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

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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

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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?

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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