28th Annual Paul F. Glenn / AFAR Grantee Conference

June 1-2, 2015 Four Seasons Biltmore Santa Barbara, California

Meeting Participants with a twitter account are encouraged to tweet at least once during the conference using the #Iamascientistbecause tag + @AFARorg

MONDAY, JUNE 1, 2015

3:30 pm - 4:00 pm	**Registration/reception**	*Alto*
4:00 pm – 4:15 pm	**Welcome** **Stephanie Lederman** Executive Director American Federation for Aging Research **Harvey Jay Cohen, MD** President, American Federation for Aging Research and Center for the Study of Aging, Duke University Medical Center	*El Mar*
4:15 pm – 5:00 pm	**Chromatin folding, age dependent memory decline and age induced haploinsufficiency.** **Giovanni Bosco, PhD** (2013 BIG recipient) Geisel School of Medicine at Dartmouth	
5:00 pm – 5:45 pm	**Rapamycin: The first longevity drug?** **Arlan Richardson, PhD** University of Oklahoma Health Science Center	
5:45 pm – 6:00 pm	**Break**	
6:00 pm – 7:00 pm	**What's new in aging biology and geroscience?** **Felipe Sierra, PhD** National Institute on Aging, National Institutes of Health	
7:00 pm – 8:30 pm	**Dinner**	*El Mar*
8:30 pm – 9:30 pm	**Social gathering, with dessert, coffee and wine**	*Alto*

Glenn Workshop on the Biology of Aging and AFAR Grantee Conference | JOINT MEETING

The Glenn Medical Foundation – 50th Anniversary
Fifty years of aging research: What have we learned, where do we go from here?

GLENN FOUNDATION FOR MEDICAL RESEARCH

Meeting Moderator: Kevin Lee

TUESDAY, JUNE 2

7:30 – 8:30 am	Breakfast	*La Marina*
8:30 – 8:45 am	**Welcome and opening remarks** **Mark Collins** President, Glenn Foundation for Medical Research	*La Veranda*
8:45 – 9:00 am	**Meeting overview and goals** **Kevin Lee, PhD** Senior Scientific & Programmatic Advisor, Glenn Foundation for Medical Research	
9:00 – 10:30 am	**Fifty Years of Aging Research: Past, Present, Future** Moderator: **Edward Lakatta, MD,** National Institute on Aging Speakers: **Steven Austad, PhD,** University of Alabama at Birmingham **George Martin, MD,** University of Washington This session will provide a backdrop, discussing major areas of inquiry over the past fifty years, lessons learned, which areas are still being investigated, emerging and promising areas, how is technology shaping research.	
10:30 – 11:00 am	Break	

11:00 am – 12:30 pm

Communicating the objectives and impact of aging research

Moderator: **Erika Check Hayden**, University of California, Santa Cruz and reporter for *Nature*

Panelists: **Richard Faragher, PhD**, University of Brighton
James Kirkland, MD, PhD, Mayo Clinic Rochester
Christopher Scott, PhD, Stanford University

Credibility of our messages hinges on the quality of scientific explanations. Findings that emerge from the aging research field are often extrapolated by the media and/or repackaged into messages promising fountains of youth. Terms such as "anti-aging, immortality, ending aging" harm the field more than they do good. This session will discuss how we can best communicate our messages — can the aging community agree on common language?

12:30 – 1:30 pm — Lunch — *Palmera Garden*

1:30 – 3:00 pm

Resistance to Aging - Optimizing damage response pathways

Moderator: **Kevin Lee, PhD**, Glenn Foundation for Medical Research

Speakers: **Judith Campisi, PhD,** Buck Institute for Research on Aging
Susan Lindquist, PhD, Whitehead Institute for Biomedical Research and Massachusetts Institute of Technology
Gary Ruvkun, PhD, Harvard University

Pathways that identify damaged molecules, organelles, and tissues and repair this damage underlie the ability to resist the effects of aging and maintain healthy function. At the same time, dysregulated or chronically activated repair pathways contribute to aging-associated pathogenesis. This session will provide an overview of our current understanding of surveillance and stress response pathways, and consider how these pathways can be optimized to strike a balance between beneficial and detrimental responses to stress and toxic insults.

3:00 – 5:30 pm — **AFAR Grantee Poster Session** — *Loggia Ballroom*

Please remove your poster at the conclusion of the session.

6:00 – 7:00 pm — Reception — *La Pacifica Terrace*

7:00 – 9:00 pm — Dinner — *La Pacifica*

Ignorance, Failure, Uncertainty, Doubt - Why Science is so Successful

Stuart Firestein, PhD, Columbia University

WEDNESDAY, JUNE 3

7:00 – 9:00 am — Breakfast — *La Marina*

The AFAR Grantee Conference adjourns following breakfast

PAUL F. GLENN

Paul F. Glenn, founder of the Glenn Foundation for Medical Research, established the foundation in 1965 to extend the healthy productive years of life through research on the mechanisms of biological aging.

GLENN FOUNDATION
FOR MEDICAL RESEARCH

The Foundation has been a leader in funding basic research in the science of aging for more than forty years and has been a key supporter of the American Federation for Aging Research.

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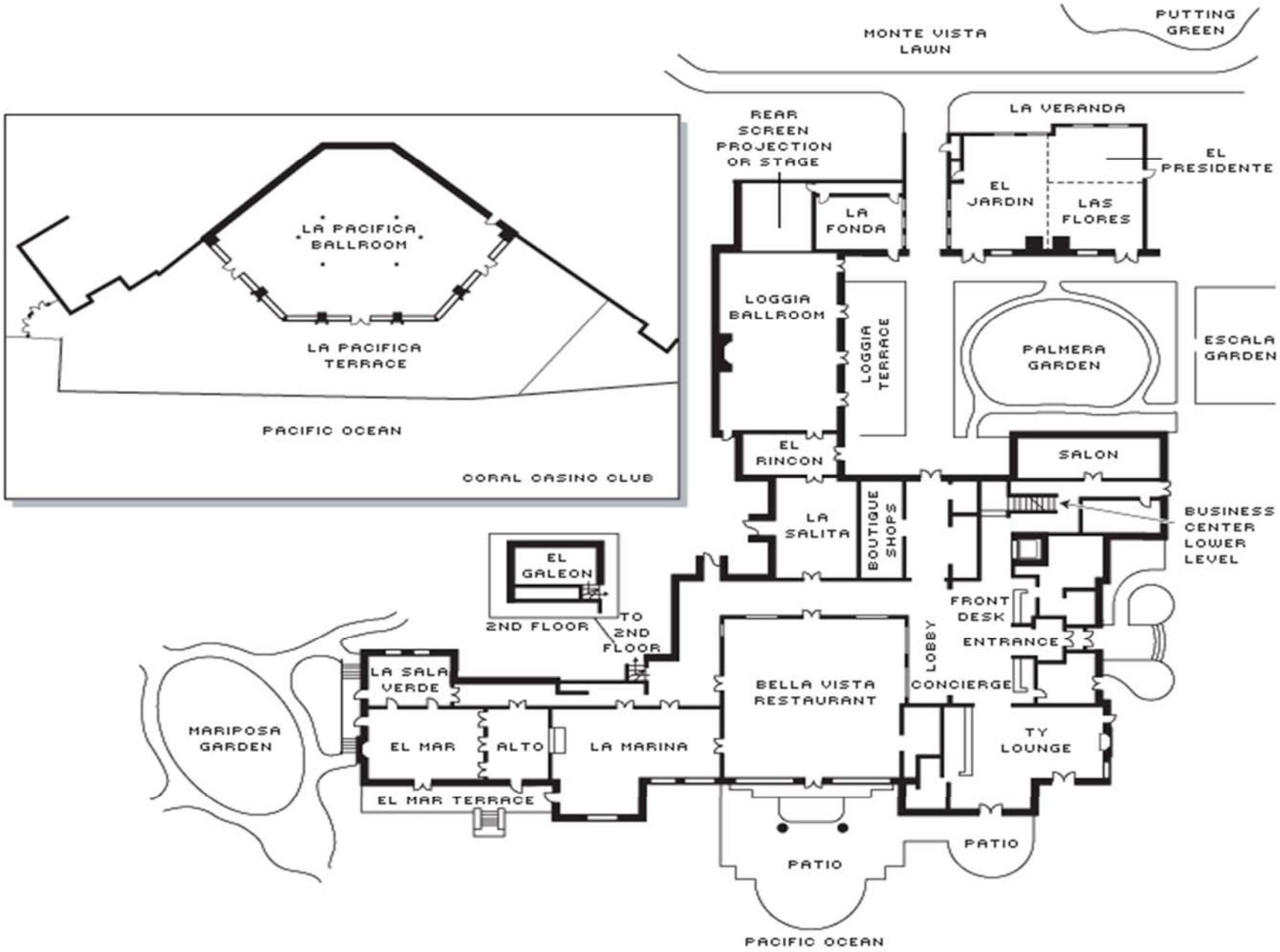
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Imaging cognitive processing in the same cell bodies and axons in mouse temporal lobe cortex across the lifespan

Christian Burgess, Ph.D.[1,2], Rohan Ramesh[1,2], Nick Jikomes[1,2], Paola Patella[2], Glenn Goldey[2], Kirsten Levandowski[2], Mark Andermann, Ph.D.[1,2]
[1]Harvard University, [2]Beth Israel Deaconess Medical Center, Harvard Medical School

One of the main goals of the proposed research is to establish a platform for evaluating neural activity and its relation to behavior, in the same mouse across months. Our proposed research aims to compare activity in early cortical areas and in more lateral cortical areas that have not been well studied in mouse models of Alzheimer's disease, but that are likely to be partially responsible for the cognitive deficits associated with many human dementias. Since receiving funding from AFAR, we have accelerated our development of methods for extending our imaging window to more lateral cortical areas including postrhinal and perirhinal cortex, and we have obtained preliminary results tracking neural responses across several months over the course of learning – a key step to evaluating how learning and recall of memory associations changes during aging and Alzheimer's disease.

We are using widefield and cellular imaging to monitor context-dependent modulation of sensory response properties across months in the same cortical neurons in awake mice, from 2 to 10 months of age. We are developing methods for extending our imaging window to more lateral cortical areas including postrhinal and perirhinal cortex, and we have obtained preliminary results tracking neural responses across several months over the course of learning. Specifically, we have begun training mice to associate various visual cues with reward, foot-shock, or no outcome. These mice express the calcium indicator GCaMP3 or, more recently, GCaMP6 in excitatory cortical neurons across all cortical areas. We have begun to image bulk neural activity in over 8 cortical areas simultaneously after implanting a chronic cranial window. We have trained these mice to enter a food-port when they see one visual cue, and to avoid entering the food-port when they see other visual cues. Our preliminary findings suggest that in postrhinal cortex (homologous to human parahippocampal region), the visual responses to the food-associated cues increase after associative learning, while responses to neutral or aversive cues stay stable. By contrast, no such biases emerge in primary visual cortex, emphasizing the importance of this work in establishing a mouse model for recording from more lateral areas that likely represent an important locus for learning-associated changes in brain activity in mouse models of aging and dementia.

More recently, we have begun to compare task-related activity in individual neurons and axons across weeks, in early visual cortex, postrhinal cortex, and in amygdalar feedback axons to cortex. We observe an emergence of increased 'delay period' activity in outside of sensory cortex provides new tools for exploring various components of sensory and cognitive modulation of neural activity in temporal lobe cortex in identified neurons, a key step towards assaying which spatiotemporal aspects of cellular and circuit activity are going awry in aging and age-associated dementias.

Structural and functional dysfunction of brain vasculature in cerebral amyloid angiopathy and Alzheimer's disease

Arbel-Ornath M., Kim A., Ramos-Rodriguez JJ., Steven Hou, Zhao L., Garcia-Alloza M., Frosch MP., Greenberg SM. and Bacskai BJ.

Alzheimer Research Unit, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, 114, 16th st. , Charlestown, MA 02129, USA

Cerebral amyloid angiopathy (CAA) is an age-related disease that frequently co-occurs with Alzheimer disease (AD). Like the plaques the deposits in CAA are comprised of amyloid β peptide. The pathological manifestations of CAA include vascular smooth muscle cell (VSMC) degeneration and intracerebral hemorrhage. There is a great need to understand the vascular components of amyloid deposition and the subsequent mechanisms that lead to the vessel wall breakdown. We took advantage of multiphoton in-vivo imaging in combination with AD/CAA mouse models, to study these mechanisms in the most relevant system, the living mouse brain. We focused on two main themes: 1) the role of impaired ISF drainage to amyloid buildup in AD and CAA and 2) the effects of amyloid progression on VSMC loss and breakdown of the vessel wall. To that end, we developed a novel approach to visualize the ISF clearance in real time and found that transgenic mice with vascular amyloid exhibit impairments in this process, suggesting the existence of a feed-forward mechanism by which amyloid deposition promotes further amyloid deposition. Thus, we propose that facilitation of Aβ clearance as a therapeutic target for AD and CAA. Additionally, by crossing the AD mouse model with mice that express EGFP specifically in VSMC, we were able to visualize individual VSMC along the progression of CAA and found that individual VSMC loss can be detected at early stages and exacerbated dramatically with age. The ability to quantify VSMC loss during CAA progression highlights the model potential for evaluation of therapeutic interventions.

The Role of Neuronal and Microglial Progranulin in Maintaining Neuronal Function with Age

Andrew E. Arrant, Anthony J. Filiano, Allen H. Young, and Erik D. Roberson

Center for Neurodegeneration and Experimental Therapeutics, Departments of Neurology and Neurobiology, University of Alabama at Birmingham

Progranulin (*GRN*) is a secreted glycoprotein that is expressed throughout the body, where it acts as a growth factor and modulates inflammation. In the brain, progranulin is expressed by neurons and microglia, and has neurotrophic and anti-inflammatory effects. Progranulin is a critical protein for maintaining neuronal function with age, as loss-of-function mutations in progranulin cause the neurodegenerative disorders frontotemporal dementia (FTD) and neuronal ceroid lipofuscinosis (NCL) in a gene-dose dependent manner. More subtle deficits in progranulin can also contribute to aging-relating disorders, as some progranulin mutations have been associated with increased risk for Alzheimer's disease. As such, understanding the mechanism by which progranulin deficiency impairs neuronal function with age could help produce treatments for diseases related to progranulin deficiency and provide insight into mechanisms affecting aging of the brain.

A basic question for how progranulin deficiency impairs neuronal function with age is whether the neurotrophic and/or anti-inflammatory effects of progranulin are key to maintaining brain health. Progranulin deficient mice ($Grn^{+/-}$ and $Grn^{-/-}$) provide a useful model to address this question, as they replicate some of the phenotypes caused by progranulin deficiency in humans. $Grn^{+/-}$ and $Grn^{-/-}$ mice develop abnormal social behavior, impaired fear conditioning, and amygdala dysfunction from 6-12 months of age. $Grn^{-/-}$ mice also develop pathology that may model that seen in NCL, with gliosis and accumulation of lipofuscin and lysosomal proteins. In this study, we generated neuron- and microglia-specific progranulin knockout lines to address the relative importance of neuronal or microglial progranulin deficiency in maintaining neuronal function with age. The lines were generated by crossing $Grn^{fl/fl}$ mice with mice expressing Cre under promoters targeting neurons (CaMKII, Nestin) or microglia (LysM). Neuronal progranulin knockout mice (N-KO) replicated most of the behavioral phenotype of $Grn^{+/-}$ and $Grn^{-/-}$ mice in a similar time course (9-16 months). In contrast, microglial progranulin knockout mice (Mg-KO) did not develop any significant behavioral phenotypes at ages 9-16 months. However, when tested at advanced ages (18-24 months) both N-KO and Mg-KO mice exhibited sociability deficits and a compulsive grooming phenotype that may model compulsive behaviors seen in FTD-*GRN* patients. None of the N-KO or Mg-KO lines developed NCL-like lipofuscin accumulation as seen in $Grn^{-/-}$ mice.

These data show that both neuronal and microglial progranulin deficiency are sufficient to produce aging related neuronal dysfunction, though there are differences in the phenotype produced by progranulin deficiency in each cell type. N-KO mice replicate more of the phenotype of $Grn^{+/-}$ and $Grn^{-/-}$ mice than do Mg-KO mice, and do so at similar ages as $Grn^{+/-}$ and $Grn^{-/-}$ mice. Mg-KO mice also develop sociability deficits, but do so at much later ages (18-20 months). These data suggest that neurotrophic support provided by progranulin is important for maintaining neuronal function earlier in life, while the anti-inflammatory effects of progranulin are important as animals reach advanced ages. This is consistent with data showing that progranulin levels increase with age in the brain of wild-type mice, largely due to increased microgliosis and inflammation with aging. Progranulin may therefore be important in restraining the inflammation that normally occurs with age, and loss of this protective effect could lead to neuronal dysfunction at advanced ages.

Regulation of pancreatic beta cell aging and proliferation

Jacqueline R. Benthuysen[1], Jeffrey N. Savas[2], Fenfen Liu[1], Tiffany Guan[1], John R. Yates III[2], and Maike Sander[1]

[1]Departments of Pediatrics and Cellular & Molecular Medicine, Pediatric Diabetes Research Center, University of California San Diego, La Jolla, CA 92093-0695, USA; [2]Department of Chemical Physiology, The Scripps Research Institute, La Jolla, CA 92037, USA

Early in life, pancreatic beta cells rapidly replicate to increase beta cell mass, however this proliferative capacity declines with age as beta cells reach quiescence. Type 2 diabetes, an age-related disease, results from reduced beta cell mass after loss of compensation to insulin resistance. Therefore, one possible strategy for improving glucose homeostasis in patients with diabetes is to increase functional beta cell mass through the stimulation of beta cell replication. However, the underlying mechanisms that regulate the age-dependent replicative senescence in beta cells are poorly understood. To identify key age-regulated pathways in beta cells, we utilized an *in vivo* quantitative proteomics approach. For this we performed Stable Isotope Labeling of Amino Acids in Mammals (SILAM) and subsequent MudPIT-mass spectrometry to quantitatively compare protein abundance in islets of Langerhans from 4-week-old and 1-year-old mice. Our statistical analysis of four biological replicates revealed 898 unique proteins displaying statistically significant differences in abundance between young and old mouse islets. Gene Ontology analysis of these statistically changed proteins revealed distinct proteome dynamics during beta cell aging. Proteins that significantly decreased with age were involved in cell cycle, chromatin modification, and mRNA processing, while proteins that increased with age were regulators of hormone metabolism, cellular secretion, and oxidative stress. From our analyses, we identified 25 candidate proteins with potential roles in regulating beta cell proliferation. One candidate we focused on was Sirtuin 2 (Sirt2), which we found upregulated with age in mouse islets. Sirt2 was of particular interest due to its metabolic sensing ability as an NAD-dependent deacetylase and its known tumor suppressor roles. To determine whether pharmacological inhibition of Sirt2 can increase beta cell proliferation, we cultured islets from aged mice with the Sirt2 inhibitor AGK2 and found that beta cell proliferation was significantly increased. Similar experiments with primary human islets showed efficacy of the inhibitor in increasing human beta cell proliferation. Furthermore, we found that Sirt2 controls beta cell proliferation by regulating the MAPK/ERK pathway. These findings suggest that Sirt2 is a novel negative regulator of age-dependent pancreatic beta cell proliferation. Thus, targeting Sirt2 activity could be a potential therapeutic strategy for increasing endogenous beta cell mass in aged diabetic patients.

Generation of neurotoxic $A\beta_{1-34}$ oligomers by reactive aldehydes targeting lysine residues: a possible molecular mechanism for the development of sporadic Alzheimer's disease?

Irene Zagol-Ikapitte[a], Roman Lazarenko[b], Taneem Amin[a], Janice A. Williams[c], Qi Zhang[b] and Olivier Boutaud[b]

Departments of Medicine[a], and Pharmacology[b]; Vanderbilt-Ingram Cancer Center[c]
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Our work provides evidence supporting a new paradigm linking inflammation/oxidative stress and sporadic Alzheimer's disease (AD).

Inflammation/oxidative stress is a pathophysiologic process that occurs early in AD. Although it is well accepted that this contributes to the disease's development, the molecular mechanism by which inflammation is contributing to AD is unclear. We have previously shown that reactive aldehydes (RAs) generated during these processes covalently modify amyloid β_{1-42}, increase its oligomerization rate and yield neurotoxic small oligomers. We hypothesized that even non-amyloidogenic species such as $A\beta_{1-34}$ would react with these RAs to form toxic oligomers in the brain. This hypothesis was tested by reacting $A\beta_{1-34}$ with the most reactive aldehyde described to these days, levuglandin E_2 (LGE_2) because levels of LGE_2 adducts on brain proteins correlate with AD severity.

Our data shows that LGE_2 causes $A\beta_{1-34}$ to form SDS-stable small oligomers that are toxic to PC12 cells differentiated into neurons. Using transmission electron microscopy (TEM), we showed that LGE_2-adducted $A\beta_{1-34}$ oligomers are small and relatively circular in forms. We have developed small molecules reacting with LGE_2 3 orders of magnitude faster than lysine residues. We showed that these RA scavengers prevent formation of the neurotoxic LGE_2-adducted $A\beta_{1-34}$ oligomers and that the $A\beta_{1-34}$ structures formed in presence of these scavenger are similar to those formed by unmodified $A\beta_{1-34}$: they are much smaller in size and less circular than the LGE_2-adducted $A\beta_{1-34}$ oligomers. These data support our hypothetical mechanism for the contribution of oxidative stress in the development of AD.

We then tested the physiological effect of $A\beta_{1-34}$ oligomers formed in the presence or absence of LGE_2 and/or RA scavengers by measuring the miniature evoked postsynaptic currents (mEPSCs) on cultured hippocampal neurons. We found that larger LGE_2-adducted $A\beta_{1-34}$ oligomers caused significant changes in the amplitude and frequency of mEPSCs, reflecting their profound impact on pre- and postsynaptic apparatuses and that these effects were prevented by the RA scavenger.

In conclusion, our results demonstrate that reactive aldehydes generated either enzymatically during inflammation or non-enzymatically during lipid peroxidation can convert benign $A\beta$ peptides to neurotoxic oligomers and impair neurotransmission. These results suggest that neuronal dysfunction caused by local generation of toxic oligomers can initiate a chain reaction leading to the propagation of synaptic dysfunction among healthy neurons nearby. Finally, we provided evidence that a small molecule scavenger can prevent the formation of the neurotoxic oligomers. Taken together, our results point to lipid-modification of $A\beta$ peptides as a possible contributor to the development of sporadic AD. They also provide evidence for targeting RAs as a novel pharmacologic approach to prevent or slow the progression of sporadic AD.

Intrinsic cellular and micro-environmental effects of aging on MSC engraftment: Implications for transplantation as a therapeutic modality

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Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104

ABSTRACT

The regenerative capacity of MSCs remains a key to their therapeutic use for degenerative diseases. It is apparent through both *ex vivo* and *in vivo* studies that the potential of MSCs to proliferate and differentiate declines over time. However, it remains unclear whether these changes in MSC function are cell autonomous, suggesting MSCs are subject to cellular aging with the possibility of losing the capacity to respond to environmental cues; or if it is the aging microenvironment itself that is affecting the ability of MSCs to function normally. To identify the effects of cellular and micro-environmental aging on MSCs we used a nonmyeloablative sex and age-mismatched transplantation model. MSCs from both young (2 month old) and old (24 month old) green fluorescent protein (GFP) – positive mice were isolated, and MSCs were infused into non-GFP^+ young and old recipients. Robust engraftment by young MSCs or their progeny was observed in the marrow, bone-lining region and in the matrix of young recipients; however, significantly lower engraftment was seen at the same sites in old recipients transplanted with old MSCs. Differentiation of transplanted MPCs strongly favored adipogenesis over osteogenesis in old recipients irrespective of MSC donor age. No GFP^+ MSCs were detected in the young mice transplanted with old MSCs. These data indicate that, at least in bone, aging alters stem cell fate by both cell intrinsic and micro-environmental effects. We are examining MSC homing and functional engraftment in other tissues after age-mismatched transplantation, including lung, heart, liver, kidneys and spleen. The ultimate goals of this approach is to determine if cell autonomous and/or non-cell autonomous aging mechanisms impair tissue renewal and if transplantation by young MSCs can contribute to regeneration .

Long-term Administration of Losartan Induces an Endurance Exercise Phenotype in Aging Mice

Tyesha N. Burks[1], Ruth Marx[1], Christopher W. Ward[2], Jeremy D. Walston[3*], Ronald D. Cohn[1,4*]
[1]Division of Geriatric Medicine and Gerontology Johns Hopkins University School of Medicine, Baltimore, MD 21205, [2]University of Maryland School of Nursing, Baltimore, MD 21201, [3]The Hospital for Sick Children University of Toronto, Toronto, ON M5G 1X8. [*]Contributed equally.

