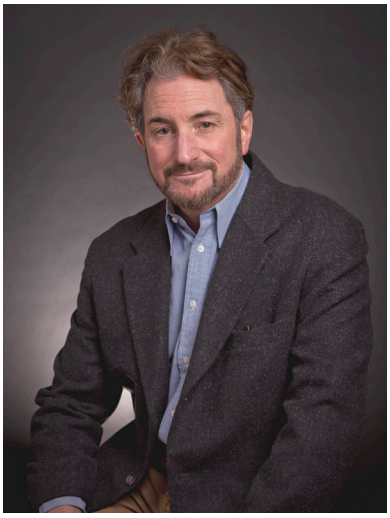
OFAS

Life's blood flows through the hourglass; the stopcock represents the alteration of aging and disease as biomedical research progresses.

My father, Norman Orentreich, founded OFAS in 1961, and for nearly 60 years, we benefitted from his guidance, genius, and generosity as he led many and diverse studies. His death, in January 2019, was a great loss to us all, but the mission he gave us endures.

We continue to refine our understanding of the mechanisms by which dietary sulfur amino acid restriction extends lifespan in laboratory animals and helps to delay the onset of aging-related diseases. As part of our commitment to bringing the benefits of this dietary intervention to the public, we have formed an Institutional Review Board (IRB) and registered with the Office of Human Research Protections so that we may begin research on human subjects. The first of these studies will be a collaborative effort with researchers from Albert Einstein College of Medicine and Penn State College of Medicine.

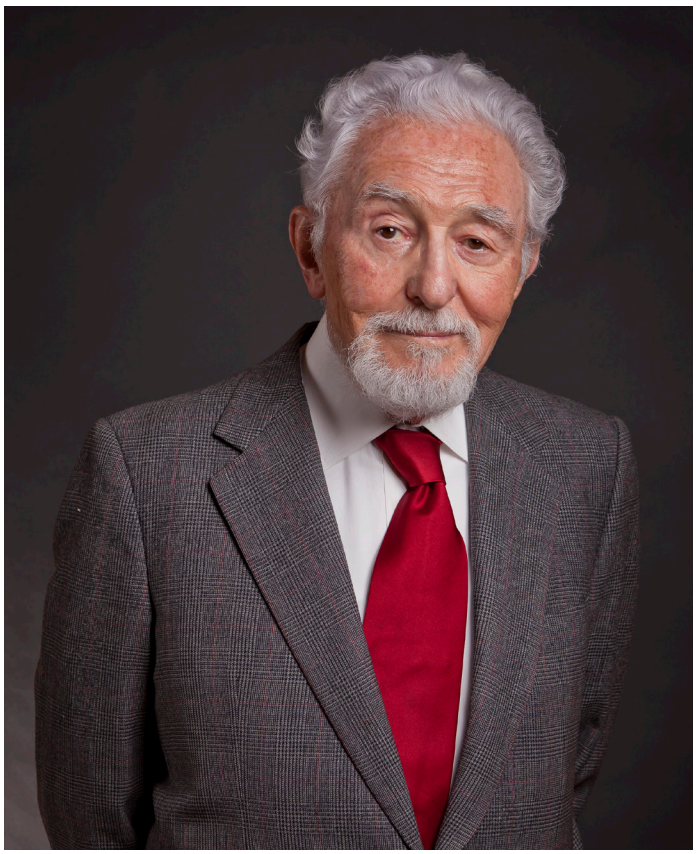
In October, we hosted our fourth biennial Symposium on Healthy Aging, featuring a keynote address from Dr. Ana Maria Cuervo of the Albert Einstein College of Medicine. Dr. Andrei Greșiță, the winner of the first Dr. Norman Orentreich Award for Young Investigator on Aging, was also featured at the symposium, as part of the award he received at the 2018 International Symposium on Neurobiology and Neuroendocrinology of Aging in Bregenz, Austria. This summer, we will both continue our support of the Symposium and present a second young investigator award.



On behalf of the dedicated staff at OFAS, we thank you for your continued support and faith in our mission. We wish you the best in 2020 and look forward to connecting with you through our communications.

