videoconferencing and socially-distanced meetings, volunteer health professionals and community members (e.g., Information Technology Technician, Psychologist, and Nurse) delivered education to older adults. Participants also met for computer training to build confidence by sharing technology accomplishments with others (e.g., online bill paying). UARC has 75 active members and conducted over 12 videoconferences and in-person programming. The UARC project serves as a model for community/academic partnerships to support mental wellness and technology use in urban older adults.

PARTICIPATORY DESIGN: AN ESSENTIAL PROCESS FOR SOCIAL ASSISTIVE ROBOTIC ACTIVITIES IN LONG-TERM CARE SETTINGS
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We conducted participatory design research for long term care (LTC) social assistive robotic activities comprised of social, cognitive and physical components and enhanced human-robot (HRI) and human-human interactions (HHI). Repeated sessions were conducted with 10 geriatric experts (physicians, activity directors, nurses, occupational therapist) and 12 LTC residents (ages 70–92). Two robots, animal and humanoid, were used in combination with virtual reality. Four collaborative activities for paired older adults were designed and evaluated: playing drums to music, completing paintings, a fishing game, and training a dog with simple commands. Within each activity, three levels of difficulty were designed. Stakeholder feedback was obtained through observations and interviews. Numerous modifications were made following each session that addressed hardware, software and activity issues. Modifications were necessary both for the HRI and HHI aspects of the activity. Our experience demonstrates the necessity for participatory design in the deployment of technology for LTC settings.

CURRENT APPLICATIONS OF PATIENT COMMUNICATION TECHNOLOGIES IN GERIATRIC CRITICAL CARE
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The availability and utility of patient-centered communication technologies in acute-critical care settings have evolved slowly over the past 30 years with wide variability, little standardization, and few randomized controlled clinical trials (RCT). The COVID-19 pandemic forced rapid expansion and use of communication technologies, particularly between patients and remote family caregivers. To capture changes responsive to the pandemic, this paper reviews current literature (< 5 years) on communication technologies in acute-critical care settings focusing on the user experience among older adult patients. We supplement these findings with case-based evidence from a pilot RCT of an electronic tablet communication application provisioned to mechanically ventilated ICU patients, and efforts toward hospital-wide implementation. Recent literature on patient communication technology consists primarily of qualitative, descriptive accounts of video communication (i.e., ICU visits) or provision of augmentative and alternative communication. Recommendations for required skills, standardization, and research regarding patient communication technology are provided.

SESSION 5091 (BIOLOGICAL SCIENCES INVITED SYMPOSIUM)

PROTEOSTASIS: NOVEL INSIGHTS AND TECHNOLOGIES
Chair: Andrew Pickering

GENETIC AND PHARMACOLOGIC PROTEASOME AUGMENTATION AMELIORATES ALZHEIMER'S-LIKE PATHOLOGY IN MICE AND FLIES
Andrew Pickering, University of Alabama at Birmingham, Birmingham, Alabama, United States

The proteasome has key roles in neuronal proteostasis, including removal of misfolded and oxidized proteins, presynaptic protein turnover, as well as synaptic efficacy and plasticity. Proteasome dysfunction is a prominent feature of Alzheimer’s disease (AD) (1–3). Artificial impairment of proteasome function can mimic many neurodegenerative phenotypes (4, 5). We report impaired proteasome function to represent an early-stage marker of AD preceding many other markers of the disease. Significantly, we show that prevention of proteasome dysfunction by genetic manipulation in fly and cell culture models of AD delays mortality, cell death, and cognitive deficits. We developed a transgenic mouse with neuronal-specific proteasome overexpression which, when crossed with a mouse model of AD showed reduced mortality and cognitive deficits. To establish translational relevance, we developed a set of novel TAT-based proteasome-activating peptidomimetics. These agonists stably penetrate the blood-brain-barrier and enhance 20S as well as 26S proteasome activity. We show that treatment with these agonists protects against cell death in a cell culture model of AD as well as both cognitive decline and mortality in fly and mouse models of AD. The protective effects observed from proteasome overexpression in our models appear to be driven at least in part by increased turnover of the amyloid precursor protein (APP) by the proteasome. We conclude that the proteasome plays an important role in AD progression. Furthermore, augmentation of proteasome function is protective against AD-like pathogenesis in diverse models of the disease, representing a new therapeutic target for treatment of AD.

