

Healthy Aging

October 25-27, 2017

Mohonk Mountain House
New Paltz, NY



To bring together scientists with an interest in diet and healthspan,
to exchange knowledge, to generate ideas for future investigations,
and to strengthen relationships within this community.



Program

Wednesday, October 25, 2017

Cocktail Reception

6:00–7:00 pm
Parlor Porch

Dinner

7:00–8:30 pm
Dining Hall

Thursday, October 26, 2017

Symposium

8:15 am–4:30 pm

Parlor

Morning Session, moderator: Jay Zimmerman, Ph.D.

- 8:15–8:30 *Welcome – David Orentreich, MD, OFAS*
- 8:30–9:30 *Keynote Address, George Martin, MD, University of Washington*
- 9:30–10:00 *John Richie, Ph.D., Penn State College of Medicine*
- 10:00–10:30 *Vishwa Dixit, Ph.D., Yale University*
- 10:30–10:45 *Break*
- 10:45–11:15 *Yousin Suh, Ph.D., Albert Einstein College of Medicine*
- 11:15–11:45 *Peter Adams, Ph.D., University of Glasgow, Scotland*
- 11:45–12:15 *Matt Kaerberlein, Ph.D., University of Washington*

Lunch

12:15–1:15 pm

Dining Hall

Afternoon Session, moderator: Arthur Cooper, Ph.D.

- 1:15–1:45 *Jay Johnson, Ph.D., OFAS*
- 1:45–2:15 *Jessica Tyler, Ph.D., Weill Cornell Medicine*
- 2:15–2:45 *Pankaj Kapahi, Ph.D., Buck Institute for Research on Aging*
- 2:45–3:00 *Break*
- 3:00–3:30 *Brad Johnson, MD, Ph.D., University of Pennsylvania*
- 3:30–4:00 *Robert Koza, Ph.D., Maine Medical Center Research Institute*
- 4:00–4:30 *Anne-Kate Shoveller, Ph.D., University of Guelph, Canada*

Group Photo

5:00 pm

Banquet Dinner

7:00–9:00 pm

East Dining Room 1



Friday, October 27, 2017

Symposium

8:15 am–12:00 pm

Parlor

Morning Session, moderator: Gene Ables, Ph.D.

8:15–8:45

Sailendra Nichenametla, Ph.D., OFAS

8:45–9:15

Peter Arvan, Ph.D., University of Michigan

9:15–9:45

Rochelle Buffenstein, Ph.D., Calico Labs

9:45–10:00

Break

10:00–10:30

Arlan Richardson, Ph.D., University of Oklahoma Health Sciences Center

10:30–11:00

Christian Sell, Ph.D., Drexel University

11:00–11:30

Holly Brown-Borg, Ph.D., University of North Dakota

11:30–12:00

Closing Remarks

Lunch

12:00–1:00 pm

Dining Hall

Symposium Adjourned

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Keynote Speaker

George M. Martin, MD
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. Other postdoctoral experiences included research in molecular biology with Francois Gros in Paris and in experimental embryology with Henry Harris and Richard Gardner at Oxford University. Honors for his research have included awards from the Gerontological Society of America, the American Federation for Aging Research, a World Alzheimer Congress Lifetime Achievement Award, an Outstanding Alumnus Award from the University of Washington School Of Medicine, and election to the National Academy of Medicine. Dr. Martin is a Past President of the Tissue Culture Society of America, the American Federation for Aging Research and the Gerontological Society of America.

Dr. Martin's research utilized genetic approaches to the study of aging and age-related diseases in mammals. His lab contributed to our understanding of a number of mechanisms for the heritable alteration of genetic information. Biochemical, cytogenetic and somatic cell genetic studies of cells from aging mammals addressed various somatic mutational theories of aging and provided the first data on mutation frequencies in human epithelial cells in aging human subjects. These studies were reinforced by investigations of a remarkable human progeroid syndrome, the Werner syndrome, resulting in the discovery of causative mutations in a member of the RecQ family of DNA helicases. Cells from these patients were shown to undergo accelerated replicative senescence. Related studies provided the first evidence for the limited replicative potential of arterial cells and its potential role in atherogenesis. Interests in the aging of post-replicative cells led to his founding of the Alzheimer's Disease Research Center at the University of Washington, research on two of the three dominant mutations that cause early onset Alzheimer's disease, and the creation of the first mouse model bearing one such mutation. His current research efforts involve tests of the hypothesis that age related increases in variegated gene expressions in homologous cell types may be regarded as a form of antagonistic pleiotropic gene action.

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



Abstracts



Dietary total sulfur amino acid restriction in healthy adults: A controlled feeding study

John P Richie, Jr¹, Raghu Sinha¹, Sailendra Nichenametla², Gene Ables², Zhen Dong¹, Amy Ciccarella³, Indu Sinha¹, Ana Calcagnotto¹, Lisa Reinhart¹, David Orentreich²

¹Penn State University College of Medicine, Hershey, PA; ²Orentreich Foundation for the Advancement of Science, Cold Spring, NY; ³Clinical Research Center, Penn State University, University Park, PA

Dietary methionine restriction (MR) delays the aging process and inhibits aging-related diseases and disorders in numerous laboratory animal models. These effects are accompanied by numerous metabolic alterations, including improvements in glucose and fat metabolism and a reduction in oxidative stress that may underlie MR's beneficial health effects. Recent studies have indicated that a restriction in both methionine and cysteine (total sulfur amino acid restriction, SAAR) is required to obtain optimal beneficial effects. While SAAR holds promise as a possible intervention for prevention of aging-related impairments and diseases, little is known about the translation of these findings to humans. Thus, our objectives were to determine the short-term (1-mo) impact of feeding MR or SAAR diets to healthy adults on relevant anthropometric, metabolic, and oxidative stress biomarkers. In this controlled feeding study, twenty healthy adults (11 females/9 males) were randomized to either MR or SAAR diet arms. Each arm consisted of 3 controlled isocaloric 4-wk feeding periods: 1) control; 2) 70% MR or 50% SAAR; 3) 90% MR or 65% SAAR, separated by 3-4-wk washout periods. Biological samples were collected before and after each feeding period. Dietary intakes of methionine and cysteine prior to and during each feeding period were confirmed by unannounced 24-hr food recall assessments and chemical analyses of actual diet samples, respectively. SAAR diets were associated with dose-dependent reductions in body weight and, with 65% SAAR, an increase in body temperature. Likewise, during SAAR diet periods, decreases in plasma cholesterol, leptin, IGF-1, and 8-isoprostane levels were observed. No adverse effects were observed for either MR or SAAR diets. These results suggest that many of the short-term effects of SAAR observed in animal models are translatable to humans. Overall, these findings support the further clinical development of this dietary intervention for health promotion and disease prevention.