David S. Orentreich, MD
Director

In Memoriam Norman Orentreich



Norman Orentreich, MD, FACP

December 26, 1922–January 23, 2019

Norman Orentreich received his MD degree from New York University College of Medicine in 1948. He became a diplomate of the National Board of Medical Examiners in 1949 and American Board of Dermatology in 1953. During his post-graduate training at New York University's Skin and Cancer Unit, Dr. Orentreich pioneered the research, creation, and performance of the very first hair transplant to treat male pattern baldness. After having established his dermatology practice (Orentreich Medical Group, LLP), in 1961 he went on to found the biomedical research organization known as the Orentreich Foundation for the Advancement of Science, Inc. (OFAS, Inc.). In 1968, Dr. Orentreich collaborated with Carol Phillips and the Lauder family to develop the internationally renowned skincare product line, Clinique. In 1970, he became the first President of the American Society for Dermatologic Surgery. Dr. Orentreich created and developed multiple procedures and treatments for skin, hair, and nail maintenance. He invented and patented medicines and medical devices for rejuvenating scarred and aging skin. He also wrote hundreds of articles and book chapters for medical textbooks and journals.

Under Dr. Orentreich's guidance, research at OFAS, Inc. expanded to encompass aging, cancer, dermatology, and serum biomarkers, resulting in an extensive list of papers in peer-reviewed publications.

Dr. Orentreich passed away on January 23, 2019; however, his legacy prevails as OFAS continues its dedication to the prevention, suspension, or reversal of those disorders that decrease the quality or length of life.

Symposium on Healthy Aging

Our fourth biennial Symposium on Healthy Aging took place October 16–18, 2019, at Mohonk Mountain House, New Paltz, NY. We host this series of symposia as part of our commitment to promoting collaborative discussion among scientists. Bringing together researchers with a common interest to exchange knowledge, generate ideas for future investigations, and strengthen relationships within this community, the series is the first to exclusively target the focused topic of nutritional restriction. The meeting's small size provides a forum in which researchers can directly engage with each other outside of the distractions of larger, more generalized meetings.

The keynote address was given by Dr. Ana Maria Cuervo (Albert Einstein College of Medicine), a leader in the field of protein degradation in relation to the biology of aging. Dr. Andrei Greșiță, the winner of the first Dr. Norman Orentreich Award for Young Investigator on Aging, presented at the 14th International Symposium on Neurobiology and Neuroendocrinology of Aging in Bregenz, Austria, was a featured presenter. This year, for the first time, we invited young researchers to present their work at a poster session; five travel awards were made to encourage and aid their participation.

Complete abstracts from all invited speakers for this and previous symposia are available online at www.orentreich.org/symposia. Highlights from the Symposium begin on page 5.

2019 Symposium attendees—Front row: Thomas Jeitner, Arthur Cooper, Tracy Anthony, Caroline Kumsta, Ana Maria Cuervo, Gene Ables, David Orentreich, Jay Zimmerman, Brian Kennedy, Richard Miller. Middle row: Vanessa Ocon, Bethany Fortier, Lucy Liaw, Diana Cooke, Dwight Mattocks, Adam Salmon, Mark Horowitz, Ignacio Gutierrez, Jason Plummer, Jay Johnson, Veronica Galvan, Sailendra Nichenametla, Virginia Malloy, Mary Bracho, Vera Gorbunova. Back row: John Newman, Jeffrey Smith, Sebastian Brandhorst, Andrei Greșiță, Derek Huffman, Spike Postnikoff, Jessica Tyler, Matt Simon, John Richie, Herbert Burack, Yang Zhao, Stephan Emmrich.

Symposium on Healthy Aging

Keynote Speaker

Ana Maria Cuervo, MD, Ph.D.
Albert Einstein College of Medicine, Bronx, NY
Selective autophagy in aging: helping with healthspan extension

Invited Speakers

Tracy G. Anthony, Ph.D.
Rutgers University, New Brunswick, NJ
Dietary sulfur amino acid restriction and the integrated stress response

Sebastian Brandhorst, Ph.D.
University of Southern California, Los Angeles, CA
Fasting-mimicking diet reduces risk factors for ageing, diabetes, cancer, and cardiovascular disease in preclinical and clinical studies

Veronica Galvan, Ph.D.
UT Health Science San Antonio, San Antonio, TX
Mechanisms linking aging to Alzheimer's disease

Vera Gorbunova, Ph.D.
University of Rochester, Rochester, NY
Mechanisms of longevity: lessons from long-lived mammals

Andrei Greșiță, MD, Ph.D. candidate
University of Medicine and Pharmacy Craiova (Romania)
Genetic conversion of proliferative astroglia into neurons after cerebral ischemia—a new therapeutic tool for the aged brain

Derek M. Huffman, Ph.D.
Albert Einstein College of Medicine, Bronx, NY
Role of one-carbon metabolism and related metabolites in aging

