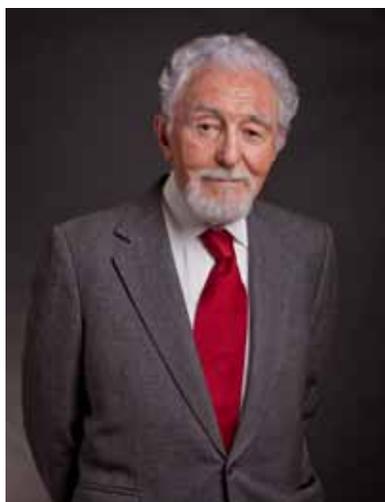


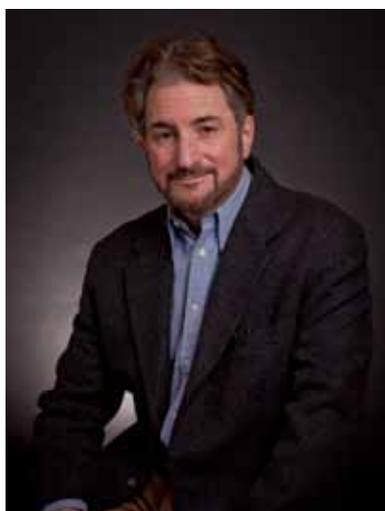
# OFAS

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



The goal of research is discovery, but even the greatest discovery, if not communicated, is of little worth. Scientists have traditionally communicated primarily through The Paper—a detailed report of methods and outcomes published in a peer-reviewed journal—and OFAS routinely communicates research in just this way. Researchers also attend various conferences, meetings, and seminars, sharing with their peers from around the world through talks and posters.

One of the chief reasons that OFAS initiated its own series of symposia two years ago was to foster the sort of collaborative discussion that can only be achieved through immediate, face-to-face communication. In September, we hosted the second biennial OFAS Symposium featuring speakers in our focal area of investigation. The gathering provided an opportunity for OFAS and other leaders in the field of aging and dietary restriction to share current research and plan future explorations. We are gratified by the impact the symposia have had within the community and look forward to continuing this unique series in the future.



Among the many tasks before us as we enter our 55<sup>th</sup> year: continuing our core research on the effects of methionine-restricted diets on aging and disease progression; concluding the clinical trial we are conducting in conjunction with Penn State University; and beginning a new partnership with the New York Academy of Sciences. This summer we will again co-sponsor the International Symposium on Neurobiology and Neuroendocrinology of Aging in Bregenz, Austria, at which our Associate Science Director, Dr Gene Ables, is among the invited speakers.

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 2016 and look forward to connecting with you through our communications.

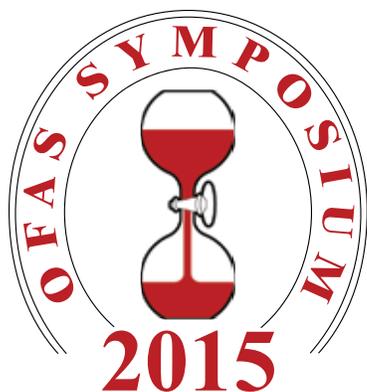


Norman Orentreich, MD, FACP  
Founder and Co-Director



David S. Orentreich, MD  
Co-Director

## Symposium 2015: Diet, Sulfur Amino Acids, and Healthspan



As part of our commitment to promoting collaborative discussion among scientists, in 2013 we inaugurated a series of symposia focused on diet and aging. With these symposia, we seek to bring together researchers with a common interest, to exchange knowledge, to generate ideas for future investigations, and to strengthen relationships within this community. The series is the first to exclusively target the focused topic of nutritional restriction. The small size of the meeting provides a forum in which researchers can directly engage with each other outside of the distractions of larger, more generalized meetings.