Caloric restriction in humans inhibits inflammation: Insights from CALERIE-II

Vishwa Deep Dixit
Yale School of Medicine, New Haven, CT

Chronic low-grade inflammation is a major driver of degenerative-chronic disease. To date, the cellular origin of age-related inflammation and the underlying molecular mechanisms are not well understood. Caloric restriction is the most robust intervention that reduces disease burden and extends lifespan; however, whether CR is relevant to human physiology remains unclear. CALERIE Phase 2 is a three-site (Pennington Biomedical Research Center, Tufts University, Washington University), single-protocol randomized clinical trial designed to test the effects of 2 years of sustained caloric restriction (CR) in healthy men (20-50 yr) and women (20-47 yr). We hypothesized that a reduction in energy intake to 75% of baseline requirement (25% CR) for 2 years will result in the same adaptive changes that occur in rodents subject to CR, with particular emphasis on the reduction in inflammation. This study investigated the impact of CR on inflammation through whole transcriptome and metabolome analyses in the s/c adipose tissue and their relationship with serum cytokines and metabolic outcomes. CR in humans did not impair the markers of adaptive immune response with no change in self-reported incidence of infections. In free living setting, instead of the intended 25% goal, only 15% CR was achieved in people. We found that the metabolic changes induced by 15% 2-year caloric restriction was sufficient to regulate the adipose-immune crosstalk within the adipose tissue to lower inflammation. These studies also reveal that CR in humans regulates several conserved longevity pathways previously identified from model organisms. Our findings suggest that drivers of CR-regulated immunometabolic response in can be harnessed for development of novel anti-inflammatory targets.



Enhancer mechanisms in human aging and disease

Yousin Suh

Department of Genetics and Medicine, Albert Einstein College of Medicine, New York, NY

Genome-wide association studies (GWAS) have achieved great success in identifying genetic variants robustly associated with increased disease risk. The vast majority (> 90%) of risk variants detected by GWAS occur in non-coding genomic regions, suggesting that they impose risk by altering promoter and enhancer elements that regulate gene expression. Understanding how non-coding variants function in pathogenesis is critically important to translate the genetic association into molecular mechanisms and, ultimately, clinical applications. Our studies have centered on enhancer mechanisms underlying a non-coding region of the genome uncovered by GWAS, the so-called gene desert at the chromosome 9p21 locus. This locus is a GWAS hotspot associated with multiple age-related diseases, including cancer, heart disease, glaucoma, Alzheimer's disease, and diabetes, suggesting a common underlying biology of aging. Indeed, the closest protein-coding genes are the two cyclin dependent kinase inhibitors, CDKN2A (encoding p16INK4A and p14ARF) and CDKN2B (encoding p15INK4B), known to be involved in tumor suppression and cellular senescence. We will discuss our approaches to elucidate the molecular mechanisms by which risk variants alter enhancer function and target gene expression, thereby conferring increased risk of aging and disease. In addition, we will present the roles of DNA binding transcription factor complexes recruited in trans in regulation of de novo enhancer networks using replicative senescence as a model of cellular aging.

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Healthy Aging

The dynamic epigenome—a challenge to healthy aging

Peter Adams

Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA and University of Glasgow, UK

Healthy aging depends on long-term maintenance of chromatin structure, for example in long-lived tumor suppressive senescent cells (e.g., nevus melanocytes), other post-mitotic cells, and quiescent stem cells. Stable chromatin is required to maintain cell phenotype, for example of a neuron, and to suppress tumorigenesis, for example in an oncogene-expressing senescent nevus melanocyte. Remarkably, in these post-mitotic cells, functional chromatin is typically maintained for several decades.

This level of chromatin stability likely represents a challenge for these cells, since chromatin structure is known to be highly dynamic. Aside from chromatin disruption linked to fundamental processes such as gene transcription, the dynamic nature of chromatin is indicated by the phenomenon of position-effect variegation (PEV), fluorescence recovery after photobleaching (FRAP) experiments, and more recent whole-genome biochemical analyses performed as part of the ENCODE project.

The Adams lab has been interested in cellular senescence, chromatin structure, cancer, and aging for several years. We are now working to understand the mechanisms by which chromatin structure is maintained, particularly in post-mitotic cells, to allow those cells to age healthily over the course of decades. However, we also hypothesize that eventual and progressive degeneration of chromatin structure with age contributes to the striking increased incidence of cancer, and other diseases, with age.



Translational geroscience: Targeting mTOR signaling for mitochondrial disease and normative aging

Matt Kaeberlein

Department of Pathology, University of Washington, Seattle, WA

A primary goal of geroscience is to improve health, longevity, and quality of life for people through basic and translational research into the biology of aging. The FDA-approved drug rapamycin is currently the most effective pharmacological intervention to increase lifespan and improve measures of healthspan in mice. Nevertheless, important questions exist regarding the translational potential of rapamycin and other mTOR inhibitors for human aging, and the optimal dose, duration, and mechanisms of action remain to be determined. Here I will report on our studies examining the effects of chronic rapamycin treatment in mice and people with severe mitochondrial disease, as well as short-term treatment with rapamycin in middle-aged mice and dogs. Rapamycin effectively rescues mitochondrial disease progression in mice, enhances cellular measures of mitochondrial function, and improves clinical parameters in patients with MELAS syndrome. During normative aging, transient treatment with rapamycin is sufficient to increase life expectancy by more than 50% and improve measures of healthspan in middle-aged mice. In companion dogs, we have defined a dose of rapamycin that is well tolerated, and initial results are consistent with improvements in age-associated cardiac function similar to those observed in rapamycin-treated mice. These data suggest that rapamycin may be suitable for translational applications in both veterinary and human medicine to treat mitochondrial disorders and to improve healthy longevity during normative aging.

October 25-27, 2017
Mohonk Mountain House, New Paltz, NY
Healthy Aging

Identification and characterization of methionine restriction mimetics that improve healthspan in yeast, cultured mammalian cells, and mice

JD Plummer, JE Johnson

Orentreich Foundation for the Advancement of Science, Cold Spring, NY

Methionine restriction (MR) is one of only a few dietary manipulations known to robustly extend lifespan in mammals. Despite this, the mechanistic basis for this extension has remained elusive. To address this, I previously developed genetically-tractable cell systems to model the benefits of MR in budding yeast and cultured mammalian cells. Using these, I have demonstrated that both dietary MR and impairment of the cell's methionine biosynthetic machinery ("genetic MR") significantly extend the chronological lifespan of yeast, while genetic MR extends the replicative lifespan of mammalian cells.

In recent work, I have identified two autophagy genes that underlie the extended lifespan of methionine-restricted cells. Consistent with this finding, I have performed genetic studies that have revealed a positive epistatic relationship between MR and autophagy, suggesting that the primary benefit of MR to yeast lifespan extension is the activation of autophagy. Usefully, I have found that enzymatic elimination of methionine, as mediated by L-methionine gamma lyase, produces the methionine-restricted state, extends yeast lifespan, and represents a powerful tool for the study of MR. I have also observed that supplementation with either of two methionine-like amino acids can extend yeast lifespan.

Recent and ongoing research in the laboratory has focused on A) dissecting the molecular mechanisms underlying the cellular benefits of MR, and B) identifying and characterizing interventions that phenocopy MR. Towards this end, we have performed genetic and biochemical studies to determine how supplementation with methionine analogues extends cellular lifespan, and whether administration of such compounds might recapitulate the benefits of MR to mice fed a methionine-replete diet. We anticipate that these studies will facilitate the eventual development of novel pharmacologic interventions that can be used to improve healthspan in humans.



