological stress and telomere biology in 2004. Over the last 13 years, her research has focused on the role of telomere maintenance in aging related diseases and risks. She optimized and developed the high throughput qPCR telomere length assay and the telomerase activity from unstimulated PBMCs. She also has extensive experience with biobanking for telomere measurements and other molecular and immunological assays for clinical research. As the director of the telomere measurement core facility in the Blackburn lab, she and her team have provided telomere measurements to over 80 research teams from 44 institutes, which include telomere length measurements for over 40,000 samples and telomerase activity measurement for over 2000 samples. She is a co-author on over 80 publications, including several invited expert review papers. Currently, she is also investigating the role of psychological stress, stress reduction on telomeres, and inflammation using *in vitro* systems.

Yie Liu
National Institute on Aging

Yie Liu, Ph.D., received her doctorate at Karolinska Institute, Sweden and then joined the University of Toronto as a postdoctoral fellow of the National Cancer Institute of Canada. She became a principal investigator at the National Institute on Aging (NIA) since 2006.

Liu's laboratory has established a hypothesize-driving research program to investigate telomere damage and repair. Her work employs a variety of in vitro and in vivo approaches, including multiple model organisms, molecular, cellular biology, and protein biochemistry to test the hypothesize that oxidative DNA lesions and inadequate resolution of unusual telomeric DNA structures alter telomere length homeostasis. Her lab focuses on the role of the Fanconi anemia (FA), RECQ helicases and base excision repair (BER) proteins in modulating resolution of unusual DNA structures and removal of oxidatively damaged DNA bases at telomeres.

Colter Mitchell
University of Michigan

Colter Mitchell is a research assistant professor in the Survey Research Center at the University of Michigan. He is the associate director of the Bio-social Methods Collaborative and is a Research Affiliate of the Population Studies Center and the Center for Human Growth and Development. His research focuses how social context interplays with an individual's genetic, epigenetic, neurodevelopment makeup to influence their behavior, wellbeing, and health. In general, this takes well-established social science research and attempts to highlight key biosocial interactions or mechanisms. For example, a key research area for demographers has been the documentation of the large behavioral and health consequences of poverty and family instability. A potential mediator in the relationship of poverty and health and behavior is biology. In some of Mitchell's work, he explores potential biomarkers and even potential mechanisms of the consequences of growing up in poverty and with family instability (e.g. changes in epigenetics signatures, brain development, and telomere length). He also explores the extent to which biology (e.g. genetics) may moderate the effect of poverty and family instability on health and behavior. His research also includes the development of new methods for integrating the collection and analysis of biological and social data. He has participated in data collection and analyses of biomarkers in multiple population-based studies, including: the Fragile Families and Child Wellbeing study, Army STARRS, the Panel Study of Income Dynamics, and the Health and Retirement Study.

Belinda Needham
University of Michigan

Belinda Needham, Ph.D., is currently an assistant professor in the Department of Epidemiology at the University of Michigan. She received her doctoral degree in sociology from the University of Texas at Austin in 2006 and was a Robert Wood Johnson Foundation Health and Society Scholar at the University of California, San Francisco and Berkeley, from 2006-2008. Her research focuses on health disparities, biosocial interactions, as well as aging and the life course. In general, members of socially disadvantaged groups have worse mental and physical health than those who have higher social status. Needham's work seeks to identify, explain, and reduce gender, socioeconomic, racial/ethnic, and sexual orientation health disparities. Her primary research goals are to use novel approaches to assess health disparities across the life course and to identify the social structural, psychological, behavioral, and physiological mechanisms by which social disadvantage leads to health disparities.

Lisbeth Nielsen
National Institute on Aging

Lisbeth Nielsen is chief of the National Institute on Aging's (NIA) Individual Behavioral Processes Branch, which supports behavioral, psychological, and integrative biobehavioral research on the mechanistic pathways linking social and behavioral factors to health in mid-life and older age. This Branch examines aging processes across the full life course, including early life influences on later life outcomes, as well as research on behavioral and social processes in midlife that play a causal role in shaping trajectories of aging. Nielsen's own portfolio supports transdisciplinary research in affective science, health psychology, and life-span developmental psychology. She coordinates NIA research initiatives on midlife reversibility of risk associated with early life adversity, conscientiousness and healthy aging, socioemotional influences on decision-making, and stress measurement. She serves on the implementation team for the trans-National Institute of Health Science of Behavior Change (SOBC) Common Fund Program, which promotes a mechanisms-focused experimental medicine approach to behavior change intervention design.

