

CELLULAR SENESCENCE AS A THERAPEUTIC TARGET FOR GEROSCIENCE-GUIDED CLINICAL TRIALS

Jamie N. Justice,¹ Anoop M. Nambiar,² Tamar Tchkonja,³ Nathan K. LeBrasseur,³ Nicolas Musi,⁴ Stephen B. Kritchevsky,⁵ and James L. Kirkland³, 1. *Wake Forest School of Medicine, Winston-Salem, North Carolina, United States*, 2. *University of Texas Health Sciences Center at San Antonio and South Texas Veterans Health Care System, San Antonio, Texas, United States*, 3. *Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, Minnesota, United States*, 4. *Barshop Institute for Longevity and Aging Studies, Center for Healthy Aging, University of Texas Health Sciences Center at San Antonio and South Texas Veterans Health Care System, San Antonio, Texas, United States*, 5. *Wake Forest School of Medicine, Winston-Salem, North Carolina, United States*

The geroscience hypothesis holds that targeting fundamental mechanisms of aging has the potential to prevent or reduce severity of multiple age-related diseases. Cellular senescence is a key mechanism that may be driving disease in human aging, including Idiopathic pulmonary fibrosis (IPF), a progressive, ultimately fatal, senescence-associated disease. Importantly, cellular senescence may be targeted therapeutically. Senolytic agents are drugs that selectively induce senescent cell apoptosis by transiently disabling anti-apoptotic pathways. Selective ablation of senescent cells using the senolytic drug combination dasatinib plus quercetin (DQ) alleviates IPF-related dysfunction in bleomycin-administered IPF mouse model. We conducted the first-in-human trial of senolytics in IPF patients, and our data indicate that short-term, intermittent administration of DQ may alleviate physical dysfunction that accompanies IPF in human aging, including clinically-meaningfully improvements in mobility ($p < 0.05$). This geroscience-guided clinical feasibility study supports evaluation of senolytics in larger randomized, controlled trials of cellular senescence-associated age-related diseases.

TORC1 INHIBITION AS AN IMMUNOTHERAPY TO DECREASE INFECTIONS IN THE ELDERLY

Joan Mannick¹, 1. *resTORbio, Boston, Massachusetts, United States*

Inhibition of TORC1 has extended lifespan in multiple preclinical species. Thus drugs inhibiting TORC1 may have therapeutic benefit for aging-related conditions in humans. An aging-related condition that improves with TORC1 inhibition in old mice is immunosenescence (the aging-related decline in immune function). Immunosenescence leads to increased rates of infections including respiratory tract infections (RTIs) in the elderly. In two Phase 2 clinical trials in over 900 elderly subjects, the TORC1 inhibitor RTB101 was observed to improve immune function and decrease the incidence of RTIs. Decreasing the incidence of RTIs is important because RTIs are the fourth leading cause of hospitalization in people age 65 and above. Based on these findings, two Phase 3 studies are underway to determine whether RTB101 given for 16 weeks during winter cold and flu season decreases relative to placebo the percentage of elderly subjects with illnesses associated with RTIs.

AGING INTERVENTIONS GET HUMAN: CAN WE EXTEND HEALTHSPAN?

Brian Kennedy¹, 1. *National University of Singapore, Not applicable, Singapore*

Understanding biologic aging will afford opportunities for novel interventions to enhance human healthspan. If ageing can be slowed, the effect would be simultaneous protection from many of the chronic diseases. One strategy is to use animal model organisms to find common pathways that modulate ageing and then to seek methods for their human manipulation. The TOR pathway is one point of convergence and a clinically approved drug targeting the TOR kinase, rapamycin, extends murine lifespan and healthspan. Many more small molecules are being added to the list of anti-ageing compounds. Here, I use examples of interventions to conceptualize how agents extending healthspan might improve human health. We are entering a stage in aging research where it is imperative to test ageing interventions in humans and several strategies are contemplated. The potential to directly impact human healthspan is emerging from ageing research and this approach, if successful, will have global impact.

AGING TREATMENT BY COUNTERACTING INTRINSIC DNA DAMAGE AND IMMUNOSENESCENCE

Andrei Gudkov

Progressive systemic poisoning by gradually accumulated damaged cells has been proposed as a major contributor to mammalian aging. Our preclinical studies support the hypothesis that this process results from a failure of innate immunity-mediated eradication of cells with DNA damaged by intrinsic mechanisms caused by the epigenetic desilencing of endogenous retroelements. This model suggests two translational approaches to improve the counteract accumulation of damaged cells: (i) by pharmacological suppression of LINE1 reverse transcriptase activities – the main driver of expansion of “retrobiome” and the trigger of damaged cell-associated inflammation and (ii) by counteracting immunosenescence by innate immunity stimulation. Preclinical proofs of concept have been obtained for both using nucleoside reverse transcriptase inhibitors and immunostimulators acting via TLR5 activation. Preparations for clinical testing of these agents in the context of age-related pathologies is in underway.