Thomas M. Jeitner, Ph.D.
Weill Cornell Medicine, New York, NY
Role of liver cystathione γ-lyase in persulfide formation and its upregulation in mice fed a methionine-restricted diet

Jay E. Johnson, Ph.D.
OFAS, Cold Spring, NY
Novel methionine-related interventions that confer healthspan benefits to yeast and rodents

Brian Kennedy, MD, Ph.D.
National University of Singapore, Singapore
Targeting human aging—can we extend healthspan

Caroline Kumsta, Ph.D.
Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA
The autophagy receptor SQSTM1/p62 promotes longevity in *C. elegans*

Lucy Liaw, Ph.D.
Maine Medical Center Research Institute, Scarborough, ME
Dietary effects of perivascular adipose tissue and implication for cardiovascular disease

Richard M. Miller, MD, Ph.D.
University of Michigan, Ann Arbor, MI
Drugs that slow aging

John Newman, MD, Ph.D.
Buck Institute for Research on Aging, Novato, CA
Ketone body signaling in health and aging

Adam Salmon, Ph.D.
UT Health Science San Antonio, San Antonio, TX
Intervention with rapamycin to improve healthy aging and longevity in a non-human primate

Jeffrey S. Smith, Ph.D.
University of Virginia, Charlottesville, VA
Caloric restriction extends yeast chronological lifespan through a cell-extrinsic mechanism

Jessica Tyler, Ph.D.
Weill Cornell Medicine, New York, NY
Identifying drivers of replicative aging and mechanisms of lifespan extension in budding yeast

Presentation Highlights

Tracy Anthony Among the known nutrient-responsive signaling pathways, the evolutionary conserved integrated stress response (ISR) is a lesser-understood candidate in mediating the hormetic effects of dietary sulfur amino acid restriction (SAAR). Dr. Anthony summarized the current understanding of how the ISR is involved in the physiological response to SAAR and detailed her lab's efforts to reveal the role of activating transcription factor 4 in this regard.

Sebastian Brandhorst The "fasting-mimicking diet" (FMD) is a nutrition-based program focused on health and longevity. In a randomized crossover-style clinical trial, the FMD reduced body weight and trunk and total body fat and lowered blood pressure in all subjects that completed the trial. A post hoc analysis demonstrated that biomarkers associated with cardiovascular disease risk were more beneficially affected in participants at risk for disease than in subjects who were not at risk.

Veronica Galvan Brain vascular dysfunction was recently identified as the earliest and most abnormal biomarker in the progression of Alzheimer's disease (AD). Dr. Galvan's findings add to growing evidence of the role of age-associated microvascular dysfunction in AD pathogenesis; suggest that propagation of pathogenic tau to brain microvascular endothelial cells may represent a novel mechanism in AD and other tauopathies; and support mTOR attenuation and tau removal as potential therapies for microvascular dysfunction in aging and AD.

Derek Huffman A comparative metabolomic screen in rodents and humans identified circulating sarcosine as being similarly reduced with aging and increased by dietary restriction (DR), while sarcosine is also elevated in long-lived Ames dwarf mice. Dr. Huffman's team found that DR significantly boosted GNMT activity in the liver. While no previously defined role has been clearly attributed to sarcosine *in vivo*, they found that sarcosine can activate autophagy in cultured cells and enhances autophagic flux *in vivo*, suggesting a potential role in autophagy induction by DR.

Thomas Jeitner The beneficial effects of dietary methionine restriction may be due, in part, to the generation of persulfide/sulfane sulfur (S0). Dr. Jeitner's study revealed that 1) the increases in cystathione λ-lyase specific activity observed in methionine-restricted mice may serve to spare sulfur for L-cysteine synthesis; and 2) cystathione λ-lyase is a source of S0, which can then be used directly to persulfidate proteins and thereby control function.