Patricia Opresko
University of Pittsburgh

Patricia L. Opresko, Ph.D., is a research associate professor in the Department of Environmental and Occupational Health at the University of Pittsburgh Graduate School of Public Health. She is affiliated with the UPMC Hillman Cancer Center and the Center for Nucleic Acid Science and Technology at Carnegie Mellon University. She received her bachelor's degree from the DeSales University in Chemistry and Biology and her doctorate from the Pennsylvania State University College of Medicine in Biochemistry and Molecular Biology. Her graduate work focused on investigating molecular mechanisms of DNA mutations associated with cancer, caused by DNA polymerase errors and carcinogens. She continued her training in genome instability and human diseases as a postdoctoral fellow at the National Institute on Aging where she studied the molecular pathology of the cancer prone progeroid disorder Werner syndrome.

Opresko started her laboratory in 2005 as a faculty member at the University of Pittsburgh. Her research program investigates the mechanisms of genomic and telomere instability associated with aging and aging related disease. Her lab is studying genetic and environmental factors that shift the rates of telomere shortening in normal aging to accelerated rates that occur in premature aging syndromes and disease. Currently, her lab is studying the role of specific DNA repair enzymes in preserving telomeres, with a focus on mechanisms of oxidative stress induced telomere alterations. Opresko is a former recipient of the Ellison Medical Foundation New Scholars Award in Aging. She also received the Outstanding New Environmental Scientist Award in 2006. She is currently a principal investigator on four active NIH grants, awarded through NIEHS, NCI and NIGMS.

Opresko is a member of the American Association for Cancer Research and the Environmental Mutagenesis and Genomics Society (EMGS). She was recently elected as an EMGS Councilor and is associate editor for the journal *Mechanisms of Development and Aging.* She has been an ad hoc member of the NCI Special Emphasis Panel for R21 and R01 applications, the Molecular Genetics B Study section, and the NIEHS panel for the ONES R01 and P30 Core Center applications. Opresko's

research in the fields of genomic integrity, telomere biology, and DNA repair has resulted in 65 peer-reviewed publications to date, achieving an h-index factor of 31. She has chaired and organized sessions focused on DNA repair and telomere biology for various international conferences, including Gordon research conferences and annual meetings of the Environmental Mutagenesis and Genomics Society (EMGS). She is greatly involved in graduate and post-doctoral mentoring across several departments at the University of Pittsburgh and teaches lectures in Genetic Toxicology, Human Genetics, Biology of Aging, and DNA Repair graduate courses.

Martin Picard
Columbia University

Martin Picard, Ph.D., received his B.Sc. Honours in neuroimmunology at McGill University in 2007. He remained at McGill for his graduate work and obtained his Ph.D. in mitochondrial biology of aging in 2012, while being a fellow in psychosocial oncology and systems biology. Picard then moved to the University of Pennsylvania for a postdoctoral fellowship in the Center for Mitochondrial and Epigenomic Medicine with Doug Wallace, who discovered that we inherit our mitochondria from our mothers and that mitochondrial DNA mutations can cause disease. There, Picard worked on mitochondria-mitochondria interactions, mitochondrial reprogramming of the nuclear transcriptome, and mitochondrial stress pathophysiology along with Bruce McEwen. In 2015, he joined the faculty at Columbia University where he established the Mitochondrial Signaling Laboratory.

Picard's NIH-funded translational research program investigates mechanisms of mind-body interactions. His group specifically seeks to identify novel principles that underlie mitochondrial responses to stressors, the maintenance of human health, and the influence of mitochondrial defects on complex cellular and physiological processes including aging. His laboratory pursues three main goals: 1) develop novel molecular, imaging, and computational methods to characterize mitochondrial health in cells and tissues; 2) use these tools to understand the link between psychosocial experiences, including emotions and stress, and mitochondrial function, (ultra)structure, and signaling; 3) establish the role of mitochondria within important stress signal transduction pathways inside and outside the cell, using genetic and molecular approaches to manipulate different facets of mitochondrial biology.