Sarcopenia, the critical loss of muscle mass and function due to the physiological process of aging, contributes to disability and mortality in older adults. The molecular mechanisms underlying sarcopenia are poorly understood, but recent evidence suggests that increased transforming growth factor-β (TGF-β) signaling contributes to the muscle phenotype. We therefore evaluated whether antagonism of TGF-β signaling via losartan, an angiotensin II type I (ATI) receptor antagonist commonly used to treat hypertension, has a beneficial impact on sarcopenia. Long-term administration of losartan caused an increased resistance to fatigue in sarcopenic muscle by inducing an endurance exercise phenotype. Losartan induced PGC-1α expression and caused a fiber type conversion toward type 1 "slow" fibers. Recent evidence suggests that a low aerobic/endurance exercise capacity is a predictor for increased morbidity and mortality in older adults. Thus, losartan, an FDA-approved drug, may prove to have clinical benefits for older adults by enhancing their endurance capacity.

MAPK-activated vascular niche inhibits functional hematopoiesis and enhances leukemic progression.

Michael C. Gutkin, Michael G. Poulos, and Jason M. Butler
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To date, most studies describing age-related alterations in the hematopoietic compartment have focused on cell-intrinsic alterations at the level of the HSC. These studies have shown that the absolute number of immunophenotypically defined HSCs increases with age but that aged HSCs exhibit decreased long-term reconstitution potential and self-renewing capabilities. Furthermore, old HSC exhibit a significant myeloid bias at the expense of lymphopoiesis and produce fewer red blood cells, leading to decreased adaptive immunity and reduced fitness. While these studies show that cell-intrinsic changes contribute to aging of the hematopoietic system, most have not adequately taken into account the effects of the aging microenvironment.

Within the hematopoietic microenvironment, we have shown that Akt-activated endothelial cells (ECs) are indispensable to supporting HSC self-renewal and differentiation into lineage-committed progeny during steady-state hematopoiesis. We have generated data demonstrating that young ECs maintain high levels of Akt signaling, whereas aged ECs demonstrate preferential signaling through MAPK while undergoing age-related senescence. Based on this data, we set out to formally test if endothelial MAPK inhibits the vascular niche from supporting functional hematopoiesis. To this end, we generated a mouse model in which MAPK was selectively overexpressed in ECs (MAPK VCC) and demonstrated that these mice exhibit a defect in phenotypic and functional HSCs, resembling phenotypes similar to aged HSCs. To directly test if the functional defects in the HSCs were due to the MAPK-activated vascular niche, we isolated BMECs from these mice and found that MAPK-activated ECs have a decrease potential to support the ex vivo expansion of functional HSCs, with less HSCs in quiescence and more differentiation into granulocytic myeloid cells. Furthermore, MAPK-activated BM ECs are endowed with the capacity to expand more primitive and aggressive acute myeloid leukemic clones, suggesting that signaling pathways within ECs can drive and dictate the BM microenvironment's role in supporting normal and malignant hematopoiesis. Taken together, our in vivo animal model and EC/HSC co-culture system will allow us to screen for angiocrine factors that support the functional attributes of the HSC, as well as factors that promote or inhibit the expansion and aggressiveness of hematopoietic malignancies.

Acute Disuse Muscle Atrophy: Investigating Mechanisms and Countermeasures in Older Adults.

Callahan D.M.[1], Toth M.J.[1,2]

Departments of Medicine[1] and Molecular Physiology and Biophysics[2], University of Vermont, College of Medicine, Burlington, VT

Introduction:

Knee osteoarthritis (KOA) is the leading cause of disability in older adults, afflicting >25% of those 63-70 years old and >40% of those > 80 years old. Total knee arthroplasty (TKA), is the final treatment option for end-stage KOA and remediates joint pain. However, muscle weakness and mobility limitations persist due to disuse-related atrophy in the early, post-surgical period (4-5 weeks post TKA). Our studies prospectively evaluate the effect of clinical disuse on mitochondrial biology and cellular-level muscle morphology and function in otherwise healthy older adults. We further test the efficacy of neuromuscular electrical stimulation (NMES) to attenuate deleterious muscle adaptations during the post-surgical period.

Methods:

Four individuals scheduled to undergo TKA have been recruited to date (2 bilateral, 2 unilateral). Volunteers were healthy by self-report and did not have uncontrolled hypertension, diabetes, heart failure or history of cancer. No participants were taking oral corticosteroids or had intra-articular injections within 3 months of study participation. Whole muscle and single fiber morphology and contractile performance were measured 2-3 weeks prior to and 5 weeks following TKA. Mitochondrial morphology was assessed using electron microscopy (n=4) and standard respirometry techniques (n=2). All measures were performed bilaterally.

Preliminary Results:

In the operative limb, whole muscle strength and size were dramatically reduced following TKA (-34% and -9% respectively). These changes were mirrored at the cellular level with single fiber atrophy, especially prominent in MHC II fibers (-33%), following TKA. Single fiber contractile tension was severely diminished following TKA (-53%) as well. NMES blunted the atrophy and contractile dysfunction responses at the cellular level following TKA (-8% and -35% respectively). NMES also limited reductions in mitochondrial density in the subsarcolemmal region (-19% in controls and +55% with NMES). Mitochondria in the intermyofibrillar region were substantially reduced following TKA in controls (-57%) and with NMES (-59%). In two participants, one with and the other without NMES, maximal state 3 (ADP stimulated) respiration was reduced 10% and 74% respectively, demonstrating the potential for NMES to limit disuse-related reductions in oxidative capacity in older adults.

Summary:

Our findings to date demonstrated significant deterioration of muscle size and function following a period of acute disuse in older adults. Importantly, our preliminary results highlight the potential for NMES to attenuate the negative impact of disuse in these older adults and provide a platform to investigate the coordination between mitochondrial biology with disuse-related alterations in the contractile apparatus.

Rapamycin induces mitochondrial remodeling to rejuvenate energy metabolism and energetics in old hearts

Ying Ann Chiao, Stephen Kolwicz, Nathan Basisty, Michael MacCoss, Rong Tian, Peter Rabinovitch
University of Washington, Seattle, WA

Recently, we showed that rapamycin (a caloric restriction mimetic) can reverse age-related cardiac dysfunction in 10 weeks, highlighting its therapeutic potential for cardiac aging. At this time-point, rapamycin reversed the age-related decrease in levels of mitochondrial proteins, without elevations of mitochondrial number or biogenesis.

Longitudinal echocardiographic analysis revealed that while diastolic function of old mice began to improve 2-4 weeks following treatment, this progressed over the course of 10 weeks. We studied whether mitochondrial remodeling had a similar time course.

Rapamycin treatment reduced phosphorylation of TORC1 target S6 and TORC2 targets AKT and PKCα in old hearts by 1 week. The mRNA expression of PCG-1α, a mitochondrial biogenesis marker, increased in the first 2 weeks of rapamycin treatment but subsequently returned to control. Autophagy (LC3 II/LC3 I ratio and ATG5 levels) increased at 1 week. Concordantly, proteomics analysis showed a mixture of increased and reduced levels of mitochondrial proteins at 1 week but an overall increase at 2 weeks of rapamycin treatment. These findings suggest that protein turnover in the first 2 weeks of rapamycin treatment rapidly remodels the cardiac mitochondrial proteome.

^{13}C NMR spectroscopy of isolated perfused heart extracts revealed that fatty acid oxidation was reduced by 30% in old control hearts, consistent with the proteomic data. Strikingly, 1 to 2 weeks of rapamycin treatment reversed the age-related decrease in fatty acid oxidation. This reversal was also accompanied by increased PCr/ATP ratio in old hearts treated with rapamycin as early as 2 weeks after treatment.

Overall, our results suggest that rapamycin induces mitochondrial remodeling in the first 2 weeks of treatment to rejuvenate energy metabolism and energetics. However, the slower rate of improvement in cardiac performance indicates that there are additional, later steps required to fully translate mitochondrial enhancement into improved cardiac function in old hearts.

Controlling Tau Aggregate Structure and Toxicity with a Twist

Chad Dickey, PhD, Associate Professor, University of South Florida Byrd Alzheimer's Institute

Controlling neurotoxicity caused by the tau protein is critical for the prevention of neurodegeneration in Alzheimer's disease (AD) and related tauopathies. Although it is known that aberrant tau accumulation drives neurotoxicity, it is unclear what controls tau assembly and metabolism, leading to its toxicity. Tau is largely a disordered protein and as such possesses many proline residues. It was previously shown that isomerization, or "twisting" of these proline residues by the cis/trans peptidyl-prolyl isomerase (PPIase) Pin1 can dramatically affect tau biology. More recently, we found that another PPIase, FK506 binding protein 51 (FKBP51) regulates tau oligomerization, aggregation and toxicity through its PPIase activity and association with heat shock protein 90. Based on these results, we predicted that other members of the PPIase enzymatic family could be important for regulating tau structure and ultimately its toxicity. Indeed, a number of PPIases can both regulate tau aggregation and metabolism, with some slowing and others enhancing these kinetics. With these tools, we are now able to assess whether modulating these PPIases is a viable strategy for regulating tau fate and downstream neurotoxicity. These PPIases could allow us to control tau structure in a way that we can ultimately identify the more toxic tau species in AD. Moreover, some of these enzymes represent interesting therapeutic candidates based on their unique structural features.

AFAR Meeting 2015, Santa Barbara, CA

Managing Cellular Trash in Aging - Cellular Regulation of Proteostasis in Neurodegeneration.

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Attenuated protein degradation and inhibition of the cellular auto-lysosomal system have been strongly associated to aging and age-related diseases like Alzheimer's (AD). Indeed, auto-lysosomal inhibition is discussed to be among the earliest changes in AD brains preceding the well-known disease hallmarks (aggregation of Tau-proteins and amyloid). My previous work shows that autolysosomal inhibition results in changes in molecular trafficking and largely affects major cellular signaling cascades as that of Wnt, a molecular pathway which has been associated with AD. Wnt signaling inhibits the cytosolic activity of Glycogen Synthase Kinase 3 (GSK3) through its sequestration into a specialized late endosomes, the multivesicular endosomes. GSK3 in turn regulates the phosphorylation and stability of many proteins, like the AD associated Tau. Especially under AD conditions, Tau phosphorylation and stability changes upon Wnt. Cells expressing AD associated Presenilin 1 (PS1) mutations show dynamic changes in responsiveness to Wnt signals which is correlates with the activity of the so called CLEAR (coordinated lysosomal expression and regulation) gene network. We find presenilin mutations to inhibit this mTOR (mammalian target of Rapamycin) regulated pathway, promoting sequestration of the Wnt mediator Disheveled leading to high GSK3 activity and pTau buildup over time. Furthermore, we find that re-activation of the clearance pathways by overexpressing of the transcription factor EB (TFEB) or transient pharmacological inhibition of mTOR reduces cholesterol levels through a process called lipophagy, restores Wnt signaling and fine-tunes GSK3 activity. This way, restoration of the mTOR/TFEB signaling inhibits the buildup of pTau in AD cells.
My startup laboratory continues to study the wide variety of effects associated with the lysosomal mTOR complex on protein synthesis and degradation in aging and AD mouse and human neurons derived from induced pluripotent stem cells.

Driving Capacity in Aging and Early Alzheimer's Disease

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***Objective*:** To assess driving performance in aging and early stage Alzheimer's disease and establish links between focal cortical atrophy and impaired driving capacity.
Background: Visuospatial impairments are a common early symptom of Alzheimer's and the loss of driving capacity is perhaps the most immediate and devastating consequence. Impaired visuospatial function is the result of selective deficits in higher order cortical processing and reflects the distribution of AD pathology in posterior cortical areas. We used a virtual-reality driving simulator to detect specific deficits in this highly complex behavior and investigate their anatomical correlates with structural MRI.
***Methods*:** Patients with early stage Alzheimer's (EAD) and older normal controls (ONC) took a virtual reality driving evaluation that incorporates multiple cognitive, visual and motor tests. Cortical thickness measures were also obtained from each participant by performing brain MRIs.
***Results*:** Based on test results, all but one of the ONC subjects were deemed safe to drive. By comparison, only one EAD subject was considered fit to drive. EADs obtained significantly lower total scores and showed specific deficits in steering, turning, braking, and detection of a looming car. There were multiple and significant correlations between individual tests scores and measures of cortical thickness and predominantly in parietal and occipital regions.
Conclusions: Even in the earliest stages, Alzheimer's significantly impairs driving capacity. Correlations with cortical thickness measures suggest a predominant role of posterior cortical atrophy in overall driving performance, as well as in specific tasks that are highly dependent on visual motion processing.

Fission Yeast Does Not Age But Has a Finite Replicative Lifespan

Ilya Finkelstein, University of Texas, Austin

Abstract:
Since the seminal observation that S. cerevisiae has a finite replicative lifespan, yeast has become a popular model organism for understanding aging in mitotically active cells. However, relatively little is known about the mechanisms of aging and longevity in fission yeast (*S. pombe).* To study replicative aging, progeny must be manually removed from the mother cell—an error-prone and low-throughput method that has not changed appreciably since its introduction in 1959. I will describe our fission yeast lifespan micro-dissector (FYLM), a microfluidic platform for performing tens of thousands of micro-dissections in well-defined culture conditions. Using FYLM, we directly observe continuous and robust replication of individual cells for over sixty cell divisions. Surprisingly, aging-associated phenotypes such as cell morphology, doubling time and daughter health do not reliably predict cell death. Genetic perturbations can further extend the replicative lifespan via an aging-independent mechanism. We conclude that fission yeast does not age and discuss how this model eukaryote achieves such remarkable longevity.

Prosaposin facilitates sortilin independent lysosomal trafficking of progranulin through M6PR

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Mutations in the Progranulin (PGRN) gene have been linked to two distinct neurodegenerative diseases, frontotemporal lobar degeneration (FTLD) and neuronal ceroid lipofuscinosis (NCL). Accumulating evidence suggests a critical role of PGRN in lysosomes and lysosomal dysfunction serves as a common mechanism for FTLD and NCL. However how PGRN is trafficked to lysosomes is still not clear. Here we report a novel pathway for lysosomal delivery of PGRN. We found that prosaposin (PSAP) interacts with PGRN and facilitates lysosomal targeting of PGRN via the cation-independent mannose 6-phosphate receptor (M6PR). Lysosomal targeting of PGRN is impaired in PSAP deficient mice and in fibroblasts derived from I cell disease patient, which are defective in the M6PR pathway. We further demonstrated that this PGRN/PSAP/M6PR interaction represents a novel mechanism of PGRN lysosomal trafficking independent of but complementary to the previously identified pathway mediated by sortilin. Our results shed light on the molecular mechanisms behind FTLD and NCL caused by PGRN mutations.

Title: Functional Characterization of Longevity Associated IGF1R Mutations
Authors: Dr. Simon C Johnson and Dr. Yousin Suh
Institution: Albert Einstein College of Medicine

While there is overwhelming evidence that reduced insulin/insulin like growth factor-1 (IGF1) signaling (IIS) extends lifespan in invertebrate and murine models, the impact of this evolutionarily conserved pathway on human longevity remains unclear. Research in the Suh lab has led to the discovery of two centenarian-enriched missense mutations in the IGF-1 receptor gene (*IGF1R*), A37T (M1) and R407H (M2), associated with decreased IIS in lymphocytes established from carriers as compared to non-carriers. While the association of the reduced-function IGF1R mutations with exceptional longevity implicates IIS in human lifespan, consistent with findings in model organisms, the in vivo effects of these mutations, including lifespan, have yet to be established. To determine thefunctional effects of centenarian associated *IGF1R* variants we have generated a series of *IGF1R* mutant knock-in cell lines carrying these centenarian associated mutations, mutations associated with disease, or homologous withnematode mutations associated with longevity. We have been characterizing the impact of these distinct disruptions of *IGF1R* to uncover the molecular functions associated with longevity associated alleles. Furthermore, to study the *in-vivo* impact of centenarian associated mutations in this gene we have generated and begun characterizing a knock-in mouse model expressing the longevity-associated human *IGF1R* M2 variant, the variant with stronger effects on IIS based on the functional studies in cell models. While *Igf1r* heterozygous and conditional knockout mice have previously been studied, reduction of IGF1R levelsin these models is not representative of naturally occurring variation and our cell-based models indicated that decreased levels of IGF1R are functionally distinct from *IGF1R* variants that alter protein structure.

Systems genetics identifies novel candidates as putative mediators of memory decline in both 'normal' aging and Alzheimer's disease

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'Normal' age-associated cognitive decline is generally less severe than that seen in pathological dementias such as Alzheimer's disease (AD), and occurs in the absence of gross neuropathological changes. However, we recently identified several candidates that are known to confer risk for AD (*Trem2 & Inpp5d*) as significantly associated with memory status in a 'normal' aging murine genetic reference group (BXD panel). This led to the hypothesis that common mechanisms may underlie both 'normal' aging and AD-related memory deficits. Using standard contextual fear conditioning, we obtained an average memory index for each of 15 aging BXD strains tested (age=14±0.7mo). Memory index varied across the population (range=0-61.4% freezing during memory test) and genetic interval mapping identified an area on chromosome 4 that suggestively modulates memory function during aging. Heterochromatin protein 1 binding protein 3 (*Hp1bp3*) was identified as a top candidate responsible for aging- and AD-related memory decline based on our data showing that: 1) age-matched BXD hippocampal transcript data identified *Hp1bp3* as *cis*-regulated, 2) HP1BP3 protein is enriched in the hippocampus of aging impaired mice, 3) *Hp1bp3* is involved in memory as *Hp1bp3*$^{-/-}$ mice are impaired on hippocampus-dependent working memory as measured on the T-maze test of spontaneous alternation [WT=91 ± 4%, KO= 49 ± 7%, $t(12)=5.095$, $p<.001$)], and, 4) *HP1BP3* transcript is enriched in the hippocampus of human AD patients as compared to age-matched non-demented controls. *Hp1bp3* has also been shown to directly interact with amyloid precursor protein (APP), a well-known gene product harboring causal mutations linked to overproduction of Aβ and AD, supporting its involvement in the pathogenesis of AD.

In order to identify targets downstream of *Hp1bp3* that are likely to mediate individual genetics differences in memory decline, we used transcript expression data from the hippocampus of BXDs to generate expression QTLs (eQTLs) that mapped to the *Hp1bp3* locus. One such eQTL was *Wdfy3*, an autophagy protein found to be enriched in the hippocampal proteome of aging mice and hippocampal transcriptome of human AD patients. Utilization of existing GWAS data confirmed *WDFY3* is nominally significantly associated with late-onset AD across a diverse human population. As dysfunction in autophagic processes has been linked to memory decline in both aging and AD, we provide a functional link between *Hp1bp3*, its downstream effector *Wdyfy3*, and memory deficits in both conditions. In addition to positional candidates, *Trpc3* was identified as significantly correlated with memory status in our BXD panel, as well as in the impaired murine hippocampal proteome and human AD hippocampal transcriptome. Subsequent studies performing intrahippocampal knockdown of *Trpc3* in the hippocampus of presymptomatic male 5XFAD mice (4mo) was sufficient to delay the onset of working memory deficits typically seen in this model at 9 mo (Ctrl = 45.3 ± 5.51%, TRPC3 KD = 58.2 ± 3.51%, $p=0.04$). These genes and additional candidates identified via our systems genetics approach will be combined with multi-layered omics data in order to create network models to better predict and understand the common mechanisms underlying memory decline in both 'normal' aging and AD. Identification of novel gene variants that compound or mitigate the onset and severity of memory decline is of major significance for biomarker development and personalized therapeutics.

Longitudinal quantification of atrophy using MRI in a mouse model of Alzheimer's disease

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A hallmark of Alzheimer's disease (AD) is the progressive nature of atrophy in the neocortex. In humans, regions comprising the hippocampal memory system show early amyloid deposition and atrophy in AD, suggesting that early signs of atrophy in the hippocampus may serve as predictors of clinical decline. Here we use the CK-p25 AD-like conditional neurodegeneration mouse model and whole-brain structural imaging to characterize longitudinal structural alterations due to p25 overexpression-induced cell death. Unlike conventional atlas-based segmentation methods, latent atlas techniques enable segmentation of brain structures that changes over time using annotation from small sample. Consequently, latent atlas-based segmentation is specifically suitable for estimating neural tissue undergoing progressive atrophy. We created a latent atlas of mouse brains undergoing neurodegeneration to estimate longitudinally the volume and shape of the forebrain. In the CK-p25 mouse model, progressive cell death results in a dramatic reduction of cortical gray matter and consequently an increased volume of the ventricles progressively throughout the degenerative process. The ventricles are thus a well-defined marker of the process. We quantified the reduction in volume and changes in the shape of the ventricles to estimate the variability of the neurodegenerative process across animals. Further, we are creating a longitudinal atlas that reflects the state of the brain as a function of the stage of the neurodegenerative process. Extending this approach to segmentation of neural structures will enable translation of these tools to humans with the animal model serving as a gold standard. We expect that such atlases will be useful to characterize the progressive nature of neurodegenerative conditions, and could potentially estimate the presence of such a condition at early stages and estimate its aggressiveness.

Peripheral circadian clocks modulate nutrient dependent changes in lifespan and fat metabolism

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Abstract

Endogenous circadian clocks orchestrate several metabolic and signaling pathways that are known to modulate lifespan, suggesting clocks as potential targets for manipulation of metabolism and lifespan. Lifespan can be extended in animal models by dietary restriction (DR), and while the underlying mechanisms are largely unknown, increases in fat metabolism are implicated. We report here that the core circadian clock genes, *timeless* and *period,* are required for the response to DR in *Drosophila*, such that null mutants of *timeless* or *period* show reduced lifespan and fat turnover under DR conditions. Consistent with the involvement of a circadian mechanism in the response to DR, we find that DR enhances the amplitude of cycling of most circadian clock genes, including *timeless,* in peripheral tissues. Furthermore, overexpression of *timeless* in peripheral tissues improves its oscillatory amplitude and extends lifespan under *ad libitum* conditions. Importantly, effects of *timeless* on lifespan appear to be mediated through increases in fat metabolism. These findings identify a critical role for specific clock genes in modulating the effects of nutrients on fat metabolism and aging.

The Mitochondrial-derived Peptide Humanin is a Potent Inducer of Autophagy

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Autophagy is a cellular process that degrades abnormal proteins and dysfunctional organelles. The increase of abnormal proteins and dysfunctional mitochondria inside cells has been shown to be a causative role in the functional deterioration of biological systems during aging and age-related diseases. Therefore, a therapeutic strategy that can accelerate the elimination of these toxic molecules via autophagy may slow down the process of aging and age-related diseases.

Humanin is a 24 amino acid peptide encoded from the 16S rRNA region of the mitochondrial DNA. The level of humanin decreases with age in human plasma and Alzheimer's disease (AD) patient brain. We also have shown that humanin has broad neuroprotective and cytoprotective effects in aging and age-related diseases**.** Two cell surface receptors have been identified for humanin: humanin can interact with either FPRL1 or CNTFR/WSX-1/gp130 receptor complex and signal through the JAK/STAT and ERK1/2 signaling pathways that are well known to regulate autophagy in response to starvation. Based on the signaling pathway, here, we demonstrate that humanin induces autophagy in several cell types including HEK293 (normal embryonic kidney cells), SH-SY5Y (neuroblastoma), and B16 (melanoma). We observed an increased level of LC3-II and p62, a marker of autophagosome by western blot and immunocytochemistry. We also observed an increase in the number of autophagosomes and autolysosomes in HEK293 cells stably expressing mRFP-GFP-LC3, a dual-tag reporter of autophagy, following humanin treatment. In addition, we investigated the signaling pathways activated by humanin using a phospho-antibody array in SH-SY5Y cells. This revealed several pathways known to regulate autophagy.

Humanin's role as an autophagy inducing peptide makes it a potential therapeutic drug and this role may be related to its apparent effects of enhancing longevity observed in other systems.

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Role of mTOR signaling in adiposity—insights from Lamin A/C-deficient mice treated with rapamycin

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Abstract:

Mammalian TOR (mTOR) signaling regulates many fundamental metabolic and physiological processes. However, the *in vivo* functions of mTOR signaling that control lipid metabolism are not well understood. Furthermore, while the role of rapamycin in suppressing both mTOR complex 1 (mTORC1) and mTORC2 signaling, as well as extending lifespan in many genetic backgrounds of mice is well known, its regulation of adiposity is still controversial.