Following on the success of the first symposium, we broadened our scope for 2015 to the effects of diet and sulfur amino acids on healthspan. The keynote address was given by Dr Caleb Finch (Davis School of Gerontology, University of Southern California), a leader in the study of aging and inflammation. Full papers from speakers will be published in the international, peer-reviewed journal *Annals of the New York Academy of Sciences*. This second biennial symposium—Diet, Sulfur Amino Acids, and Healthspan—was held September 21-22, 2015, at the Tarrytown House Estate & Conference Center in Tarrytown, NY.

Highlights from the Symposium appear on page 4. Complete abstracts from all invited speakers are available online at [www.orentreich.org/symposia](http://www.orentreich.org/symposia).



2015 Symposium attendees—Front Row: Heidi Kitlas, Gene Ables, David Orentreich, Norman Orentreich, Caleb Finch, Bernardita Calinao, Jay Zimmerman, Arthur Cooper. Second Row: Sailendra Nichenametla, Maria Figueiredo-Pereira, Julie Hens, Diana Cooke, Rochelle Buffenstein, Jay Mitchell, Virginia Malloy, Herbert Burack. Third Row: James Mullen, Vadim Gladyshev, Suresh Tyagi, Robert Koza, Dwight Mattocks, Joseph Kemnitz, Jason Plummer, Tsang-hai Huang. Fourth Row: Tiffany Mitchell, Miri Park, Martha Stipanuk, Mark Horowitz, Jacob Selhub, Warren Kruger, Sean Adams. Back Row: John Richie, Holly Brown-Borg, George Roth, Jason Locasale.

## Keynote Speaker

Caleb E Finch, PhD

Davis School of Gerontology, University of Southern California, Los Angeles, CA

*APOE alleles, diet, and infection in the evolution of human life histories*

## Invited Speakers

Gene P Ables, PhD

OFAS, Cold Spring, NY

*Methionine restriction beyond lifespan extension*

Sean H Adams, PhD

University of Arkansas for Medical Sciences, Little Rock, AR

*Intersections between fat metabolism and amino acids*

Holly M Brown-Borg, PhD

University of North Dakota, Grand Forks, ND

*Impact of dietary methionine on aging: Dependence on growth hormone status*

Rochelle Buffenstein, PhD

Calico Labs, South San Francisco, CA

*Maintenance of glutathione redox status in the naked mole-rat heart under conditions of high oxidative stress*

Maria E Figueiredo-Pereira, PhD

Hunter College (CUNY), New York, NY

*Prostaglandin J2: A potential target for halting inflammation-induced neurodegeneration*

Vadim N Gladyshev, PhD

Harvard Medical School, Boston, MA

*Understanding control of lifespan through comparative genomics and methionine status*

Tsang-hai Huang, PhD

National Cheng Kung University, Tainan, Taiwan

*Dietary restrictions, bone density, and bone quality*

Joseph W Kemnitz, PhD

University of Wisconsin, Madison, WI

*Diet, calorie restriction, and aging in rhesus monkeys*

Robert A Koza, PhD

Maine Medical Center Research Institute, Scarborough, ME

*Molecular correlates for the development of adiposity in male C57BL/6J mice after short-term exposure to an obesogenic diet*

Warren Kruger, PhD

Fox Chase Cancer Center, Philadelphia, PA

*The effect of dietary modulation of sulfur amino acids on cystathionine- $\beta$ -synthase deficient mice*

Jason Locasale, PhD

Duke University, Durham, NC

*Dynamics of histone methylation mediated by the status of methionine metabolism*

Jay Mitchell, PhD

Harvard T H Chan School of Public Health, Boston, MA

*Dietary sulfur amino acid control of endogenous hydrogen sulfide production*

James M Mullin, PhD

Lankenau Institute for Medical Research, Wynnewood, PA

*Improvement of epithelial barrier function by methionine restriction*

John P Richie, Jr, PhD

Penn State University, Hershey, PA

*Dietary sulfur amino acid restriction in healthy adults*

George S Roth, PhD

GeroScience, Inc, Pylesville, MD

*Manipulation of healthspan and function by dietary restriction mimetics*

Jacob Selhub, PhD

Tufts University, Boston, MA

*The atherogenic effect of methionine*

Martha H Stipanuk, PhD

Cornell University, Ithaca, NY

*Blocking metabolism of cysteine to cysteinesulfinate: Consequences of taurine depletion and hydrogen sulfide overproduction*

