FUNCTIONAL MODULATORS OF RESILIENCE TO AGE-ASSOCIATED DOPAMINERGIC NEURODEGENERATION IN C. ELEGANS
Guy Caldwell, The University of Alabama, Tuscaloosa, Alabama, United States

The societal costs of neurodegenerative diseases demand a sense of urgency and innovative strategies toward therapeutic intervention. We have exploited the experimental attributes of roundworm, C. elegans, as a model to expedite discovery of genetic and chemical modifiers of the age-dependent progressive neurodegeneration of dopaminergic neurons commonly associated with Parkinson’s disease (PD). Our model of transgenic nematodes overexpressing the misfolding-prone familial PD gene product, alpha-synuclein, has proven prescient in illuminating key aspects of PD pathology, including vesicular trafficking, autophagy, stress response, lipid dynamics, as well as the first evidence of endolysosomal function in effecting dopaminergic neurodegeneration. Subsequent chemical-genetic analyses reveal a mechanism whereby dopamine transport intersects with epigenetic control of gene expression through proteins functioning in endocytic regulation to modulate neuroprotection. We theorize this reflects a “tunable” nexus of gene-by-environmental regulation where dopamine levels, which impact alpha-synuclein misfolding, are coordinately controlled with epigenetic response to mediate resilience to age-dependent neurodegeneration.

SESSION 6520 (SYMPOSIUM)

MICROBIOME: LIVING WELL AND THRIVING WITH YOUR BACTERIA
Chair: Meng Wang
Co-Chair: William Ludington

This symposium aims to invite speakers who are the leading experts in the field of microbiome and longevity, and select short talks from abstracts submitted by young investigators, postdoctoral fellows and graduate students. We will discuss new progress in this exciting research area and raise new questions for future studies. Confirmed speakers include Evgeny Nudler from NYU, William Ludington from Carnegie, Paul O’Toole from University College Cork, Ireland, and Meng Wang from Baylor College of Medicine.

MICROBIOME-MITOCHONDRIA COMMUNICATION IN THE REGULATION OF HOST LONGEVITY
Meng Wang, Baylor College of Medicine/HHMI, Houston, Texas, United States

Mitochondria are ancient relatives of bacteria in eukaryotic cells and dynamically interconnected through organelle fusion and fission. Given the close relationship between bacteria and eukaryotic mitochondria during evolution, my group is interested in understanding the critical role of their communication in regulating host’s longevity. We have conducted genome-scale screens to decipher how bacterial genetic composition impacts host longevity, leading to the discovery of specific bacteria-secreted metabolites that fine-tune the mitochondrial fusion-fission balance and consequently promotes longevity across different host species. We have further developed optogenetic approaches to manipulate bacterial gene expression and metabolite production inside the gut of live organisms, in order to investigate the microbiome-mitochondria communication in time and space. Our studies demonstrate a novel mode of signaling communication between bacteria and mitochondria, revealing its vital impacts on host healthy aging, and provide new methods to decipher the spatiotemporal relationship between the microbiome and the host.

INTER-SPECIES INTERACTIONS IN THE FLY GUT MICROBIOME SHAPE AGING
William Ludington, Carnegie Institution, Baltimore, Maryland, United States

Gut bacteria affect key aspects of host fitness, including fecundity and lifespan. However, it is unclear to what extent individual species versus complex interactions drive host fitness. We dissected the natural microbiome of Drosophila melanogaster and revealed that interactions between bacteria shape host fitness through life history tradeoffs. Empirically, we made germ-free flies and colonized them with each possible combination of the five core species of bacteria. We measured the microbiome and fly fitness traits including reproduction and lifespan. Notably, flies that reproduced more died sooner. Removing bacteria after reproduction extended lifespan in most cases, suggesting an indirect tradeoff. However, in certain cases, antibiotics did not extend lifespan, indicating a metabolic memory of the microbiome. Overall, complex interactions within the microbiome had significant effects on host fitness. We suggest that model systems with reduced complexity will be instrumental in elucidating mechanisms of microbiome-host interactions.

GENOMICS AND ECOLOGY OF GASTROINTESTINAL BACTERIA IN HUMAN HEALTHSPAN
Paul O’Toole

BACTERIAL TOXIC OXIDANTS IN HEALTHY AGING AND DISEASE
Evgeny Nudler

SESSION 6525 (SYMPOSIUM)

PHYSIOLOGY AND AGING: NEW UNDERSTANDING OF ORGANS THAT AFFECT THE PHYSIOLOGY OF AGING
Chair: Daniela Drummond-Barbosa

As organisms age, many changes occur to their physiology, which in turn impact the function of multiple tissues. It is therefore critical to investigate the fundamental mechanisms of how endocrine organs shape our physiology, and how changes in our physiology affect stem cell lineages, which generate new cells for maintenance and repair of tissues/organs throughout life. This symposium will highlight the research in the laboratories of Dr. Gerard Karsenty (Columbia University) on the multiple endocrine functions of bone, of Dr. Nicholas Buchon (Cornell University) on the role of host-microbe interactions in intestinal homeostasis, of Dr. Jane Hubbard (NYU/Skirball Institute) on the physiological control of the germline, and of Dr. Daniela Drummond-Barbosa (Johns Hopkins University) on how diet and adipocyte factors regulate oogenesis. As research by
these and other groups illustrate, the complex physiological regulation of tissue/organ maintenance and function is not only a fascinating biological problem, but it also has implications for many diseases and other conditions that are tightly linked to our endocrine state, including aging.

