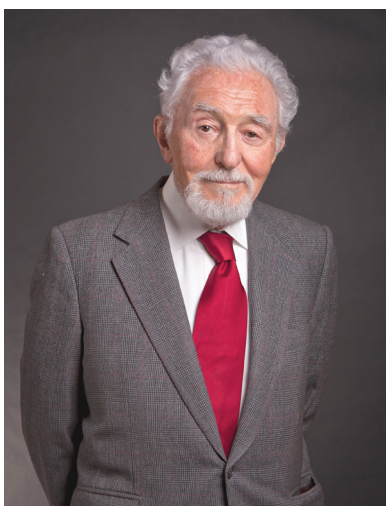


OFAS

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



As 2017 draws to a close, we reflect upon our achievements and look ahead to what the new year will bring.

Our third biennial Symposium was held in October and brought together leading researchers on aging from prestigious institutes such as Yale University, the Buck Institute for Research on Aging, and Weill Cornell Medicine to share their current research and to plan future investigations.

Our clinical trial on dietary restriction in conjunction with Penn State College of Medicine concluded; the results indicate that many of the positive benefits seen in animal models from methionine restriction and total sulfur amino acid restriction do translate to humans.

This summer, we intend to continue our long-standing support of the International Symposium on Neurobiology and Neuroendocrinology of Aging in Bregenz, Austria. In addition to sponsoring a session on Nutrition and Aging, we will be presenting the first Norman Orentreich Award for Young Investigator on Aging.

Furthermore, we will continue to focus the broad scope and depth of our research on pursuing our mission to develop interventions that prevent, halt, or reverse disorders that decrease the quality or length of life.

On behalf of the dedicated staff at OFAS, we thank you for your continued support and interest in our mission. We wish you the best in 2018 and look forward to connecting with you in the months ahead.




Norman Orentreich, MD, FACP
Founder and Co-Director



David S Orentreich, MD
Co-Director

Symposium 2017: Healthy Aging

In 2013 we inaugurated a series of symposia focused on diet and aging to reflect our commitment to promoting collaborative discussion among scientists. We successfully established an exclusive and intimate forum in which scientists and researchers who are interested in the topic of nutritional restriction can exchange knowledge, generate ideas for future investigations, and strengthen relationships within this community.

Steadily broadening the scope of the symposia, this year we chose the topic of healthy aging. The keynote address was given by Dr. George Martin (University of Washington), a pioneer in the study of aging and age-related diseases through genetic approaches. Full papers from speakers will be published in the international, peer-reviewed journal *Annals of the New York Academy of Sciences*. This third biennial symposium on Health Aging was held October 25-27, 2017, at Mohonk Mountain House, New Paltz, NY.



Highlights from the Symposium begin on page 4. Complete abstracts from all invited speakers for this and previous symposia are available online at www.orentreich.org/symposia.



2017 Symposium attendees—Front Row: Matt Kaeberlein, Yousin Suh, Diana Cooke, Zhen Dong, Anna Kate Shoveller, Gene Ables. Second Row: Dwight Mattocks, Arlan Richardson, Marie Rusin. Third Row: Spike Postnikoff, Peter Adams, Bernardita Calinao, Aileen Lee. Fourth Row: Robert Kozca, Zie-Jie Shen, Jay Johnson, Jessica Tyler, Pankaj Kapahi. Fifth Row: Virginia Malloy, Brad Johnson, Sailendra Nichenametla, Rochelle Buffenstein. Back Row: Jay Zimmerman, Christian Sell, Peter Arvan, David Orentreich, Norman Orentreich, Arthur Cooper, George Martin, John Richie, Holly Brown-Borg, Jamie Cifuentes, Vishwa Dixit.

