insights into how biological age differs across adulthood and contributes to overall health.

DISTINGUISHING SUBJECTIVE EXPERIENCE FROM OBJECTIVE FACTORS IN DECISION MAKING AND PERCEIVED EFFORT

RIchard Gonzalez,[1] Patricia Abbott,[1] James Ashton-Miller,[1] and Jacqui Smith[1], *1. University of Michigan, Ann Arbor, Michigan, United States*

We use self-reported and behavioral data from the HomeLab to comment on the theoretical and methodological implications of integrating objective and subjective measures of experience. To illustrate, we will focus on two domains that vary in the nature of objective and subjective measurements examined. One domain will be decision making where subjective measures include subjective probability and utility and the respective objective measures include probability and actual outcomes. The second domain will be activities of daily living where the subjective measure is perceived effort and the objective measures include various data from sensor such as EDA (arousal) and EMG (muscle contraction). The presentation will discuss the benefits of conducting such research in a realistic standardized context such as the HomeLab, which is a fully connected, fully functioning apartment set up as a standardized lab in order to study activities of daily living.

SESSION 3195 (SYMPOSIUM)

INTERVENING IN THE LONGEVITY NETWORK

Chair: Alexander Mendenhall, *University of Washington, Seattle, Washington, United States*
Co-Chair: George L. Sutphin, *University of Arizona, Tucson, Arizona, United States*

This session will focus on interventions to delay biological aging with the goal of in increasing lifespan and healthspan.

TARGETING TRYPTOPHAN-KYNURENINE METABOLISM TO EXTEND LIFESPAN AND TREAT AGE-ASSOCIATED DISEASE

George L. Sutphin,[1] and George L. Sutphin[1], *1. University of Arizona, Tucson, Arizona, United States*

The kynurenine pathway, the major route for tryptophan catabolism, becomes dysregulated with age and in many age-associated pathologies in humans. Interventions targeting kynurenine metabolism are being pursued for neurodegeneration, cardiovascular disease, and chronic kidney disease. By manipulating kynurenine pathway enzymes and metabolites, we have extended lifespan up to 40% in Caenorhabditis elegans. Our most promising single target is the metabolite 3-hydroxyanthranilic acid dioxygenase (3HAA). Elevating physiological 3HAA by directly supplementing 3HAA or inhibiting the enzyme 3HAA dioxygenase (HAAO) extends worm lifespan by ~30% while reducing oxidative stress by directly degrading hydrogen peroxide. In rodents, anti-inflammatory activity of 3HAA improves outcomes in models of cardiovascular disease, asthma, and autoimmune encephalomyelitis. We are now beginning to validate our C. elegans work in mice and investigating a mechanistic model in which 3HAA acts to extend healthy lifespan by slowing age-associated accumulation of oxidative damage and repressing chronic inflammation.

INCREASED LIFESPAN THROUGH ALTERED GCN4 / ATF-5 IN S. CEREVISIAE AND C. ELEGANS

Mark McCormick,[1] Christine Robbins,[1] Olivia Heath,[1] and Marissa Westenskow[1], *1. University of New Mexico Health Sciences Center, Albuquerque, New Mexico, United States*

In a whole-genome screen for deletions that increase lifespan in S. cerevisiae, we identified increased Gcn4 signaling as a mediator of increased lifespan. Gcn4 is a nutrient-responsive transcription factor whose entire pathway is functionally conserved from yeast through humans. Accumulation of uncharged tRNAs has been shown to upregulate Gcn4, and its mammalian ortholog, ATF4. Here we demonstrate that chemical inhibitors of tRNA synthetases significantly extend lifespan in both yeast and the nematode C. elegans, in a dose- and Gcn4-dependent manner.

LEVERAGING DRUG-DRUG INTERACTIONS FOR PHARMACOLOGICAL EXTENSION OF HEALTHY LIFESPAN

Jan Gruber[1], *1. Yale-NUS, Singapore, Singapore*

Traditional approaches aimed at delaying or preventing age-dependent diseases view each disease as a distinct entity, resulting from separate pathophysiological chains of events. However, it is becoming increasing clear that even in adult animals there remains significant plasticity in terms of ageing trajectories and lifespan, suggesting that targeting ageing processes directly may be a promising alternative strategy. However, to date effects of even the most efficacious pharmacological interventions are smaller than those of ageing mutations, even when targeting the same ageing pathways. Interestingly, it has been shown that simultaneously targeting multiple ageing pathways can result in lifespan benefits that are synergistic (more than additive). We have recently shown that dramatic lifespan and healthspan extension can also be archived by leveraging interactions between drugs targeting distinct subsets of the gene-regulatory network controlling ageing of C. elegans. These interventions were highly efficacious, even when animals were treated only as adults.

UNDERSTANDING AGING IN TERMS OF PHYSIOLOGICAL STATES

Alexander Mendenhall,[1] Nikolay Burnaevskiy,[1] Soo Yun,[1] and Bryan Sands[1], *1. University of Washington, Seattle, Washington, United States*

The "network" of homeostatic systems fails in distinct ways in individual isogenic animals during the aging process. We believe that understanding these distinct physiological states, the transitions between them, and how they relate to homeostatic system functions will allow us to better affect change in the aging process. Work in yeast showed that fixing an initial system failure, loss of vacuole acidification capacity, could increase cellular lifespan. Here we showed how the long-lived physiological state conferred by high expression of the hsp-16.2 promoter based lifespan/penetrance biomarker correlates with differences in the expression of other genes, and the structure and function of lysosomes. We found that vacuole acidification failure is not a major initial proximal cause of aging in C. elegans – at least not in their intestine cells.