PROTEOSTASIS: NOVEL INSIGHTS AND TECHNOLOGIES
Constanza Cortes, University of Alabama at Birmingham, Birmingham, Alabama, United States

Skeletal muscle has recently arisen as a novel regulator of Central Nervous System (CNS) function and
aging, secreting bioactive molecules known as myokines with proteostasis and metabolism-modifying functions in targeted tissues, including the CNS. Myokine secretion is heavily modified by exercise, suggesting that myokine signaling in the periphery may underlie the well-documented geroprotective benefits of exercise on the brain. The following studies address muscle proteostasis, a pathway highly activated during exercise, as a potential new regulator of the neurocognitive benefits of exercise. We have recently generated a novel transgenic mouse with enhanced muscle proteostasis via moderate overexpression of Transcription Factor E-B (TFEB), a powerful master regulator of cellular clearance and proteostasis. We have discovered that the resulting enhanced skeletal muscle proteostasis function can significantly ameliorate proteotoxicity and reduce neuroinflammation in the aging CNS. We derived cTFEB;HSA-Cre transgenic mice in the P301S MAPT background and we detected a significant reduction in hyperphosphorylated tau at T8 phospho-tau antibody in whole hippocampal lysates and in the dentate gyrus of cTFEB;HSA-Cre;P301S mice compared to their single transgenic P301S littermate controls. Nanostring nCounter®AD panel analysis revealed reduced microglia activation modules in P301S MAPT/cTFEB;HSA-Cre hippocampi, suggesting reduced neuroinflammation. We also determined that these CNS benefit sin P301S MAPT/cTFEB;HSA-Cre mice were accompanied by activation of exercise-associated neurotrophic signaling and reduced markers of advancing tau-associated pathologies in the hippocampus. These provocative results suggest that enhanced skeletal muscle proteostasis modifies the accumulation of pathogenic tau isoforms and reduces neuroinflammation in the CNS of P301S MAPT mice via activation of exercise-associated signaling in the CNS.

INTERPLAY BETWEEN LOSS OF PROTEOSTASIS AND CELLULAR SENESCENCE: A SPOTLIGHT ON MISFOLDED PROTEIN QUALITY CONTROL
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Loss of protein homeostasis (‘proteostasis’) and onset of cellular senescence are two conserved hallmarks of ageing. Healthy proteostasis relies on tightly-regulated intracellular quality control circuits that co-ordinate clearance of potentially toxic misfolded proteins arising from various internal or external stresses throughout an organism’s lifespan. Proteostasis imbalances are mechanistically linked to a broad range of ageing-associated diseases, and are also characteristic of cellular senescence—a permanent cell cycle arrest that prevents uncontrolled proliferation during development, injury repair, and tumorigenesis, but drives ageing-associated frailty, degeneration, and therapy resistance. Across a range of replicative and stress-induced senescence models in primary human cells, we have discovered differences in how misfolded proteins are triaged when compared with proliferating, quiescent, or immortalised cells—especially at the level of ubiquitin-mediated protein clearance systems. Given recent findings that proteostasis modulators act as senolytics with geroprotective properties, our work highlights the need for an improved fundamental understanding of how different ageing hallmarks are inter-connected in order to drive advances in human healthspan.

PARALLEL MEASUREMENTS OF PROTEIN AND CELL TURNOVER REVEAL HOW TISSUE CONTEXT AND AGING SHAPE PROTEIN LIFETIMES
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The lifespans of proteins can range from moments to years within mammalian tissues. Protein lifespan is relevant to organisational aging, as long-lived proteins can accrue damage over time. It is unclear how protein lifetime is shaped by tissue context, where both cell division and proteolytic degradation contribute to protein turnover. We have developed turnover and replication analysis by 15N isotope labeling (TRAIL) for parallel quantification of protein and cell lifetimes. We have deployed TRAIL over 32 days in 4 mouse tissues to date to quantify cell proliferation with high precision and no toxicity and determine that protein lifespan varies independently of cell lifespan. Variation in protein lifetime is non-random: multiprotein complexes such as the ribosome have consistent lifetimes across tissues, while mitochondria, peroxisomes, and lipid droplets have variable lifetimes across tissues. To model the effects of aging on tissue homeostasis, we apply TRAIL to a mouse model of Hutchinson-Gilford progeria syndrome and uncover fat-specific alterations in cell lifetime and proteome composition, as well as a broad decrease in protein turnover flux. These data indicate that environmental factors influence protein turnover in vivo and provide a framework to understand proteome aging in tissue context.

PHOSPHORYLATION OF ULK1 AT S555 IS REQUIRED FOR METABOLIC ADAPTATIONS TO CALORIC RESTRICTION
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Unc-51 Like Autophagy Activating Kinase 1 (ULK1) is responsible for initiating selective degradation of damaged/dysfunctional mitochondria (mitophagy) once phosphorylated at S555 in response to energetic stress. Mitophagy is integral for mitochondrial health and Ulk1 has been implicated to be important for metabolic adaptation to exercise. Caloric restriction (CR), which extends lifespan and healthspan, has profound metabolic benefits, including improved mitochondrial health. However, the contribution of Ulk1 in adaptation to CR is unknown. To decipher a functional role of Ulk1(S555) in adaptations to CR we used CRISPR-Cas9 generated, loss-of-function Ulk1(S555A) mice, in which Ulk1 cannot be phosphorylated at S555. 6-month-old, male and female homozygous Ulk1(S555A) mice and C57BL6J (wild type, WT) mice were placed on a 40% CR diet for 8 weeks. Body mass in both male and female Ulk1(S555A)