An integrative analysis of replicative aging in budding yeast

Jessica Tyler
Weill Cornell Medicine, New York, NY

Mitotic aging in budding yeast uses conserved aging pathways and serves as an excellent model for understanding the aging of human stem cells. We have been performing an integrative analysis of the replicative aging process, using the mother enrichment program to isolate unprecedented numbers of old yeast. Deep sequencing and mapping DNA damage sites by gammaH2A ChIPseq identified significant increases in chromosomal translocations, amplification of chromosomal arms, retrotransposition, and nuclear transfer of mitochondrial genomes in old cells. There are also more DNA double-strand breaks (DSBs) in old cells, which is partially due to the defect in DSB repair that we have uncovered in old cells. We have determined the mechanistic basis for this defect and reverse this defect to extend lifespan, demonstrating that the DNA repair defect is a cause of aging. We observe elevated rDNA instability during aging accompanied by insertion of the rDNA repeats into other chromosomes, and this rDNA instability leads to global genomic instability. We have uncovered a defect in sister chromatin cohesion in old cells, with the potential to cause chromosomal loss, aneuploidy, and further genomic instability. By mapping nucleosome occupancy over the aging genome, we find a loss of approximately half the nucleosomes with age, leading to transcriptional upregulation of the entire transcriptome. Conversely, our ribo-seq analyses show that most protein synthesis is reduced during aging, and we have discerned the molecular basis for this defect. Our metabolomics analyses find that amino acids are the most reduced metabolites during aging, indicating a defect in both amino acid uptake and amino acid synthesis in old cells, which activates the amino acid sensor Gcn2. Further mimicking the effect of amino acid depletion by tRNA overexpression was found to extend lifespan. Taken together, our studies are revealing novel molecular defects that occur during, and cause, replicative aging.

October 25-27, 2017
Mohonk Mountain House, New Paltz, NY
Healthy Aging

Uncoupling of diet-related effects on longevity and healthspan in *Drosophila melanogaster*

Kenneth A Wilson, Christopher S Nelson, Jennifer N Beck, Rachel B Brem, Pankaj Kapahi
Buck Institute for Aging Research, Novato, CA

Aging affects all individuals and is a risk factor for a myriad of diseases, as well as death. A number of interventions have been suggested to improve overall lifespan and health, with one of the most successful being in the form of dietary restriction. Despite the generally well-accepted health and longevity benefits of dietary restriction, cases remain in model organisms where some genotypes are not affected or are negatively impacted by dietary restriction. Further, it is often seen that individuals of different genotypes display a range of longevity and health phenotypes under different dietary conditions, indicating a role for natural genetic variation in the regulation of longevity and health as they pertain to diet. With the use of the *Drosophila* Genetic Reference Panel, we identify a new set of diet-dependent genes, the expressions of which vary naturally, which impact longevity and health. Further, our measures indicate that longevity and health, as measured by *Drosophila* climbing ability, are distinct traits that are not necessarily correlated and are regulated through genetically distinct mechanisms. Associated with diet-dependent longevity is the gene CG34351, which has a previously unreported function. Through case-control analysis for long-lived fly lines, we have also identified *Fdxh*, which is known to regulate iron-sulfur clustering in the mitochondria, as genes that regulate extreme longevity. We have also found that CG33690, a previously little-characterized gene, has a role in climbing fitness, and thus propose the new name “hiker”. Through alteration of the expression of these genes via gene disruption and RNAi, we have validated their roles in diet-dependent effects on lifespan or climbing ability. In addition to ascribing novel functions to these genes, our results underline that lifespan and healthspan may be regulated through distinct mechanisms in response to changes in diet.



The potential for Wnt pathway agonists to ameliorate pathology driven by telomere dysfunction

Rafael J Fernandez, Qijun Chen, F Brad Johnson

Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Through studies of the intestinal stem cell niche in mice and in cultured human intestinal organoids, we have identified a positive feedback loop through which the capping of telomeres and the expression of multiple components in the canonical Wnt signaling pathway support one another (*Nat Commun* 2017, 8:14766; *Cell Stem Cell* 2016, 19(3):397). Thus, on the one hand, if telomeres are in a capped state, Wnt signaling is active, and this in turn reinforces telomere capping. On the other hand, if telomeres begin to uncap, e.g., due to critical shortening, Wnt signaling declines, leading to further uncapping. The mechanisms underlying the loop include 1) upregulation of miR34a by uncapped telomeres, which inhibits expression of Wnt pathway factors, and 2) Wnt-dependent expression of several shelterins, including TRF2.

We have exploited the Wnt-telomere loop to use Wnt pathway agonists to restore telomere capping and tissue homeostasis in the intestines of late generation mice lacking telomerase (mTR mutants) and in cultured human intestinal organoids derived from cells from people suffering from the telomerase deficiency disorder dyskeratosis congenita (DKC1 mutants). We will discuss the therapeutic potential of this approach for the treatment of dyskeratosis congenita, and describe our new efforts to use it to ameliorate pathology driven by telomere dysfunction in other tissues, including lung.

October 25-27, 2017
Mohonk Mountain House, New Paltz, NY
Healthy Aging

Cardioprotective effects of rapamycin treatment on adult female C57BLKS/J-db/db mice

Peter C Reifsnnyder², Sergey Ryhzov¹, Kevin Flurkey², Rea P Anunciado-Koza¹, Ian Mills¹, David E Harrison², Robert A Koza¹

¹Center for Molecular Medicine, Maine Medical Center Research Institute, Scarborough, ME;

²The Jackson Laboratory, Bar Harbor, ME

Rapamycin (RAPA), an inhibitor of mTORC signaling, has been shown to extend lifespan in mice and other organisms. Recently, animal and human studies suggest that inhibition of mTORC signaling can alleviate or prevent the development of cardiomyopathy. In view of this, we used a murine model of type-2-diabetes (T2D), C57BLKS/J-db/db, to determine whether RAPA treatment can mitigate the development of T2D-induced cardiomyopathy in adult mice. Female C57BLKS/J-db/db fed diet supplemented with RAPA from 11 to 27 weeks of age showed reduced weight gain and significant reductions of fat and lean mass compared with untreated mice. No differences in plasma glucose or insulin levels were observed between groups; however, RAPA-treated mice were more insulin sensitive ($P < 0.01$) than untreated mice. Kidney weights and urine ACR were lower in RAPA-treated mice, suggesting reduced diabetic nephropathy and improved kidney function. Echocardiography showed significantly reduced left ventricular wall thickness in mice treated with RAPA compared to untreated mice ($P=0.02$) that was consistent with reduced heart weight/tibia length ratios, reduced myocyte size measured by histomorphology, and reduced mRNA expression of *Coll1a1*, a marker for cardiomyopathy. Our results suggest that inhibition of mTORC signaling is a plausible strategy for ameliorating complications of obesity and T2D, including cardiomyopathy.



Examining potential mechanisms of healthy aging with preventative nutrition approaches

AK Shoveller, LM McKnight, KM Wood, J Cant

Centre of Nutrition Modeling, Department of Animal Biosciences, University of Guelph, ON, Canada

Dietary restriction (DR) increases median lifespan and protects against age-related disease development. Extension of lifespan can be achieved by restricting intake of dietary energy, protein, or specific amino acids like methionine (Met) and tryptophan. We investigated a purported DR mimetic, mannoheptulose (MH), and its effects on metabolism. MH inhibits hexokinase and produces transient hyperglycemia with high doses of intravenous delivery. We predicted that limiting glucose availability via glycolytic inhibition would consequently increase fatty acid oxidation, which is beneficial for weight management. To support whole body outcomes, we hypothesized a role for AMP-activated protein kinase (AMPK) in the switch from oxidation of glucose to fatty acids. These studies focused on glucose metabolism in response to MH feeding in different breeds of dogs consuming diets of different macronutrient profiles. The impact of MH on protein metabolism and specifically on the control of the mechanistic target of rapamycin complex 1 (mTORC1) remains to be explored. The mTORC1 signaling network regulates protein synthesis and degradation, lipogenesis and cell growth, proliferation, differentiation, and metabolism in response to hormones, amino acids, and cellular energy status. Inhibition of mTORC1 signaling with rapamycin or genetic mutation increases median lifespan in model organisms, and mTORC1 inhibition may be responsible for some of the lifespan extending effects of energy, protein, and Met restriction. Met restriction also results in a reduction in mitochondrial production of reactive oxygen species and improved insulin sensitivity in adipose tissue. Low-Met diets can be formulated with high levels of cyst(e)ine in order to meet total sulfur amino acid requirements for growth. However, dietary cysteine supplementation reverses the lifespan extending effects of Met restriction. These results indicate that amino acid requirements need to consider more than just support of whole body protein synthesis and should include secondary measures related to tissue-specific and whole-body metabolism. Studies assessing energy and Met restriction need to explore energy, protein synthetic, and oxidative stress associated pathways concurrently.