Keynote Speaker

George M. Martin, MD

University of Washington, Seattle, WA

Genomic and epigenomic instabilities as mechanisms of biological aging

Invited Speakers

Peter D. Adams, PhD

Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA

The dynamic epigenome—a challenge to healthy aging

Peter Arvan, MD, PhD

University of Michigan, Ann Arbor, MI

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

Holly M. Brown-Borg, PhD

University of North Dakota, Grand Forks, ND

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

Rochelle Buffenstein, PhD

Calico Labs, South San Francisco, CA

Proteostatic mechanisms of the extremely long-lived naked mole rat

Vishwa Deep Dixit, PhD

Yale University, New Haven, CT

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

F. Brad Johnson, MD, PhD

University of Pennsylvania, Philadelphia, PA

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

Jay E. Johnson, PhD

OFAS, Cold Spring, NY

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

Matt Kaeberlein, PhD

University of Washington, Seattle, WA

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

Pankaj Kapahi, PhD

Buck Institute for Research on Aging, Novato, CA

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

Robert A. Koza, PhD

Maine Medical Center Research Institute, Scarborough, ME

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

Sailendra Nichenametla, PhD

OFAS, Cold Spring, NY

Effect of methionine restriction on protein synthesis

Arlan Richardson, PhD

University of Oklahoma Health Science Center, Oklahoma City, OK

Effect of dietary restriction on DNA methylation

John P. Richie, Jr, PhD

Penn State University, Hershey, PA

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

Christian Sell, PhD

Drexel University, Philadelphia, PA

Metabolic interventions may delay or block key aspects of cellular senescence

Anna Kate Shoveller, PhD

University of Guelph, Guelph, ON, Canada

Examining potential mechanisms of healthy aging with preventative nutrition approaches

Yousin Suh, PhD

Albert Einstein College of Medicine, New York, NY

Enhancer mechanisms in human aging and disease

Jessica Tyler, PhD

Weill Cornell Medicine, New York, NY

An integrative analysis of replicative aging in budding yeast

John Richie, Penn State College of Medicine: Recent animal studies indicate that total sulfur amino acid restriction (SAAR) is required to obtain optimal improvements in glucose and fat metabolism and reduced oxidative stress shown on methionine-restricted diets. However, little is known about the translation of these findings to humans. Therefore, we conducted short-term trials feeding SAAR diets to healthy adults to discover their impact on relevant anthropometric, metabolic, and oxidative stress biomarkers. Our results suggest that many of the short-term effects of SAAR do translate to humans, supporting further clinical development of this dietary intervention.

Christian Sell, Drexell University: Although DNA damage is classically associated with induction of senescence, multiple lines of evidence also support a connection between metabolic imbalance and activation of the senescence program. Metabolic interventions that extend lifespan, such as caloric restriction, methionine restriction, and rapamycin treatment, reduce the burden of senescent cells in model organisms. We examined the potential mechanisms that link metabolic pathways with the senescence program and 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.

Holly Brown-Borg, University of North Dakota: We are evaluating the effects of simple dietary interventions on the incidence of Alzheimer's Disease (AD) pathology and physiological decline in mouse models of AD and in mice that exhibit accelerated aging. Differences in behavioral measures were apparent in mice on rapamycin and methionine restriction. This study demonstrates that treating an age-related disease with interventions that slow and prevent aging processes also slows disease progression.

Matt Kaeberlein, University of Washington: 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. Our 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.

Yousin Suh, Albert Einstein College of Medicine: Our studies have centered on enhancer mechanisms underlying a non-coding region of the genome, the so-called gene desert at

the chromosome 9p21 locus. This locus is associated with multiple age-related diseases, including cancer, heart disease, glaucoma, Alzheimer's disease, and diabetes, suggesting a common underlying biology of aging. We 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.

Jessica Tyler, Weill Cornell Medicine: We have performed an integrative analysis of the replicative aging process in budding yeast, using the mother enrichment program to isolate unprecedented numbers of old yeast cells. Deep sequencing and mapping DNA damage sites revealed a defect in DSB repair in old cells, whereas ribo-seq analyses showed that protein synthesis is reduced during aging. We determined the mechanistic basis for many of these defects, and found that reversing them extends lifespan. Taken together, our studies reveal novel molecular defects that are causative of replicative aging.

Arlan Richardson, University of Oklahoma Health Science Center: Because early life dietary restriction (DR) is known to increase lifespan even when DR is discontinued, we have explored whether DR retards aging through an epigenetic mechanism—DNA methylation. We measured DNA methylation in the promoter regions of several genes whose expression is dramatically altered within months of DR implementation and whose expression remains altered after returning the mice to an *ad libitum* diet. Our data demonstrate that DR induces changes in DNA methylation, which has the potential of altering gene expression and having a memory effect.