Previously, we demonstrated that rapamycin reverses elevated mTORC1 signaling and extends lifespan in lamin A/C-deficient mice (*Lmna*$^{-/-}$ mice). Because *Lmna*$^{-/-}$ mice are runts and were noted to lack fat, we speculated that signaling pathways in lipid metabolism might be dysregulated and contribute to the short lifespan of *Lmna*$^{-/-}$ mice. Here, we applied *Lmna*$^{-/-}$ mice as a model to evaluate the role of mTOR signaling in lipid metabolism mediated by rapamycin in adipose tissues.

We reported that life extension by rapamycin is associated with increased body weight and fat content in *Lmna*$^{-/-}$ mice. This increased adiposity came with suppressing elevated energy expenditure by rapamycin in *Lmna*$^{-/-}$ mice. These metabolic phenotypes, as well as life extension, can be partially captured by increasing housing temperature (30 ^{o}C) in *Lmna*$^{-/-}$ mice. At the molecular level, increased adiposity is associated with increased Lipin 1 expression, a target protein of mTOR, in white adipose tissue. These beneficial effects, however, were not observed in long-lived *Lmna*$^{-/-}$ mice lacking one copy of S6K1 (*Lmna*$^{-/-}$ *S6K*$^{+/-}$ mice), one of the major targets of mTORC1 signaling. *Lmna*$^{-/-}$ mice overexpressing 4EBP1 (*Lmna*$^{-/-}$ *4EBP1* mice), the other downstream target of mTORC1 signaling, manifested reduced adiposity and surprisingly an even shorter lifespan. The beneficial effects by rapamycin, such as life extension, were not captured in mice carrying *Lmna* H222P missense mutation (*Lmna*$^{H222P/H222P}$ mice), the other mouse model for muscular dystrophy and dilated cardiomyopathy without lipodystrophy.

These findings show that rapamycin-mediated mTOR signaling contributes to accumulating adiposity, which plays a partial role in life extension by rapamycin in *Lmna*$^{-/-}$ mice. Together, these findings point to the link between reduced A-type lamin function and lipid metabolism, and provide one potential avenue for clinical intervention that could benefit patients with diseases associated with reduced lamin A function.

Regulation of Ubiquitin Metabolism by a Direct Phosphorylation Mechanism

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There is mounting evidence that many human diseases – particularly diseases related to protein misfolding and aggregation such as neurodegenerative disorders - are associated with diminished function of the ubiquitin-proteasome system (UPS) and altered ubiquitin homeostasis. Given the emerging consensus that dysregulation of ubiquitin homeostasis is a key feature of neurodegeneration, some have proposed restoring ubiquitin levels as a potential therapeutic strategy. However, very little is known about regulation of ubiquitin homeostasis in physiological conditions, during cellular aging, in response to cellular stress, or in states of disease. Thus, there is a critical need to dissect the basic mechanisms responsible for regulating ubiquitin metabolism and to identify new pathways which may be targeted to facilitate precise manipulation of ubiquitin homeostasis in the context of disease cells.

Here, we summarize our recent findings that phosphorylation of ubiquitin regulates its metabolism in the cell. Based on our results from live cell imaging, reconstitution biochemistry, and biophysical experiments we propose that direct phosphorylation of ubiquitin prevents the recycling of ubiquitin conjugates from substrates during degradation, and that the cellular concentration of ubiquitin is tightly regulated by a ubiquitin phosphoregulatory cycle. These results have important implications for how cells maintain ubiquitin homeostasis and may reveal therapeutic strategies for restoring ubiquitin levels in the context of aging and disease.

Neurocognitive Characterization of Cognitive Control in Older Adults with Exceptional Memory

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Abstract

While most people associate human aging with declines in long-term memory function the most striking change with advancing age is the dramatic increase in variability across older adults. Understanding the factors contributing to this variability may be key in helping people cope with decline in their memory functioning including the dramatic changes that are a hallmark of Alzheimer's disease. We have recently identified a cohort of individuals 80 years and older with memory function typical of much younger adults. These SuperAgers (SAs) are unremarkable in other non-memory neuropsychological tests. However, SA individuals are typically APOe4 negative and their brains show preserved cortical thickness and volume typical of 30-year younger adults. SA's also have thicker left anterior cingulate cortices (ACC) as compared to even much younger adults with typical memory ability (Rogalski et al., 2012).

To explore the neurocognitive significance of differences in SA brain structure we asked SAs and age-matched controls with age-typical memory function to perform a cognitive control task while we monitored their brain waves using scalp electroencephalography (EEG). In our version of the Go NoGo task participants one letter presented 70% of the time cues a response while another letter presented 30% of the time cues withholding the response. This task is dependent on the ACC and areas of prefrontal cortex associated with cognitive control. A recent study (Cid-Fernandez, Lindin & Diaz, 2014) of patients with amnestic mild cognitive impairment (aMCI) found patients to be behaviorally impaired at a similar task. Likewise, cognitive control event-related potentials (ERPs) calculated from EEG recordings during the task were reduced for the aMCI patients. In our study SA's task accuracy and response time did not differ from controls; however, NoGo error rate was significantly correlated with several measures of long-term memory performance across groups. ERPs known to originate from the ACC and surrounding cortical areas (P2, and N2/P3) dramatically differed between groups with SA ERPs being much larger in left fronto-central electrodes. In general SAs appeared to engage both hemispheres while doing the task while controls favored the right hemisphere. SA ERPs showed the opposite pattern observed in aMCI patients relative to controls and were characteristic of ERPs of much younger adults suggesting that the differences in SA brain structure, particularly their larger ACC, may have functional significance.

To further explore the functional significance of differences in brain structure, we calculated Global Field Synchronization (GFS; Koenig et al., 2001) in both resting-state and task-related EEG recordings as a measure of functional connectivity. A previous study found that GFS was associated with cognitive decline during Alzheimer's disease (Koenig et al., 2005). Using GFS we found no differences during rest between SAs and controls. In contrast, we found that SAs showed an increase in GFS during Go-NoGo task engagement while controls showed a decrease with respect to rest. Likewise, the degree to which an individual showed an increase in task GFS relative to rest was strongly correlated with memory performance across groups ($r=0.70$).

We believe these results suggest that differences in SA cortical thickness and ACC structure 1) may contribute to preserved neural functioning of areas associated with cognitive control and 2) preserve functional connectivity particularly during task engagement. While the ACC is not typically considered to be a part of the long-term memory network it is a critical site for the transmodal integration of multiple limbic and neocortical functions including attention and motivation, which are essential for proper memory function and may be critical for attention monitoring during learning. While the origins of the structural and functional differences observed in SAs are still unknown our neurocognitive characterization of these differences provide a useful target for training in middle- and older-aged adults.

miR-29: A novel biomarker and regulator of aging

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MicroRNAs (miRNAs), which regulate a diverse array of genes and block gene expression post-transcriptionally, have the ability to promote aging by affecting multiple pathways. In addition, miRNAs offer significant advantages as biomarkers because they are highly stable and can be detected with high sensitivity and specificity. We and others have identified miR-29 as a miRNA that is continually induced with age during the entire lifespan of the animal. In particular, we have observed miR-29 induction with age in various tissues isolated from 2-month and 2-year old wildtype mice. We are also currently investigating whether miR-29 could serve as a reliable biomarker of aging in humans. To do this, we have isolated blood, serum and buccal swab samples from individuals 0-99 years of age and have isolated RNA from these samples in order to measure miR-29 levels.

Furthermore, to investigate whether miR-29 could be a molecular timer that regulates lifespan, we generated transgenic mice that overexpress miR-29 under a tetracycline-inducible promoter (miR-29TG). Induction of miR-29 at birth resulted in striking signs of premature aging, including alopecia, sclerotic skin, kyphosis, infertility, and reduced lifespan. miR-29TG mice also show a marked increase in senescence-associated (SA)-β-gal staining as seen during normal aging and decreased proliferation in the skin, intestine and spleen. Together, our results show that miR-29 could serve as a reliable biomarker of aging and that induction of miR-29 is sufficient to drive aging *in vivo*.

Genetic suppression of β2-adrenergic receptors ameliorates tau pathology in a mouse model of tauopathies

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Accumulation of the microtubule-binding protein tau is a key event in several neurodegenerative disorders referred to as tauopathies, which include Alzheimer's disease, frontotemporal lobar degeneration, Pick's disease, progressive supranuclear palsy, and corticobasal degeneration. Thus, understanding the molecular pathways leading to tau accumulation will have a major impact across multiple neurodegenerative disorders. To elucidate the pathways involved in tau pathology, we removed the gene encoding the beta-2 adrenergic receptors (β2ARs) from a mouse model overexpressing mutant human tau. Notably, the number of β2ARs is increased in brains of AD patients and epidemiological studies show that the use of beta blockers decreases the incidence of AD. The mechanisms underlying these observations, however, are not clear. We show that the tau transgenic mice lacking the β2AR gene had a reduced mortality rate compared to the parental tau transgenic mice. Removing the gene encoding the β2ARs from the tau transgenic mice also significantly improved motor deficits. Neuropathologically, the improvement in lifespan and motor function were associated with a reduction in brain tau immunoreactivity and phosphorylation. Mechanistically, we provide compelling evidence that the β2AR-mediated changes in tau were linked to a reduction in the activity of GSK3β and CDK5, two of the major tau kinases. These studies provide a mechanistic link between β2ARs and tau and suggest the molecular basis linking the use of beta-blockers to a reduced incidence of AD. Furthermore, these data suggest that a detailed pharmacological modulation of β2ARs could be exploited to develop better therapeutic strategies for AD and other tauopathies.

Cholinergic contributions to PASA and functional compensation

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Neuroimaging studies have indicated increased recruitment of prefrontal regions coupled to reduced activation of posterior regions in task-performing older adults. This shift of activity in cortical networks is described as posterior-to-anterior shift in aging (PASA). What cellular mechanisms contribute to PASA and how it provides functional compensation for age-related decline in cognitive capacities remains unknown? Cortically-projecting forebrain cholinergic neurons modulate cortical networks and facilitate attentional processes. Here we examined whether cortical cholinergic inputs contribute to PASA expression and maintenance of attentional capacities in aging. Young (3 months) and aged (24 months) Wistar rats were trained in a sustained attention task (SAT) that requires them to distinguish between signal and non-signal events. After attaining criterion performance (≥70% correct responses for 3 consecutive sessions), rats received bilateral infusions of cholinoselective immunotoxin 192-IgG SAP either into the prefrontal cortex (PFC) or posterior parietal cortex (PPC) to produce partial cholinergic deafferentation. Control animals were infused with saline. Following behavioral testing 4 weeks post-surgery, animals were perfused 45-min after the last session to examine changes in neuronal activity in the PFC and PPC using c-fos immunohistochemistry. Partial prefrontal cholinergic deafferentation in aged rats produced robust deficits in response accuracy on signal trials as compared to aged sham ($p=0.04$) and young lesion ($p=0.03$) rats. In general, c-fos expressing neurons were higher in the PFC of aged rats as compared to young rats. Although prefrontal neuronal activity did not differ between the aged sham and PFC lesion group, there was a trend for a higher neuronal activity in the PPC of the latter. Surprisingly, attentional performance displayed a negative correlation with the prefrontal activity. Neuronal activity in the PPC did not correlate with performance. PPC-infused aged rats displayed no lesion effect on SAT and performed better than aged rats infused with 192 IgG-SAP into the PFC ($p=0.04$). Moreover, partial loss of cholinergic inputs into the PPC reduced PFC recruitment as compared to PFC lesioned aged rats. Collectively, these data suggest that reduced cortical activity in young rats compared to aged rats may represent better neural capacity, or the efficient utilization of normal brain regions, for task performance. Moreover, PASA is not triggered by prefrontal cholinergic inputs, but these inputs may regulate the reciprocal interactions between the PFC and PPC networks to maintain optimal attentional performance in aging.

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IRE1α is an endogenous substrate of endoplasmic reticulum-associated degradation

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Our laboratory (http://www.human.cornell.edu/dns/qilab/index.cfm) aims to explore the physiological role of ER stress response and inflammation in the context of several disease models using genetic and cellular biological tools and to produce new insights into the etiology of these diseases. Endoplasmic reticulum-associated degradation (ERAD) represents a principle quality control (QC) mechanism to clear misfolded proteins in the ER; however its physiological significance and the nature of endogenous ERAD substrates remain largely unknown. In a recent study, we discover that IRE1α, the sensor of unfolded protein response (UPR), is a bona fide substrate of the Sel1L-Hrd1 ERAD complex. Mechanistically, ERAD-mediated IRE1α degradation occurs at the steady state and is attenuated in response to ER stress. Both intramembrane hydrophilic residues of IRE1α and lectin protein OS9 are required for IRE1α degradation. ERAD deficiency causes IRE1α accumulation and mild activation, leading to cellular hypersensitivity to ER stress and inflammation. In vivo, enterocyte-specific Sel1L-knockout mice (*Sel1L*$^{\Delta IEC}$) are viable and appear normal, indistinguishable from their wildtype littermates in terms of body weight and colonic epithelial morphology. IRE1α is significantly stabilized and accumulates in colonic epithelium in the absence of Sel1L. The *Sel1L*$^{\Delta IEC}$ mice are more susceptible to experimental colitis in an IRE1α-dependent but CHOP-independent manner. Collectively, these results demonstrate that Sel1L-Hrd1 ERAD serves a distinct, essential function in restraint of IRE1α signaling in vivo by managing its protein turnover.

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Serotonergic Circuits Mediate Protein Valuation and Aging

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Dietary restriction has long been studied in several experimental systems as a robust manipulation that extends lifespan and improves health. It has been appreciated only recently, however, that changes in the consumption of specific nutrients rather than total calories *per se* is important, and dietary protein has emerged as a key parameter in this response. In certain instances, however, nutrient effects on lifespan are independent of consumption, leading us to test the hypothesis that perceptive, cell non-autonomous processes may be important aging regulators.

We report that components of a neural circuit that specify the value of ingested protein significantly alter lifespan. Using a newly designed continuous feeding monitor, we found that the fruit fly, *Drosophila melanogaster,* exhibits a transient feeding preference for protein-containing food after modest starvation. We exploited this behavioral phenotype to perform a reverse genetic screen to identify genes and specific neurons that are required for this choice behavior, which would implicate them in either perception of protein availability or recognition of value of the protein meal. In result, we identified serotonin, serotonin receptor 2a, and the solute carrier 7-family amino acid transporter, JhI-21, are required to establish the value of ingested protein in an energy state-dependent manner. Disruption of any one of these genes abrogated protein-feeding preference and increased lifespan, independent of food intake. Reduced serotonin synthesis or loss of 5HT2a nearly doubled fly lifespan when the animals were maintained in a complex nutritional environment. These findings establish that evolutionarily conserved neuromodulatory systems that govern nutrient assessment are also capable of orchestrating rapid and reversible effects on aging.

Together, our data provide, to our knowledge, the first evidence that the perception or ingestion of dietary protein is systemically regulated in the fly, and they implicate a specific amino acid transporter and the serotonin/serotonin receptor 2a axis in this regulation.

Role of mitochondrial matrix peptidase ClpP in mitochondria and stress resistance

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Mitochondrial dysfunction is an important contributor to aging and age-related diseases. Studies have shown that maintenance of mitochondrial homeostasis through the mitochondrial unfolded protein response (mtUPR), extends lifespan in *C.elegans*.[1] The mtUPR is a stress response pathway that activates transcription of nuclear-encoded mitochondrial chaperone genes to promote protein homeostasis in the mitochondria.[2] One key component of the mtUPR response is the mitochondrial matrix caseinolytic peptidase P (ClpP), the endopeptidase component of the mitochondrial matrix ATP-dependent ClpXP protease[2]. Importantly, inhibition of ClpP using RNAi attenuates mtUPR-mediated lifespan extension in *C.elegans* mit mutants.[1] This suggests a critical role of ClpP in the maintenance of mitochondrial homeostasis and longevity. However, no information is available about the function of ClpP in mitochondria or its role in stress resistance in mammals. Skeletal muscle is one of the tissues that predominantly express ClpP and in order to understand the functions of ClpP at cellular level, we have generated a stable cell line of ClpP knockdown in C2C12 muscle cells. A reduction in ClpP by ~70% alters mitochondrial morphology that is characterized by round-shaped and smaller mitochondria than control cell mitochondria. While mitochondrial fusion proteins are unaffected by the decline in ClpP, level of mitochondrial fission protein Drp1 is elevated in ClpP KD cells. Reduced levels of ClpP decreased basal (~23%) and maximal respiration (~54%) and elevated glycolysis. ClpP knockdown reduced activities of electron transport chain (ETC) complexes I and II (~40% and ~22%, respectively) and also decreased expression levels of ETC complex subunits. In addition, ClpP knockdown cells have elevated levels of reactive oxygen species (ROS) generation (~4.6- and ~2.4-folds by complexes I and II-linked substrates, respectively) and lower membrane potential (~15%) than control cells. Reduction in ClpP also reduces cell proliferation, alters cell morphology and inhibits cytosolic protein translation. ClpP knockdown cells exhibited reduced response to mtUPR induction, assessed by the expression of mitochondrial heat shock protein Hsp60. Decline in ClpP made cells more susceptible to oxidative stress mediated cell death by H_2O_2 and paraquat. Together, our study demonstrates for the first time the critical role of mitochondrial protease ClpP in the maintenance of mitochondrial function and resistance to oxidative stress.

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Human and fly genetics implicate a *CD2AP* susceptibility network at synapses in Alzheimer's disease

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Genomewide associations scans have identified 22 loci associated with Alzheimer's disease (AD) risk. Based on a functional validation strategy examining gene candidates in *Drosophila*, our studies implicate a susceptibility network comprised of *CD2AP* and related mediators of adhesion (*CASS4*, *FERMT2, PTK2B*) and endocytosis (*PICALM*, *BIN1*, *AP-2α, RIN3*). Genetic manipulation of fly homologs for many of these loci alters the neurotoxicity of Tau, which forms neurofibrillary tangle pathology in AD. In order to better define the nervous system function of this putative regulatory pathway, we have studied *cindr*, the single conserved fly homolog of the *CD2AP* SH3-domain adaptor protein. Cindr is highly expressed in neurons, showing enrichment at both peripheral and central synapses. Immunoprecipitation of Cindr from adult brains confirms an interaction with Actin and identifies novel associations with synaptic proteins, including the Ca^{2+} sensor, Synaptotagmin, the synaptic vesicle reserve pool marker, Synapsin, and multiple core mediators of clathrin-dependent endocytosis, including AP-2σ, EPS-15, and Hsc-70, which regulate synaptic vesicle recycling. We have also generated a *cindr* deletional null allele through transposable element-mediated recombination. Since global development and maintenance of the brain appeared normal, we explored a synaptic regulatory role. Studies at the larval neuromuscular junction reveal a "ghost bouton" phenotype, consistent with pre- and post-synaptic membrane uncoupling. Further, electrophysiologic studies show preserved basal neurotransmission but increased facilitation following high-frequency stimulation, consistent with altered synaptic vesicle release probability and impaired plasticity. We are currently extending our studies to mouse models, beginning with confirmation of the CD2AP synaptic localization and examination of hippocampal neurophysiology in knockout animals. Based on our results, we postulate that dysfunction within the CD2AP susceptibility network attenuates synaptic efficacy, and leads to enhanced vulnerability to Tau-induced neuronal injury in AD.

The role of glycosphingolipids in renal aging.

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With increasing age, there is a general decline in organ function and their ability to respond to physiological and pathophysiological stimuli. With regards to the kidney, there is an age-associated progressive decline in renal function even in the absence of obvious renal diseases. With normal aging, a number of functional and structural changes occur in the kidney both in humans and in laboratory animals, including decreased renal blood flow and glomerular filtration rate, changes in tubular function that impair the ability to concentrate urine, glomerulosclerosis, and tubulointerstitial fibrosis. Furthermore, as drug excretion is also reduced in the aged kidney, the pharmacokinetics and pharmacodynamics of many drugs used by the elderly are altered, making them more likely to suffer long-term consequences following acute kidney injury. Thus, the aged kidney has increased exposure to renal stressors, enhanced susceptibility to injury, and decreased ability to repair itself following injury. As a result, the elderly have an increased incidence of renal disease than younger adults, including chronic kidney disease and end-stage renal disease.

Caloric restriction (CR), without a reduction in essential nutrients, preserves kidney function during aging. As compared to kidneys from young animals, aging kidneys from *ad libitum* (AL) fed, but not CR animals, have increased levels of apoptosis, necrosis, fibrosis, and inflammation, processes mediated in part by sphingolipids. During aging, sphingolipid levels are altered in several different organs and tissues in mammals, including the brain and liver. However, the role of sphingolipids in kidney aging is largely unknown. We hypothesized that alterations in kidney sphingolipids play a role in the declining kidney function that occurs during aging. To test this hypothesis, we measured the sphingolipid profile in young (3 mo.), middle aged (9 mo.) and old (17 and 24 mo.) C57BL/6 male mice. Specific species of glycosphingolipids were elevated as much as 10-14 fold during aging in the kidney cortex. The kidney was the source of these glycosphingolipids as their levels were not elevated in the blood. Importantly, CR prevented accumulation of glycosphingolipids during aging, suggesting that these lipids are important mediators of the aging process. To begin to elucidate a role for glycosphingolipids in the aged kidney, we studied their impact on kidney cells (mesangial and proximal tubule) in culture. In mesnagial cells, elevated glycosphingolipids were sufficient to increase expression of inflammatory cytokines as well as induce cellular hypertrophy. Alternatively, in proximal tubule cells, elevated glycosphingolipids induced mitochondrial dysfunction and apoptosis. Taken together, our data indicate novel roles for glycosphingolipids in renal aging and suggest that caloric restriction maintains kidney function during aging at least in part by regulating sphingolipid metabolism. Importantly, there is potential for translation to humans as there are FDA approved inhibitors glucosylceramide synthase currently utilized for the treatment of Gaucher disease. Thus, glycosphingolipids represent compelling novel targets for the development of therapeutics that can preserve kidney function during aging as well as treat a wide variety of kidney diseases both in the elderly and in the general population.

The contribution of age-related complement dysfunction on T cell immunity to infection

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2013 AFAR Research Grant

Age-associated immune senescence results in increased susceptibility to infection and decreased vaccine efficacy, at a staggering cost to our health-care system. Upon infection, the immune system must: (1) limit the spread of the pathogen; (2) identify the class of pathogen to direct the appropriate immune response; and (3) provide long-lived immunity to protect against re-infection. With aging, these functions break down. Our *long-term goal* is to identify areas of intervention that will improve immunity in the elderly. The *objective of this project* has been to determine if complement-mediated early immune coordination is compromised in late life, impairing downstream adaptive immunity.

Proteolytic complement (C') proteins are activated within minutes of microbial entry into the host. The three C' pathways intersect at the C3 protein, resulting in C3 cleavage and deposition of the C3b fragment on the pathogen surface. Since C3b deposition is critical for opsonization of pathogens to promote their phagocytosis, we hypothesize that this process plays a key coordinating role between the innate and adaptive immune systems by targeting microbial pathogens specifically to dendritic cells (DCs). $C3^{-/-}$ mice mount poor T cell responses to many microorganisms, suggesting a broad role for C' in coordinating cellular immunity. Adaptive immunity is particularly hard-hit in the elderly, and there are many age-associated diseases associated with defective complement function. Yet, how aging affects C' pathways has been mostly unexplored.

We hypothesize that C3 functions broadly to target pathogens to DCs for antigen uptake and presentation to the adaptive immune system. We propose that this is a key coordination point between the innate and adaptive responses that becomes less efficient with aging. Our preliminary data shows an age-associated reduction in serum C3 levels in mice and humans. After *in vitro* incubation with *Listeria monocytogenes* (*Lm*), C3b deposition on the bacteria is significantly reduced when sera originate from aged mice or humans. This correlates with reduced *in vivo* delivery of *Lm* into DCs of old mice, which can be restored by *in vitro* pretreatment with adult serum. Using adoptive transfer of adult naïve OT-I TCR transgenic CD8 T cells (specific for the $H\text{-}2K^{b}\text{-}OVA_{257\text{-}264}$ SIINFEKL epitope) to evaluate the impact of the old "priming environment" on T cell responses to *Lm*-OVA, we find that adult OT-I cells show impaired expansion in old animals following infection with Lm-OVA, which is restored to adult levels if the bacteria are pre-coated with adult serum prior to infection.

A better understanding of this early C'-mediated immune coordination, and its impact upon immune function in late life may establish an innovative framework for broad new approaches to enhance cellular immune responses in the elderly.

Dynamic changes in chromosome conformation during neuronal differentiation.