October 25-27, 2017
Mohawk Mountain House, New Paltz, NY
Healthy Aging

Effect of methionine restriction on protein synthesis

Sailendra N Nichenametla, Dwight AL Mattocks, Virginia L Malloy
Orentreich Foundation for Advancement of Science, Cold Spring, NY

Although numerous studies confirm that a methionine-restricted (MR) diet confers multiple health benefits, such as lifespan extension and the amelioration of diabetes and obesity, the mechanisms by which it does so remain unclear. In addition to being a precursor for a number of metabolic intermediates (e.g., S-adenosylmethionine, homocysteine, cysteine, and glutathione), methionine is an essential and starting amino acid for the translation of mRNA into protein. Previous studies found MR induced changes in markers of protein synthesis and breakdown, such as total plasma protein, lean mass, and 3-methylhistidine. Despite a strong association between proteostasis and aging, there is no information on whether an MR diet affects the kinetics of proteostasis, and if such effects confer any benefits. We will discuss findings from our ongoing studies in rodents on the effect of an MR diet on rates of protein synthesis and if these changes confer any benefits.



Mutant *INS* gene-induced diabetes of youth (MIDY)

Peter Arvan

Division of Metabolism, Endocrinology & Diabetes, University of Michigan, Ann Arbor, MI

Healthy pancreatic β -cells can synthesize 6000 proinsulin molecules every second. The dominant feature of β -cells is the presence of stored insulin secretory granules, but mitochondria, Golgi stacks, and autophagosomes are also abundant. β -cells do not reserve a specific cytoplasmic region for the endoplasmic reticulum (ER); nevertheless, this is where all proinsulin is initially made. Ordinarily, proinsulin in the ER rapidly folds to the native state, including three evolutionarily conserved disulfide bonds (B7-A7, B19-A20, and A6-A11) that are catalytically accelerated.

In states of increased metabolic demand, as proinsulin synthesis is upregulated, there is an increase of misfolded proinsulin that is disposed of by mechanisms such as ER-associated degradation. However, beyond a certain threshold, accumulation of misfolded proinsulin molecules may interfere with normal intracellular transport of “bystander” proinsulin, leading to diminished insulin production and hyperglycemia, and provoking ER stress.

We have bioengineered three proinsulin mutants, each with the potential to form only one native proinsulin disulfide bond. “Keep-B7/A7”, “keep-B19/A20”, and “keep-A6/A11” can never advance from the ER, but analysis from these mutants establishes that B19-A20 initiates covalent B-chain/A-chain interaction. Moreover, certain uncommitted Cys residues can function as “interlopers”, forming mispaired disulfides that disrupt the fidelity of native proinsulin disulfide pairings. These realizations provide the underpinnings of our studies on MIDY: an autosomal dominant form of diabetes that masquerades as several different diabetes syndromes. The *INS* gene coding sequence mutations causing this disease can involve various conserved residues of proinsulin, triggering misfolding, disulfide mispairing, aggregation, enhanced proinsulin interaction with ER molecular chaperones, and diminished insulin production.

Folding defects may also occur in type 2 diabetes or other conditions when beta cells need to greatly increase proinsulin production. Our work provides several encouraging preclinical therapies that may ameliorate this problem.

Proteostatic mechanisms of the extremely long-lived naked mole-rat

Rochelle Buffenstein, Vikram Narayan, Peter Janki, Kaitlyn N Lewis
Calico Life Sciences, South San Francisco, CA

When compared to the four-year maximum life span (MLSP) of laboratory mice, the MLSP of more than thirty years for the naked mole-rat (*Heterocephalus glaber*) is astonishing. Strikingly, not only do naked mole-rats live an order of magnitude longer than similar-sized mice, they do so for most of their lives in cancer-free, good health. When compared to the deterioration of the human body during aging, this hairless rodent shows little age-associated physiological decline, maintaining heart health, bone quality, and reproductive capacity for more than 75% of its known lifetime. With a greater emphasis in aging research on mechanisms that may prolong healthspan, rather than lifespan, and an ever increasing demand to determine how to improve quality of life into old age, understanding how animals with exceptional longevity, like the naked mole-rat, are able to resist the vagaries of aging may provide pivotal insights into mechanisms that may prolong good health and attenuate age-related diseases. Here, we review some of the idiosyncratic pedomorphic traits of naked mole-rats as well as the diverse suite of mechanisms that may contribute to the maintenance of protein homeostasis and genomic integrity. Newfound interest in their basic biology of aging serves to remind us that studying animals with unusual traits often sheds light on the more difficult biological and biomedical questions that have eluded scientists for years.



Effect of dietary restriction on DNA methylation

Arlan Richardson^{1,3,4}, Willard M Freeman^{2,3}, Niran Hadad^{2,3}, Archana Unnikrishnan^{1,3}

¹Department of Geriatric Medicine, ²Department of Physiology, and ³Reynold Oklahoma Center on Aging at the University of Oklahoma Health Science Center, Oklahoma City, OK;

⁴Oklahoma City VA Medical Center, Oklahoma City, OK

Dietary restriction (DR) to date is the most consistent nutritional intervention to increase lifespan and retard aging in a wide variety of organisms; however, the molecular basis of DR's life-extending action is still unknown. Because early life DR has been shown to increase lifespan even when restriction is discontinued, we have explored whether DR retards aging through an epigenetic mechanism—DNA methylation. Alterations in DNA methylation at specific genes is critical during development and is a mechanism by which the transcriptional potential of cells can be altered for the life of an organism. In our first series of experiments, we measured the DNA methylation in the promoter regions of several genes whose expression is dramatically altered within months after the implementation of DR and whose expression remains altered after returning the mice to an *ad libitum* diet. We found that the methylation at three specific CG sites in the promotor of the Nts1 gene was correlated with the increased expression of Nts1 in the intestinal mucosa of mice fed a DR diet. Both the hypomethylation and increased expression of Nts1 gene persisted even when DR was discontinued and mice fed AL. The changes in DNA methylation in the Nts1 gene are likely to occur in intestinal stem cells and could play a role in preserving the intestinal stem cell pool in DR mice. In a second series of experiments, we used bisulfite oligonucleotide capture sequencing to measure DNA methylation genome-wide in base-specific sites in the hippocampus of young and old mice and old mice fed DR. Over 18,000 mCpGs and 30,000 mCpHs sites were significantly altered with age, and 34 to 40% of these sites of DNA methylation were prevented by DR. We also observed that DR induced specific changes in methylation at ~25,000 CpG sites and ~80,000 CpH sites, which were not significantly altered by age. Our data demonstrate that DR induces changes in DNA methylation, which has the potential of altering gene expression and having a memory effect.