Brandon Pierce
The University of Chicago

Brandon Pierce, Ph.D., is an assistant professor in the Departments of Public Health Sciences and Human Genetics at the University of Chicago. Pierce is a genetic and molecular epidemiologist interested in understanding gene-environment relationships and their role in the etiology of cancer. His research focuses on identifying biomarkers that are related to susceptibility to environmental exposure. Pierce's research interests include 1) telomere length as a biomarker of exposures, aging and cancer risk, 2) methods for assessing causal relationships among risk factors, biomarkers, and disease, and 3) susceptibility to the effects of environmental exposure to arsenic, a known carcinogen. The long-term goals of Pierce's work are to understand toxicity mechanisms and disease biology, and to improve our ability to predict disease and target interventions to high-risk

sub-populations. Pierce a principal investigator of several ongoing projects including a study of telomere length in an arsenic-exposed Bangladeshi cohort and a study of telomere length and chromosomal Instability across many human tissue types.

Chandra Reynolds
University of California, Riverside

Chandra Reynolds, Ph.D., is professor of psychology at the University of California Riverside. She received her doctorate in psychology from the University of Southern California (USC) in 1994. She held postdoctoral positions at the Institute for Behavioral Genetics, University of Colorado at Boulder (1994-1995), and the Andrus Gerontology Center, USC Davis School of Gerontology (1996-1997). Reynolds' research focus considers lifespan developmental psychology and quantitative genetic methods, particularly as they inform understandings of: 1) growth and declines in cognitive abilities (including normative changes versus dementia-related changes), 2) how earlier life factors impact later life cognition, health and well-being, and 3) the coaction and interplay of genes and environments in shaping how individuals age cognitively, and maintain health and well-being. Understanding the dynamic etiologies contributing to individual differences includes focus on biomarkers as indexes (or residues) of gene-environment interplay, including telomere length and DNA methylation.

Necessarily, attention to measurement, longitudinal design, and probing designs to illuminate gene-environment interplay have been of importance to projects that Reynolds has undertaken. She has led multi-site collaborative efforts (AG28555, Reynolds), considering genes in the cholesterol pathway, intermediate lipid biomarkers, and ultimate behavioral and clinical cognitive phenotypes measured in Swedish case-control and four related twin samples (GENDER, OCTO-Twin, SATSA and Harmony). She has also led and contributed to projects on childhood and social factors that predict life course patterns of health, well-being, and longevity (AG02700, Terman Life Cycle Study, Reynolds, Friedman; HD010333, Colorado Adoption Project, Wadsworth). Currently, she serves as a co-investigator on the VETSA Longitudinal Twin Study of Cognition and Aging (VETSA 3) (AG018386; Kremen, Lyons, MPIs). She is a co-Investigator and site PI for the *Gene-Environment Interplay of Social Contexts and Aging-Related Outcomes* (AG037985; IGEMS consortia, Pedersen), in which current projects include longitudinal studies of DNA methylation change in Swedish and Danish samples. She serves as contact PI of the MPI project *Colorado Adoption/Twin study of Lifespan behavioral development and cognitive aging*, CATSLife (AG046938; Reynolds, Wadsworth, MPIs), which is evaluating the unique saliency of early life versus proximal factors on how well individuals build and maintain cognitive functioning as they approach midlife.

Janine Santos
National Institute of Environmental Health Sciences

Janine Santos, Ph.D., received her doctorate in genetics and molecular biology from the Federal University of Rio Grande do Sul in Porto Alegre, Brazil. During her Ph.D. studies. Santos worked on Genetic Toxicology using Drosophila melanogaster as a model system to understand the effects of dietary compounds under conditions of genotoxic stress. She then moved to North Carolina for her post-doctoral fellowship at NIEHS to work on mitochondrial DNA metabolism.

In 2006, Santos became faculty at the New Jersey Medical School. Following her discovery that telomerase is also in the mitochondria, her work in New Jersey established several connections between mitochondria and telomeres. In 2013, she returned to NIEHS, and since then her focus has been on defining the impact of mitochondrial metabolism to the epigenome and transcriptome.

Sharon Savage
National Cancer Institute

Sharon A. Savage, M.D., is the chief of the Clinical Genetics Branch in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute (NCI). She leads clinical, genetic, and epidemiologic studies of individuals and families at high risk of cancer. Her comprehensive approach combines genomics with clinical genetics and molecular biology to improve understanding of cancer etiology and the lives of patients with complex cancer-prone disorders.

Savage leads NCI's clinical and genetic study of Li-Fraumeni syndrome (LFS), a highly penetrant cancer susceptibility syndrome often caused by germline mutations in *TP53*, that is evaluating pediatric and adult cancer-screening regimens and studying the underlying molecular biology of LFS. Savage led the first genome-wide association study (GWAS) of osteosarcoma, the most common primary malignant bone cancer of children and adolescents, which discovered novel genetic risk factors.