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Transcriptional networks in fetal and early postnatal cortical development have indicated that chromatin-remodeling complexes have distinct expression patterns during neural differentiation and are implicated in multiple disorders during brain development, including autism, intellectual disability, and schizophrenia. However, how concerted action of chromatin remodelers define chromosomal organization in neural differentiation has not been elucidated.
Hi-C combines chromosome conformation capture technology and high-throughput sequencing to comprehensively map the genome-wide architecture of chromosomes. Here, we obtained Hi-C data from germinal zone (GZ) and cortical plate (CP) of a fetal brain (gestation week 17-18).
Principal component analysis revealed that inter-chromosomal structure is largely conserved between CP and GZ. Interchromosomal structure is highly correlated to GC content, gene number, and chromatin accessibility (DNaseI hypersensitivity; DHS), indicating that chromosome conformation reflects global genomic features related to gene regulation. Genes in regions with the most dynamic chromatin structure changes are enriched for neuronal genes, emphasizing the functional relevance of global chromosome architecture during neural development. As well as interchromosomal conformation, regions with dynamic intrachromosomal compartment changes are associated with gene expression changes and epigenetic modifications. Moreover, genes in highly interacting regions tend to share co-expression pattern, which is mediated by epigenetic regulation. Collectively, these results suggest that chromatin architecture can provide novel insights about gene regulatory landscape during neuronal differentiation.

The role of cellular senescence in age-related tissue dysfunction and diseases

Ming Xu Mayo Clinic PD14059

Aging is the biggest risk factor for most of the chronic diseases that account for morbidity, mortality, and health expenditures, including diabetes, cardiovascular disease, cancers, and neurodegenerative diseases. Although fundamental mechanisms responsible for aging are only just beginning to be understood, cellular senescence appears to be an important driver of age-associated dysfunction and diseases. We hypothesize that age-associated dysfunction can be induced by transplanting senescent *vs*. non-senescent cells. We induced cellular senescence in rat preadipocytes (fat cell progenitors) by irradiation. Twenty days after irradiation, these rat preadipocytes had increased senescence-associated beta-galactosidase (SABG) activity and developed a senescence-associated secretory phenotype (SASP). We then transplanted approximately 2 million senescent cells or healthy non-senescent cells into the intraperitoneal (IP) cavity of healthy young Long Evans rats. We observed that both transplanted control and senescent cells were still present in the IP cavity 3 weeks after transplantation. Compared to rats transplanted with non-senescent cells, rats transplanted with senescent cells developed glucose intolerance starting at 5 days after transplantation that lasted for at least 3 months. These rats also had cardiovascular dysfunction 1 month after transplantation. We are currently making several lentivirus comprising luciferase for tracking the transplanted cells *in vivo* and a drug-inducible "suicide" gene or shRNA to specifically kill or manipulate the transplanted cells *in vivo*. This novel senescent cell transplantation model could be a valuable tool for understanding the roles and mechanisms of cellular senescence in aging and age-associated diseases.

Ameliorating age-related biophysical deficits in dorsal CA1 through viral overexpression of CREB protein

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Humans and animals often display learning and memory impairments as they age, however the underlying mechanisms of these impairments are poorly understood. Identifying the molecular pathways that mediate these impairments will allow us to design therapeutics to prevent or reverse these deficits. One important brain region for learning and memory is the hippocampal CA1 region. The Disterhoft laboratory has shown that CA1 pyramidal neurons from cognitively-impaired aged rats are less excitable than those from young and cognitively-unimpaired aged animals. These and many other experiments suggest that an age-related decrease in the excitability of CA1 pyramidal neurons mediates age-related cognitive impairments. Previous studies have shown that both excitability of CA1 pyramidal neurons and learning and memory can be enhanced in young adult animals by increasing levels of cAMP response element binding protein (CREB). Additionally, our recent experiments have revealed that basal levels of phosphorylated CREB (pCREB) are decreased in dorsal hippocampus with age, and that pCREB levels correlate with behavioral performance during a hippocampal-dependent spatial learning task. Together, these results suggest that elevating pCREB levels in aged animals will ameliorate both the excitability and learning and memory deficits. Therefore, this project used an adeno-associated virus to overexpress CREB in CA1 of young and aged rats. The viral infection was found to be widespread in the anterior-posterior axis of CA1. RNA extracted from infected CA1 tissue showed increased CREB mRNA levels in both young and aged animals, confirming that our virus mediated overexpression of CREB. Furthermore, as predicted, we found that infected cells were more excitable than control cells. On-going experiments are being conducted to confirm that increases in total and activated CREB protein will ameliorate age-related learning and memory deficits.

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Steven N. Austad, PhD

Dr. Steven N. Austad is a Distinguished Professor and Chair of the Department of Biology, University of Alabama at Birmingham (UAB). At UAB, he also serves as Associate Director of the Comprehensive Center for Healthy Aging, a Senior Scientist of the Nutrition Obesity Research Center and the Center for Exercise Medicine, and on the Executive Committee of the Comprehensive Neuroscience Center. Originally trained in evolutionary biology, Dr. Austad became interested in aging during field studies on the common opossum in Venezuela, where he discovered that opposums do not live significantly longer than mice. Dr. Austad's current research uses a variety of nontraditional animal species to seek to discover underlying causes of aging with a long-term goal of developing medical interventions that slow the age-related decay in human health. His work spans levels of analysis from cells to populations. He is the author of more than 150 scientific papers covering nearly every aspect of the biological aging process and has co-edited with Dr. Edward J. Masoro, the 5th (2001), 6th (2006), and 7th editions of the *Handbook of the Biology of Aging*. Dr. Austad is also a fellow of the Gerontological Society of America, a recipient of that Society's Robert W. Kleemeier Award for outstanding research. He has also received the Geron Corporation-Samuel Goldstein Distinguished Publication Award, the Nathan A. Shock Award from the Gerontological Research Center of the National Institute on Aging, the Irving S. Wright Award from the American Federation for Aging Research, and the Fondation IPSEN Longevity Prize.

Dr. Austad also serves as Scientific Director of the American Federation for Aging Research and the External Advisory Committee of the Mayo Clinic's Kogod Center on Aging. Dr. Austad maintains a keen interest in communicating science to the general public, and in that capacity has served on the Science Advisory Board of National Public Radio, written a regular newspaper column for the San Antonio Express-News (*On Aging*) and has been a consultant to the Oregon Museum of Science and Industry (Portland, Oregon), the Perot Museum of Nature and Science (Dallas, Texas), and the American Museum of Natural History (New York City). He has written popular science articles for numerous publications including *Natural History* magazine, *Scientific American*, *National Wildlife*, and *International Wildlife*. His trade book, *Why We Age* (1997), has been translated into eight languages.

Pre-aging research life:
Prior to entering aging research, Dr. Austad with a degree in English literature was a newspaper reporter, trained wild animals for the Hollywood film industry, and drove a taxi cab in New York City, and hustled pool nation-wide. With a PhD in evolutionary ecology, he has done biological field research in several parts of the United States, Venezuela, England, Kenya, Micronesia, and Papua New Guinea.

Dr. Darren Baker received his Ph.D. in Cell Biology at the University of Nijmegen and is currently an Assistant Professor of Biochemistry, Molecular Biology and Pediatrics at Mayo Clinic. He is one of the co-directors of the Glenn Laboratories of Mayo Clinic.

The aging related work of the Baker lab has focused on the progeroid gene BubR1, which encodes a core component of the mitotic checkpoint whose level of expression markedly declines with aging. About 10 years ago, the lab discovered that BubR1 hypomorphic mice that begin life with low amounts of the mitotic checkpoint protein BubR1 protein die early and develop multiple progeroid and age-related disorders. Shortly thereafter, others demonstrated that loss of function mutations in BubR1 cause mosaic-variegated aneuploidy, a human syndrome that is characterized by aneuploidy, cancer predisposition and several progeroid traits. These observations led to the idea that depletion of BubR1 with age is a key determinant of longevity and age-related disorders. His lab went on to test this hypothesis using BubR1 transgenic mice in which age-related decline of BubR1 is prevented. These mice are resistant to tumorigenesis, have an extended lifespan and delayed age-related decline in several tissues and organs important to human health in the absence of any overt negative side effects. These findings identify BubR1 and its regulator(s) as therapeutic targets for treatment of a broad spectrum of human cancers and key age-related disorders that dictate health- and lifespan.

In addition, using the BubR1 progeroid model, the Baker lab was the first to show an in vivo link between p16-induced cellular senescence and the development of age-related pathologies. Then, in collaboration with several laboratories in the Kogod Center on Aging, including the van Deursen, Kirkland and LeBrasseur labs, his lab went on to show that clearance of p16-positive senescent cells from BubR1 progeroid mice delays the onset of age-related disease, further confirming the causal link between senescence and aging and demonstrating that removal of senescent cells can prevent or delay tissue dysfunction and extend healthspan. Work in the Baker laboratory now focuses on the involvement and relevance of senescent cells in age-related diseases and normative aging.

Biosketch – Nir Barzilai, M.D.

Dr. Barzilai is a chaired Professor of Medicine and Genetics and the Director of the Institute for Aging Research at the Albert Einstein College of Medicine the home of the Nathan Shock Center of Excellence in the Biology of Aging and the Glenn center for the Biology of Human Aging. His interests focus on several basic mechanisms in the biology and genetics of aging. He is the recipient of an NIH a Merit Award the extend the healthy life span in rodents by biological interventions. He also studies families with centenarians that have provided genetic/biological insights on the protection against aging. Several drugs are developed based, in part, on these paradigm-changing studies. He is a recipient of numerous prestigious awards, including the recipient of the 2010 Irving S. Wright Award of Distinction in Aging Research. Dr. Barzilai is in the board of the American Federation for Aging Research, is its co-scientific director, and has served on several NIA study section. He is also a founder of CohBar Inc., a biotech that develops mitochondrial derived peptides as therapy for aging and its diseases. He is co-PI on the R24 Geroscience (Apollo) grant that is an effort to move the field of aging to translation. He is leading the TAME (Targeting/Taming Aging with Metformin multi central study. the His work has been profiled by major outlets, including the New York Times, the BBC and PBS' NOVA science Now, and TEDx talk.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Giovanni Bosco	Associate Professor, Genetics
eRA COMMONS USER NAME (credential, e.g., agency login) gbosco	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Boston University, Boston, MA	B.A.	1983-1988	Biology
Brandeis University, Waltham, MA	Ph.D.	1991-1998	Molecular Biology
Whitehead Institute/MIT, Cambridge, MA	Postdoc	1998-2001	Molecular Genetics

A. Personal Statement: The goal of my current research is to elucidate the molecular mechanisms through which dynamic changes in nuclear morphology and chromosome structure impinge on cellular functions such as proliferation and replicative senescence. A unique contribution we have made in recent years has been to show that condensins modulate both chromatin compaction, nuclear size and shape in interphase Drosophila and human cells. My lab's focus has recently shifted to projects that seek to elucidate molecular mechanisms of aging and senescence and age impaired memory. We have made use of Drosophila, human cell lines, wild-type primary cells and primary cells from progeria patients in order to understand the interplay of chromosome structure, nuclear lamin function and changes in gene expression that cause laminopathies and associated age dependent phenotypes. In a related project, my lab also is interested in understanding how changes in chromatin and other epigenetic factors contribute to maintenance of long term memory and mechanisms of age dependent memory decline.

B. Positions and Honors

Positions and Employment

1984-1986 & 1988: Undergraduate student researcher, Boston University
1988-1990: Technician, Univ. of Colorado, Boulder
1990-1991: Technician, Harvard Genome Lab, Harvard University
1991-1998: Ph.D. student, Brandies University
1998-2002: Post-doctoral fellow, Whitehead Institute for Biomedical Research & MIT
2002-2009: Asst. Professor, Dept. of Molecular and Cellular Biology, University of Arizona
2009-2012: Associate Professor (w/Tenure), Dept. of Molecular and Cellular Biology, University of Arizona
2009-2012: Chair, Genetics Graduate Interdisciplinary Program, University of Arizona
2012-present: Associate Professor, Dept. of Genetics, Geisel School of Medicine at Dartmouth

Honors and Fellowships

1987-1988 National Science Foundation Undergraduate Research Fellow, Dept. of Biology, Boston University, Boston, MA
1990 (summer) National Aeronautics and Space Administration (NASA) Planetary Biology Internship Award, Dept. of Zoology, University of California at Davis, Davis, CA
1998-2000 Margaret and Herman Sokol Post-doctoral Fellow, Whitehead Institute for Biomedical Research, Cambridge, MA
1999-2001 Damon Runyon-Walter Winchell Post-doctoral Fellow of the Cancer Research Fund
2002 MIT/Merck Post-Doctoral Fellowship, Whitehead Institute for Biomedical Research, Cambridge, MA

C. Selected peer-reviewed publications (out of 32)**.**

Most relevant to the current application (in chronological order).

1. Tom A. Hartl, Sarah J. Sweeney, Peter J. Knepler and Giovanni Bosco. (2008). Cap-H2 resolves chromosomal associations to enable anaphase I segregation in *Drosophila* male meiosis. ***PLoS Genet.*** Oct;4(10):e1000228 **PMID: 18927632**
2. Tom A. Hartl, Helen F. Smith and Giovanni Bosco. (2008). Chromosome alignment and transvection are antagonized by condensin II. ***Science 322(5906):1384 – 1387*** **PMID:19039137**
3. Christopher R. Bauer, Tom A. Hartl and Giovanni Bosco. (2012). Condensin II promotes the formation of polyploid chromosome territories by inducing axial compaction of interphase cells. ***PLoS Genet. 2012 Aug;8(8):e1002873.*** **PMID: 22956908**
4. Daniel W. Buster, Scott G. Daniel, Huy Q. Nguyen, Sarah L. Windler, Lara C. Skwarek, Maureen Peterson, Meredith Roberts, Joy H. Meserve, Tom Hartl, Joseph E. Klebba, David Bilder, Giovanni Bosco and Gregory C. Rogers (2013). SCF^{Slimb} ubiquitin-ligase suppresses condensin II-mediated nuclear reorganization by degrading Cap-H2. ***Journal of Cell Biology. Apr 1; 201(1):49-63*** **PMID:23530065**
5. Helen F. Smith, Meredith A. Roberts, Huy Q. Nguyen, Maureen Peterson, Tom A. Hartl, Xiao-Jun Wang, Joseph E. Klebba, Gregory C. Rogers and Giovanni Bosco. (2013). Maintenance of interphase chromosome compaction and homolog pairing in Drosophila is regulated by the condensin Cap-H2 and its partner Mrg15. ***GENETICS***. **195(1):127-146. PMID: 23821596.**
6. Carolyn M. George, Julianna Bozler, Huy Q. Nguyen and Giovanni Bosco. (2014). Condensins are required for maintenance of nuclear architecture. ***Cells. 22;3(3):865-882. PMID: 25153163.***

Additional publications related to the proposal (in chronological order).

1. Giovanni Bosco, Wei Du and Terry L. Orr-Weaver. (2001). DNA replication control through interaction of E2F-RB and the Origin Recognition Complex. ***Nature Cell Biol.*** 3:289-295 **PMID: 11231579**
2. Julie M. Claycomb, Matt Benasutti, Giovanni Bosco, Douglas D. Fenger and Terry Orr-Weaver. (2004). Gene amplification as a developmental strategy: Isolation of two developmental amplicons in Drosophila. ***Dev Cell.*** Jan;6(1):145-55. **PMID: 14723854**
3. Tom Hartl, Carl Boswell, Terry Orr-Weaver and Giovanni Bosco. (2007). Developmentally regulated histone modifications in Drosophila follicle cells: initiation of gene amplification is associated with histone H3 and H4 hyperacetylation and H1 phosphorylation. ***Chromosoma*** 116:197-214. **PMID: 17219175**
4. Giovanni Bosco, Paula Campbell, Joao T. Leiva-Neto and Therese A. Markow (2007). Analysis of *Drosophila species* genome size and satellite DNA content reveals significant differences among strains as well as between species. ***Genetics***. **Nov;177(3):1277-90. PMID: 18039867**
5. Celine Hayden and Giovanni Bosco. (2008). Comparative genomic analysis of novel conserved peptide upstream open reading frames and associated major open reading frames in Drosophila melanogaster reveals an overrepresentation of mitochondria-targeted proteins, ***BMC Genomics*****. Feb 1;9:61. PMID: 18237443**
6. Sarah Sweeney, Paula Campbell and Giovanni Bosco. (2008). Drosophila *sticky/citron kinase* is a regulator of cell cycle progression and epigenetic gene silencing. ***Genetics***. **Mar;178(3):1311-25. PMID: 18245345**.
7. Joseph Ahlander, Xioa-Bo Chen, Paula Campbell and Giovanni Bosco. (2008). The retinoblastoma family protein RBF1 interacts with ORC and localizes to chromatin in an E2F independent manner. ***PLoS-ONE.*** **30;3(7):e2831 PMID: 18665226**
8. Joseph Ahlander and Giovanni Bosco. (2009). Sqd interacts with the Drosophila retinoblastoma tumor suppressor Rbf. ***Biochem Biophys Res Commun. 2009 Jun 5;383(3):363-7. Epub 2009 Apr 11.*** **PMID: 19364495**
9. Maureen Peterson, Vicki L. Chandler and **Giovanni Bosco**.(2013). High SINE RNA Expression Correlates with Post-transcriptional Downregulation of BRCA1. ***GENES*** **2013, *4*(2), 226-243;doi:10.3390/genes4020226**

D. Research Support. List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects

ACTIVE

Breakthroughs in Gerontology (PI: G. Bosco) 07/01/2013 – 06/30/2015 American Federation of Aging Research
Title: Condensins and mechanisms of cellular senescence and aging

Department of Defense/DARPA (PI: G. Bosco) 04/01/2015-02/28/2017
Title: Genetic Memory

National Science Foundation (PI: C. Greene. co-PI: G. Bosco) 06/01/2015-05/30/2017
Title: ABI Development: A critical assessment of protein function annotation

COMPLETED

Arizona Center on Aging (co-PIs: F. Goodrum, G. Bosco, K. Knox)2009-2010
Title: Nuclear dysorganization and viral persistence as coordinated drivers of aging in humans

K18 GM097732-01 (PI: G. Bosco)
K18 NIH Basic Behavioral and Social Science Opportunity Network (OppNet) Short-term Mentored Career Development Awards. “Career development in epigenetic control of memory maintenance.”

1 RO1 GM069462 (PI: G. Bosco) 2009 NIH/GM
Title: Developmental control of replication by Drosophila RB

UA Center for Insect Sciences (PI: G. Bosco, Co-PI: Pak Kim Wong, Aerospace and Mech. Engineering)
Development of elctrokinetic/microfluidic devices for studying chromatin structure

AZCC ACS IRG (PI: G. Bosco) 2004
Proteomic analysis of RB interacting proteins.

2 R01 GM069462 (PI: G. Bosco) 07/01/2004 – 06/30/2013 (thru 06/30/2014 No Cost Extension) NIH/GM
Title: Chromosome pairing and condensins

Judith Campisi, Short Biosketch

Judith Campisi received a PhD in Biochemistry from the State University of New York at Stony Brook, and postdoctoral training in cell cycle regulation and cancer at the Dana-Farber Cancer Institute and Harvard Medical School. As an Assistant Professor at the Boston University Medical School, she began studying the role of cellular senescence in suppressing the development cancer. However, she soon became convinced that senescent cells also contributed to aging. She left Boston University as an Associate Professor to accept a Senior Scientist position at the Lawrence Berkeley National Laboratory in 1991. In 2002, she established a laboratory at the Buck Institute for Age Research, where she is a Professor. At both institutions, Campisi established a broad program to understand various aspects of aging, with an emphasis on the interface between cancer and aging. Her laboratory made several pioneering discoveries in these areas, and her research continues to challenge and alter existing paradigms.

In recognition of the quality of her research and leadership, Campisi has received numerous awards. These include two MERIT awards from the US National Institute on Aging, awards from the AlliedSignal Corporation, Gerontological Society of America and American Federation for Aging Research, the Longevity prize from the international IPSEN Foundation, the Bennett Cohen award from the University of Michigan, the Schober award from Halle University (Germany) and the international Olav Thon prize from the University of Oslo. She is an elected a fellow of the American Association for the Advancement of Science, and serves on numerous national and international editorial and scientific advisory boards.

Erika Check Hayden

Erika is a San Francisco-based reporter for the science journal *Nature* and teaches in the University of California Santa Cruz Science Communication program.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Dillin, Andrew G.	Professor
eRA COMMONS USER NAME (credential, e.g., agency login) andydillin	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Nevada, Reno, NV	B.S.	05/93	Biochemistry
University of California, Berkeley, CA	Ph.D.	06/98	Molecular & Cell Biology
University of California, San Francisco, CA	Postdoctoral	1998-2002	Genetics

A. Personal Statement

The goal of the proposed research is to identify the source and signal of a newly identified signaling pathway that connect distal cell types to coordinate endoplasmic reticulumn proteotoxicity. My lab has a strong backgroud in proteotoxicity in both worms and mice, and perhaps, an even longer standing in issues related to metabolic flux. This proposal is centered around multiple methodoligies using the nematode *C. elegans*, many of which have been pioneered in my lab and my collaborators labs. As a group leader, I have always encouraged my postdocs and graduate students to explore new areas of biology and reach out of their collective comfort zone. This approach has allowed my laboratory to make seminal discoveries in many areas, including diet restriction mediated longevity, insulin/IGF1 signaling, mitochondrial biology and protein homeostasis. In summary, I have demonstrated both a strong record of creative scientific achievements and preparing students and postdocs for the next level of their respective careers. The proposed studies use almost every biological tool available to us, and when the expertise is not present in the lab, we actively collaborate to get the job done and done right.

f B. Positions and Honors

Positions and Employment

1990-1991 Undergraduate Student with Dr. Jeff Seemann, University of Nevada. Regulation of RUBISCO in the spinach plant.
1991-1993 Undergraduate Student with Dr. Ardythe McCracken, University of Nevada. ER associated protein degradation.
1993-1998 Graduate Student with Dr. Jasper Rine, University of California, Berkeley. Studies of transcriptional repression, regulation of replication initiation and mitosis in yeast.
1998-2002 Postdoctoral Fellow with Dr. Cynthia Kenyon, University of California, San Francisco, Determinants of longevity in the nematode *Caenorhabditis elegans.*
2002-2007 Assistant Professor, The Salk Institute for Biological Studies, Molecular and Cell Biology Laboratory La Jolla, CA
2007-2011 Associate Professor, The Salk Institute for Biological Studies, Molecular and Cell Biology Laboratory, La Jolla, CA
2007-2012 Adjunct Associate Professor, University of California, San Diego, CA
2008-present Investigator, Howard Hughes Medical Institute
2009-2012 Director, Glenn Center for Aging Research at the Salk Institute
2011-2012 Professor, The Salk Institute for Biological Studies, Molecular and Cell Biology Laboratory, La Jolla, CA
2012-present Professor, University of California at Berkeley, Molecular and Cell Biology Department

C. Peer-reviewed publications or manuscripts in press

Most Relevant to the Current Application

1. Cohen, E., Bieschke, J., Perciavalle, R., M., Kelly, J. W. & Dillin, A. (2006). Opposing activities protect against age-onset proteotoxicity. Science, 313(5793),1604-1610.
2. Cohen, E. Paulsson, J.F., Blinder, P., Burstyn-Cohen, T., Du, P., Estepa, G., Adame, A., Pham, H.M., Holzenberger, M., Kelly, J.W., Masliah, E. & Dillin, A. (2009). Reduced IGF-1 Signaling Delays Age-Associated Proteotoxicity in Mice. Cell, 139(6),1157-69. PMCID: PMC3017511.
3. Durieux, J. Wolff, S. & Dillin A. (2011). The cell non-autonomous nature of electron transport chain-mediated. Cell, 144(1), 79-91. PMCID: PMC3062502.
4. Vilchez D, Morantte I, Liu Z, Douglas PM, Merkwirth C, Rodrigues AP, Manning G, & Dillin A. (2012). RPN-6 determines C. elegans longevity under proteotoxic stress conditions. Nature, 489(7415), 263-8. PMC Journal – In Process.
5. Taylor, R. & Dillin, A. (2013). XBP-1 is a cell-nonautonomous regulator of stress resistance and longevity. Cell,153(7), 1435-47. PMC Journal – In Process.
6. Riera, C., Huising, M., Follett, P., Leblanc, M., Halloran, J., Van Andel, R., Filho, C., Merkwirth, C., Dillin, A (2014). TRPV1 Pain Receptors Regulate Longevity and Metabolism by Neuropeptide Signaling. Cell, 157 (5), 1023-1036.