(continued on page 6)

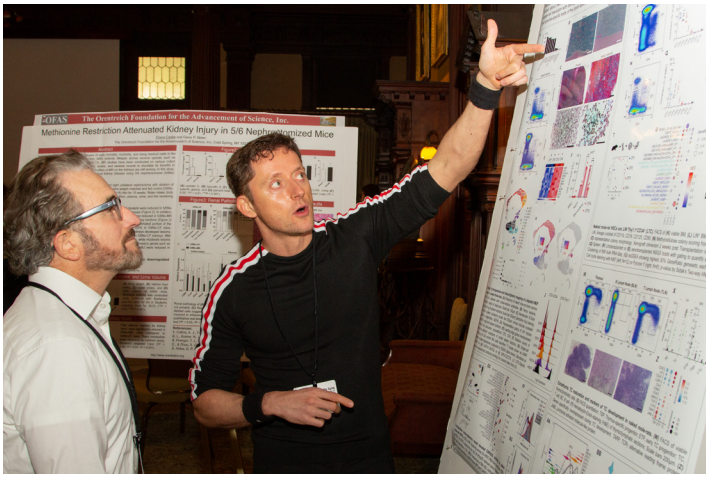
Spanning undergraduate to post-doctoral levels, early-career researchers joined the Symposium this year. (l-r) Spike Postnikoff, Ignacio Gutierrez, Matt Simon, Vanessa Ocon, Yang Zhao, Bethany Fortier, Stephan Emmrich.

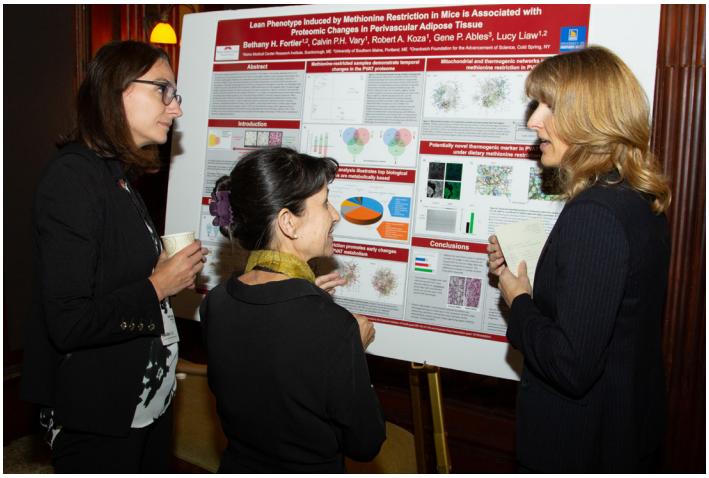
Symposium on Healthy Aging

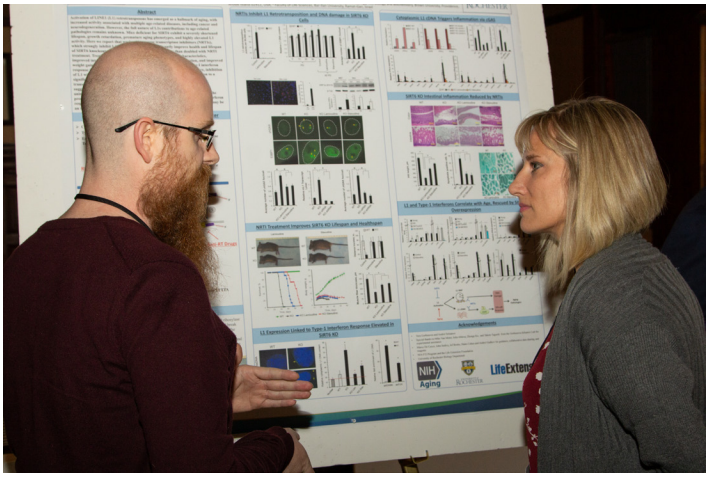
Caroline Kumsta Mammalian SQSTM1/p62 acts as a selective autophagy receptor for substrates such as ubiquitinated protein aggregates. Overexpression of SQST-1 in *C. elegans* extends lifespan in an autophagy-dependent manner and improves the lifespan of temperature-sensitive folding mutants, indicating that SQST-1 mediates lifespan and proteostasis in *C. elegans*. The autophagy receptor SQST-1 has tissue- and context-specific roles in mediating autophagy, proteostasis, and lifespan in *C. elegans*.