Savage's research program in telomere molecular epidemiology incorporates population-based studies of telomere length and disease with genetic studies of telomere biology. Dyskeratosis congenita (DC), cancer-prone inherited bone marrow failure syndrome, is caused by germline mutations in telomere biology genes. To date, Savage has discovered four genetic causes of DC. This work has formed the basis for numerous basic science studies of the function of telomere biology genes. Her clinical studies of DC have led to improvements in the diagnosis of DC and seek to advance understanding of the clinical complications of DC and the related telomere biology disorders.

Idan Shalev
Pennsylvania State University

Idan Shalev, Ph.D., is an assistant professor in the Department of Biobehavioral Health at Penn State University. Shalev received his bachelor's degree in Biology from the Ben-Gurion University of the Negev in Israel. He then moved to the Hebrew University in Jerusalem and completed his master's and doctoral degrees in Neuroscience and Genetics under the supervision of Richard Ebstein, Ph.D. His work entailed an interdisciplinary investigation into the genetic underpinning of social stress in healthy human subjects. He worked at the Department of Psychology at the National University of Singapore as a Research Associate before moving to Duke University as a Postdoctoral Fellow. At Duke, Shalev worked with Professors Terrie Moffitt and Avshalom Caspi where he focused his research on telomeres, a promising new biomarker of stress and aging. In the Spring of 2014, Shalev joined the Department of Biobehavioral Health and the Child Maltreatment Solutions Network at Penn State University. The Network, which began in response to a recommendation

from the Presidential Task Force on Child Maltreatment in the Fall of 2012, aim to strengthen the University's research efforts in the area of child maltreatment.

Shalev's research entails an interdisciplinary approach to identify mechanisms underpinning the biological embedding of stress across the lifespan. His research combines the disciplines of molecular genetics, endocrinology, neurobiology, and psychology. This systems approach integrates data sources across multiple levels of genomic, biomarkers, and phenotypic data. Specifically, using innovative research designs, his research tests the effects of stress from early life on change in telomere length and other biomarkers of aging across the life course, and the consequences of change in telomere length for physical and mental health problems.

In the first study of children, Shalev and colleagues showed that cumulative violence exposure was associated with accelerated telomere erosion, from age 5 to age 10 years, for children who experienced violence at a young age. This finding provided initial support for a mechanism linking cumulative childhood stress to telomere maintenance, observed already at a young age, with potential impact for life-long health. Shalev is the Mark T. Greenberg Early Career Professor for the Study of Children's Health and Development and an author of more than 40 scientific articles and chapters.

Pathik Wadhwa
University of California, Irvine

Pathik Wadhwa, M.D., Ph.D., is a professor of Psychiatry & Human Behavior, Obstetrics & Gynecology, Pediatrics, and Epidemiology at the University of California, Irvine, School of Medicine, and the founding director of the University of California Irvine Development, Health and Disease Research Program. Wadhwa received his medical degree from the University of Poona, India, in 1985, and his doctorate in social ecology (behavioral medicine concentration) from the University of California, Irvine, in 1993. His research examines the interface between biological, social and behavioral processes in human pregnancy, with an emphasis on outcomes related to fetal development, birth, and subsequent newborn, infant and child development and health. In particular, this work focuses on the interplay between maternal-placental-fetal neuroendocrine, immune, metabolic and genetic/epigenetic processes as putative mechanisms that mediate the effects of the maternal environment (and particularly prenatal stress and stress-related processes) on early human development. Wadhwa has published over 100 peer-reviewed scientific papers and lectured extensively at scientific meetings and universities across North America, Europe, and Australia. His program has been continuously supported by several research grants from the National Institutes of Health and other agencies. Wadhwa is the recipient of numerous national honors and awards, including recognition for his early- and mid-career contributions from the Academy of Behavioral Medicine, the Perinatal Research Society, the National Institutes of Health, and the World Health Organization.

Nan-Ping Weng
National Institute on Aging

Nan-ping Weng, M.D., Ph.D., received his medical degree from Fudan University Shanghai Medical College (formerly Shanghai First Medical College) in 1984 and doctorate in Immunology from Baylor College of Medicine in 1993. He obtained his postdoctoral training (1994 – 1997) at the National Cancer Institute (NCI). He joined the National Institute of Aging (NIA) as a tenure-track investigator in 1997 and was tenured in 2006. Weng's lab focuses on understanding age-associated decline of T cell functions with focus on three specific areas: 1) roles of telomere and telomerase in human immune function; 2) epigenetic regulation of transcription, function, and aging of CD8+ T cells; and 3) general and antigen-specific T-cell receptor (TCR) repertoires: diversity, distribution, and age-associated change.