Peter Arvan, University of Michigan: Accumulation of misfolded proinsulin molecules may interfere with normal intracellular transport of “bystander” proinsulin, leading to diminished insulin production and hyperglycemia. By bio-engineering and experimenting with proinsulin mutants, we gained an understanding of the mechanisms involved. Our work provides several encouraging preclinical therapies that may ameliorate mutant INS gene-induced diabetes of youth (MIDY), type 2 diabetes, and other conditions when beta cells need to greatly increase proinsulin production.

Anna Kate Shoveller, University of Guelph: We investigated a purported dietary restriction mimetic, mannoheptulose (MH), and its effects on metabolism. The studies focused on glucose metabolism in response to MH feeding in different breeds of dogs consuming diets of different macronutrient profiles. Our 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.

Symposium 2017: Healthy Aging



George Martin delivering the keynote address.



Keynote Speaker George Martin with Co-Directors David Orentreich (left) and Norman Orentreich (seated).



This was our first Symposium at which younger researchers took part. Zie-Jie Shen & Spike Postnikoff (post-docs in Jessica Tyler's lab) & Aileen Lee (Vishwa Dixit's graduate student) with the Orentreichs.



Vishwa Dixit, Aileen Lee, Holly Brown-Borg, & Matt Kaerberlein at a casual gathering after the first day of sessions.



Jay Zimmerman, Anna Kate Shoveller, John Richie, & Arthur Cooper relaxing in the Carriage Lounge.



The Symposium was held at the historic Mohonk Mountain House.

Human Trial Update: MR in Healthy Adults

In laboratory animal models, the effects of methionine restriction (MR) are accompanied by numerous metabolic changes that may underlie MR's beneficial health effects, including improvements in glucose and fat metabolism and a reduction in oxidative stress. Recent studies have indicated that a restriction in both methionine and cysteine [i.e., total sulfur amino acid restriction (SAAR)] is required to obtain optimal beneficial effects. While SAAR holds promise as a possible intervention for reducing aging-related impairments and diseases, little is known about the translation of these findings to humans. Thus, we have conducted an interventional study in healthy subjects with Penn State College of Medicine to determine the short-term (1-month) impact of both MR and SAAR diets. In this study, healthy adults were randomized to either MR or SAAR diets, each consisting of 3 controlled feeding groups—1) control; 2) 70% MR or 90% MR; 3) 65% SAAR or 50% SAAR—separated by washout periods. 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 to promote health and to prevent disease in humans.

Metabolism

Building on his previous research to determine the roles of fibroblast growth factor 21 (FGF21) and adiponectin in MR, Dr. Ables and his team are studying MR in the absence of both of these hormones. FGF21 attenuates obesity and insulin resistance, and adiponectin increases insulin sensitivity, so the increased levels of both seen with MR may be thought to contribute to MR's effects on insulin resistance and sensitivity. Preliminary results in mice lacking both hormones, however, show that MR continues to have these beneficial effects, pointing to another yet to be discovered mechanism by which MR achieves these results.

Searching for additional possible mechanisms by which dietary restriction works, Dr. Nichenametla hypothesized that restriction of both methionine and cysteine (SAAR) alters protein synthesis by modulating the environment in which proteins act. Energy is required for protein synthesis and folding and for the breaking down of misfolded and damaged proteins that could lead to disease. SAAR slowed protein synthesis, and proteins involved in folding and repair were more

numerous. Slower production and more efficient folding may result in improved proteostasis in SAAR.

MR Mimetics

The primary aim of Dr. Johnson's research is the identification and characterization of MR mimetics that improve healthspan. Toward this end, Dr. Johnson and his group make use of multiple experimental model systems, ranging from baker's yeast to laboratory mice, in order to assess the effects of various dietary, chemical, and genetic interventions on both cellular and organismal lifespan. To better understand the molecular mechanisms underlying the benefits of MR, they have explored the involvement of autophagy (a process whereby extraneous or damaged cellular components are recycled) in the extension of cellular lifespan observed for methionine-restricted cells. In a parallel approach, Dr. Johnson's lab has also sought to identify compounds that confer the extended longevity and improved healthspan associated with MR while under the methionine-replete conditions of a normal diet. It is hoped that such compounds will form the basis of novel dietary or pharmacologic interventions that will improve healthy lifespan in mammals, including humans.