October 25-27, 2017
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Metabolic interventions may delay or block key aspects of cellular senescence

Ashley Azar, Christian Sell

Department of Pathology, Drexel University College of Medicine, Philadelphia, PA

The process of cellular senescence contributes to aging and age-related dysfunction in multiple organ systems. The burden of senescent cells increases with age, and strategies to selectively target senescent cells (senolytics) improve late-life function in animal models. Although DNA damage has been classically associated with induction of senescence, multiple lines of evidence also support a connection between metabolic imbalance and activation of the senescence program. Mitochondrial stress can induce senescence, while altered metabolism and mitochondrial dysfunction are features of senescence induced by specific insults such as DNA damage. Metabolic interventions that extend lifespan, such as caloric restriction, methionine restriction, and rapamycin treatment, reduce the burden of senescent cells in model organisms. In human cell culture models, both rapamycin treatment and methionine restriction delay senescence; however, the molecular connections between metabolism and regulation of the senescence program have not been fully elucidated. Guided by a transcriptome-wide analysis, we examine the potential mechanisms that link metabolic pathways with the senescence program and discuss the possibility that senostatic therapies that block, rather than eliminate, senescent cells may be developed through a greater understanding of the intersection between metabolism and senescence.



The effects of dietary intervention on accelerated aging and age-related disease

HM Brown-Borg¹, CK Combs¹, C Sell²

¹Department of Biomedical Sciences, University of North Dakota School of Medicine & Health Sciences, Grand Forks, ND; ²Department of Pathology, Drexel University, Philadelphia, PA

Aging is the major risk factor for many diseases [Alzheimer's (AD), diabetes, cancer). Dietary interventions have been shown to delay aging and extend health and lifespans in model organisms. As such, these interventions exhibit the potential to reduce disease burden and health care costs by significantly postponing or preventing the pathology and symptoms associated with age-related disease. We are currently evaluating the effects of simple dietary interventions on the incidence of AD pathology and physiological decline in mouse models of AD and in mice that exhibit accelerated aging. Male and female APP/PS1, growth hormone transgenics, and corresponding wild type mice were subjected to one of four diets for 8 weeks beginning at 8 weeks of age: control, 80% methionine-restriction, rapamycin, or 80% methionine-restriction/rapamycin. Measures of behavior included tests for anxiety, working memory, and general locomotion. Liver, kidney, visceral fat, hind limb skeletal muscle, hippocampus, cortex, and plasma were collected to determine effects of diet on nutrient signaling, metabolism, detoxification, and stress resistance. Measures indicative of AD include APP, BACE, PSD95, pAKT, AKT, p-tau, and tau protein as well as immunohistochemistry to evaluate pathology. Differences in behavioral measures were apparent in mice on rapamycin and methionine restriction. Several components of methionine metabolism were affected by the diets in both the AD mice and the GH transgenic mice. A detailed description of the results will be presented. This study demonstrates that treating an age-related disease with interventions that slow and prevent aging processes also slows disease progression.

October 25-27, 2017
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Healthy Aging



Speaker Biographies

Peter D. Adams obtained his Ph.D. from Imperial Cancer Research Fund London in 1993 and did post-doctoral work with William G. Kaelin, Jr. at Dana-Farber Cancer Institute Boston, 1993-1999. Dr. Adams had his own lab at Fox Chase Cancer Center Philadelphia from 1999-2008, and then moved to the Beatson Institute for Cancer Research (BICR), Glasgow, where he was head of the Epigenetics Unit at University of Glasgow and BICR (2008-2017). Recently, he relocated to Sanford Burnham Prebys Medical Discovery Center, San Diego, although he still has a lab in Glasgow. Over the years, he has studied signal transduction, cell cycle control, cell senescence, and its control by chromatin and epigenetics, mostly in the context of cancer. Dr. Adams is now passionate to understand the molecular mechanisms underlying the exponential increase in cancer incidence with age—an important but understudied problem. In particular, he is interested in the contribution of age-associated epigenetic changes to onset of age-associated cancer, and the mechanisms by which cells harness the dynamic epigenome to permit phenotypic stability and healthy aging (a process for which his lab coined the term “chromostasis”, for chromatin homeostasis). He is also exploiting the new generation of small molecule epigenetic inhibitors for development of novel cancer therapies. In the UK, his lab is funded by CRUK, BBSRC, and MRC and in the US by NIA. Dr. Adams is co-editor-in-chief of *Aging Cell*.

Peter Arvan is Chief of the Division of Metabolism, Endocrinology & Diabetes (MEND), Professor of Medicine and Physiology, and the Brehm Professor of Diabetes Research at the University of Michigan. Dr. Arvan received his bachelor's degree from Cornell University and his MD and Ph.D. degrees from Yale University School of Medicine. Following residency training in internal medicine, Dr. Arvan completed fellowship training in Endocrinology at Yale. Dr. Arvan joined the faculty at Harvard Medical School in 1988. He moved to Albert Einstein College of Medicine in 1996 and became Division Chief at Michigan in 2003. Dr. Arvan's research has focused on how polypeptide hormone precursors are processed into bioactive hormones, especially insulin synthesis and thyroid hormone synthesis. He is specifically interested in understanding how hormone precursors are made and converted into biologically-active hormones, and how these steps go wrong in various disease states. Dr. Arvan's work focuses increasingly on protein misfolding in the endoplasmic reticulum (ER), leading to a problem called “ER stress”. Dr. Arvan was a PEW scholar in the Biomedical Sciences and is an elected member of the American Society for Clinical Investigation and the American Association of Physicians. He won the R.R. Bensley (AAA) and Van Meter (ATA) awards, and was a Pfizer Visiting Professor, a Burroughs-Wellcome Visiting Professor, and the Sidney Ingbar Lecturer (Harvard). His research is funded by public (NIH) as well as private support.

Holly Brown-Borg received BS and MS degrees from the University of Nebraska-Lincoln and a Ph.D. in physiology from North Carolina State University. She completed postdoctoral fellowships as an ARS Research Associate at the USDA Research Center in Nebraska and as a Research Associate in the Department of Physiology at Southern Illinois University School of Medicine. Dr.

Brown-Borg is currently a Professor in the Department of Biomedical Sciences at the University of North Dakota School of Medicine and Health Sciences. Her research interests focus on the role of the endocrine system in aging and life-span as it relates to metabolism, stress resistance, mitochondrial function, and DNA methylation. She is a Past-President of the American Aging Association, a Fellow of the American Aging Association and the Gerontological Society of America, and a Past-Chair of the Biological Sciences section of the GSA. She has served as the Chair of the Research Committee for the American Federation for Aging Research and serves on the editorial boards of several journals. She has organized several scientific meetings including AGE, GSA (Biological Sciences), Biology of Aging Gordon Research Conference, and currently organizes the International Symposium on Neurobiology and Neuroendocrinology of Aging held biennially in Bregenz, Austria.