Additional recent publications of importance to the field (in chronological order)

1. Venable, J.D., Dong, M.Q., Wohlschlegel, J., Dillin, A. & Yates III, J.R. (2004). Automated approach for quantitative analysis of complex peptide mixtures from tandem mass spectra. Nature Methods, 1(1), 39-45.
2. Wolff, S., Ma, H., Burch, D., Maciel, G., Hunter, T. & Dillin, A. (2006). SMK-1, an essential regulator of DAF- 16 mediated longevity. Cell,124(5),1-15.
3. Cohen, E., Bieschke, J., Perciavalle, R., M., Kelly, J. W. & Dillin, A. (2006). Insulin-like signaling couples the aging process and toxic protein aggregation by regulating opposite detoxification activities. Science, 313(5793), 1604-1610.
4. Panowski, S., Wolff, S., Aguilaniu, H. & Dillin, A. (2007). PHA-4/FOXA1 is essential and specific for DR-mediated longevity in *C. elegans*. Nature, 447(7144), 550-556.
5. Dong, M.Q., Venable, J.D., Au, N., Xu, T., Park, S.K., Cociorva, D., Johnson, J.R., Dillin, A. & Yates, J.R. 3rd (2007). Quantitative mass spectrometry identifies insulin signaling targets in C. elegans. Science, 317(5838), 603-604.
6. Carrano, A., Liu, Z., Dillin, A. & Hunter, T. (2009). A conserved ubiquitination pathway determines longevity in response to diet restriction. Nature, 16(7253), 369-399. PMCID: PMC2746748.
7. Cohen, E. Du, D. Joyce, D. Kapernick, EA. Volovik, Y. Kelly, JW. & Dillin, A. (2010). Temporal requirements of insulin/IGF-1 signaling for proteotoxicity protection. Aging Cell, 9(2), 126-34. PMCID: PMC3026833.
8. Mair, W., Morantte, I., Rodrigues, A.P.C., Manning, G., Montminy, M., Shaw, RJ., Dillin, A. (2011) CRTC-1 couples energy homeostasis to longevity. Nature, Feb; 470(7334):404-8. PMCID:21331044.
9. Volovik, Y., Maman, M., Dubnikov, T., Bejerano-Sagie, M., Joyce, D., Kapernick, E. A., Cohen, E. & Dillin, A. (2012). Temporal requirements of heat shock factor-1 for longevity assurance. Aging Cell, 11(3), 491–499. PMCID: 22360389.
10. Vilchez D, Boyer L, Morantte I, Lutz M, Merkwirth C, Joyce D, Spencer B, Page L, Masliah E, Berggren WT, Gage FH, Dillin A. (2012). Increased proteasome activity in human embryonic stem cells is regulated by PSMD11. Nature, 489(7415), 304-8.

D. Research Support

Ongoing Research Support

7 R37 AG024365-07 (Dillin, PI) 09/01/2004-08/31/2016
NIH/NIA
The Perception of Mitochondrial Stress in Receiving Cells
The major goal of this project is to determine how distal tissues can sense mitochondrial stress in other tissues, and how their own form and function might change in response to distal mitochondrial signaling.
Role: PI

7 R01 ES021667-02 (Dillin, PI) 10/19/2012-12/31/2016
NIH/NIEHS
Distal Mitochondrial Signaling in a Multicellular Organism
The major goal of this project is to discover how mitochondria within the nervous system can communicate a signal that will ensure the survival of an animal under conditions of stress.
Role: PI

1 R01AG042679-01A1 (Dillin, PI) 03/15/2013-02/28/2018
NIH/NIA
The Cell Non-Autonomous Nature of UPR Signaling
The major goal of this project is to discover how the UPR within the endoplasmic reticulum with neurons can communicate with distal tissues to increase the chance of survivorship as the organism ages.
Role: PI

-- (Dillin, PI) 09/01/2008-08/31/2017
Howard Hughes Medical Institute
Molecular Pathways of Aging
The major goal of this project is to perform high risk, innovative research towards the understanding of aging and age-related diseases.
Role: PI

RB5-06974 (Dillin, PI) 03/01/2014-02/28/2017
California Institute for Regenerative Medicine
A Requirement for Protein Homeostasis in the Mediation of Stem Cell Health
The major goal of this project is to understand the behaviors and regulation of UPR and stress responses in stem cells.
Role: PI

Completed Research Support

7 R01 AG027463-06 (Dillin, PI) 07/01/2008-06/30/2014
NIH/NIA
Genetic Regulation of the Response to Dietary Restriction
The major goal of this project is to understand the molecular mechanism by which a core-signaling pathway, that responds to and integrates an organism's response to reduced caloric intake, perceives and interprets the environmental signals that ultimately result in increased longevity. [Funds shared by two investigators.]
Role: PI

5 P01 AG031097-05 (Kelly, PI) 02/01/2009-01/31/2014
NIH/NIA
Molecular Mechanisms Linking Aging, Abeta Proteotoxicity, and Neurodegeneration
The major goal of Project 3, Age-Associated Neuroprotection by Insulin/IGF-1 Signaling: From Worm to Mouse, is to investigate the molecular mechanisms that prevent proteotoxicity during early life that become compromised with age.
Role: PI, Project 3

RC1 AG036024-02 (Morimoto, PI) 09/30/2009-08/31/2011
NIH/NIA
Protostasis Sensors to Assess the Cellular Protein Folding Capacity
The major goal of this project is to develop a molecular toolbox of folding sensors that provide real-time living cell imaging to quantify the health of the proteome in the face of acute stress, chronic expression of damaged proteins, and aging. [ARRA funding.]
Role: Co-Investigator

R01 DK070696-05 (Dillin, PI) 03/01/2005-01/31/2011

NIH/NIDDK
Specifying Insulin/IGF-1 Signaling in C. elegans
The major goal of this project is to determine how DAF-2 controls distinctive signaling pathways to regulate C. elegans development, reproduction and aging. [This grant includes an extended, unfunded, one-year period.]
Role: PI

5 R01 DK074798-04 (Yates, PI) 03/01/2007-02/28/2011
NIH/NIDDK
Proteomic Analysis of C. elegans Insulin Signaling
The major goal of this project is to utilize mass spectrometry-based protein identification and quantification technologies developed in our laboratory to identify and characterize protein complexes and novel components of the C. elegans insulin signaling pathway.
Role: Co-Investigator

Research Grant (Dillin, PI) 02/01/2007-01/31/2011
McKnight Endowment Fund for Neurosciences
Age-associated neuroprotection regulated by insulin/IGF-1 signaling: from worm to mouse
The major goal of this project is to understand the molecular mechanisms that prevent proteotoxicity during early life that become compromised with age. [This grant includes an extended, unfunded, one-year period.]
Role: PI

5 R21 AG032560-02 (Dillin, PI) 09/01/2008-08/31/2010
NIH/NIA
The Study of E3 Ligases and Longevity
The major goals of this project are to identify substrates of human and worm ubiquitin ligases using our new purification strategies and to use C. elegans genetics to study the involvement of ligases and potential substrates of ligases suggested to be involved in aging, and to validate the most biologically significant substrates identified.
Role: PI

Scholar Award AG-NS-0260-04 (Dillin, PI) 08/01/2004-07/31/2008
The Ellison Medical Foundation
Regulation of Aging by Insulin/IGF-1 and Mitochondrial Signaling Pathways
The major goal of this project is to determine how the mitochondrial electron transport chain sets the rate aging.
Role: PI

Biographical Sketch

PERSONAL DETAILS

Forenames: Richard George Arthur Surname: Faragher

Email: rgaf@brighton.ac.uk

POSITION

Professor of Biogerontology, University of Brighton

EDUCATION/TRAINING

1986–1989 Imperial College, London. BSc (Hons) Biochemistry, 2(i)

1989–1993 University of Sussex. D.Phil. *The cell kinetics of Werner's syndrome.* Supervisor: Professor Sydney Shall.

1994 -1996	Postdoctoral Fellow, Department of Pharmacy, University of Brighton, Brighton, Sussex. led directly to the marketing of *Proclear* contact lenses (now sold by CooperVision).
1997-2000	School Research Fellow, School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, Sussex. HEFCE-funded tenure-track special appointment.

POSITIONS & EMPLOYMENT

2000-2003	Senior Fellow, School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, Sussex
2003-2005	Principal Fellow, School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, Sussex.
2005-2009	Reader in Gerontology, School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, Sussex.
2009-date	Chair of Biogerontology, School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, Sussex.
2010-2014	Assistant Head [Research] School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, Sussex.

OTHER EXPERIENCE & PROFESSIONAL MEMBERSHIPS

1999-2003	Treasurer, British Society for Research on Ageing
2004-2008	BBSRC-EPSRC Programme Director (35 project network)
2004-2011	Member, Research Advisory Council of Research Into Ageing
2009-2014	Chair British Society for Research on Ageing
2011-2015	Member, BBSRC Bioscience for Health Strategy Advisory Panel (Strategic oversight of ~50% of BBSRC budget, typically £500 million pa)
2010-	Executive Director and Board Member, American Aging Association

2015- Chair, Scientific Advisory Board, British Society for Research on Ageing

HONOURS

2002 Royal Pharmaceutical Society Conference Science Medal for outstanding scientific achievement in ageing research.

2005 Help the Aged *Living Legend* Award for services to ageing research and the needs of older people. First ever scientist to be the recipient of this award.

2010 Paul F Glenn Award for research in biological mechanisms of ageing.

WORKSHOP RELEVANT PUBLICATIONS

Wyllie FS Jones CJ, Skinner JW, Haughton MF, Wallis C, Wynford-Thomas D, Faragher RGA (corresponding), Kipling D. (2000). Telomerase prevents the accelerated cell ageing of Werner syndrome fibroblasts. Nature Genetics 24: 16-17.

Kipling D, Ostler E.L., Davis T. & Faragher R.G.A. (2004) What can progeroid syndromes tell us about human aging? Science 305:1426-31

Kipling D, Faragher RGA (2009) Microarray analysis of senescent vascular smooth muscle cells: A link to atherosclerosis and vascular calcification. Exp Gerontol. 44(10):659-65.

Faragher RGA (2009) Back to the future? Transatlantic collaboration on ageing research. Age (Dordr) 31(4):257-9.

Sheerin AN *et al.* (2011) Characterisation of cellular senescence mechanisms in human corneal endothelial cells. Aging Cell 11(2):234-40.

Faragher RG & Yeoman M (2012) Use of model organisms to study CNS ageing. Nature Reviews Neuroscience 13(6):435-45.

Faragher R, Frasca D, Remarque E, Pawelec G (2014) Better immunity in later life: a position paper. Age (Dordr). 36:9619

Burton DG, Faragher RGA (2015) Cellular senescence: from growth arrest to immunogenic conversion. Age (Dordr) 37(2):27.

Faragher RGA (2015) Should we treat ageing as a disease? The consequences and dangers of miscategorisation. Frontiers in Genetics doi: 10.3389/fgene.2015.00171

OTHER RELEVANT ACTIVITIES

Funded by the Glenn Foundation co-scripted *Live longer live well* (2014) integrating our knowledge of the biology of ageing with economic analyses of the benefits of improved healthspan(viewable on http://www.youtube.com/watch?v=2v34Dt6wBkE)

Delivered plenary lecture to the Institute and Faculty of Actuaries at their annual symposium (summary document on http://www.actuaries.org.uk/sites/all/files/Longevity%20symposium%20Publication.pdf).

Sole contributor selected to attend the press conference launching Legal and General's *What is ageing* (with Professor Sir Colin Blakemore and Dame Karen Dunnell DCB). Sample coverage can be accessed at http://www.thetimes.co.uk/tto/science/article4243307.ece and the report itself at http://www.longevitypanel.co.uk/viewpoint/what-is-ageing-can-we-delay-it/

STUART FIRESTEIN

Dr. Stuart Firestein is the former Chair of Columbia University's Department of Biological Sciences where his colleagues and he study the vertebrate olfactory system, possibly the best chemical detector on the face of the planet. Aside from its molecular detection capabilities, the olfactory system serves as a model for investigating general principles and mechanisms of signaling and perception in the brain. The olfactory system represents a unique opportunity for these studies as it processes sensory information over a very short neural pathway – giving rise to striking perceptions and memories with much less processing than the visual system requires, thus making it a more tractable system to understand. The laboratory has published over 100 scientific articles on their research. His laboratory seeks to answer that fundamental human question: How do I smell?

Dedicated to promoting the accessibility of science to a public audience Firestein serves as an advisor for the Alfred P. Sloan Foundation's program for the Public Understanding of Science, where he reviews scripts for the Ensemble Studio Theatre/Sloan Science and Technology Program, and for the Tribeca and Hamptons International Film Festivals. Recently he was awarded the 2011 Lenfest Distinguished Columbia Faculty Award for excellence in scholarship and teaching. He is a Fellow of the AAAS, an Alfred Sloan Fellow and a Guggenheim Fellow. His book on the workings of science for a general audience called *Ignorance*, *How it drives Science* was released by Oxford University Press in 2012. His new book, *Failure: Why Science is So Successful,* will be released in September.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Leonard Pershing Guarente leng01	POSITION TITLE Professor; Director of the Paul F. Glenn Lab for Science of Aging

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
Massachusetts Institute of Technology, Cambridge, MA	B.S.	1974	Biology
Harvard University, Cambridge, MA	Ph.D.	1978	Molecular Genetics

A. Personal Statement

I have had a long-term interest in studying the role of sirtuins in mediating the increased longevity caused by calorie restriction in species ranging from yeast to mammals. Recently, my research has focused on SIRT1, the most studied sirtuin in mammals. It has led us to investigations of a great many processes that we have found may be regulated by SIRT1, including neuroprotection, cancer cell growth, mitochondrial function, and mammalian fuel metabolism, as well as a variety of diseases, many of them associated with the metabolic syndrome. There has been a strong connection made between SIRT1 and protection against neurodegenerative diseases. In mouse models, we showed that SIRT1 over-expression in the brain protected against pathology in the most commonly used models of Alzheimer's, Huntington's, or Parkinson's disease. Moreover, the recent literature suggests that the SIRT1 cosubstrate NAD+ may itself play an important in the pathophysiology of aging and neurodegenerative diseases. Recent data shows that NAD+ is depleted in normal aging. Thus increasing SIRT1 expression and supplementing NAD+ might be a potent one-two punch for aging and related diseases.

Recently, a strong connection has been made between SIRT1 and the circadian clock. First, the core clock machinery stages metabolic processes diurnally by regulating NAD+ synthesis and SIRT1 in a circadian way. Second, SIRT1 feeds back on the core clock machinery to regulate its amplitude in the brain and peripheral tissues. This proposal will study how this SIRT1/circadian link may influence the effects of diet on health.

B. Positions and Honors

Appointments

1978-1981 - Jane Coffin Childs Postdoctoral Fellow, Harvard University, Cambridge, MA
1981-1985 - Assistant Professor of Biology, Massachusetts Institute of Technology, Cambridge, MA
1985-1991 - Associate Professor of Biology, Massachusetts Institute of Technology, Cambridge, MA
1991-present - Professor of Biology, Massachusetts Institute of Technology, Cambridge, MA
2000-present - Novartis Professor of Biology, Massachusetts Institute of Technology, Cambridge, MA
2008-present - Director Glenn Labs for Science of Aging at MIT, Cambridge, MA
2010-present - Affiliate Koch Institute for Integrative Cancer Research

Professional Activities

Editorial Board, *Cell* 2009-present
Editorial Board *Cell Metabolism* 2011-present
Editorial Board, *Developmental Cell* 2001-2012
Editorial Board, *Genes and Development* 1989-present
Editorial Board, *Aging* 2009-present
Editorial Board, *Trends in Genetics* 1989-present
Editorial Board, *EMBO Reports* 2010-present
Editorial Board, *Experimental Gerontology* 2003-present
Editorial Board, *Science* Magazine SAGE KE, 2000-2004
Editorial Board, *Molecular and Cellular Biology* 1986-1991

Founder & Board Member, Elixir Pharmaceuticals 1999-2006
SAB Co-chair, Sirtris/GSK 2007-present
Author of *Ageless Quest,* CSH Press 2003
Editor *Molecular Biology Of Aging*, CSH Press 2007
A.C.S. Microbiology and Virology Study Section 1987-1991
N.I.H. Molecular Biology Study Section 1994-1998
N.I.H. Board of Scientific Counselors, NIA 1999-2008

Awards & Lectureships

AFAR Irving S. Wright Award 2015
Feodor Lynen Award, Miami Winter Symposium 2012
Charles H. Best Lectureship and Award/U of Toronto 2011
Elected French Academie des Sciences 2009
Dart/NYU Biotechnology Achievement Award 2009
Dr. Kenneth S. and Audrey S. Gould Lecture, Rutgers 2009
Garland Lecture, British Society of Cell Biology 2008
McLean Lecture, Baylor College of Medicine 2008
Elected to American Academy of Arts and Science 2004
Founding Instructor, MBL Aging Course 1999-2003
Academy of the American Society for Healthy Aging Investigator of 2001
Ida Beam Distinguished Lecturer 2001
Ellison Medical Foundation Senior Scholar 1999-2002
Earle P. Charlton Lectureship 1998
Elected, to American Academy of Microbiology 1998
Presidential Young Investigator National Science Foundation 1984-1989
Thomas D. and Virginia W. Cabot Career Professorship 1989-1992

C. Publications (2011-present)

Simic, P., Zainabadi, K., Bell, E., Sykes, D., , Saez, B., Lotinun, B.,, Baron, R.,, Scadden, D., Schipani, E.,, and Guarente, L. SIRT1 regulates differentiation of mesenchymal stem cells by deacetylating β-catenin. (2013). *EMBO Mol. Med.* 3, 430-440 Epub Jan 30.

Simic, P., Williams, EO, Bell, E., Gong, JJ, Bonkowski, M., and Guarente, L. (2013). SIRT1 suppresses the epithelial to mesenchymal transition in cancer metastasis and organ fibrosis. *Cell Reports* 3;1175-86 April 10 Epub.

Chang, H-C., and Guarente, L., (2013). SIRT1 mediates central circadian control in the SCN by a mechanism that decays with aging. *Cell* 153, 1448-1460.

Mouchiroud, L., Houtkooper, R. Moullan, N., Katsyuba, E., Ryu, D., Canto, C., Mottis, A., Jo, Y., Viswanathan, M., Schoonjans, K., Guarente, L., and Auwerx, J. (2013). The NAD+/Sirtuin pathway modulates longevity through activation of the mitochondrial UPR and FOXO signaling. *Cell* 154, 430-441.

Guarente L. (2013). Introduction: sirtuins in aging and diseases. *Methods Mol Biol*. 1077:3-10. doi: 10.1007/978-1-62703-637-5_1.

Guarente L. (2013). Calorie restriction and sirtuins revisited. *Genes Dev*. 27 :2072-85. doi: 10.1101/gad.227439.113.

Hasegawa K, Wakino S, Simic P, Sakamaki Y, Minakuchi H, Fujimura K, Hosoya K, Komatsu M, Kaneko Y, Kanda T, Kubota E, Tokuyama H, Hayashi K, Guarente L, Itoh H. (2013). Renal tubular Sirt1 attenuates diabetic albuminuria by epigenetically suppressing Claudin-1 overexpression in podocytes. *Nat Med*. Oct 20. doi: 10.1038/nm.3363. [Epub ahead of print].

Sinclair DA, Guarente L. (2013). Small-Molecule Allosteric Activators of Sirtuins. *Annu Rev Pharmacol Toxicol*. 2013 Oct 16. [Epub ahead of print].

Chang, H-C. and Guarente, L. (2013). SIRT1 and other sirtuins in metabolism. *Trends Endocrin. And Metab.* published online Dec. 31.

Guarente, L. (2014). Sirtuins and the Warburg effect. *Nature Med.* 20, 24-26

Herskovits, A. and Guarente, L. (2014). SIRT1 in neurodevelopment and brain senescence. *Neuron* 81, 471-483.

Chalkiadaki, A., Igarashi, M., Nasamu A., Knezevic, J., and Guarente, L. (2014). Muscle-Specific SIRT1 Gain-of-Function Increases Slow-Twitch fibers and Ameliorates Pathophysiology in the Mouse Model of Duchenne Muscular Dystrophy. PLoS Genetics, Jul 17;10(7):e1004490. doi: 10.1371/journal.pgen.1004490. eCollection 2014 Jul. PMID: 25032964

Imai, S., and Guarente, L. (2014). NAD+ and sirtuins in aging and disease. *Trends in Cell Biol*. 24, 464-471. doi: 10.1016/j.tcb.2014.04.002. Epub 2014 Apr 29.

Bell EL, Nagamori I, Williams EO, Del Rosario AM, Bryson BD, Watson N, White FM, Sassone-Corsi P, Guarente L. (2014). SirT1 is required in the male germ cell for differentiation and fecundity in mice. *Development*. 2014 Sep;141(18):3495-504. doi: 10.1242/dev.110627. Epub 2014 Aug 19

Guarente L. (2014). Aging research-where do we stand and where are we going?
Cell. 2014 Sep 25;159(1):15-9. doi: 10.1016/j.cell.2014.08.041.

D. Support

CURRENT

5-R01 AG015339-14 (PI: L. Guarente) 2/1/2010-1/31/2015 1.00 Summer Months
National Institutes of Health $237,488 Direct Costs
"Function of Mammalian SIRT1 in Aging"

This project studies the functions of mammalian sirtuins with an emphasis on SIRT1, to suggest new strategies to treat aging diseases.

5-R01 AG011119-21 (PI: L. Guarente) 4/1/2012-3/31/2017 1.00 Summer Months
National Institutes of Health $249,102 Direct Costs
"Function of SIRT1 in Growth and Reproduction"

This grant studies the role of SIRT1 in central neuro-endocrine control and in germ cells.

Agreement Dated 4/30/12 (PI: L. Guarente) 5/1/2012-6/30/2014 0.00 Calendar Months
Jain Foundation $90,909 Direct Costs
"Identification of Genetic Suppressors of C. Elegans fer-1"

This project will generate mutations in genes that ameliorate conditions associated with the lack of fer-1, a C. elegans homolog of human Dysferlin, which is mutated in patients with Limb-Girdle Muscular Dystrophy 2B.

Glenn Foundation for Medical Research – The Glenn Award has helped support the lab for six years. Renewal application is pending.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Karlseder, Jan	Professor
eRA COMMONS USER NAME (credential, e.g., agency login) karlseder	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Innsbruck, Austria		09/87-07/89	Biology
University of Vienna, Austria		09/89-07/92	Molecular Genetics
University Hospital, Vienna, Austria	M.S.	07/92	Molecular Oncology
Institute for Molecular Biology, Austria	Ph.D.	05/95	Molecular Biology
Center for Applied Genetics, Austria	Postdoctoral	06/95-06/96	Molecular Biology
Rockefeller University, New York, NY	Postdoctoral	07/96-03/02	Cell Biology

A. Personal Statement

The Karlseder laboratory is interested in telomere dynamics during the cell cycle, aging, senescence and cancer formation. We are focusing on telomere maintenance pathways and their regulation during cellular transformation, telomere structure, telomere replication, the interaction between the checkpoint machinery with telomeres, the impact telomeres have on nuclear structure, telomere localization and telomere driven epigenetic changes during cellular and organismal aging and transformation. The laboratory's recent discovery that mitotic inhibition leads to telomere dysfunction promotes the hypothesis that side effects associated with treatment of mitotic inhibitors, such as accelerated aging phenotypes, could be due to telomere deprotection.

B. Positions and Honors

Positions and Employment

1990-1991 Scientific co-worker, Dept. for Molecular Oncology, University Hospital Vienna, Austria
1995-1996 Postdoctoral Fellow, Center for Applied Genetics, University BOKU, Vienna, Austria
1996-1997 Postdoctoral Associate, Rockefeller University, New York, NY
1997-2002 Postdoctoral Fellow, Rockefeller University, New York, NY
2002-2007 Assistant Professor, The Salk Institute for Biological Studies, La Jolla, CA
2003-2007 Adjunct Assistant Professor, University of California San Diego, La Jolla, CA
2007-2011 Associate Professor, The Salk Institute for Biological Studies, La Jolla, CA
2007-present Adjunct Associate Professor, University of California San Diego, La Jolla, CA
2011-present Professor, The Salk Institute for Biological Studies, La Jolla, CA
2013-present Director, Glenn Center for Aging Research, Salk Institute, La Jolla, CA

Other Experience and Professional Memberships

2007-present Editorial Board, Aging Cell
2007-present Editorial Board, Aging
2007-present Member, Moores Cancer Center, University of California San Diego, La Jolla, CA
2007-present Scientific Advisory Board, The William Guy Forbeck Research Foundation
2007-present Conference Organizer, 'Models and Mechanisms of Cancer', Salk Institute
2009-2011 Organizer, Annual Mahajani Symposium, Salk Institute
2009-present CPRIT Advisory and Review Panel
2010 Organizer, 'Cancer and Stem Cell Symposium', Salk Institute
2010-2014 Organizer, 'Telomeres and Genome Stability', EMBO Conference, Europe

2012-present Permanent Member, CG Study Section, NCI
2015-present Editorial Board, Science Advances

Awards

1992	Austrian Fellowship, Universite de Montpellier, France
1993	EMBO Fellowship, Universite de Montpellier, France
1995	Austrian Society for Senology
1997	Human Frontiers Science Program, Long-term Fellowship
1999	Charles H. Revson Fellowship in Biomedical Research
2002	The V-Foundation Award for Developing Scientists
2002	Forbeck Scholar Award
2009	Glenn Award for Research in Biological Mechanisms of Aging

C. Selected peer-reviewed publications (out of 53 total)

Verdun, R.E. and Karlseder, J. (2006) The DNA damage machinery and homologous recombination pathway act consecutively to protect human telomeres. Cell 127:709-720.