STEM CELLS, DIET, AND PHYSIOLOGY
Daniela Drummond-Barbosa, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States

Nutrient availability, stresses, and aging affect tissue stem cells in multicellular organisms; yet, the underlying physiological mechanisms in vivo remains largely unexplored. Dr. Drummond-Barbosa pioneered using Drosophila to study the physiology of tissue stem cell regulation. Her laboratory played a major role in delineating how diet, brain insulin-like peptides, and the TOR nutrient sensor control the germline stem cell (GSC) lineage. They also discovered that adipocyte-specific disruption of amino acid transport, other nutrient signaling, and metabolic pathways causes distinct germline phenotypes. They also showed that nuclear receptors act in multiple tissues to affect the GSC lineage through direct and indirect mechanisms. More recently, her group has been exploring how other physiological stresses affect the GSC lineage. Her group’s studies point to extensive communication between the brain, adipocytes, hepatocyte-like cells, and the germline, and underscore the complexity of the physiological network that modulates stem cell lineage behavior.

THE IMPACT OF BONE ON THE BIOLOGY OF AGING
Gerard Karsenty, Columbia University, New York, New York, United States

We hypothesized that bone may secrete hormones that regulate energy metabolism and reproduction. Testing this hypothesis revealed that the osteoblast-secreted specific protein osteocalcin is a hormone regulating glucose homeostasis and male fertility by signaling through a GPCR, Gprc6a, expressed in pancreatic β cells and Leydig cells of the testes. The systematic exploration of osteocalcin biology revealed that it regulates an unexpectedly large spectrum of physiological functions in the brain and peripheral organs and that it has most features of an antigeromic molecule. As will be presented at the meeting, this body of work suggests that harnessing osteocalcin for therapeutic purposes may be beneficial in the treatment of age-related diseases such as depression, age-related memory loss and the decline in muscle function seen in sarcopenia.

AGING GERMLINE STEM CELLS IN C. ELEGANS
E. Jane Hubbard, Skirball/NYU, New York, New York, United States

Failure to maintain stem cells with age is associated with conditions such as tissue degeneration and increased susceptibility to tissue damage. We use the C. elegans germline stem cell system as a model to study stem cell aging. This system combines a well-established model for aging with an accessible stem cell system, providing a unique opportunity to understand how aging influences stem cell dynamics. The germline stem/progenitor pool in C. elegans becomes depleted over time. At the cellular level, aging influences both the size of the stem cell pool and the proliferation rate of stem cells. The flux of differentiated cells also affects how aging impacts the pool. This depletion is partially alleviated in mutants with reduced insulin/IGF-like signaling via inhibition of the transcription factor DAF-16/FOXO. In this role, DAF-16 does not act in the germ line, and its anatomical requirements are different from its previously described roles in larval germline proliferation, dauer control, and lifespan regulation. We found that DAF-16/FOXO is required in certain somatic cells in the proximal part of the reproductive system to regulate the stem cell pool. We also find that the degree to which various age-defying perturbations affect lifespan does not correlate with their effect on germline stem cell maintenance. We are investigating additional aspects of aging germline stem cells using this system.

HOSTMICROBE GENETIC NETWORK INTERACTIONS GOVERN THE RESPONSE TO MICROBES
Nicolas Buchon, Cornell University, Ithaca, New York, United States

MOLECULAR AND CELLULAR NETWORKS THAT DRIVE SLEEP
Amita Sehgal, University of Pennsylvania, Philadelphia, Pennsylvania, United States

CIRCADIAN REGULATION OF MITOCHONDRIAL UNCOUPLING AND LIFESPAN
Matthew Ulgherait, CUMC, New York, New York, United States

Because old age is associated with defects in circadian rhythm, loss of circadian regulation is thought to be pathogenic and contribute to mortality. We show instead that loss of specific circadian clock components Period (Per) and Timeless (Tim) in male Drosophila significantly extends lifespan. This lifespan extension is not mediated by canonical diet-restriction longevity pathways, but is due to altered cellular respiration via increased mitochondrial uncoupling. Lifespan extension of per mutants depends on mitochondrial uncoupling in the intestine. Moreover, up-regulated uncoupling protein UCP4C in intestinal stem cells and enteroblasts is sufficient to extend lifespan and preserve proliferative homeostasis in the gut with age. Consistent with inducing a metabolic state that prevents over-proliferation, mitochondrial uncoupling drugs also extend lifespan and inhibit intestinal stem cell overproliferation due to aging or even tumorigenesis. These results demonstrate that circadian-regulated intestinal mitochondrial uncoupling controls longevity in Drosophila and suggest a new potential anti-aging therapeutic target.