Rochelle (Shelley) Buffenstein received her Ph.D. from the University of Cape Town, South Africa. In 2015, she joined Calico, a research and development company specifically focused on understanding the biology of aging and the factors that control lifespan. Prior to that position, she was a Professor at the Sam and Anne Barshop Institute for Aging and Longevity Studies at UTHSCSA. She has also been a professor in the Department of Biology at The City College of New York and spent 10 years at the Medical School of the University of Witwatersrand, South Africa. She is a comparative biologist who pioneered the use of the naked mole-rat as a model of exceptional bio-gerontological interest. Her research strives to determine the molecular mechanisms used in nature to modulate both species lifespan and healthspan. Using a multidisciplinary mechanistic approach, she specifically examines why some mammals, such as mice, age extremely rapidly, exhibiting pronounced declines in all aspects of their biology, and how other species, such as naked mole-rats, bats, and whales can maintain physiological function and disease-free good health for a larger proportion of their long lifespans. Elucidating these mechanisms may lead to therapeutic targets to retard the aging process and delay the onset of age-associated disability and diseases such as cardiovascular disease, cancer, diabetes, and Alzheimer's disease.

Vishwa Deep Dixit is a Professor of Comparative Medicine and Immunobiology at the Yale School of Medicine. He did Ph.D. research at University of Hannover, Germany, and postdoctoral research at the NIH. Before joining Yale, he held faculty positions at the Pennington Biomedical Research Center, Baton Rouge. Dr. Dixit studies immunometabolism with the goal to reveal targets that can be harnessed to improve healthspan. He has discovered that pro-longevity hormone FGF21 protects against thymic degeneration and T cell senescence. His lab has helped to define the role of innate immune sensor NLRP3 inflammasome in lipid metabolism, insulin-resistance, type 2 diabetes, age-related inflammation, and immune-senescence. Dr. Dixit identified that ketone metabolite β -hydroxybutyrate serves as a therapeutic target to lower the NLRP3 inflammasome-dependent inflammatory diseases. His work has been published in prominent journals including *Nature*, *Nature Medicine*, *Nature Immunology*, *PNAS*, *JCI*, and *Cell Metabolism*. He has received



numerous awards for his research including the Nathan Shock Award from National Institute on Aging, Glenn Award for Aging Research, Nathan Shock Young Investigator Awards from Gerontological Society of America and NIA, and Young Investigator Award from the Endocrine Society. He received Honorary Masters of Arts from Yale University in 2014. The Dixit Laboratory is funded in part by the NIH (NIA, NIAID, NIAMS), Glenn Foundation for Aging Research, and Cure Alzheimer's Fund.

Brad Johnson is an associate professor in the Department of Pathology and Laboratory Medicine in the Perelman School of Medicine at the University of Pennsylvania. He serves as Assistant Director of the Clinical Immunology Laboratory at the Hospital of the University of Pennsylvania, where his expertise is in transplant-related testing, and as Assistant Director of the Penn Institute on Aging. Dr. Johnson's laboratory investigates the biology of telomeres, how they are maintained, and how enhancing these natural mechanisms may help ameliorate age-related diseases. He is an editorial board member at *Mechanisms of Ageing and Development*, at *Frontiers of Genetics (Aging)*, and at *Aging Cell*, and is chair of the NIH Cellular Mechanisms of Aging and Development Study Section. Dr. Johnson earned his BS at Yale in 1987, and an MD and a Ph.D. in biochemistry at Stanford University in 1995.

Jay Johnson received his doctorate in Molecular Biology from Case Western Reserve University, where his thesis work focused on the molecular mechanisms underlying cell division in prokaryotes. His postdoctoral work in the lab of Dr. Dominique Broccoli, at Fox Chase Cancer Center (Philadelphia), used a liposarcoma model system to investigate the maintenance of telomeres, important nucleoprotein structures with roles in aging and cancer. Dr. Johnson then joined the lab of aging researcher Dr. Brad Johnson, at the University of Pennsylvania (Philadelphia). There, his early published work explored cellular defects in patients with Werner and Bloom's syndromes, genetic diseases characterized by accelerated aging and cancer predisposition. Dr. Johnson's current work, as a Senior Scientist at the Orentreich Foundation for the Advancement of Science, focuses on understanding the molecular basis of the longevity-promoting benefits of the dietary intervention methionine restriction. Towards this end, Dr. Johnson makes use of a variety of highly tractable model systems, including *S. cerevisiae* (baker's yeast), cultured mouse and human cells, and lab mice. The ultimate aim of his studies is to develop pharmacological interventions that phenocopy methionine restriction and improve human healthspan.

Matt Kaeberlein is a Professor of Pathology, Adjunct Professor of Genome Sciences, and Adjunct Professor of Oral Health Sciences at the University of Washington. His research focuses on understanding the fundamental mechanisms of aging. His work has been recognized by several prestigious awards, including a Breakthroughs in Gerontology Award from the Glenn Foundation, an Alzheimer's Association Young Investigator Award, and an Ellison Medical Foundation New Scholar in Aging Award. In 2011, he was named the Vincent Cristofalo Rising Star in Aging

Research by the American Federation for Aging Research. His contributions have also been recognized with Fellow status in the American Aging Association (AAA) and the Gerontological Society of America (GSA). Dr. Kaeberlein is a past president of the AAA and has served on their Executive Committee and Board of Directors since 2012. He is also a member of the FASEB Board of Directors and is the Chair-elect of the Biological Sciences Section of the GSA. Dr. Kaeberlein currently serves on the editorial boards of a number of noted journals. His research has been featured by numerous media outlets both nationally and internationally. In addition to his primary appointments, Dr. Kaeberlein served as a Distinguished Visiting Professor of Biochemistry at the Aging Research Institute of Guangdong Medical College in Dongguan, China, from 2009-2014. He is currently the co-Director of the University of Washington Nathan Shock Center of Excellence in the Basic Biology of Aging, the founding Director of the Healthy Aging and Longevity Research Institute at the University of Washington, and founder and co-Director of the Dog Aging Project.

Pankaj Kapahi is interested in understanding the role of nutrition and energy metabolism in lifespan and disease. The overall goal of his lab is to understand how different tissues orchestrate responses to nutrients to integrate physiological changes that influence health and disease. In his research, Dr. Kapahi looks for clues to longevity. His work confirms the finding that diet plays a major role in aging and age-related diseases. The Kapahi lab explores molecular mechanisms in a search for strategies to extend healthy lifespan in people. For example, his lab found that a low-protein diet could lengthen the lives of fruit flies, a result that challenged the wisdom of the high-protein Atkins diet for weight loss. He was the first to demonstrate that the TOR pathway (a growth signaling pathway named for the Target of Rapamycin) mediates the effects of dietary restriction. The benefits of dietary restriction are seen across all species; humans share the cellular mechanisms that link diet to longevity in fruit flies. Dr. Kapahi received his Ph.D. from the University of Manchester in England and completed postdoctoral studies at the University of California, San Diego and at the California Institute of Technology. He joined the Buck Institute in 2004. He is the recipient of numerous honors and awards, including the Ellison Medical Foundation New Scholar Award, the Eureka Award from the NIH, and the Nathan Shock New Investigator Award from the American Gerontological Society.