Crabbe, L., Jauch, A., Naeger, C.M., Holtgreve-Grez, H. and Karlseder, J. (2007) Telomere dysfunction as a cause of genomic instability in Werner syndrome. Proc Natl Acad Sci USA 104:2205-2210.

Raices, M., Verdun, R., Compton, S., Haggblom, C., Griffith, J., Dillin, A. and Karlseder, J. (2008) *C. elegans* telomeres contain G-strand and C-strand overhangs that are bound by distinct proteins. Cell 132:745-757. Accepted for publication prior to April 7, 2008

O'Sullivan, R.J., Kubicek, S., Schreiber, S.L. and Karlseder, J. (2010) Reduced histone biosynthesis and chromatin changes aging arising from a damage signal at telomeres. Nat Struct Mol Biol. 17:1218-1225. PMCID: PMC2951278

Flynn, R.L., Centore, R.C., O'Sullivan, R.J., Rai, R., Tse, A., Songyang, Z., Chang, S., Karlseder, J. and Zou, L. (2011) TERRA and hnRNPA1 orchestrate an RPA-to-POT1 switch. Nature 471:532-536. PMCID: PMC3078637

Lackner, D., Durocher, D. and Karlseder, J. (2011) A siRNA-based screen for genes involved in chromosome end protection. PLoSONE 6:e21407. PMCID: PMC3121770

Oganesian, L. and Karlseder, J. (2011) Mammalian 5' C-rich telomeric overhangs are a mark of recombination-dependent telomere maintenance. Mol Cell 42:224-236. PMCID: PMC3082866

Barefield, C. and Karlseder, J. (2012) The BLM helicase contributes to telomere maintenance through processing of late-replicating intermediate structures. Nucleic Acids Res 40:7358-7367. PMCID: PMC3424559

Hayashi, M.T., Cesare, A.J., Fitzpatrick, J.A.J., Lazzerini-Denchi, E. and Karlseder, J. (2012) A Telomere Dependent DNA Damage Checkpoint Induced by Prolonged Mitotic Arrest. Nat Struct Mol Biol 19:387-94. PMCID: PMC3319806

Crabbe, L., Cesare, A.J., Kasuboski, J.M., Fitzpatrick, J.A. and Karlseder, J. (2012) Human telomeres are tethered to the nuclear envelope during postmitotic nuclear assembly. Cell Rep. 2:1521-1529. PMCID: PMC3694759

Hayashi, M.T. and Karlseder, J. (2013) DNA damage associated with mitosis and cytokinesis failure. Oncogene. 32:4593-4601. PMCID: PMC3681845

Oganesian, L. and Karlseder, J (2013) 5' C-rich telomeric overhangs are an outcome of rapid telomere truncation events. DNA Repair. 12:238-245. PMCID: PMC3594334

Cesare, A.J., Hayashi, M.T., Crabbe, L. and Karlseder, J. (2013) The telomere deprotection response is functionally distinct from the genomic DNA damage response. Mol Cell. 51:141-155. PMCID: PMC3721072

O'Sullivan, R.J., Arnoult, N., Lackner, D.H., Oganesian, L., Haggblom, C., Corpet, A., Almounzi, G. and Karlseder, J. (2014) Rapid induction of alternative lengthening of telomeres by depletion of the histone chaperone ASF1. Nat Struct Mol Biol 21:167-174. PMCID: PMC3946341

Lackner, D.H., Hayashi, M.T., Cesare, A.J. and Karlseder, J. (2014) A genomics approach identifies senescence-specific gene expression regulation. Aging Cell 13:946-950. PMCID: PMC4172521

Hayashi, M.T., Cesare, A.J., Rivera, T., Karlseder, J. (2015) Cell death during crisis is mediated by mitotic telomere deprotection. Nature, in press.

D. Research Support

ACTIVE

5 R01 CA174942-02 (Karlseder, PI) 04/01/2013-03/31/2018
NIH/NCI
The role of histone chaperone Asf1 in Alternative Lengthening of Telomeres
The major goal of this project is to understand the molecular mechanisms underlying the ALT pathway, providing a reliable diagnostic tool and eventually allowing the specific targeting of cancer cells that rely on ALT for telomere maintenance.
Role: PI

2 R01 GM087476-05 (Karlseder, PI) 07/01/2014-06/30/2018
NIH/NIGMS
Understanding ALT activation in C. elegans and human cells
The major goal of this project is to investigate how Alternative Lengthening of Telomeres (ALT) is regulated, employing the genetically tractable C. elegans system as well as mammalian approaches, with the goal of developing diagnostic markers and inhibitors for cancer therapy.
Role: PI

COMPLETED

5 R01 GM087476-04 (Karlseder, PI) 09/30/2009-06/30/2014
NIH/NIGMS
C. elegans as a Model for Telomere Maintenance in Cancer
The major goal of this project is to define and characterize regulators of Alternative Lengthening of Telomeres (ALT) in nematodes and mammals, and to provide, for the first time, a regulated multicellular model for ALT. [This grant included an extended, unfunded, 10-month period.]
Role: PI

Dr. Brian Kennedy is internationally recognized for his research in the basic biology of aging and is a visionary committed to translating research discoveries into new ways of delaying, detecting, preventing and treating age-related conditions. He leads a team of 20 principal investigators at the Buck Institute – all of whom are involved in interdisciplinary research aimed at extending healthspan, the healthy years of life.

The inventor on several patents, Dr. Kennedy is co-founder of two U.S. companies aimed at developing treatments for age-related chronic disease. He is actively involved in aging research in the Pacific Rim, which features the largest elderly population in the world. He is a visiting professor at the Aging Research Institute at Guangdong Medical College in China. In the past year he lectured in Korea, Russia, China, Chile, Austria, Italy and the United Kingdom. In conjunction with the University of Southern California, he also launched the nation's first PhD Program in the Biology of Aging.

Dr. Kennedy has published over 140 manuscripts in prestigious journals including *Science* and *Nature* and has been quoted in *The Wall Street Journal*, *The New York Times* and *The Boston Globe*, among others. He is co-Editor-in Chief of *Aging Cell* and serves as a consultant for biotech and pharmaceutical companies. His own research has led to the discovery of Sirtuins and the mTOR pathway as key regulators of aging, with current studies involving an intensive focus that is unusual in the field – his work seeks to move discoveries from simple organisms into mammalian animal models as quickly as possible in order to develop new approaches to alleviate age-associated diseases in humans.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Kirkland, James L.	Professor of Medicine and Physiology Director, Robert and Arlene Kogod Center on Aging
eRA COMMONS USER NAME (credential, e.g., agency login) JKirkland	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Toronto	M.D.	06/77	Medicine
Toronto General Hospital	Resident	07/77-07/80	Medicine
University of Manchester	Fellow	08/80-12/82	Geriatrics
University of Manchester	M.Sc.	12/82	Physiology
University of Toronto	Ph.D.	06/90	Biochemistry

A. Personal Statement

My research focus is on age-related fat tissue stem cell dysfunction, causes and consequences of fat tissue inflammation with aging, mechanisms of cellular senescence, and age-related metabolic dysfunction. I am PI on R01s and other foundation-funded grants. I have been involved in PPG and Center grants in several capacities, as a Subproject leader, Core leader, External Advisory Committee member, Reviewer, and Review Committee Chair. I lead the NIH-funded Geroscience Apollo Network, (R24 AG044396) which brings together personnel from the basic biology of aging and clinical geriatrics to translate healthspan interventions from bench to the bedside and to identify and begin to develop the infrastructure including personnel and training requirements to support this translation. I have mentored multiple Master's and Ph.D. students and post-doctoral fellows. I have five currently in my laboratory. As a board-certified geriatrician, I also care for elderly patients and teach medical students, interns, residents, and fellows about geriatrics and aging.

B. Positions and Honors

Positions and Employment:

1977 Issei Prize in Medicine and Surgery, University of Toronto
1977-1980 Resident in Medicine, Toronto General Hospital, Toronto, Canada
1980-1982 Research Registrar, Division of Geriatric Medicine, University of Manchester, England
1982-1984 Guest Worker, National Institute on Aging, NIH
1983-1984 Instructor, Department of Medicine, John Hopkins University
1985-1990 Lecturer, Department of Medicine, University of Toronto
1988-1992 Research Director, Division of Geriatrics, University of Toronto
1990-1994 Assistant Professor, Department of Medicine, University of Toronto
1994-2007 Associate Professor, Departments of Medicine and Biochemistry, Boston University
1997-present Co-Founder and Scientific Advisor, AdipoGenix, Inc
1997-2007 Director, Adipocyte Core, Boston Obesity Nutrition Research Center
2007-present Noaber Foundation Professor of Aging Research, Mayo Medical School
2007-present Director, Robert and Arlene Kogod Center on Aging, Mayo Clinic

Awards and Other Professional Activities:

1980-present Certificate in Internal Medicine, American Board of Internal Medicine
1982 Toronto Fund Award for Postgraduate Medical Research
1985-present Certificate in Endocrinology and Metabolism, American Board of Internal Medicine
1988-present Specialist Certificate in Geriatric Medicine, American Board of Internal Medicine
1988 Anderson Award, Toronto General Hospital
1989, 1991 Member, Ad-hoc Initial Review Committee for Pepper Research Centers, NIH
1994 Outstanding Teacher Award, Division of Geriatrics, University of Toronto
1996-present Fellow, American College of Physicians
2002 Associate Editor and Editorial Board, Obesity Research

2002-2010	Member, Ad hoc NIH Special Emphasis Panels ZAG1 ZIJ(O4); ZAG1 ZIJ-6(M2); ZAG1 ZEIEJ-7(O2); ZAG1 ZIG-2 (J3) 2, IPOD *ad hoc*, ZAG1 ZIJ-2 M2, ZAG1 ZIG-2 03 1, ZAG1 ZIJ-2 (Chair)
2009-present	Member, Newcastle University Institute of Ageing and Health Scientific Advisory Board, UK
2010-present	Member, Buck Institute External Advisory Board, California
2010- present	Editorial Board, Aging Cell
2010	Co-Vice Chair, Gordon Research Conference on the Biology of Aging; Co-Chair for 2012
2011-present	Ellison Foundation Senior Scholar
2011-2014	Chair-Elect and Chair, Biological Sciences Section, Gerontological Society of America
2012	Excellence in Research Award, Division of General Internal Medicine, Mayo Clinic
2012	Honorary Professor; Chair, Healthy Ageing and the Pathobiology of Mammalian Ageing. University of Groningen, the Netherlands
2014	Clinical Trials Advisory Panel (CTAP), National Institute on Aging
2014	Board of Directors, American Federation for Aging Research
2014	National Advisory Council on Aging, National Institute on Aging

C. Contributions to Science

1. My early publications are related to adipose tissue biology and focus on the role of different adipose depots in health and disease. Fat, the largest organ in humans, is now acknowledged to play a central role in age-related dysfunction and modulating healthspan. Over the past 15 years my laboratory has uncovered many insights in adipose tissue biology and its relevance to the aging process. Four papers listed below, together with 10 other publications, demonstrate that preadipocytes, the cells from which new fat cells constantly arise throughout the lifespan from different fat depots, are separate cell subtypes. Thus, different fat depots are effectively distinct mini-organs. Collectively, these papers show that inherent properties of fat cell progenitors contribute to regional differences in fat tissue function. This is important for understanding the development of the metabolic syndrome, in explaining how and why fat distribution changes with aging and its clinical consequences, and defining upstream mechanisms responsible for distinct patterns of fat tissue growth.
   a. Tchkonia T, Lenburg M, Thomou T, Giorgadze N, Frampton G, Pirtskhalava T, Cartwright A, Cartwright M, Flanagan J, Karagiannides I, Gerry N, Forse RA, Tchoukalova Y, Jensen MD, Pothoulakis C, Kirkland JL. Identification of depot-specific human fat cell progenitors through distinct expression profiles and developmental gene patterns. Am J Physiol Endocrinol Metab 2007 Jan;292(1):E298-E307.
   b. Tchkonia T, Giorgadze N, Pirtskhalava T, Thomou T, DePonte M, Koo A, Forse RA, Chinnappan D, Martin-Ruiz C, von Zglinicki T, Kirkland JL. Fat depot-specific characteristics are retained in strains derived from single human preadipocytes. Diabetes 2006 Sep; 55(9):2571-8.
   c. Tchkonia T, Thomou T, Zhu Y, Karagiannides I, Pothoulakis C, Jensen MD, Kirkland JL. Mechanisms and metabolic implications of regional differences among fat depots. Cell Metab. 2013 May 7; 17(5):644-56. Epub 2013 Apr 11. PMID:23583168. PMCID:3942783. DOI:10.1016/j.cmet.2013.03.008.
   d. Kirkland JL, Hollenberg CH, Gillon WS. Age, anatomic site, and the replication and differentiation of adipocyte precursors. Am J Physiol. 1990 Feb; 258(2 Pt 1):C206-10. PMID:2305864.

2. In addition to the contributions described above, my laboratory demonstrated that preadipocyte and hence fat tissue dysfunction with aging is related to activation of cellular stress responses. This led us to discover that in both aging and obesity, senescent preadipocytes are generated that express cellular senescence markers and mediators (senescence associated beta galactosidase, phosphorylated p53, and gamma-H2AX) with restricted replicative potential, short telomeres, an aberrant secretory phenotype, and impaired adipogenesis. We have tested the hypothesis that the fat tissue dysfunction of aging and obesity share this mechanism. We are currently elucidating the molecular pathways involved in senescence, the roles of fat depot origin, developmental genes, and epigenetic processes in this, and the nature and impact of the consequent preadipocyte secretory and chemokine profiles on adipogenesis and function with aging.
   a. Karagiannides I, Thomou T, Tchkonia T, Pirtskhalava T, Kypreos KE, Cartwright A, Dalagiorgou G, Lash TL, Farmer SR, Timchenko NA, Kirkland JL. Increased CUG triplet repeat-binding protein-1 predisposes to impaired adipogenesis with aging. J Biol Chem 2006 Aug 11; 281(32):23025-33.
   b. Cartwright MJ, Schlauch K, Lenburg ME, Tchkonia T, Pirtskhalava T, Cartwright A, Thomou T, Kirkland JL. Aging, depot origin, and preadipocyte gene expression. J Gerontol A Biol Sci Med Sci. 2010 Mar; 65(3):242-51. Epub 2010 Jan 27. PMID:20106964. PMCID:2904595. DOI:10.1093/gerona/glp213.

c. Tchkonia T, Morbeck DE, Von Zglinicki T, Van Deursen J, Lustgarten J, Scrable H, Khosla S, Jensen MD,Kirkland JL. Fat tissue, aging, and cellular senescence. Aging Cell. 2010 Oct; 9(5):667-84. Epub 2010 Aug 15. PMID:20701600. PMCID:2941545. DOI:10.1111/j.1474-9726.2010.00608.x.

3. We are leveraging these findings to target basic aging mechanisms and combat age-related comorbidities as a group. We have developed numerous sophisticated approaches in adipose tissue biology that are being used by investigators worldwide. We found that aging results in adipose tissue and preadipocyte senescence and a pro-inflammatory senescence-associated secretory phenotype (SASP). My laboratory initiated testing of the hypothesis that clearing senescent cells enhances healthspan. We have since demonstrated that clearing senescent cells through genetic and pharmacological approaches enhances healthspan in mice. We found that the senescent cells can be selectively eliminated pharmacologically in vitro and in vivo using our first agents termed Senolytics.
   a. Kirkland JL. The biology of senescence: potential for prevention of disease. Clin GeriatrMed. 2002 Aug; 18(3):383-405. PMID:12424865.
   b. Tchkonia T, Morbeck DE, Von Zglinicki T, Van Deursen J, Lustgarten J, Scrable H, Khosla S, Jensen MD,Kirkland JL. Fat tissue, aging, and cellular senescence. Aging Cell. 2010 Oct; 9(5):667-84. Epub 2010 Aug 15. PMID:20701600. PMCID:2941545. DOI:10.1111/j.1474-9726.2010.00608.x.
   c. Baker D.J., Wijshake T., Tchkonia T., LeBrasseur N.K., Cilds B.G., van Sluis B., Kirkland J.L., van Deursen J.M. Clearance of p16 Ink4a-positive senescent cells delays aging-associated disorders. Nature, (7372):232-6, 2011. PMCID: 22048312
   d. Zhu, Y., Tchkonia, T., Pirtskhalava, T., Gower, A., Ding, H., Giorgadze, N., Palmer, A.K., Ikeno, Y., Borden, G., Lenburg, M., O'Hara, S.P., LaRusso, N.F., Miller, J.D., Roos, C.M., Verzosa, G.C., LeBrasseur, N.K., Wren, J.D., Farr, J.N., Khosla, S., Stout, M.B., McGowan, S.J., Fuhrmann-Stroissnigg, H., Gurkar, A.U., Zhao, J., Colangelo, D., Dorronsoro, A., Ling, Y.Y., Barghouthy, A.S., Navarro, D.C., Sano, T., Robbins, P.D., Niedernhofer, L.J., Kirkland, J.L. The Achilles' heel of senescent cells: From transcriptome to senolytic drugs. Aging Cell. 2015 Mar 9. doi: 10.1111/acel.12344. [Epub ahead of print]

D. Research Support

Ongoing Research Support

R24 AG044396 Kirkland (PI) 9/30/2013-6/30/2016
NIH/NIA
Geroscience Network
The aims of this grant are to: 1) establish an interdisciplinary network comprising aging centers across the nation as the basis for a Geroscience Initiative to understand and exploit links between aging and genesis of chronic disease, 2) use retreats and working groups to design and initiate strategies, translational paradigms, and resources needed to test our hypothesis, and 3) use faculty exchanges to catalyze further development of the strategies, translational paradigms, curricula, and resources needed to test our hypothesis.

R01 AG013925 Kirkland (PI) 8/15/2008-7/13/2014
NIH/NIA
Effect of Aging on Preadipocyte Differentiation
The aims are: 1) to test if dysfunctional preadipocytes accumulate with aging, dissect responsible mechanisms, and test fat depot-dependence in humans, 2) to define the aging preadipocyte secretory phenotype, the impact of replicative history and depot origin upon it, and its effect on chemotaxis, 3) to test if dysfunctional preadipocytes contribute to impaired adipogenesis with aging, define responsible mechanisms, and, based on these, test molecular interventions.

P01 AG31736 Bartke (PI) 4/1/2009-3/31/2014
The Somatotrophic Axis and Healthy Aging: A search for mechanism
Project 4 Kirkland (PI) IGF-1's Influence on Preadipocytes
The aims are to test if decreasing IGF-1 will: 1) reduce subcutaneous preadipocyte utilization with aging, preserving adipogenic capacity and delaying stress-responsive anti-adipogenic factor expression, and impair visceral preadipocyte development into fat, 2) delay age-related development of a metabolically unfavorable preadipocyte secretory profile with increased inflammatory cytokine, chemokine, and matrix remodeling protein production, and 3) generation of senescent preadipocytes is delayed by reducing life-long IGF-1 exposure.
Role: PI Project 4

AG-SS-2711-11-1 Kirkland (PI) 11/1/2011-10/31/2015
Ellison Medical Foundation
Aging and Adult "Stem" Cell Transplantation: Seed *vs.* Soil
The aims are: 1) In order to enhance adipose-derived stem cell (ADSC) transplant success, we will compare eliminating senescent cells from the "seed" to eliminating them from the "soil". 2) In order to enhance ADSC transplant success, we will ameliorate the senescence-associated secretory phenotype.
Role: PI

P30 DK50456 Levine (PI) 4/5/2011-4/4/2016
NIH/NIDDK
Minnesota Obesity Center
Director, Adipocyte Subcore of the Molecular and Cellular Basis of Obesity Core
The aims of the Adipocyte Subcore are to develop, store, and provide mouse and human adipocyte cell strains for use by NIH-funded investigators.
Role: Adipocyte Subcore PI

P01-AG041122 Kirkland (PI) 5/1/2012-4/30/2017
NIH/NIA
Cellular Senescence and Aging
Core A (Administrative Core)
Subproject 2
The hypothesis of this program project is that preventing the accumulation of senescent cells or their effects can restore age-related decrements in function. The following Aims are to determine effects on healthspan of: 1) eliminating senescent cells in a novel animal model (Subproject 1, van Deursen, PI), 2) Inhibiting the senescence-associated secretory phenotype (SASP) by manipulating Jak/Stat (Subproject 2, Kirkland, PI), and 3) Inhibiting the SASP by manipulating mTOR (Subproject 3, Campisi, PI).

Glenn/AFAR Breakthroughs in Gerontology Award Kirkland (PI) 07/1/2012-06/30/2014
Glenn Foundation/AFAR
INK-ER-Cre Mice: A Novel Tool for Uncovering How Senescent Cells Cause Age-Related Dysfunction
The aims are: 1) To generate *INK-ER-Cre* mice, which can be crossed to mice with floxed alleles to eliminate expression of specific genes only after administering tamoxifen and only in senescent cells and 2) To test transgene functionality and demonstrate proof of principle that SASP components can be targeted.
Role: PI

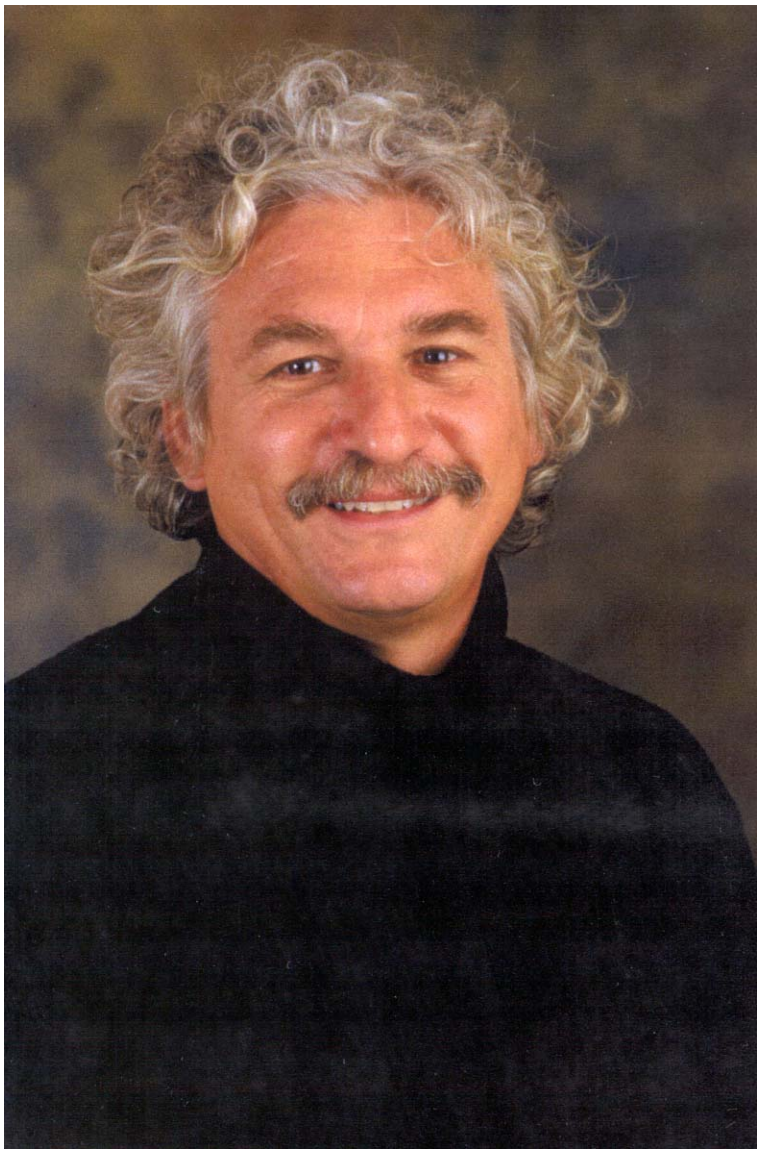
HL111121 Miller (PI) 1/4/2013-11/30/2017
NIH
Role of SIRT6 in calcific aortic valve disease
To determine the roles of oxidative stress and SIRT6-dependent epigenetic modifications in the initiation and progression of calcific aortic valve disease in mice.
Role: Co-I

AG19899 Bartke (PI) 5/1/2012-04/30/2017
NIH
Longevity genes and calorie restriction: early post-natal effects
The hypothesis is that the first few weeks of postnatal life represent a developmentally malleable period in which the pace of aging is set for each mouse, triggered by a combination of factors including GH/IGF-1 levels and nutritional signals. The aims are: 1) To extend our original study of lifespan extension in the "crowded litter" protocol by assessment of dose and timing effects, healthspan outcomes, and candidate mechanisms. 2) To identify the candidate mechanisms of longevity reversal in Ames dwarf mice given a brief exposure to GH early in postnatal development. 3) To evaluate the crowded litter model for effects on the growth hormone-insensitive, GH receptor-deleted (GHR-*/-*; Laron dwarf) mice.
Role: Co-I

PO1 AG04875 Khosla (PI) 7/1/2009-6/30/2014
Pathophysiology of Osteoporosis
The major goals of this project are to use the human as the experimental model to address key, unresolved issues regarding E action on bone, including definitively establishing whether follicle-stimulating hormone

modulates bone resorption in the setting of E deficiency and defining mechanisms for the age-related decrease in bone formation.
Role: Co-I

MNP IF #14.06 Kirkland (Co-PI with Arriaga) 05/2014-05/2016
Minnesota Partnership for Biotechnology
Mass Cytometry Infrastructure for Fundamental and Translational Research in Minnesota
Provides support for investigators in cellular senescence and additional aging research fields for conducting single cell mass spectrometry.