Suresh C Tyagi, PhD

University of Louisville, Louisville, KY

*Mitochondrial division/mitophagy inhibitor (Mdivi) ameliorates pressure overload-induced heart failure*

*Vadim Gladyshev, Harvard Medical School:* We sequenced the genomes of several mammals of exceptional lifespan, including mole-rats and microbats, and identified genes that may contribute to their longevity. We also carried out analyses of gene expression and metabolites across a large panel of mammals. These studies point to both lineage-specific and common adaptations to longevity involving various pathways. One pathway that emerges as relevant to the control of lifespan is methionine availability.

*Rochelle Buffenstein, Calico Labs:* Unlike all other mammals studied to date, not only can the naked mole-rat achieve an extraordinary lifespan, but it is also able to maintain cardiovascular function for at least 75% of this extraordinary longevity. Oxidative stress is largely implicated in both the age-associated decline in cardiovascular function already evident in middle age and in cardiovascular disease.

*Robert Koza, Maine Medical Center Research Institute:* Heterogeneity in high fat diet (HFD)-induced obesity within a population of inbred mice has been shown to be associated with changes of gene expression in adipose tissue. A gene with a large degree of variation among mice, mesoderm specific transcript (Mest), has also been shown to be highly inducible after short-term exposure to dietary fat, and its expression in adipose tissue prior to HFD-feeding is predictive of individual susceptibility to the development of obesity.

*Jay Mitchell, Harvard T H Chan School of Public Health:* We recently linked functional benefits of dietary restriction, i.e., reduced food intake without malnutrition, on stress resistance and longevity in model organisms to increased transsulfuration pathway activity and endogenous hydrogen sulfide production.

*Suresh Tyagi, University of Louisville:* Several studies have reported the evidence of cardiac autophagy, involving removal of cellular organelles like mitochondria (mitophagy), peroxisomes, etc., in the pathogenesis of heart failure. However, little is known regarding the therapeutic role of mitochondrial division inhibitor (Mdivi) in pressure overload induced heart failure. We hypothesize that treatment with Mdivi inhibits abnormal mitophagy in a pressure overload heart and thus ameliorates heart failure condition.

*Sean Adams, University of Arkansas for Medical Sciences:* The mitochondrial branched-chain ketoacid dehydrogenase complex is a primary regulator of BCAA and cysteine oxidative catabolism, and the enzyme is inhibited under conditions of increased fatty acid oxidation.

*Martha Stipanuk, Cornell University:* Cysteine homeostasis is dependent on the regulation of cysteine dioxygenase (CDO) in response to sulfur amino acid intake. Knockout of the murine Cdo1 gene results in elevated cysteine levels, severe impairment in ability to synthesize taurine, and an increased catabolism of cysteine to hydrogen sulfide.

*Warren Kruger, Fox Chase Cancer Center:* The Tg-I278T Cbs<sup>-/-</sup> mouse model of cystathionine- $\beta$ -synthase (CBS) deficiency has undetectable levels of CBS activity, extremely elevated levels of plasma tHcy, modestly elevated plasma methionine, and low plasma cysteine. It exhibits several easily discernible phenotypes, including osteoporosis, loss of fat mass, reduced lifespan, and facial alopecia.

*Jason Locasale, Duke University:* Our findings demonstrate that flux through methionine metabolism and the sensing of methionine availability may be configured to allow for direct communication to the chromatin state in cells.

