ASSESSING LIFESPAN AND AGING PHENOTYPES RESULTING FROM FOXO3 INDUCTION USING MOUSE MODELS

Jesse Owens,[1] Brian Hew,[1] Christopher Tran,[1] Kristal Xie,[1] and Bradley Willcox,[2] *1. Kuakini Medical Center, Honolulu, Hawaii, United States, 2. Kuakini Medical Center, Kuakini Medical Center/Honolulu, Hawaii, United States*

Environmental signals, including caloric restriction and oxidative stress, trigger FoxO3 to upregulate genes involved in stress resistance, metabolism, cell cycle arrest, and apoptosis that may help mitigate age-related diseases. Activation of FoxO3 has been shown to have a profound life-extending effect on model organisms. Protective SNPs in FOXO3 are strongly associated with exceptional longevity in humans. The objective of this study is test the relation between FoxO3 and longevity using mouse models. We generated a mouse line containing an extra copy of FoxO3 that can be induced at any age. In our model, FoxO3 remains driven by its natural promoter to avoid mis-expression in inappropriate cells and to maintain the gene's ability to respond to signals such as stress. We are utilizing this new model to assess survival endpoints and test a panel of aging phenotypes reflecting healthspan throughout the mouse lifespan and compare these to similar human phenotypes.

ANALYSIS OF CELL AND MOLECULAR PHENOTYPES OF A HIGHLY REPLICATED LONGEVITY-ASSOCIATED FOXO3 VARIANT IN OLDER ADULTS

Philip Davy,[1] Randi Chen,[1] Richard Allsopp,[1] and Bradley Willcox,[2] *1. Kuakini Medical Center, Honolulu, Hawaii, United States, 2. Kuakini Medical Center, Kuakini Medical Center/Honolulu, Hawaii, United States*

Aging demographics in the US, and other industrialized nations, are resulting in rapidly increasing health care costs from age-related diseases. New therapeutic interventions to extend healthspan in older adults requires understanding connections between basic aging biology and human longevity factors. Using clinical samples from the Kuakini Honolulu Heart Program (HHP) and their Offspring, we are examining potential links between molecular and cellular mechanisms of aging and the longevity associated FOXO3 genotype (carriage of SNP rs2802292 "G" allele). Telomere dynamics in leucocytes (LTL) have shown strong correlation with multiple lifestyle and health factors. We previously demonstrated a significant protective relation between FOXO3 longevity genotype and LTL in a cross-sectional study. Now we are assessing a longitudinal relation, at three time points over 20+ years, in older men. We are also exploring stem cell frequency and differentiation capacity in neurological and peripheral blood samples to assess FOXO3 genotype and human cell dynamics.

FOXO3, TELOMERE DYNAMICS, AND HEALTHY BRAIN AGING: A COBRE STUDY

Kalpana Kallianpur,[1] Bradley Willcox,[2] Kamal Masaki,[1] and Richard Allsopp,[1] *1. Kuakini Medical Center, Honolulu, Hawaii, United States, 2. Kuakini Medical Center, Kuakini Medical Center/Honolulu, Hawaii, United States*

Human longevity is linked to genetic, cellular, and other complex biological and psychosocial traits. Aging is typically accompanied by gradual brain atrophy and cognitive decline, but the mechanisms are unclear. Cellular aging, characterized by telomere shortening and altered telomerase activity, is related to mortality and brain aging. Decelerated brain aging is associated with greater peripheral blood leukocyte telomere length (LTL) and, we hypothesize, may be linked to FOXO3 genotype. We will use MRI to assess brain structure and function cross-sectionally in 100 Kuakini Honolulu Heart Program Offspring. Atrophy and disrupted functional connectivity, markers of brain aging, will be examined in relation to FOXO3 and LTL. Associations between brain structural and functional differences, FOXO3 genotype and LTL will be investigated over a wide range of ages, controlling for other biological and psychosocial factors. Results may provide insight into mechanisms influencing the rate of brain aging, and may eventually extend human healthspan.

THE IMPACT OF APOE AND FOXO3 GENOTYPE ON THE RISK OF INTRACEREBRAL HEMORRHAGE AMONG AMERICAN MEN OF JAPANESE ANCESTRY

Kazuma Nakagawa,[1] Randi Chen,[2] Steven Greenberg,[3] G. Ross,[4] Bradley Willcox,[5] and Kamal Masaki,[2] *1. University of Hawaii and Kuakini Medical Center, Honolulu, Hawaii, United States, 2. Kuakini Medical Center, Honolulu, Hawaii, United States, 3. Massachusetts General Hospital, Boston, Massachusetts, United States, 4. VA Pacific Islands Health Care System, Honolulu, Hawaii, United States, 5. Kuakini Medical Center, Kuakini Medical Center/Honolulu, Hawaii, United States*

This study assessed the impact of APOE e2, e4 minor alleles and the FOXO3 longevity-associated genotype (carrier of SNP rs2802292 "G" allele) on 34-year incidence of intracerebral hemorrhage (ICH). Cox regression models were performed to assess the impact of the APOE e2, e4 and FOXO3 G alleles on the incidence of ICH. A total of 6483 participants were eligible for the analyses. 213 participants developed ICH. Cox-regression model showed neither APOE minor allele vs. common genotype (APOE e3/e3: RR 0.89, 95% CI: 0.64-1.22, p=0.46) nor FOXO3 G carrier status (RR 0.97, 95% CI: 0.72-1.29, p=0.82) was associated with incident ICH. Conversely, both hypertension (RR: 1.46, 95% CI: 1.07-2.00, p=0.02) and low cholesterol level (RR: 0.99, 95% CI: 0.99-1.00, p=0.001) were associated with incident ICH. Carriage of APOE e2 or E4 alleles and the FOXO3 G allele do not appear to impact risk of ICH over 34 years in this cohort.

Session 3420 (Symposium)

LEVERAGING ACL FUNDING TO IMPLEMENT AN EVIDENCE-BASED FALLS PREVENTION PROGRAM IN THREE GWEPS

Chair: Ellen Flaherty
Discussant: Nina Tumosa

Primary care practices have a robust capacity to screen older adults for falls risk and refer them to evidence-based falls prevention programs delivered by Community Based Organizations (CBOs). However, due to a difference in the culture and nature of the work done in these two systems of care, there is often a lack of coordination and communication. Dartmouth has worked to bridge this gap for the past five years through our Health Resources and Services