Ami Zota
The George Washington University

Ami Zota, Sc.D., is an assistant professor in the Department of Environmental & Occupational Health at the George Washington University (GWU) Milken School of Public Health. Her research examines population exposures to environmental chemicals, their effects on women and children's health, and implications of these risks for health disparities. She received a K99/R00 career development award from National Institutes of Environmental Health Sciences to identify how environmental hazards may interact with social disadvantage and psychosocial stressors to exacerbate health disparities during pregnancy.

Zota is equally committed to developing innovative approaches for science translation so that her research can more effectively be used to inform decision-making at the individual and collective level. Her research has been featured in high-impact national and international media publications, including the Washington Post, Los Angeles Times, USA Today, Huffington Post, and the Atlantic Monthly. She has helped shape health and safety standards for flame retardants and other consumer product chemicals by participating in legislative briefings, providing technical assistance to the non-governmental organization (NGO) community, and writing commentaries for popular media.

Before joining GWU, Zota studied human exposure and health effects of endocrine-disrupting chemicals at the Silent Spring Institute and then later at the University of California, San Francisco's Program on Reproductive Health and the Environment. She received her master's and doctorate in environmental health at the Harvard School of Public Health.

She is an associate editor of Journal of Exposure Science and Environmental Epidemiology and on the Editorial Board of Environmental Health Perspectives and Environmental Epigenetics.
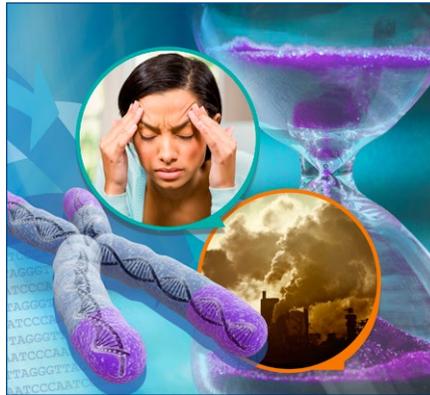
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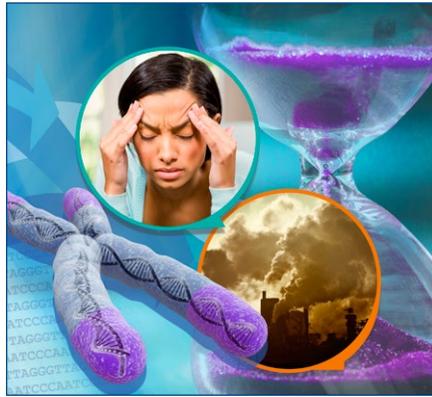
Participant List

Workshop Participant List

Ahmed, Shawn	University of North Carolina at Chapel Hill	shawn@med.unc.edu
Aiello, Allison	University of North Carolina at Chapel Hill	aaiello@unc.edu
Armanios, Mary	Johns Hopkins University	marmani1@jhmi.edu
Arnette, Robin	NIEHS	arnetter@niehs.nih.gov
Artandi, Steven	Stanford University	sartandi@stanford.edu
Aviv, Abraham	Rutgers University	aviab@njms.rutgers.edu
Bailey, Susan	Colorado State University	sbailey@colostate.edu
Belsky, Daniel	Duke University	dbelsky@duke.edu
Bertuch, Alison	Baylor College of Medicine	abertuch@bcm.edu
Birnbaum, Linda	NIEHS	birnbaumls@niehs.nih.gov
Caglayan, Melike	NIEHS	melike.caglayan@nih.gov
Carlin, Danielle	NIEHS	danielle.carlin@nih.gov
Collman, Gwen	NIEHS	collman@niehs.nih.gov
Copeland, Bill	NIEHS	copelan1@niehs.nih.gov
Cowell, Whitney	Columbia University	wc2449@cumc.columbia.edu
Degtyareva, Natalya	NIEHS	natalya.degtyareva@nih.gov
Demanelis, Kathryn	University of Chicago	kdemanelis@bsd.uchicago.edu
Drury, Stacy	Tulane University	sdrury@tulane.edu
Epel, Elissa	University of California, San Francisco	elissa.epel@ucsf.edu
Factor-Litvak, Pam	Columbia University	prf1@columbia.edu
Ferguson, Kelly	NIEHS	kelly.ferguson2@nih.gov
France, Suzanne	NIEHS contractor: MDB, Inc.	sfrance@michaeldbaker.com
Freeman, Kenda	NIEHS Contractor: MDB, Inc.	kfreeman@michaeldbaker.com
Gaston, Symielle	NIEHS	symielle.gaston@nih.gov
Gordenin, Dmitry	NIEHS	gordenin@niehs.nih.gov
Griffith, Jack	University of North Carolina at Chapel Hill	jdg@med.unc.edu
Guidry, Virginia	NIEHS	virginia.guidry@nih.gov
Guo, Max	National Institute on Aging	Max.Guo@nih.gov
Hagg, Sara	Karolinska Institutet	sara.hagg@ki.se
Heacock, Michelle	NIEHS	heacockm@niehs.nih.gov
Henry, Heather	NIEHS	henryh@niehs.nih.gov