SESSION 4095 (SYMPOSIUM)

ACTIVITY SELECTION AND ENGAGEMENT IN OLD AGE: MOTIVATIONAL AND GOAL-BASED INFLUENCES

Chair: Thomas M. Hess, *North Carolina State University, Raleigh, North Carolina, United States*

Discussant: Christopher Hertzog, *Georgia Institute of Technology, Atlanta, Georgia, United States*

Research from a variety of perspectives has emphasized the central role played by activity in supporting a variety of positive outcomes in later life. For example, participation in activities that place demands on personal resources has been shown to be beneficial in promoting brain, cognitive, and

physical health. From another perspective, older adults may also engage in certain activities to promote specific outcomes (e.g., emotional) in service of psychological well-being. Such findings highlight the adaptive significance of activity selection and engagement processes. Using a variety of approaches, the presentations in this symposium focus specifically on goal-based and motivational factors that may facilitate or impede such processes. Moored and colleagues examine adaptive characteristics—including motivational ones—of individuals whose activity patterns are protective against dementia. Using longitudinal data from the Health and Retirement Study, Lothary and colleagues explore the degree to which intrinsic motivation to engage cognitive resources mediates the effect of personal resources (e.g., physical and emotional health) on participation in challenging everyday activities. Growney and colleagues present research demonstrating that subjective perceptions of difficulty affect decisions to engage in challenging activities, but that such perceptions may reflect biases associated with negative aging attitudes as opposed to actual effort expenditure. Finally, Lind and Isaacowitz examine selection associated with affective aspects of the activities, finding that both middle-aged and older adults exhibited similar biases toward positive activities in congruence with emotion-regulation goals, though age differences were observed in non-affective aspects of the activities. The discussion by Hertzog will highlight common themes.

AGING STEREOTYPES MODERATE THE RELATIONSHIP BETWEEN COSTS AND DISCOUNTING

Claire Growney,¹ Erica L. O'Brien,¹ Jesse DeLaRosa,¹ and Thomas M. Hess,¹ *1. North Carolina State University, Raleigh, North Carolina, United States*

Aging is associated with normative declines in cognitive resources that increase the costs associated with mobilizing resources in cognitively demanding activities. Selective Engagement Theory (Hess, 2014) hypothesizes that changes in costs influence the motivation to engage in such activities in everyday life. We used an economic discounting task to examine the relationship between both objective estimates (systolic blood pressure responses) and subjective estimates (NASA Task Load Index) of cognitive costs in 78 older adults' (ages 64-85) decisions to engage in more or less demanding activities. Perceptions of costs were meaningfully tied to actual costs (SBP), but further influenced by personal or primed attitudes about aging. Interestingly, decisions to engage in demanding activities—as reflected in discounting decisions—were less influenced by effort expenditure in the activity than by perceptions of difficulty. These results underscore the role that negative stereotypes play in undermining motivation to engage in potentially beneficial activities.

EXAMINING WHETHER LIFESTYLE ACTIVITY PATTERNS PREDICT DEMENTIA INCIDENCE AMONG COMMUNITY-DWELLING OLDER ADULTS

Kyle Moored,¹ Kyle Moored,² Jeanine Parisi,² and Michelle Carlson,² *1. Johns Hopkins, Baltimore, United States, 2. Johns Hopkins University, Baltimore, Maryland, United States*

Engagement in lifestyle activities can be neuroprotective, but it remains unclear what aspects of engagement are most beneficial. Examining activity patterns may better characterize both quantitative (e.g., number) and qualitative (e.g., characteristic/motivational) differences in engagement. We used a novel, latent class analysis (LCA) to characterize subgroups with distinct activity patterns and examined whether they have differential risk of incident dementia. We compared these findings to models including standard activity frequency and variety metrics. Using the Ginkgo Evaluation of Memory Study (N=3,069), we fit Cox regressions of each activity metric on time to dementia, adjusting for intervention group and demographics. For the LCA, we derived group/class indicators for Cox regression. Variety predicted incident dementia and will be compared to LCA activity metrics in predicting risk. Activity metrics that are most protective against dementia inform intervention design. Unlike standard activity metrics, LCA may further identify subgroups with common motivations to sustain activity.

MOTIVATION AS A MECHANISM: THE LONGITUDINAL RELATIONSHIP BETWEEN PERSONAL RESOURCES AND ACTIVITY ENGAGEMENT

Allura F. Lothary,¹ Tara L. Queen,² and Thomas M. Hess,¹ *1. North Carolina State University, Raleigh, North Carolina, United States, 2. University of North Carolina at Chapel Hill, Carrboro, North Carolina, United States*

Past research has demonstrated an association between health and cognitive resources, intrinsic motivation, and activity participation in older adulthood, both cross-sectionally and from a daily perspective (e.g., Queen & Hess, 2018; Hess et al., 2018). This highlights the potential importance of motivation as a mediator of the impact of changing personal resources on engagement in cognitively beneficial activities. This study expanded on prior research by examining these relationships longitudinally in a large representative sample of adults over 50. Specifically, we used data from the Health and Retirement Survey (N = 5600) to create two 4-year longitudinal assessments, with multi-level structural equation modeling used to test the mediating role of motivation on everyday activity engagement. Consistent with expectations from Selective Engagement Theory (Hess, 2014), motivation served as a partial mediator of the impact of changing resources on engagement, with the effect being selective based on the cognitive demands of the activity.

THE ROLE OF AGE AND EMOTION REGULATION IN CHOICE OF EMOTIONAL ACTIVITY IN EVERYDAY LIFE

Majse Lind,¹ and Derek Isaacowitz,¹ *1. Northeastern University, Boston, Massachusetts, United States*

Situation selection is a form of activity selection focused on the affective tone of potential choices. We investigated this type of emotional activity selection in everyday life during a longitudinal multi-burst study of middle-aged and older adults. In each burst, participants were asked to complete six phone-based assessments per day across five consecutive days, including a situation selection question about what type of emotional situation they would want to engage