Robert A. Koza obtained his Ph.D. in Biochemistry at the University of New Hampshire where he studied the role of polyamines in cellular growth and proliferation under the mentorship of the late Dr. Edward J. Herbst. During postdoctoral studies at the Wistar Institute (Philadelphia) and the Lankenau Medical Research Center (Wynnewood, PA) with Dr. Thomas O'Brien, he was involved in investigating the role for polyamines in the development and progression of epidermal carcinogenesis. In 1994, Dr. Koza joined Dr. Leslie P. Kozak at The Jackson Laboratory as a Research Associate, and moved with Dr. Kozak's laboratory to the Pennington Biomedical Research Center (PBRC) as an instructor in 1998. From 1994-2002 Dr. Koza's research focused on the metabolic mechanisms and genetic regulation of energy expenditure and Ucp1 thermogenesis; in addition,



he was involved in establishing and directing the Genomics Core Research Facility at PBRC. In 2002, as an Assistant Professor, Dr. Koza developed a research program to study mechanisms associated with non-genetic variation of metabolic disease that was supported by funding from the NIDDK. In addition to being on the editorial board for the *International Journal of Obesity*, Dr. Koza has served as an ad hoc reviewer for both NIH/NIDDK and NIEHS review panels and is a standing member of the Cellular Aspects of Diabetes and Obesity Study Section (NIDDK). Dr. Koza joined the Maine Medical Center Research Institute as a Faculty Scientist in 2013 and is an adjunct associate professor at PBRC, Tufts Medical School and a faculty member for the Graduate School of Biomedical Science and Engineering at the University of Maine at Orono.

Sailendra (Nath) Nichenametla is a Senior Scientist at Orentreich Foundation for the Advancement of Science. He joined the Foundation in 2013 after his postdoctoral training at South Dakota State University, Department of Nutrition, and Hershey Medical College, Department of Public Health Sciences. Prior to this, he completed his undergraduate and graduate training in Veterinary Medicine & Animal Husbandry at the College of Veterinary Science, India, Food Science & Toxicology at University of Idaho, and Integrative Biosciences at Penn State University. During and after his graduate training, he investigated how genetics and environment (food components in particular) affect risk for diseases such as cancer and metabolic syndrome. Currently, he is studying the molecular mechanisms underlying the health benefits induced by dietary restriction of sulfur amino acids methionine and cysteine (SAAR). His current research primarily focuses on understanding how changes in the concentrations of methionine metabolites cysteine and glutathione induce biochemical changes that lead to health benefits. In an effort to understand the translational potential of this intervention, he is also involved in human studies employing the SAAR diet.

Arlan Richardson earned his Ph.D. in chemistry/biochemistry from Oklahoma State University, and for the past 40 years he has devoted his career to aging research. He is currently Professor of Geriatric Medicine and the Donald W. Reynolds Endowed Chair of Aging Research at Oklahoma University Health Science Center and Senior VA Career Scientist at the OKC VA Medical Center. Dr. Richardson has mentored and directed the research of more than 50 Ph.D. graduate students, postdoctoral fellows, and junior faculty and is the author of over 260 peer-reviewed scientific publications. His research has focused on various aspects of aging, e.g., the effects of aging and dietary restriction on gene expression in rats and mice; and 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. His group was the first to show dietary altered gene expression at the level of transcription through changes in specific transcription factors. He is currently studying the mechanism responsible for genotype differences in the response of mice to dietary restriction and the potential role DNA methylation might play in the life-extending mechanism of dietary restriction. He has served as president of the Gerontological Society of America (GSA) and the American Aging Association (AAA). Among the honors for his scientific contributions are the

GSA's Robert W. Kleemeier Award, the Lord Cohen Medal for Services to Gerontology from British Society for Research on Ageing, the AAA's Harman Research Award for research contributions in the field of aging and dietary restriction, and the Irving S. Wright Award of Distinction from the American Federation for Aging Research. In addition, Dr. Richardson served on the Board of Scientific Counselors at the National Institute on Aging from 2002–2007, and he was a member of the National Advisory Council on Aging from 2010–2013.

John Richie is Professor of Public Health Sciences and Pharmacology at Penn State University College of Medicine in Hershey, PA. For the past 30 years, his research goal has been to understand the link between the biological aging process and the development of aging-related diseases and disorders, including cancer. Using an interdisciplinary research approach, he focuses on the role of oxidative stress, generated both endogenously and from environmental exposures, as a mechanism for enhanced susceptibility during aging. His research has also investigated the impact of both endogenous and dietary antioxidants in protection against oxidative stress and its resulting damage, with the ultimate goal of designing and developing targeted prevention strategies. Dr. Richie received his Ph.D. in Biochemistry from the University of Louisville in 1985. Prior to joining Penn State College of Medicine, he developed and led a Program on Cancer Susceptibility and Aging at the American Health Foundation (Institute for Cancer Prevention) in Valhalla, NY.

Christian Sell obtained his undergraduate training at the State University of New York in Binghamton. He obtained his Ph.D. at the Albany Medical College and postdoctoral training at Temple University and Thomas Jefferson University. He joined the Faculty of the Medical College of Pennsylvania in 1994 as an Assistant Professor. He moved his research to the Lankenau Institute for Medical Research (Wynwood, PA) in 1998 and subsequently joined the faculty of the Drexel University College of Medicine (Philadelphia). His early research work focused on the role of IGF-1 signaling in cancer. He identified the IGF-1 receptor as critical for the transformed phenotype and as an antiapoptotic factor. This work led to the use of anti-IGF strategies as anticancer therapy and set the stage for multiple clinical studies on the potential for anticancer therapies targeting the IGF-I signaling pathway. The basic biology of aging and cellular senescence has been a research focus in Dr. Sell's laboratory for a number of years. He has performed studies on the influence of the growth hormone/IGF-1 axis on longevity, the comparative biology of aging, and the lifespan extending properties of rapamycin on human cells. His work has been featured on *60 Minutes* and in multiple publications, including *Philadelphia Magazine*. He has published over 80 articles and book chapters and is the editor of the book, *Exceptional Longevity, Single Cell Organisms to Man*. Dr. Sell's work has been cited over 9,000 times in the scientific literature.

Anna Kate Shoveller received her BSc, Honours in Animal Biology from the University of Guelph in 1997 and her Ph.D. in Nutrition and Metabolism from the University of Alberta in 2004. In 2009, Shoveller was selected by the American Society for Nutrition to receive the Peter J. Reeds



Memorial Young Investigator Award, recognizing her contributions to the understanding of neonatal sulfur amino acid metabolism and specifically for the changes made in the parenteral feeding industry due to knowledge developed in her Ph.D. Dr. Shoveller served as the provincial equine nutritionist for Alberta Agriculture, Food, & Rural Development prior to joining the University of Guelph as a postdoctoral fellow in companion animal nutrition (2004-2007), where she validated the indicator amino acid oxidation technique to the domestic dog. From 2007-2014 she worked for Procter & Gamble Research & Development, where she was involved in discovery and clinical trials, communicating scientific results and teaching nutrition throughout the organization, developing and executing intellectual property strategy, leading multiple academic collaborations, and mentoring junior technologists. Dr. Shoveller is also the recipient of P&G's John G. Smale Innovation Award for innovative thinking. She joined the Department of Animal Biosciences at the University of Guelph in 2015 and now leads a laboratory focused on comparative animal nutrition, specifically on protein and energy metabolism. Dr. Shoveller employs indirect calorimetry and isotope dilutions methodologies across monogastric species and additionally considers behavior outcomes, particularly for her work with dogs, cats, and horses. In addition to her research, teaches Companion and Equine Nutrition, serves on the University Senate, and is a scientific reviewer for the Animal Care and Utilization Committee. Dr. Shoveller has published over 50 scientific articles, contributed to books, and is a co-inventor on a number of patents.