Humble, Michael	NIEHS	humble@niehs.nih.gov
Jackson, Chandra	NIEHS	Chandra.Jackson@nih.gov
Kar, Anirban	University of North Carolina at Chapel Hill	anirbank@email.unc.edu
Kovi, Ramesh	NIEHS	ramesh.kovi@nih.gov
Kresovich, Jacob	NIEHS	jacob.kresovich@nih.gov
Lansdorp, Peter	British Columbia Cancer Agency	plansdor@bccrc.ca
Lee, Mi Kyeong	NIEHS	mikyeong.lee@nih.gov
Lin, Jue	University of California, San Francisco	jue.lin@ucsf.edu
Liu, Yie	National Institute on Aging	liuyie@mail.nih.gov
Mashal, Ahmed	NIEHS	ahmed.mashal@nih.gov
Mathura, Emilie	NIEHS	emilie.mathura@gmail.com
McAllister, Kim	NIEHS	mcallis2@niehs.nih.gov
Meier, Helen	University of Wisconsin-Milwaukee	meierh2@uwm.edu
Mitchell, Colter	University of Michigan	cmsm@umich.edu
Nadalutti, Cristina	University of North Carolina at Chapel Hill	llcrna@email.unc.edu
Needham, Belinda	University of Michigan	needhamb@umich.edu
Nielsen, Lisbeth	National Institute on Aging	nielsenli@nia.nih.gov
Opresko, Patricia	University of Pittsburgh	plo4@pitt.edu
Park, Yong-Moon	NIEHS	mark.park@nih.gov
Peters, June	National Cancer Institute	petersju@mail.nih.gov
Picard, Martin	Columbia University	mp3484@columbia.edu
Pierce, Brandon	University of Chicago	brandonpierce@uchicago.edu
Reinlib, Les	NIEHS	reinlib@niehs.nih.gov
Reynolds, Chandra	University of California, Riverside	chandra.reynolds@ucr.edu
Rodriguez, Yesenia	NIEHS	yesenia.rodriguez@nih.gov
Sandler, Dale	NIEHS	sandler@niehs.nih.gov
Santos, Janine	NIEHS	janine.santos@nih.gov
Savage, Sharon	National Cancer Institute	savagesh@mail.nih.gov
Schurman, Shepherd	NIEHS	schurmansh@mail.nih.gov
Shalev, Idan	Pennsylvania State University	ius14@psu.edu
Shaughnessy, Dan	NIEHS	Shaughn1@niehs.nih.gov
Thomas, Duncan	Duke University	dthomas@econ.duke.edu

Thomas, Laura	NIEHS	laura.thomas@nih.gov
Thomas, Sam	Rose Li and Associates, Inc.	samuel.thomas@roseliassociates.com
Tyson, Frederick	NIEHS	tyson2@niehs.nih.gov
Voelker, Kerri	NIEHS Contractor: MDB, Inc.	kvoelker@michaeldbaker.com
Wadhwa, Pathik	University of California, Irvine	pwadhwa@uci.edu
Weng, Nan-ping	National Institute on Aging	wengn@mail.nih.gov
Witt, Kristine	NIEHS/NTP	witt@niehs.nih.gov
Worth, Leroy	NIEHS	worth@niehs.nih.gov
Woychik, Rick	NIEHS	rick.woychik@nih.gov
Xu, Miaofei	NIEHS	miaofei.xu@nih.gov
Zota, Ami	George Washington University	azota@gwu.edu

**Telomeres as Sentinels for Environmental Exposures,
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111 T.W. Alexander Drive • Research Triangle Park, NC 27709