Methodology

In his goal to elucidate the role of the transsulfuration pathway in mediating the protective effects of MR, Dr. Ables collaborated with scientists at Yale University and New York Medical College to develop a means by which to measure hydrogen sulfide (H_2S). Preliminary results suggest that measurements of H_2S in tissues are possible through the use of gas chromatography coupled with mass spectroscopy.

Walkability

Dr. Calinao's current focus is on the use of walkability as a tool to identify placemaking opportunities and sidewalk improvements that could encourage people to walk more, thus improving their health and well-being, reducing their carbon footprint, strengthening community bonds, and supporting local economies. She recently measured walkability in neighborhoods surrounding three senior housing locations in Manhattan (Hell's Kitchen, East Harlem, and Lower East Side). Hell's Kitchen had the greatest walkability, followed by East Harlem and Lower East Side. Using an automated rule-based microscale assessment tool, Dr. Calinao discovered that comfort and safety were low across all three neighborhoods, posing unnecessary risks that deter residents from a more active lifestyle. Next steps include determining the impact neighborhood walkability has on health outcomes, making preliminary designs of placemaking opportunities, and exploring ways to apply the microscale method at a larger scale.

Publications, Posters, & Presentations

Cooke D, Ouatarra A, Ables GP.

Dietary methionine restriction modulates renal response and attenuates kidney injury in mice.

FASEB Journal, in press.

Ables GP, Johnson JE.

Pleiotropic response to methionine restriction.

Experimental Gerontology 2017; 94: 83-8.

Mattocks DA, Mentch SJ, Shneyder J, Ables GP, Sun D, Richie JP Jr, Locasale JW, Nichenametla SN.

Short term methionine restriction increases hepatic global DNA methylation in adult but not young male C57BL/6J mice.

Experimental Gerontology 2017; 88:1-8.

Horowitz MC, Berry R, Holtrup B, Sebo Z, Nelson T, Fretz JA, Lindskog D, Kaplan JL, Ables GP, Rodeheffer MS, Rosen CJ.

Bone marrow adipocytes.

Adipocyte 2017; 6: 193-204.

Postnikoff SDL, Johnson JE, Tyler JK.

The integrated stress response in budding yeast lifespan extension.

Microbial Cell 2017; 4: 368-375.

Cooke D, Ables GP.

Methionine restriction attenuated kidney injury in 5/6 nephrectomized mice. (poster)

American Aging Association 46th Annual Meeting in Brooklyn, NY, USA.

Park M, Plummer J, Malloy VL, Hens J, Ables GP.

Methionine restriction with cisplatin treatment attenuated non-small cell lung cancer tumor growth. (poster)

Targeting Cancer Metabolism and Signaling, New York, NY, USA.

Calinao B, Rusin M.

Measuring neighborhood walkability around three senior housing in Manhattan, New York. (poster)

Walk 21 Conference, Calgary, Alberta, Canada.

Calinao B, Rusin M.

Measuring neighborhood walkability around three senior housing in Manhattan, New York. (presentation)

The Walking Summit, St. Paul, Minnesota, USA.

Calinao B, Rusin M.

Measuring degrees of walkability to reduce obesity using GIS. (presentation)

ESRI User Conference, San Diego, California, USA.

Norman Orentreich Award for Young Investigator on Aging

OFAS is a long-time supporter of the International Symposium on Neurobiology and Neuroendocrinology of Aging, held biennially in Bregenz, Austria. For the past 10 years, we have supported a session on Aging and Nutrition. At the next meeting, OFAS will additionally provide an award to one graduate student or post-doctoral fellow presenting at the Symposium. It is our goal to inspire young investigators to continue aging research, as well as to acknowledge the potential of their work. The Awards Committee will judge eligible submissions based on research focus, research potential, and presentation. One award will be made to one of the oral presenters. As part of receiving this award, the awardee will provide OFAS with research updates and, contingent upon satisfactory progress, the awardee may also be invited to present at the biennial OFAS Symposium.



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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