Biosketch: Edward G. Lakatta, M.D.

Dr. Lakatta is the founder and Director of the Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health. He also holds adjunct appointments as Professor, Department of Physiology, University of Maryland School of Medicine, and Professor, Cardiology Division, Johns Hopkins School of Medicine.

He has made a sustained 40-plus-year commitment to a broad-based research career. His studies range from molecules to humans, including translation of novel findings into the clinical realm. The overall goals of his research program are 1) to identify age associated changes that occur within the cardiovascular system and to determine the mechanisms for these changes; 2) to determine how aging of the heart and vasculature interacts with chronic disease states to enhance the risk for CV diseases in older persons; 3) to study basic mechanisms in excitation-contraction coupling and how these are modulated by surface receptor signaling pathways in cardiac cells; 4) to elucidate mechanisms of pacemaker activity in sinoatrial nodal cells; 5) to elucidate mechanisms that govern cardiac and vascular cell survival; 6) to establish the potentials and limitations of new therapeutic approaches such as changes in lifestyle, novel pharmacologic agents or gene or stem cell transfer techniques in aging or disease states.

Dr. Lakatta is recognized as both nationally and internationally as an expert in cardiovascular research. He has authored over 450 original publications in top peer-reviewed cardiovascular journals, written over 250 invited reviews/book chapters, and delivered over 450 invited lectures. He is a member of multiple scholarly societies and journal editorial boards. Based upon his accomplishments, Dr. Lakatta has received numerous awards, among which are the Allied Signal Achievement Award in Aging, the Novartis Prize in Gerontology, the Irving Wright Award of Distinction of the American Federation for Aging Research (AFAR), the Frank J. O'Hara Alumni Award from the University of Scranton, and the Distinguished Leader Award of the International Society of Heart Research (ISHR).

Kevin J. Lee, Ph.D.

Dr. Lee is Senior Scientific and Programmatic Advisor to the Glenn Foundation for Medical Research. In that capacity he assists in guiding and coordinating the Foundation's scientific mission to extend the healthy, productive years of life through research on the biological mechanisms of aging. Prior to joining the Glenn Foundation, he has served as Executive Director of the Lawrence Ellison Foundation (formerly the Ellison Medical Foundation), a philanthropic organization supporting biomedical research on the fundamental mechanisms of aging, age-related diseases, and neuroscience. The Foundation was established by Lawrence Ellison, the Executive Chairman and founding CEO of Oracle Corporation.

Dr. Lee is a graduate of the University of Michigan and received his Ph.D. in biology from the Massachusetts Institute of Technology. His career spans over 25 years of research experience in molecular genetics and neurobiology in biotechnology, academic research and not-for-profit settings. He served previously as Deputy Executive Director of the Ellison Medical Foundation from 2007-2012. Prior to joining the Ellison Medical Foundation, Dr. Lee was Executive Vice President-Research of Sentigen Biosciences. He was responsible for the start-up and development of this New York City-based biotechnology company leading to its acquisition by Invitrogen Corporation in 2006. He has served as a member of the Scientific Review Board for the Simons Foundation Autism Research Initiative in New York. Dr. Lee's scientific research career employed genetic approaches to learn how neurons in the brain are "wired up" during development to make functional circuits that relay sensory information and control behavior. He worked with Dr. Thomas Jessell in the Center for Neurobiology and Behavior at Columbia University, where he studied the specification, axonal projection, and functional connectivity of nerve cells in the spinal cord. He is the recipient of biotechnology patents and is the author of numerous research publications.

Susan Lindquist is a Member and former Director (2001-2004) of the Whitehead Institute for Biomedical Research, an Investigator of the Howard Hughes Medical Institute and a Professor of Biology at MIT. She investigates many diverse aspects of protein folding using biochemical, cell biological and genetic methods. Her work has influenced a variety of areas including mechanisms for the rapid evolution of new traits and the influence of protein homeostasis on cancer, drug resistance and neurodegenerative disease. Previously she was the Albert D. Lasker Professor of Medical Sciences (from 1999-2001), and a member of the faculty in the Department of Molecular Biology, University of Chicago. Lindquist received her undergraduate degree in Microbiology from the University of Illinois, and a PhD in Biology from Harvard University. She co-founded FoldRx, a biotech company developing drug therapies for diseases of protein misfolding and amyloidosis, and recently co-founded Yumanity, a biotech company identifying and developing new therapies for neurodegenerative diseases caused by protein misfolding. She is a member of the Board of Directors of Johnson & Johnson. Her honors include membership in the National Academy of Sciences, the American Academy of Arts and Science, the American Philosophical Society and the Institute of Medicine. She has been awarded the Dickson Prize in Medicine, the Otto-Warburg Prize, the Genetics Society of America Medal, the FASEB Excellence in Science Award, the Max Delbrück Medal, the Mendel Medal, the E.B. Wilson Medal, a Vallee Professorship and the Vanderbilt Prize. In 2009, she was the recipient of the National Medal of Science.

GEORGE M. MARTIN, M.D.

Professor of Pathology Emeritus (Active); Director Emeritus, Alzheimer's Disease Research Center; Adjunct Professor of Genome Sciences (Retired), University of Washington

Dr. Martin received his BS and MD degrees from the University of Washington and has been a member of its faculty since 1957. After an internship at the Montreal General Hospital and a residency in anatomic pathology at the University of Chicago, he pursued postdoctoral research in somatic cell genetics under Professor Guido Pontecorvo at Glasgow University, where he worked with *Aspergillus nidulans* and human cell cultures. Other postdoctoral experiences have included research in molecular biology with Francois Gros in Paris and in experimental embryology with Henry Harris and Richard Gardner at Oxford University. He has also done medical genetics fieldwork in India. Honors for his research have included the Brookdale, Kleemeier and Paul Glenn Foundation awards of the Gerontological Society of America, the Allied-Signal Corporation Award, the Irving Wright Award of the American Federation for Aging Research, the American Aging Association Research Medal and Distinguished Scientist Award, the Pruzanski Award of the American College of Medical Genetics, and a World Alzheimer Congress Lifetime Achievement Award. He has also received an Outstanding Alumnus Award from the University of Washington School of Medicine. He was elected to the Institute of Medicine of the National Academy of Sciences and now serves as a Senior Member. Dr. Martin was a member of the National Advisory Council, the Board of Scientific Counselors of the National Institute on Aging, and the Scientific Advisory Board of the Ellison Medical Foundation. He served as the Scientific Director of the American Federation for Aging Research for 18 years and is now its Scientific Director Emeritus. Dr. Martin was the Founding Editor-in-Chief of an AAAS/Science WEB site for research on the biology of aging (SAGE KE). He is a Past President of the Tissue Culture Society of America, the American Federation for Aging Research and the Gerontological Society of America (GSA) and continues to serve on the President's Cabinet of the GSA

Dr. Martin's research has for many years been concerned with genetic approaches to the study of aging and age-related diseases in mammals. One theme has been the plasticity of the genome of somatic cells. His lab has contributed to our understanding of a number of mechanisms for the heritable alteration of genetic information (Nature, 1967; Science, 1969; Chromosoma, 1973; Proc Natl Acad Sci USA, 1983; Cytogenet Cell Genet, 1983; Somatic Cell Mol Genet, 1984 & 1986; J Exp Path, 1986; Dev Genet, 1987; J Biol Chem , 1989). During this period a parallel series of biochemical, cytogenetic and somatic cell genetic studies on cells from aging mammals addressed various somatic mutational theories of aging; these have demonstrated the importance of relatively large scale chromosomal types of mutation (summarized, in part, in *Molecular Biology of Aging: Gene Stability and Gene Expression*, 1985). An offshoot of this work provided the first data on mutation frequencies in human epithelial cells in aging human subjects (Human Mol Genet, 1996).

These studies were reinforced by a long series of investigations of a remarkable human progeroid syndrome, the Werner syndrome, a recessive mutation that Dr. Martin's group and Japanese investigators mapped to chromosome 8. This led to the positional cloning of the Werner syndrome gene and its identification as a member of the *RecQ* helicase family (Science, 1996). Dr. Martin and colleagues have provided molecular evidence for the importance of intragenic deletions in the somatic cells of Werner syndrome subjects (Proc Natl Acad Sci USA, 1989). Cells from these patients were also shown to undergo accelerated "aging *in vitro*" (Lab Invest, 1970). This latter line of research provided the first evidence for the limited replicative potential of cells of the vascular wall (Exp Mol Path, 1973). Together with Drs. Tom Norwood and William Pendergrass, the Martin lab also carried out the first cell fusion experiments for the

investigation of dominance/recessivity relationships between old cells, young cells and "immortal" cells (Proc Natl Acad Sci USA, 1974; J Cell Biol, 1975) and demonstrated that the decline of growth potential involved gradual and variable attenuations of clonal growth (Am J Path, 1974).

At a more clinical level, Dr. Martin has systematized our knowledge of human genetic disorders from the point of view of their rich potential to elucidate specific aspects of the senescent phenotype (Birth Defects, 1978) and used this analysis to make inferences concerning the polygenic basis of aging.

Later in his career, Dr. Martin turned his attention to mechanisms of the aging of post-replicative cells, again using genetic approaches. He assembled a team of investigators to carry out a linkage analysis of familial Alzheimer disease, an effort that led to the assignment of the commonest form to chromosome 14 (Science, 1992) and to the mapping and positional cloning of a related locus on chromosome 1 (Science, 1995). New candidate genes were sought using the yeast protein interaction trap methodology. This work has led to a series of papers on an adaptor protein (FE65) that is of importance in the modulation of the function of the beta amyloid precursor protein; polymorphisms at that locus were shown to play a role in the susceptibility to Alzheimer disease in very old individuals (Hum Mol Genet, 1996; Hum Genet, 1998; J Neurosci Res, 1999; J Neurosci Res, 2000; Human Mol Genet, 2002; J Neurosci Res, 2004; J Biol Chem, 2005; J Biol Chem, 2006; J Neurochem, 2010).

These studies were complemented by attempts to develop cell culture (Biochem Biophys Res Commun, 1992) and transgenic (Exp Neurol, 1994; Amer J Path, 1996) models for the study of Alzheimer disease and the pathobiology of aging, including the synthesis of the first “knock-in” and “conditional “knock-out” transgenic mouse models of human presenilin 1 dysfunction (Nature Med, 1999; Neuron, 2001). The latter study demonstrated an intriguing correlation, in presenilin deficient mice, between diminished hippocampal stem cell replication and aberrations in memory.

Evolutionary biological theories of aging have been important components of his research throughout much of his career (Fed Proc, 1979; Nature Genet, 1996; Neurobiol Aging, 2002; Archiv Neurol, 2002; Exp Gerontol, 2006; Ann NY Acad Sci 2007) and currently occupies most of his attention (Aging Cell, 2009; Molecular Neurodegen, 2012; Mech Ageing and Develop, 2012). Current research addresses the role of variegated gene expression and age-related epigenetic drifts in the genesis of quasi-stochastic distributions of a wide range of geriatric pathologies, including the origins of neoplasms and the canonical lesions of major neurodegenerative disorders (PNAS, 2005; Aging Cell, 2009; Mech Aging Dev, 2012; Ann Rev Gerontol Geriatr, 2014).

Dr. Martin is certified by the American Board of Medical Genetics (Clinical Cytogenetics) and the American Board of Pathology. He has participated in the service functions of the Department of Pathology of the University of Washington since 1957, initially as a surgical pathologist and, for many years, as a cytogeneticist. His major teaching contributions at the University of Washington have involved the founding directorships of the Medical Scientist Training Program and the “Genetic Approaches to Aging Research” Institutional Training Grant of the National Institute on Aging. He continues to serve on the Executive Committee of that program and the Nathan Shock Center of Excellence for Basic Research on the Biology of Aging, both of which are under the directorship of his former graduate student, Professor Peter S. Rabinovitch.

RICHARD A. MILLER

Richard A. Miller, M.D., Ph.D., is a Professor of Pathology at the University of Michigan, and the Director of Michigan's Paul F. Glenn Center for Aging Research. He received the BA degree in 1971 from Haverford College, and MD and PhD degrees from Yale University in 1976-1977. After postdoctoral studies at Harvard and Sloan-Kettering, he moved to Boston University in 1982 and then to his current position at Michigan in 1990. Dr. Miller has served in a variety of editorial and advisory positions on behalf of the American Federation for Aging Research and the National Institute on Aging, and served as one of the Editors-in-Chief of Aging Cell. He is the recipient of the Nathan Shock Award, the AlliedSignal Award, the Irving Wright Award, an award from the Glenn Foundation, and the Kleemeier Award for aging research, was a Senior Scholar of the Ellison Medical Foundation, and is a Fellow of the American Association for the Advancement of Science. At Michigan, he directs the Geriatrics Center's Biogerontology program, and the Paul F. Glenn Center for Aging Research. His research program includes ongoing studies of the mechanisms that link stress, nutrients, and hormones to delayed aging in mice, development of new approaches to slow aging and disease through drugs, early life dietary restriction, and targeted mutations, and studies of the ways in which cells from long-lived birds, rodents, and primates may differ from those of short-lived species.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Coleen T Murphy	POSITION TITLE Associate Professor of Molecular Biology and Genomics, Princeton University
eRA COMMONS USER NAME ctmurphy	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Houston	B.S.	06/92	Biochemical & Biophys.
U. T. Southwestern Medical School	Post-baccalaureate	1992-1993	Structural Biology
Stanford University	Ph.D.	06/99	Biochemistry
University of California, San Francisco	Postdoctoral training	2000-2005	Biology of Aging

A. Personal Statement

My group studies aging and the quantitation of quality of life with age, including the decline of cognitive capacities with age. We develop genomic, genetic, biochemical, robotic, microfliuidic, and computational approaches to address these questions, using the nematode *C. elegans* as our model system. I am a member of the Center for Quantitative Biology, the Integrated Science Program, and the Princeton Neuroscience Institute. I am also the Director of the Glenn Center for Quantitative Aging Research at Princeton, which fosters collaborations between biology, neuroscience, computational, and engineering groups to address aging research questions, with a focus on quantitative approaches.

My lab and I have a strong track record for developing new approaches to address important questions in the field of aging research, combining genomic approaches with genetics and novel behavioral assays, including the full-genome identification of insulin signaling/FOXO transcriptional targets (Murphy, et al. ***Nature*** 2003) and the identification of PQM-1 as an antagonist of FOXO transcription (Tepper, et al. ***Cell*** 2013); the identification of TGF-β signaling as a primary regulator of reproductive aging (Luo, et al. ***Cell*** 2010) and insulin signaling as a regulator of cognitive aging and CREB-regulated long-term memory (Kauffman, et al. ***PLoS Biology*** 2010; Lakhina, et al. ***Neuron*** 2015), and the discovery that signaling from males drives pro-aging pathways that kill mothers after reproduction (Shi & Murphy, ***Science*** 2014).

Recently my lab developed a method to isolate adult *C. elegans* cells that allows us to carry out transcriptional studies with unprecedented refinement (Kaletsky, et al., submitted). We have used this method to isolate specific tissues, single cells, and subcellular compartments, including pre- and post-synapses, for RNA-seq analysis. Coupled with our behavioral assays for learning and memory and our work in longevity/aging, we will use this approach to identify key regulatory mechanisms for the maintenance of cognitive function and neuromuscular junction (NMJ) with age.

B. Positions and Honors

Assistant Professor of Molecular Biology and Genomics, Princeton University (2005)
Associate Professor of Molecular Biology and Genomics, Princeton University (2012)
Director, Glenn Center for Quantitative Aging Research at Princeton University (2012)

Selected Honors:

National Merit Scholar (1987)

Rhodes Scholarship Semi-Finalist (1992)
Howard Hughes Medical Institute Pre-Doctoral Fellowship (1994-1999)
NSF Pre-doctoral Fellowship (1994, declined)
Life Sciences Research Foundation Postdoctoral Fellowship (2000-2003)
American Cancer Society Fellowship (2000 declined)
Ellison Medical Foundation/American Federation for Aging Research, Senior Postdoct.Fellowship (2003-2005)
Burroughs-Wellcome Career Awards in the Biomedical Sciences Finalist (2003)
Sloan Research Fellowship (2006-08)
Ellison Medical Foundation New Scholar in Aging (2006, declined)
Pew Biomedical Scholar (2006-10)
Basil O'Connor Starter Scholar Research Award (2008-10)
American Society for Cell Biology Women in Cell Biology Jr. Award (2008)
McKnight Scholars Award (2008-11)
Keck Distinguished Young Scholars in Medical Research Award (2008-13)
National Institute on Aging Lab. of Neurosciences *Disting. Lect. in Neuroscience and Aging* (2009)
NIH New Innovators Award (2008-13)
NIH Research Partnership in Cognitive Aging Award (R01, 2009)
Glenn Award for Research in Biological Mechanisms of Aging (2010)
Princeton Molecular Biology Innovation Award (2014)
NIH Pioneer Award Finalist (2014)

C. Contributions to Science

My lab works on several areas that are all related to understanding how aging and longevity are regulated. Everything we call a "longevity pathway" functions to couple the timing of reproduction, based on information the organism perceives about its environment and nutrient status, with somatic health; all of the selection for any longevity pathway has to act at the level of reproduction, not late in life. For those reasons, and because I am fundamentally interested in reproductive and cognitive decline with age, and how they are regulated both cell autonomously and non-autonomously, the work in my lab incorporates several lines of research that are unified by this reasoning.

1. ***Regulation of Longevity****:* I first became interested in the question of aging as a postdoc, when it was known that insulin signaling mutants, such as the *daf-*2 insulin receptor mutant, were long-lived and required the activity of the FOXO transcription factor DAF-16, but the downstream targets were unknown. To solve this problem, I built my own *C. elegans* microarrays and used them to carry out a transcriptional analysis of *daf-2* and *daf-16;daf-2* mutants in early aging (Murphy, et al. 2003). These results not only answered the original question, showing that DAF-16 activates a large suite of genes that keep proteins and cells functional, but also identified a motif, the "DAF-16 Associated Element" that is associated with the opposing activity, growth, which we later found is regulated by the PQM-1 transcription factor (Tepper, et al., 2013). Our 2003 results enabled us and other researchers to study particular targets, co-factors, and mechanisms in greater detail, and is still a source of aging research, including our new findings regarding collagen upregulation (Ewald, et al. 2014). The genomic analysis also revealed that other factors and pathways, such as TGF-β signaling and HSF-1, are closely connected with IIS/DAF-16 activity (Shaw, et al. 2007; Hsu, et al. ***Science*** 2003), and all of the pathways we have studied are conserved through mammals, thus our work will have a lasting impact.

Murphy, CT., McCarroll, S., Bargmann, CI., Fraser, A., Kamath, RS., Ahringer, J., Li, H.,& Kenyon, C.; "Genes that Act Downstream of DAF-16 to Influence the Lifespan of *C. elegans*." (2003) ***Nature*** 424:277-83;
• *Featured in* ***News and Views***, Nature **424**: 259-61. (cited >1300 times, *Google Scholar*)

Shaw W.M., Luo S., Landis J, Ashraf J, **Murphy C.T.**."The *C. elegans* TGF-β Dauer pathway regulates longevity via insulin signaling." ***Current Biology.*** (2007) Oct 9;17(19):1635-45.

Ewald, C., Landis, J., Abate, J. and **Murphy*, C.T.** & Blackwell*, TK. "Dauer-independent insulin/IGF-1 signalling implicates extracellular matrix remodelling in longevity." ***Nature***, 2014 ***co-corresponding authors**

Tepper, R., Ashraf, J.A., **Murphy*, C.T.,** and Bussemaker*, H., "PQM-1 complements DAF-16 as a Key Transcriptional Regulator of DAF-2-mediated development and longevity." ***Cell,*** 2013 Aug 1; PMCID: PMC3763726 ***co-corresponding authors**

2. Regulation of Reproductive Aging: One of the earliest age-related declines humans experience is the loss of female reproductive ability. When I started my lab, I realized that the causes of reproductive decline were not known, no treatments that can slow this decline are available, and the aging field in general has not yet focused on this issue, despite the fact that reproductive status and longevity are intimately linked (Luo, et al. 2009). To address the question of reproductive aging, my lab has carried out unbiased genetic screens (Kaletsky, et al. in preparation), and genetic and genomic analyses (Luo, et al. 2009; Luo et al 2010). We discovered that mutants of the conserved TGF-β pathway slow reproductive decline, and do so by maintaining oocyte quality with age (Luo, et al. ***Cell*** 2010). Despite differences in time scales, *C. elegans* and mammalian oocyte quality decline is due to the loss of transcription of the same set of genes; this suggests that mechanisms and compounds that slow worm reproductive decline could also extend women's reproductive period. I am now interested in discovering biomarkers of reproductive decline that are present in oocytes, blood, and other tissues that would allow me to develop a diagnostic of reproductive age (provisional patent).

Luo, S., Shaw, W. M., Ashraf, J., **Murphy, C. T**. (2009). "TGF-β Sma/Mab signaling mutations uncouple reproductive aging from somatic aging." ***PLoS Genet.*** 2009 Dec. 5 (12)

Luo, S., Kleemann, G.A., Ashraf, J.M., Shaw, W.M., and **Murphy, C.T**., "TGF-β and Insulin Signaling Temporally and Spatially Regulate Reproductive Aging via Germline Quality Maintenance." ***Cell*** 2010 Oct 15;143(2):299-312.

- *Featured in **Cell**'s PaperClip, Oct. 15, 2010*
- ***New York Times**, Oct. 15, 2010*
- ***News & Views**, Nature* **468**: 386-387

Murphy, C.T., US Provisional Patent # 62/089,604: *Biomarkers of Oocyte Quality*

3. Regulation of Cognitive Aging: The loss of cognitive abilities is one of the most devastating effects of aging. While *C. elegans* has been used to study regulation of longevity, it had not been well-studied as a model for cognitive aging. My lab developed new assays to study *C. elegans'* learning, short-term, and long-term associative memory (Kauffman, et al. 2010; Kauffman, et al. 2011), and found that long-lived IIS *daf-2* mutants have extended learning and short-term memory, and increase long-term memory through increased levels of CREB. We went on to identify the genetic components of short-term memory (Stein & Murphy, 2014), and to identify the set of genes that CREB activates upon long-term memory training (Lakhina, et al. ***Neuron*** 2015). Together, these studies show that worms use and lose their cognitive abilities via similar mechanisms as humans, and that their abilities can be maintained under specific longevity conditions. Worms will therefore be a good system to explore additional conditions and treatments that may slow cognitive decline with age.

Kauffman, A.L., Ashraf, J.A., Corces-Zimmerman, M.R., Landis, J.L., and **Murphy, C.T**., (2010) "Insulin Signaling and Caloric Restriction Differentially Influence the Decline of Learning and Memory with Age." ***PLOS Biology***, 8(5): PMCID: PMC2872642

- *Featured in **Nature Reviews Neuroscience**, June 9, 2010*.