Yousin Suh is a Professor of Genetics and Medicine at Albert Einstein College of Medicine. She investigates the (epi)genetic component that underlies the interface of intrinsic aging and disease. The approach she follows is based on the identification of (epi)genome sequence variants associated with age-related disease risk or its opposite, i.e., an unusual resistance to such disease. For this purpose her target populations are either cohorts of middle-aged individuals followed longitudinally for signs of all major age-related diseases, or cohorts of extremely long-lived individuals who managed to ward off such diseases. To tackle the key problem of identifying the functional impact of any observed association, she applies specific functional tests, including *in silico* modeling, cell culture assays, and mouse models. Discoveries thus far include novel, rare alleles associated with extreme longevity; sirtuin variants that confer risk for heart disease; longevity-associated miRNAs; and epigenetic signatures of cellular senescence. Her contributions in the field have been recognized by the Glenn Award for Research in Biological Mechanisms of Aging. She has organized numerous international symposia on functional genomics of aging, is on the Editorial Boards of numerous journals, and participates in advisory committees for several research institutions and companies.

Jessica Tyler pursued her Ph.D. at the Medical Research Council Virology Unit in Glasgow, Scotland. In 2000, after completing a post-doctoral fellowship in Epigenetics in the laboratory of Dr. James Kadonaga at the University of California San Diego, she started an independent laboratory as Assistant Professor in the University of Colorado School of Medicine Department of Biochemis-

try & Molecular Genetics. Following her identification of the key chromatin assembly factor Anti-silencing Function 1, her laboratory showed that chromatin assembly and disassembly not only accompanies DNA replication, but also occurs during and regulates gene expression, DNA repair, the DNA damage response, and aging. Her lab continues to delineate the molecular mechanisms of how chromatin assembly and disassembly regulates these key processes and their dysfunction in disease. Their hypothesis-driven research uses a variety of approaches, combining molecular genetics in budding yeast and flies with tissue culture, genomics, biochemistry, and structural biology. Although research is her priority, Dr. Tyler is committed to education, directing several graduate courses and a graduate program, and winning multiple teaching and mentorship awards. She has been particularly involved in facilitating the success women. Dr. Tyler's achievements in research and the advancement of women in science were recognized by the AACR-Women in Cancer Charlotte Friend memorial lectureship in 2009. She was promoted to full Professor in the same year. As a Program Leader in the NCI designated Cancer Center at the University of Colorado, she built and led their flagship Program in Molecular Carcinogenesis. Dr. Tyler moved in 2010 to the University of Texas MD Anderson Cancer Center (Houston), having been recruited as a Cancer Prevention Research Institute of Texas Rising Star. There, she co-directed the Center for Cancer Epigenetics and held the Edward Rotan Distinguished Professorship in Cancer Research. In 2015, Dr. Tyler moved her lab to the Department of Pathology and Laboratory Medicine at Weill Cornell Medicine where she runs a joint laboratory with her partner Barry Sleckman. Dr. Tyler serves on the editorial board of multiple journals and is a Senior Editor of *eLIFE*.

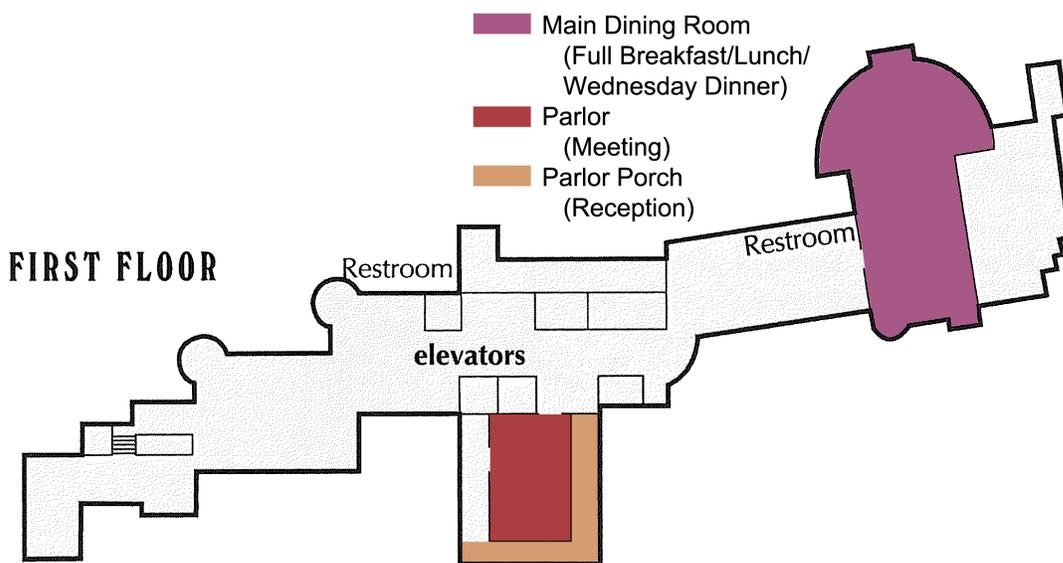
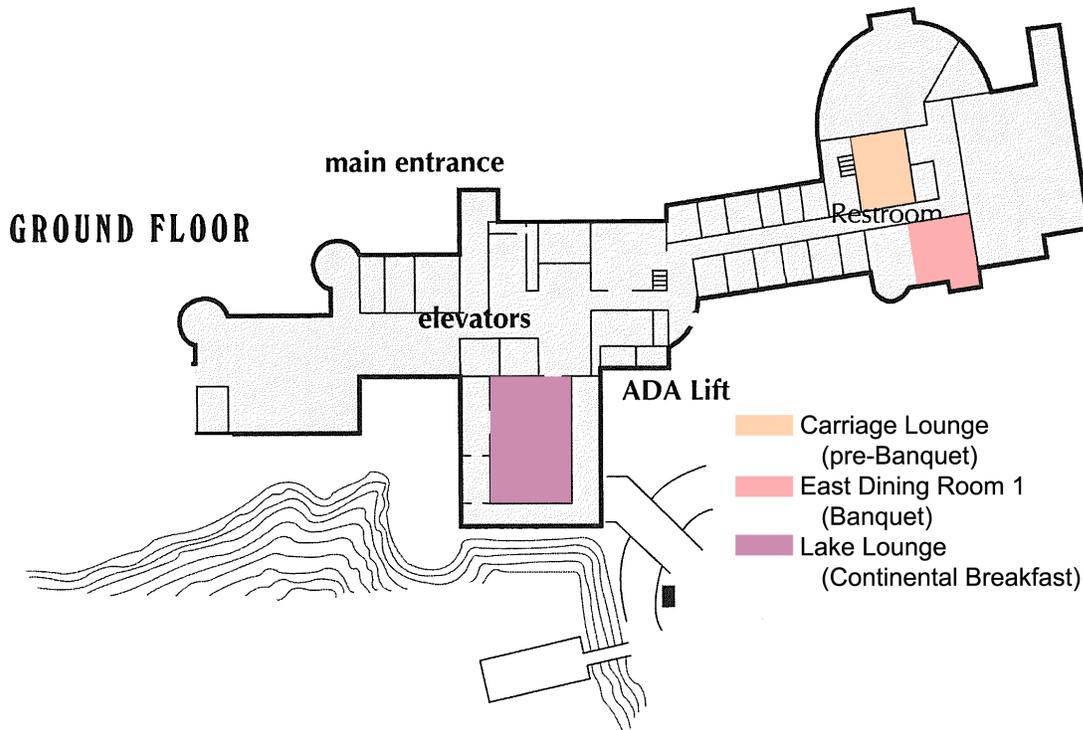
If you have any questions on the Symposium, please contact:

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Event Locations

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