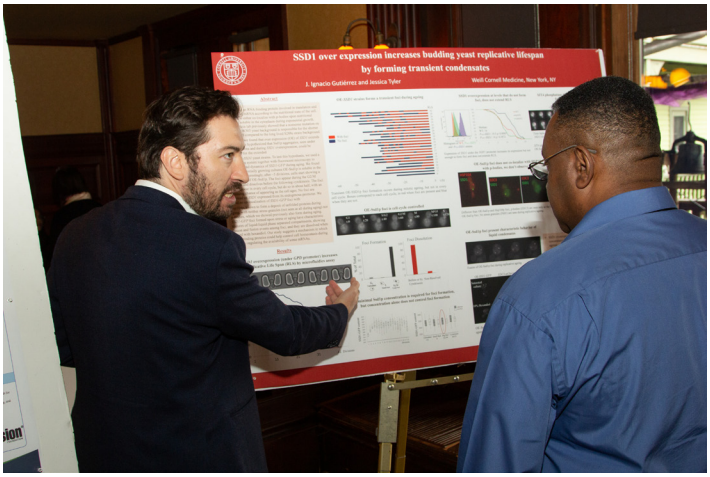
Lucy Liaw Dr. Liaw's laboratory is focused on a specialized adipose depot, perivascular adipose tissue (PVAT), which resides within the vascular microenvironment and is a paracrine regulator of vascular function. Despite continuation on a high-fat diet, reduction in dietary methionine is sufficient to revert the PVAT phenotype, concomitant with reduced body weight and reversion to a lean phenotype. Dr. Liaw is interested in the mechanisms by which these dietary changes affect adipocyte differentiation in PVAT, as well as changes in its secretion profile.

Richard Miller The NIA Interventions Testing Program (ITP) evaluates agents proposed to extend mouse lifespan by retardation of aging or postponement of late-life diseases. Thirty-seven experiments have involved comparative tests of multiple doses of effective agents, variable starting ages, or alternative dosing schedules. Significant effects on longevity, in one or both sexes, have been documented and then confirmed for NDGA, rapamycin, acarbose, and 17-α-estradiol (17aE2), with significant (but currently unconfirmed) effects also noted for Protandim, glycine, and, in an interim analysis, canagliflozin. Lifespan trials are now underway for 18 new agents. ITP survival results have





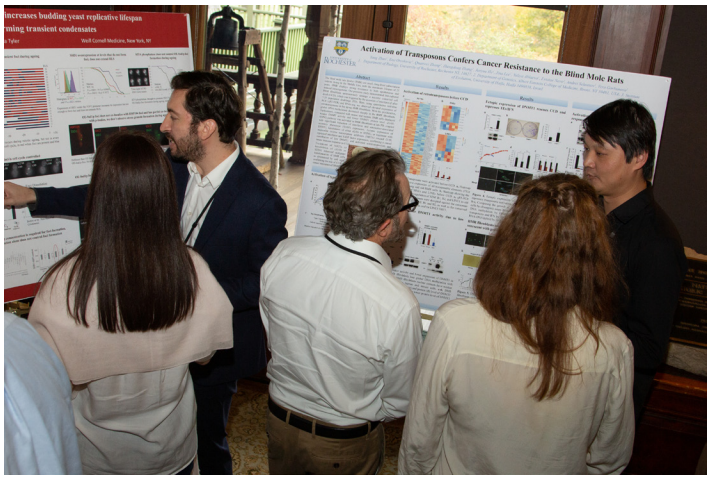




also documented longevity benefits from three agents started in middle-age: rapamycin, acarbose, and 17aE2.

John Newman A normal part of human metabolism, ketone bodies are small molecules made by the body during fasting, exercise, or other times when carbohydrates become scarce. Dr. Newman's lab helped to identify ketone bodies as endogenous histone deacetylase inhibitors; they also showed that exposing mice to ketone bodies long-term using a non-obese ketogenic diet can extend healthy lifespan, and identified a new mechanism by which ketone bodies affect Alzheimer's disease.

Adam Salmon Dr. Salmon's team has an ongoing long-term study testing whether rapamycin treatment can extend lifespan and delay the progression of age-related disease in a short-lived non-human primate species, the common marmoset (*Callithrix jacchus*). As an aging model, the marmoset offers many advantages over other non-human primates, including relatively short life and small size. Marmosets exhibit many of the same age-related pathologies and diseases that occur naturally with age in humans.