Stein GM and **Murphy CT.** "The intersection of aging, longevity pathways, and learning and memory in *C. elegans."* ***Frontiers in Genetics*** **3**:259. (2012) doi: 10.3389/fgene.2012. 0259; PMCID: PMC3509946

Stein, GM and **Murphy, CT**. "*C. elegans* Positive Olfactory Associative Memory is a Molecularly Conserved Behavioral Paradigm." ***Neurobiol Learn Mem***, 2014 Aug 7; DOI: 10.1016/j.nlm.2014.07.011; PMID: 25108196

Lakhina, V., Arey, R.A., Kaletsky, R., Kauffman, A., Stein, G. Keyes, W., Xu, D., and **Murphy, C.T. "**Genome-wide Functional Analysis of CREB/Long-Term Memory-Dependent Transcription Reveals Distinct Basal and Memory Gene Expression Programs." ***Neuron*** 2015 Jan 21;85(2):330-45.

4. ***Post-mating Changes in Physiology and Behavior:*** We discovered serendipitously that mating kills C. *elegans* mothers just after having produced the male's progeny, possibly due to sperm competition (death prevents any later matings). Remarkably, the mechanisms that males use to kill the mothers is by reversing

pathways that we normally think of as pro-longevity: insulin signaling is turned up "high," removing DAF-16 from the nucleus, and NHR/DAF-12 signaling is also shut off. Together these result in the worms losing all stress protection, causing shrinking and rapid death. Thus, the males have hijacked the same pathways that females normally use slow reproduction and extend somatic lifespan in times of low nutrients, driving them in the opposite direction. The effect is also conserved in true female/male species, such as *C. remanei*, meaning that females must always have a shortened lifespan if they reproduce. Moreover, we observe major shifts in behavior after mating, suggesting that neuronal signals are also changed. Our current studies focus on identifying the sperm and seminal fluid components that induce these effects, the signals between the germline and soma, the signal to the neurons, and the gene expression changes in neurons that mediate the behavioral shifts we observe.

Shi C, **Murphy CT**. "Mating induces shrinking and death in *Caenorhabditis* mothers." ***Science***. 2014 Jan 31; 343(6170):536-40.

- *Featured in* ***Current Biology*** **2014** Mar 3;24(5):R196-8.
- *Featured in* ***Science.*** 2014 Jan 31;343(6170):491-2.
- *Featured in* ***Jezebel***, http://jezebel.com/sex-is-kiss-of-death-for-female-worms-because-patriar-1488279886

5. Tissue Specificity and adult C. elegans tissue profiling: Although lifespan is a whole-organism phenotype, differerent tissues can age at different rates, tissue-specific phenotypes develop at different ages, and cell non-autonomous effects are important in the regulation of longevity. Therefore, my lab is interested in being able to determine where all genes are expressed. However, this is not a simple problem; adult worms have a tough outer cuticle that prevents easy dissociation of cells. In order to explore localized gene expression, we first leveraged the available whole-animal gene expression data, and used known gene expression profiles (10% of the genome) to predict where the remaining genes are likely to be expressed (Chikina, et al. 2009). More recently, we developed a chemo-mechanical method to dissociate adult worm cells. I believe that this method will be widely adopted by the *C. elegans* field (judging from the number of requests for the protocol) because it will help answer many different gene expression questions in adults that were not previously addressible. We are using this technique to study gene expression changes in adults with age and in longevity mutants, isolating tissues (muscles, neurons, intestine, hypodermis), neuron types, individual neurons, and pre- and post-synaptic compartments, including the NMJ.

Chikina, M.D., Huttenhower, C., **Murphy, C.T**.* and Troyanskaya, O.G., "Global Prediction of Tissue Specific Gene Expression and Context-Dependent Gene Networks in *C. elegans*." ***PLoS Comput Biol.*** 2009 Jun;5(6). ***co-corresponding authors.**

Kaletsky, R., Williams, A., Lakhina, V., Arey, R., Landis, J., and **Murphy, C.T.,** "Transcriptional profiling of dissociated adult *C. elegans* neurons identifies a new IIS/FOXO-dependent regulator of axon regeneration," *Submitted* (***Science***)

My Bibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/coleen.murphy.1/bibliography/42228466/public/?sort=date&direction=descending

D. Research Support (past three years)

Ongoing Research Support:

Source: Glenn Foundation **Period**: 8/1/12-7/31/17

Title: Glenn Center for Quantitative Aging Research at Princeton University

Major Goals: The mission of the Glenn Laboratories for Aging Research at Princeton is the establishment of collaborative projects between labs with different areas of interest and expertise to carry out innovative aging research. C.T. Murphy is the Director of the Glenn Center at Princeton.

Source: NIH **ID:** R01 AG034446 **Period:** 8/15/09-7/31/15

Title: Molecular Mechanisms Regulating Age-Related Cognitive Decline in *C. elegans*
Major Goals: We use genomic and genetic approaches to identify age-related changes in neuronal function, and to distinguish those changes that are functionally deleterious from those that may be an adaptive response to aging. C.T. Murphy is the PI.

Source: March of Dimes **Period:** 6/1/14-5/31/17
Title: Identification of Genes and Small Molecules to Prevent Maternal Age-Dependent Oocyte Decline and Aneuploidy
Major Goals: *C. elegans* is an excellent model to rapidly and thoroughly dissect mechanisms underlying reproductive aging. We will perform genetic and drug screens to fully define the repertoire of reproductive aging regulators and to identify potential therapeutics. C.T. Murphy is the PI.

Source: Princeton Dean of Research Molecular Biology Innovation Fund **Period**: 2/1/14-1/31/15
Title: "The Wheat from the Chaff: Sorting Neurons from Animals with Differences in Learning and Memory Ability"
Major Goals: The goal is to develop a system to distinguish 'smart' from 'dumb' worms in an isogenic population, and to determine the underlying molecular components that are responsible for this difference.

Completed Research Support:
Source: Keck Foundation's Distinguished Young Scholars **Period:** 7/1/08-6/30/14
Title: Molecular Characterization of Long-Term Memory Maintenance with Age
Major Goals: The goal of our proposed work is to identify critical neuronal maintenance genes in *C. elegans*, leading eventually to the development of therapeutics to improve cognitive function in the elderly.

Source: NIH, Director's New Innovator Award **ID:** 1DP2OD004402-01 **Period:** 9/30/08-6/30/13
Title: Slowing the Ticking Clock: *C. elegans* Screens for Reproductive Aging Regulators
Major Goals: We developed methods to prevent and treat age-related reproductive problems. These approaches will expand our knowledge of the causes of reproductive aging, and will help identify candidates for the treatment and prevention of age-related reproductive decline.

Source: McKnight Scholar Award **Period:** 7/1/08-6/30/13
Title: Molecular Characterization of Long-Term Memory Maintenance with Age
Major Goals: Using *C. elegans* as a model organism we propose to 1-quantiative the age sensitivity of neuronal processes, 2-characterize various longevity pathways' effects on neuronal function and 3-perform a genetic screen to identify genes that maintain memory function with age.

Source: Glenn Foundation **Period:** 6/18/10-6/17/12
Title: Glenn Award for Research in Biological Mechanisms of Aging
Major Goals: Award to augment aging research in Prof Murphy's laboratory.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: RICHARDSON, ARLAN

eRA COMMONS USER NAME (agency login): Richardsona

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Peru State College, Peru, Nebraska	BA	08/1963	Chemistry/Biology
Oklahoma State University, Stillwater, Oklahoma	PHD	08/1968	Biochemistry
University of Minnesota, St. Paul, Minnesota	Postdoctoral Fellow	08/1971	Biochemistry

A. PERSONAL STATEMENT

Over the past 35 years, my research has focused on various aspects of aging, e.g., (i) the effects of aging and dietary restriction on gene expression in rats and mice, (ii) testing the oxidative stress theory of aging by measuring the effect of alterations in the antioxidant defense system on the lifespan and pathology of transgenic and knockout mice, and (iii) most recently, studying the effect of rapamycin on aging and age-related diseases. Currently, my research is focused on two areas. First, the role of cell senescence in the mechanism of accelerated aging observed in Sod1 knockout mice. Second, the effect of genotype and level of restriction on the anti-aging mechanism of dietary restriction.

Since 1971 I have mentored/directed the thesis research of 32 graduate students who received MS degrees and 26 graduate students who have received PhD degrees at either Illinois State University of the University of Texas Health Science Center at San Antonio. I also have trained 25 post-doctoral fellows and served as a mentored on NIH, VA, and Beeson grants for 16 junior faculty. In addition I am the PI on an NIA Summer Workshop for training junior faculty interested in pursuing a research career in aging (see description of grant below) and have been involved in the Summer Workshop for the past 20 years.

B. POSITIONS AND HONORS

Positions and Employment

1968 - 1969	Assistant Professor, Fort Lewis College, Department of Chemistry, Durango, CO
1971 - 1974	Assistant Professor, Illinois State University, Department of Chemistry, Normal, IL
1975 - 1979	Associate Professor, Illinois State University, Department of Chemistry, Normal, IL
1980 - 1990	Professor , Illinois State University, Department of Chemistry, Normal, IL
1990 - 2012	Research Career Scientist, Audie L. Murphy Memorial VA Medical Center, GRECC, San Antonio, TX
1990 - 2012	Professor, University of Texas Health Science Center at San Antonio, Department of Medicine (1990-1995), San Antonio, TX
1996 - 2012	Director, Barshop Institute on Longevity and Aging Studies, University of Texas Health Science Center at San Antonio, San Antonio, TX
2013 -	Senior Research Career Scientist, Oklahoma City VA Medical Center, Oklahoma City, OK
2013 -	Professor, University of Oklahoma Health Sciences Center, Department of Geriatric Medicine, Oklahoma City, OK

Other Experience and Professional Memberships

1980 - 1981	President, American Aging Association
1982 - 1983	President, American Aging Association
1985 - 1988	Member of Council, Gerontological Society of America
1986 - 1987	Chair of Biological Sciences Section, Gerontological Society of America

1991 - 1991	Chair, Gordon Conference on the Biology of Aging
1998 - 1999	President, Gerontological Society of America
2002 - 2007	Member, Board of Scientific Counselors of NIA
2008 - 2008	Chair, Keystone Symposium of Metabolic Pathways of Longevity
2010 - 2013	Member, National Advisory Council on Aging (NIA)

Honors

1986	Distinguished Professor, Illinois State University
1993	Nathan W. Shock Award, Gerontology Research Center of NIA
1995	Robert W. Kleemeier Award, Gerontological Society of America
2001	Denham Harman Research Award, American Aging Association
2008	Irving Wright Award of Distinction in Aging Research, American Federation for Aging Research
2008	Lord Cohen Medal for Services to Gerontology, British Society for Research on Ageing
2010	Faculty Leadership Award, Faculty Senate, University of Texas Health Science Center at San Antonio
2010	Presidential Distinguished Senior Research Scholar, University of Texas Health Science Center at San Antonio

C. SELECTED PEER-REVIEWED PUBLICATIONS (from 256 with 25 since 2013)

To test directly the oxidative stress theory of aging, my laboratory has generated over the past 15 years a wide variety of transgenic and knockout mouse models that over or under express various antioxidant enzymes. While these animals show the expected alterations in sensitivity to oxidative stress and the accumulation of oxidative damage, only one, out of 18 mouse models showed any significant change in lifespan: *Sod1* knockout mice. The data my laboratory generated has led to the field re-evaluating the role oxidative damage plays in aging.

- H. Van Remmen, Y. Ikeno, M. Hamilton, M. Pahlavani, N. Wolf, S.R. Thorpe, N.L. Alderson, J.W. Baynes, C.J. Epstein, T.-T. Huang, J. Nelson, R. Strong, and **A. Richardson**. "Lifelong reduction in MnSOD activity results in increased DNA damage and higher incidence of cancer but does not accelerate aging." *Physiol. Genomics,* **16:** 29-37, 2003. PubMed PMID: 14679299. .
- V. I. Pérez, H. Van Remmen, A. Bokov, C.J. Epstein, J. Vijg, and **A. Richardson**. "The overexpression of major antioxidant enzymes does not extend the lifespan of mice." *Aging Cell,* **8:** 73-75, 2009. PubMed PMID: 19077044; PubMed Central PMCID: PMC2667893.
- Y. C. Jang, V. I. Pérez, W. Song, M. S. Lustgarten, A. B. Salmon, J. Mele, W. Qi, Y. Liu, H. Liang, A. Chaudhuri, Y. Ikeno, C. J. Epstein, H. Van Remmen, and **A. Richardson**, "Overexpression of Mn superoxide dismutase protects against oxidative stress but does not increase lifespan in mice." *J. Gerontol. A Biol. Sci. Med. Sci.,* **64:**1114-25, 2009. PubMed PMID: 19633237; PubMed Central PMCID: PMC2759571.
- A. B. Salmon, V. I. Pérez, A. Bokov, A. Jernigan, G. Kim, H. Zhao, R. L. Levine, and **A. Richardson**. "Lack of methionine sulfoxide reductase A in mice increases sensitivity to oxidative stress but does not diminish lifespan." FASEB J., **23:** 3601-8, 2009. PubMed PMID: 19487311; PubMed Central PMCID: PMC2747676.
- Y. Zhang, Y. Ikeno, W. Qi, A. Chaudhuri, Y. Li, A. Bokov, C. Epstein, **A. Richardson**, and H. Van Remmen. "Mice deficient in both manganese superoxide dismutase and glutathione peroxidase-1 have increased oxidative damage and a greater incidence of pathology that do not lead to a reduction in longevity." *J Gerontol A Biol Sci Med Sci. Dec;***64**:*1212-1220*, *2009.* PubMed PMID: 19776219; PubMed Central PMCID: PMC2781787.
- Y. Zhang, Y. Ikeno, A. Bokov, J. Gelfond, C. Jaramillo, H.M. Zhang, Y. Liu, W. Qi, G. Hubbard, **A. Richardson**, and H. Van Remmen. "Dietary restriction attenuates the accelerated aging phenotype of Sod1$^{-/-}$ mice." *Free Radic. Biol. Med*., **60:** 300-306, 2013. PubMed PMID: 23459073; PubMed Central PMCID: PMC3696984.
- G.K. Sakellariou, C.S.Davis, Y.Shi, M.V.Ivannikov, Zhang Y., Vasilaki A., Macleod G. T., **Richardson A.**, Van Remmen H., Jackson M. J., McArdle A, Brooks S. V. Neuron-specific expression of CuZnSOD prevents the loss of muscle mass and function that occurs in homozygous CuZnSOD-knockout mice. *FASEB J*., **28**:1666-81, 2014. PubMed PMID: 24378874; PubMed Central PMCID: PMC3963022.

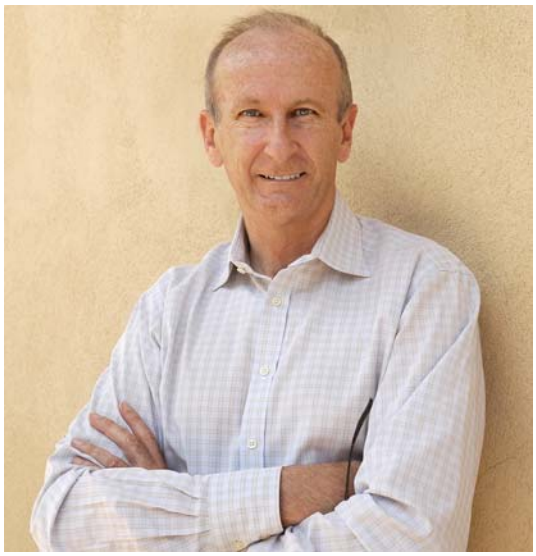
Aging research of Gary Ruvkun 2015

Dr. Ruvkun's research has explored two major themes: control of longevity and metabolism by insulin and other endocrine pathways and developmental regulation by microRNA genes and other tiny RNAs. Dr. Ruvkun's laboratory discovered that an insulin-like signaling pathway controls *C. elegans* metabolism and longevity. Recent insulin signaling mutant analyses in mouse and humans have validated the generality of these discoveries to other animals. Dr. Ruvkun's lab has also used full genome RNAi libraries to explore the complete set of genes that regulate aging and metabolism. Many of the gene inactivations that cause increased survival encode the core conserved elements of cells that are targeted by antibiotics produced by fungi and microbes. These core genetic pathways may be surveilled for toxin and virulence factor inhibition so that a decrement in function is interpreted as a microbial attack. The immune surveillance endocrine states that are normally induced by poisons or genetic variation in these surveillance pathways may underlie a variety of autoimmune and other diseases.

Dr. Ruvkun's research revealed that the first microRNA discovered by the Ambros lab, *lin-4,* regulates the translation of a target gene, *lin-14*, to which it base pairs. The Ruvkun lab identified a second microRNA, *let-7*, which also regulates translation of its target gene via imperfect base pairing to the 3' untranslated region of that mRNA, and showed that the sequence and regulation of the *let-7* microRNA is conserved across animal phylogeny including humans. Thousands of miRNAs have subsequently been discovered and are now implicated in control of gene expression of across eukaryotic phylogeny. Saturation genetic analysis of the miRNA and RNAi pathways by the Ruvkun lab has revealed many of the protein cofactors that may mediate other steps in how miRNAs and siRNAs engage their targets. Some of these components may be developed as drug targets to enhance RNAi in mammals, a technical improvement that may be necessary to elevate a laboratory tool to a therapeutic modality.

Biography

PROGRAM ON STEM CELLS IN SOCIETY
STANFORD CENTER *for* BIOMEDICAL ETHICS



Christopher Thomas Scott, MLA, PhD, is Director of the Stanford University Program on Stem Cells in Society, a faculty and senior research scholar at the Stanford Center for Biomedical Ethics, and a member of the Stanford Institute for Stem Cell Biology and Regenerative Medicine. He is an associate faculty of the University of British Columbia's National Core on Neuroethics and a fellow at King's College London.

His research centers on the ethical, legal, and social implications of new biotechnologies. Scott is widely published in peer-reviewed journals such as *Cell, Cell Stem Cell, Science, Nature, The Hastings Center Reports, Nature Biotechnology*, and the *American Journal of Bioethics*. His introductory text, *Stem Cell Now* (Penguin/Plume) has been translated into four languages. He directs undergraduate, graduate, and medical school courses. He is a contributing editor at *Nature Biotechnology* and serves on the editorial boards of several journals.

A former cell biologist, Scott was the Assistant Vice Chancellor at the University of California, San Francisco (UCSF). He co-founded Acumen Sciences, a research consulting company based in San Francisco, and was formerly the President and CEO of The Stem Cell Advisors, a public benefit non-profit company providing oversight and guidance for stem cell research.

He is regularly featured in national media coverage of science policy and bioethics, including ABC, BBC, NBC, PBS, UPI, Fox, The New York Times, The Boston Globe, Time, The Atlantic Monthly, Nightline, Talk of the Nation, Science Friday, Al Jazeera's Fault Lines, and NPR's Fresh Air with Terry Gross.

CURRICULUM VITAE

Personal data:

Name: **Luis Felipe SIERRA**
Date of birth: October 4, 1953
Citizenship: Chile, USA

Education:

1977: Licensed in Biochemistry (with Distinction), Universidad de Chile
1977: Biochemist (with Maximal Distinction), Universidad de Chile
1983: Ph. D. in Biochemistry and Molecular Biology, University of Florida

Work History:

1983-1987: Post-doctoral fellow, ISREC and University of Geneva, Switzerland
1987-1992: Molecular Biology Specialist, Nestlé Research Center, Switzerland
1992-1998: Assistant / Associate Professor, Medical College of Pennsylvania/ Hahnemann University, Philadelphia, PA
1999-2002: Assistant / Associate Investigator, Lankenau Institute for Medical Research, Wynnewood, PA and Associate Professor, ICBM, Universidad de Chile, Santiago, Chile
2002-2006: Health Science Administrator, NIH/NIA, Bethesda, MD

2006-present: Director, Division of Aging Biology, NIA

Lectures while at the NIH:

A comprehensive list has not been kept up to date. On average, I give 12-16 lectures a year, on three primary topics:

- The current status and prospects for research on the basic biology of aging
- Funding by the NIH/NIA – things you need to know
- Geroscience and the GeroScience Interest Group

Publications:

- **Prior to joining the NIH:**

40 peer reviewed papers
4 reviews
5 chapters in books
1 monographic book

- **Since joining the NIH (and related to NIH activities):**

6 peer reviewed papers
7 reviews
5 chapters in books

Program Development

A. Announcements / Requests for Applications

PA-03-069 - The Biological Basis of Hutchinson-Gilford Syndrome (HGS): Relationship to mutations in the lamin A/C gene (lmna) and to other laminopathies.

PA-03-145 - Ubiquitin and ubiquitin-like modifications regulating disease processes. PA from NIDDK, Dr. Sierra is the NIA contact.

RFA-AG-04-006 - Proteomics of Aging and Age-related Diseases. Released October 7, 2003, in conjunction with Dr. Brad Wise (NNA).

PA-05-136 - Testing Stem Cell Therapy in Mouse Models of Premature Senescence. Released July 13, 2005.

PA-05-155 & PA-06-138 - The Secretory Pattern of Senescent Cells. Released August 15, 2005

TPA-05-055 - Targeting Diseases Caused by Protein Misfolding or Misprocessing. PA from NIDDK, Dr. Sierra was the NIA contact.

RFA-AG-08-001 – Protein homeostasis and aging: repair and degradation. Released June 13, 2007.

RFA-AG-09-013 – Limited Competition Renewal of Aging Intervention Testing Program. Released November 13, 2008.

PAR-AG-11-266 – Network Infrastructure Support for Emerging Areas of Research in the Basic Biology of Aging. Released July 20, 2011.

RFA-AG-12-010 – Caenorhabditis Intervention Testing Program (CITP). Released September 11, 2012.

PAR-AG-13-233 – Inflammation and Age-related Disease. Released May 30, 2013.

RFA-AG-15-005 – Nathan Shock Centers of Excellence in Basic Biology of Aging. Released August 8, 2014.

B. Other trans-NIH activities

2011 – Created and directs the Trans-NIH Geroscience Interest Group, with representatives from 20 different ICs. The goal is to promote awareness (and increase funding) about the role of aging as the major risk factor driving the large majority of chronic diseases of interest across the NIH.

David A. Sinclair, Ph.D.
ONE PAGE BIOSKETCH
(2015)

David A. Sinclair, Ph.D. is a tenured Professor of Genetics at Harvard Medical School, co-Director of the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging at Harvard, and a Professor at the University of New South Wales. His postdoctoral training was with Dr. Lenny Guarente at M.I.T., where he worked on the cause of yeast aging and a family of longevity regulators that become known as the sirtuins. He is known for his work on understanding why we age and how to slow its effects, including molecules that can slow or reverse aspects of aging in mammals. He has founded a number of biotechnology companies in areas of aging, diabetes, vaccines, and bioinformatics. He also co-founded and serves as co-chief editor of the scientific journal *Aging* and his work is featured in four books and two documentary movies. Dr. Sinclair has received awards including the Australian Commonwealth Prize, the Thompson Prize, a Helen Hay Whitney Postdoctoral Award, A Charles Hood Fellowship, a Leukemia Society Fellowship, a Ludwig Scholarship, a Harvard-Armenise Fellowship, an American Association for Aging Research Fellowship, The Nathan Shock Award from the National Institutes of Health, Ellison Medical Foundation Junior and Senior Scholar Awards, The Merck Prize, a Genzyme Outstanding Achievement in Biomedical Science Award, the Bio-Innovator Award, the David Murdock-Dole Lectureship, the Fisher Honorary Lectureship at UCLA, the Les Lazarus Lectureship, the ASMR Medal, and TIME 100, TIME magazine's list of the "100 most influential people in the world."

Bruce A. Yankner, M.D., Ph.D. is Professor of Genetics and Neurology at Harvard Medical School, Director of the Harvard Neurodegeneration Training Program, and Co-Director of the Paul F. Glenn Laboratories for Biological Mechanisms of Aging. Dr. Yankner graduated from Princeton University, received his M.D. and Ph.D. from Stanford University, and did a residency at Massachusetts General Hospital. His work has contributed to understanding pathogenic mechanisms in Alzheimer's disease, Down's syndrome and Parkinson's disease, beginning with the initial observation that amyloid beta protein is a toxic molecule, and later with investigations into the roles of presenilin proteins, Notch and Wnt in neuronal signaling and pathology. Recent work from his laboratory has defined the transcriptome of the aging brain, its evolution from mouse to man, and the role of the transcriptional regulator REST/NRSF in brain aging and Alzheimer's disease. He has received the Major Award for Medical Research from the Metropolitan Life Foundation, the Derek Denny-Brown Neurological Scholar Award from the American Neurological Association, the Irving S. Cooper Award from the Mayo Clinic, the Ellison Medical Foundation Senior Scholar Award, the Nathan W. Shock award from the National Institute on Aging, and an NIH Director's Pioneer Award.