## Symposium 2015: Diet, Sulfur Amino Acids, and Healthspan

A casual dinner on the first night of the Symposium allowed participants time to relax and network.



Bernardita Calinao, Norman and David Orentreich



Jason Locasale, John Richie



Jacob Selhub, Jay Zimmerman



Diana Cooke, Suresh Tyagi



Mark Horowitz, David Orentreich, Jay Zimmerman, Arthur Cooper, John Richie



Caleb Finch



Julie Hens, Jay Mitchell



Suresh Tyagi, Gene Ables, Sailendra Nichenametla, Jason Locasale



Joseph Kemnitz, Holly Brown-Borg, Rochelle Buffenstein, George Roth

Our 3<sup>rd</sup> biennial symposium  
will be held in October 2017 at  
Mohonk Mountain House, New Paltz, NY.



Aging is marked by the body's decreasing ability to respond to environmental challenges, manifested in the form of frailty and disease. Some seemingly innocuous issues in the elderly—imbalances of blood glucose, insulin, body fat, triglycerides, and chemically reactive oxygen molecules—can gradually snowball into formidable diseases like cancer. Rats and mice fed diets low in methionine are better able to handle such imbalances, outliving those fed standard diets. As methionine is essential for proper growth and reproduction until adulthood, it is perplexing that low levels of this protein would help one to live a longer, healthier life. Hence, our Senior Scientists are leading investigations to elucidate the role of methionine in promoting healthy aging.

### Methionine Restriction (MR) Across Lifespan

Dr Nichenamela is working to understand how animals process methionine at different stages of life. Specifically, he is currently investigating how methionine restriction (MR) affects 1) the synthesis of proteins, essential for growth and reproduction; 2) the synthesis of cysteine, essential for combating reactive oxygen molecules; and 3) the interactions of methionine with nucleic acids and proteins, which regulate glucose, insulin, and fat levels.

### Cancer

The focus of Dr Hens' research is the applicability of a MR diet to improving the outcomes of various cancers. She and her team are examining the molecular mechanisms of how dietary MR can regulate organ function and affect cancer. They are examining how MR alters microRNAs (miRNA) in different tissues, and whether these miRNA changes can improve healthspan. Her most recent studies on metastatic breast cancer in animal models (mouse cancer models, patient-derived cancer xenograft murine models, and human cell lines) indicate that there are several miRNAs and their downstream protein targets that are altered by MR, and that these changes can hinder metastases. These altered miRNAs could become possible targets for cancer therapies. In the coming year, her team will investigate the effects of MR on non-small cell lung cancer.

### Obesity

Dr Ables and his team have recently concluded research that indicates that MR induces accumulation of beige

adipose tissue in the white adipose tissue, which could explain the improved metabolism observed in mice fed this diet. They have also identified a potential signaling cascade in the hypothalamus of mice that regulates appetite in MR mice. Dr Ables' upcoming projects will investigate the effects of MR in a mouse model of amyotrophic lateral sclerosis (ALS), and elucidate the role of adiponectin, a hormone known to promote insulin sensitivity, in MR mice.

### Molecular Mechanisms of MR

Our newest Senior Scientist, Dr Johnson, will explore the molecular mechanisms underlying the benefits of MR at a cellular level. For this purpose, he has developed three novel genetically-tractable cell systems to model MR in 1) budding yeast, 2) cultured mouse cells, and 3) cultured human cells. Using these, Dr Johnson has demonstrated that both classical MR and impairment of the cell's methionine biosynthetic machinery ("genetic MR") significantly extend the lifespan of yeast and render them resistant to a variety of stresses. Similarly, he has shown that genetic MR of cultured mouse and human cells significantly extends their replicative capacity and resistance to stress. As improvements in cellular lifespan and stress tolerance likely support, at least in part, the increased healthspan of methionine-restricted rodents, Dr Johnson will identify the specific pathways engaged by MR to confer such benefits.