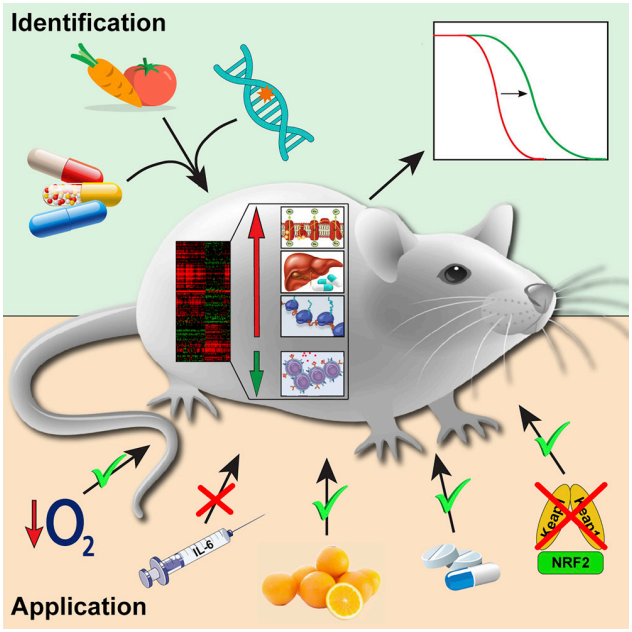


Jeffrey Smith Dr. Smith utilizes chronological lifespan (CLS) of the budding yeast *Saccharomyces cerevisiae* as a cellular model for calorie restriction (CR), whereby glucose in the growth medium is reduced from 2% (non-restricted; NR) to 0.5% (CR). Serine showed the strongest relative CR enrichment. Serine supplementation extended CLS of NR cultures in a dose-dependent manner.

Jessica Tyler Elucidation of the causes of aging has been greatly facilitated by the use of model organisms. In particular, the budding yeast *Saccharomyces cerevisiae* has been invaluable in the identification of conserved molecular and cellular determinants of aging and for the development of approaches to manipulate these aging determinants to extend lifespan. Dr. Tyler's laboratory uses the unique advantages of yeast as an experimental organism to elucidate conserved mechanisms that decay during aging, in order to identify novel ways to achieve lifespan extension that are likely to drive therapeutic approaches to extend human lifespan and healthspan in the future.

Methionine Restriction in Neurological Disease

Dr. Gene Ables has been examining the effects of methionine restriction (MR) on neurodegenerative diseases using a mouse model for amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease. ALS is a progressive and fatal neuromuscular disease characterized by neuroinflammation progressing to neurodegeneration. No cure for ALS has yet been identified, and the lack of proven and effective therapeutic interventions is an ongoing challenge. In connection with this, it is well established in rodents that methionine restriction (MR) delays onset of disease and extends lifespan. However, the neurological effects of MR, particularly during ALS, have not yet been examined. Dr. Ables is utilizing transgenic mice transfected with the G93A human superoxide dismutase 1 mutation. He hypothesizes that MR will delay onset of disease or suppress disease progression by attenuation of inflammation and oxidative stress markers in the spinal cord. Characterization of the effects of MR in this ALS disease model is a first step to guide future investigations on how MR may affect other neurological diseases.



Dr. Gene P. Ables collaborated with Dr. Vadim Gladyshev of Harvard Medical School on a comprehensive analysis of 17 known lifespan-extending interventions in mice to generate gene expression signatures associated with longevity. Methionine restriction was one of these interventions. © Elsevier Inc. Reprinted by permission from Cell Metabolism *30(3): 573-593, 2019*

In addition, Dr. Ables is involved with ongoing collaborations with Drs. Lucy Liaw and Rob Koza from Maine Medical Center Research Institute; they are working to identify underlying mechanisms in adipose tissues during weight loss in obese mice.

In the coming year, Dr. Ables and his team will engage in translational research studies about dietary sulfur amino acid consumption in humans. These include a joint study with epidemiologist Dr. Zhen Dong, OFAS's newest scientist, to determine the associations between consumption of sulfur amino acids and aging-related health outcomes in humans.

Methionine Restriction Mimetics

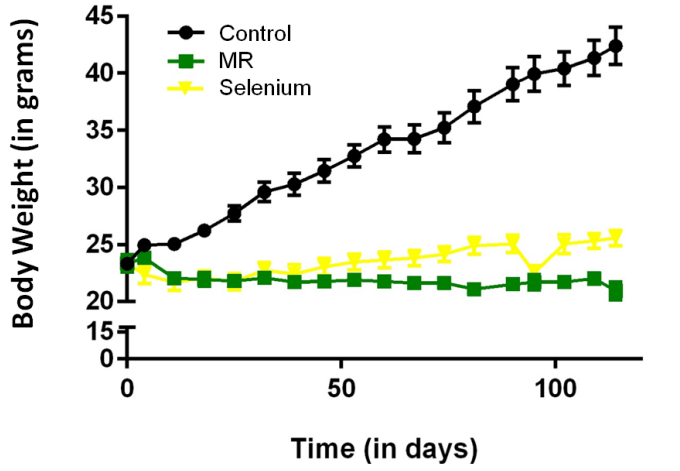
The dual aims of Dr. Jay Johnson's research have been 1) the characterization of the mechanisms underlying the benefits of MR, and 2) the identification of novel MR-like interventions that improve healthspan. For such efforts, Dr. Johnson's team has made use of multiple experimental model systems, including baker's yeast, cultured mouse and human cells, and laboratory mice.

In published studies, Dr. Johnson has demonstrated that dietary MR, genetic MR (i.e. impairment of the cell's methionine biosynthetic machinery), and enzymatic MR (i.e. enzymatic depletion of intracellular methionine) all significantly extend the lifespan of yeast. In addition, Dr. Johnson's team has explored the role of autophagy, a process whereby cellular components are recycled, in supporting MR-dependent cellular lifespan extension. They found that, of the many specialized forms of autophagy known, the autophagic recycling of mitochondria (i.e. mitophagy) is alone required for the benefits of MR to yeast. Furthermore, Dr. Johnson's team observed substantial alterations in energy metabolism for yeast undergoing MR, and obtained evidence that such changes are likely directly responsible for the extended lifespan of these cells. Ongoing studies

will reveal whether such metabolic alterations might be causally related to MR-mediated improvements in healthspan for mammals, and if so, whether they might be engendered in the context of a normal, methionine-replete diet.

As part of such efforts, recent research in Dr. Johnson's lab has produced three novel MR-like interventions with efficacy in mice. Two of these interventions are performed in the context of a normal, methionine-containing diet and achieved by oral supplementation with various methionine-like compounds; the third is a novel, intermittent variant of the classical methionine-restricted diet. In the past year, Dr. Johnson has found that these interventions not only mimic the ability of continuous MR to protect mice against diet-induced obesity, but also confer additional beneficial effects. Future studies will determine 1) whether these interventions, like MR, might produce an extension of mouse longevity, and 2) whether they might be translated to similarly benefit humans.

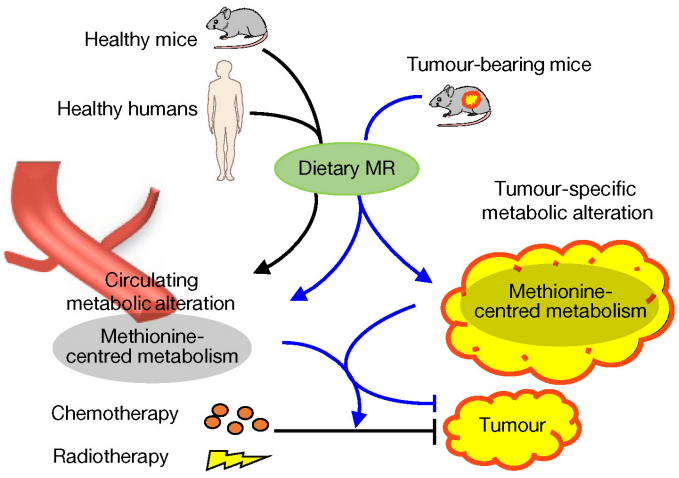
Selenium supplementation prevents obesity in mice



Mice fed a high-fat diet (Control) typically become obese over time, whereas mice that eat a methionine-restricted high-fat diet (MR) remain lean. Supplementation of a normal high-fat diet with a selenium source (Selenium) similarly protects mice against diet-induced obesity.

Sulfur Amino Acid Restriction

In short-term studies of laboratory models, several interventions have been documented to extend lifespan. But, evolutionary theories suggest that such an extension almost always trades off with other characteristics of life, including growth rates, fecundity, and disease resistance. While numerous studies show that sulfur amino acid restriction (SAAR) extends lifespan in rats and mice, it is unknown whether this extension compromises other biological aspects of life. This information is crucial to translate SAAR to humans. Dr. Sailendra Nichenametla is investigating trade-offs in SAAR with two critical aspects, growth rates and the ability to cope with various physiological stresses. Preliminary data from his studies show that while SAAR slows down growth rates, it does not compromise the ability to cope with physiological stresses. When initiated at later stages of life, SAAR was less efficient in inducing the benefits compared to initiations at earlier stages. Surprisingly, data indicate that animals on SAAR had greater resistance to certain types of stresses compared to those on a regular diet. While this data, as such, is encouraging, his future studies will focus on increasing the efficiency of SAAR for late-life onsets.