### Clinical Trial Update: MR in Healthy Adults

Laboratory studies confirm the lifespan and healthspan extension benefits of low-methionine diets. Observational studies in humans also suggest that at least some of the health benefits conferred by low-protein diets such as vegan or vegan-like diets could be due to low methionine. However, few interventional studies of low-methionine diets conducted in humans have resulted in benefits as robust as those observed in laboratory animals. Key issues in translating the diet to humans are: 1) using natural foods with the exact dietary composition used in rodent studies and 2) low dietary compliance. Minimizing these issues, we are currently conducting an interventional study in healthy subjects with Penn State University. Findings from this study will help in designing low-methionine diets and translating the benefits observed in rodents to humans.

Huang TH, Su IH, Lewis JL, Chang MS, Hsu AT, Perrone CP, Ables GP. Effects of methionine restriction and endurance exercise on bones of ovariectomized rats: A study of histomorphometry, densitometry, and biomechanical properties. *Journal of Applied Physiology* 2015; 119(5): 517-26.

Ables GP, Ouatarra A, Hampton TG, Cooke D, Perodin F, Augie I, Orentreich DS. Dietary methionine restriction in mice elicits an adaptive cardiovascular response to hyperhomocysteinemia. *Scientific Reports* 2015; 5:8886.

Mentch SJ, Mehrmohamadi M, Huang L, Liu X, Gupta D, Mattocks D, Gómez Padilla P, Ables G, Bamman MM, Thalacker-Mercer AE, Nichenametla SN, Locasale JW. Histone methylation dynamics and gene regulation occur through the sensing of one-carbon metabolism. *Cell Metabolism* 2015; 22(5): 861-73.

Plummer J, Perodin F, Horowitz M, Orentreich D, Hens J. Dietary restriction of methionine affects bone structure differently in young male and female mice (abstract). *Journal of Bone and Mineral Research* 2015; 30 (Suppl 1).

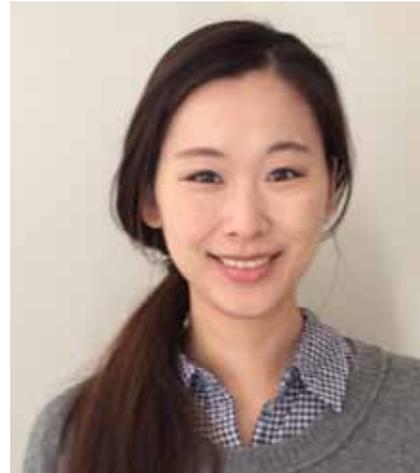
Mattocks D, Nichenametla SN, Orentreich DS, Ables GP. Low methionine diet induced weight loss and reversed nonalcoholic fatty liver disease in obese mice due to Fibroblast Growth Factor 21 (FGF21) (poster). Keystone Symposia “Obesity & the Metabolic Syndrome” in Whistler, BC, Canada

Plummer J, Perodin F, Orentreich DS, Hens J. Dietary restriction of methionine alters the miRNA expression profile in the mammary gland (poster). Keystone Symposia “MicroRNAs and Noncoding RNAs in Cancer” in Keystone, CO, USA.

## New Staff

**Jay Johnson, PhD**

Jay received his PhD in Molecular Biology from Case Western Reserve University. He previously worked as a Research Associate at the University of Pennsylvania and was a Post-Doctoral Fellow at the Fox Chase Cancer Center. His recent work focused on exploring the mechanistic basis of the benefits of methionine restriction in *S. cerevisiae* and cultured mouse and human cells. Jay joins us as a Senior Scientist.

**Miri Park, PhD**

Miri received her PhD in Biomedical Engineering from the University of Delaware earlier this year. Prior to working on her degree, she was a Research Assistant to professors at both Columbia University and Massachusetts Institute of Technology. Miri joins us as a Senior Research Associate.



*The Orentreich Foundation for the Advancement of Science, Inc.,  
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those disorders that decrease the quality or length of life.*

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