Model of the influence of dietary methionine restriction on tumor-cell metabolism. Reprinted from Nature *572, 397-401, 2019.*

Walkable Urban Environments for Older Populations

Dr. Calinao's team is investigating aging and active living. According to the Centers for Disease Control and Prevention, only half of US adults get the physical activity recommended to help reduce and prevent chronic diseases. Inactive adults have a higher risk for early death, heart disease, stroke, type 2 diabetes, depression, and some cancers. As populations move increasingly to cities, it is necessary to structure the urban environment to support active lifestyles, especially for older adults who may rely more on casual or unstructured activity.

Three senior housing units in New York City were selected for study. Dr. Calinao aimed to a) apply a microscale assessment approach to measure walkability; b) map the quality of sidewalks and relationships among third places, walk zones, and soft edges using geographic information systems (GIS); and c) identify opportunities for placemaking and active living. A total of 394 block faces were studied stretching approximately 63.3 linear miles. A handheld field audit device was employed to measure 197 sidewalk indicators, and a rule-based rating system was used to rate sidewalks from high to low walkability.

Results show that, while the neighborhoods varied widely in terms of overall walkability (Hell's Kitchen 71% walkable, East Harlem 65%, Lower East Side 54%), comfort and safety scores are low across neighborhoods. Using a microscale method and GIS mapping tools was found to be objective, cost-effective, and efficient. Identifying the quality of the walking environment through GIS marks the first step to improving sidewalks for older adults. The figures below show how walkability can be enhanced.

Aesthetic transformation of a street with added shading and seating, planters, tree pits, and solar-powered waste receptacles.

Enhancing walkability through safety measures (bike lane), aesthetic upgrades (tree pit, foliage), increased comfort (seating, awning), improved wayfinding, and energy-generating pavement.

Publications & Presentations

Komninou D, Malloy VL, Zimmerman JA, Sinha R, Richie JP Jr. Methionine restriction delays aging-related urogenital diseases in male Fischer 344 rats. *GeroScience*, in press.

Plummer JD, Johnson JE. Extension of cellular lifespan by methionine restriction involves alterations in central carbon metabolism and is mitophagy-dependent. *Frontiers in Cell & Developmental Biology* 2019; 7: 301.

Gao X, Sanderson SM, Dai Z, Reid MA, Cooper DE, Lu M, Richie JP Jr, Ciccarella A, Calcagnotto A, Mikhael PG, Mentch SJ, Liu J, Ables G, Kirsch DG, Hsu DS, Nichenametla SN, Locasale JW. Dietary methionine influences therapy in mouse cancer models and alters human metabolism. *Nature* 2019; 572: 397-401.

Sebo ZL, Rendina-Ruedy E, Ables GP, Lindskog DM, Rodeheffer MS, Fazeli PK, Horowitz MC. Bone marrow adiposity: basic and clinical implications. *Endocrine Reviews* 2019; 40: 1187-1206.

Tyshkovskiy A, Bozaykut P, Borodinova AA, Gerashchenko MV, Ables GP, Garratt M, Khaitovich P, Clish CB, Miller RA, Gladyshev VN. Identification and application of gene expression signatures associated with lifespan extension. *Cell Metabolism* 2019; 30: 573-593.e8.

Cooke D, Ruseskas J, Izquierdo B, Ables GP. Methionine restriction reduces circulating IGF-1 and preserves muscle function in mice (poster). Gordon Research Conference: The Impact of IGF and Insulin on Life-Long Health, Ventura, CA.

Plummer JD, Postnikoff SDL, Tyler JK, Johnson JE. Novel methionine-related interventions that confer healthspan benefits to yeast and rodents (oral presentation). Gerontological Society of America 2019 Annual Scientific Meeting, Austin, TX.

Calinao B, Bracho M. Walkable cities and baby boomers: how GIS maps walkable routes for active living (oral presentation). Walk21 2019, Rotterdam, Netherlands

New Staff

Zhen Dong, DrPH

Dr. Dong received her doctorate in Public Health from Penn State College of Medicine (Hershey, PA) under OFAS consultant Dr. John Richie. Her doctoral research examined the effects of dietary sulfur amino acid restriction (SAAR). Dr. Dong previously worked with OFAS on the development of a SAAR app. As she concludes this project, she will begin a study with Associate Science Director Gene Ables on the associations between consumption of sulfur amino acids and aging-related health outcomes in humans. She joins our team as a Scientist.

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The Orentreich Foundation for the Advancement of Science, Inc. is dedicated to biomedical research to prevent, halt, or reverse those disorders that decrease the quality or length of life.

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