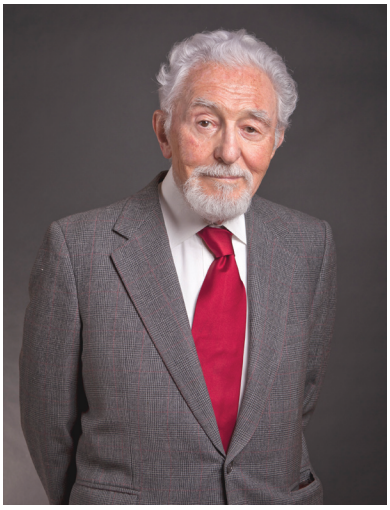
Report of the Directors 2018

OFAS

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



Founded 57 years ago, OFAS is dedicated to biomedical research to prevent, halt, or reverse those disorders that decrease the quality or length of life. In the most recent 25 years, we have investigated a very promising means of achieving this: a diet low in the essential sulfur amino acid methionine. (Of the 20 standard amino acids required for good health, the 9 "essential" amino acids must be consumed; the remaining 11 are made in the body.) During this time, we have seen how a low-methionine diet can increase lifespan and delay onset of age-related diseases; examined the interplay of methionine with cysteine (another sulfur amino acid); and sought to understand the mechanisms by which these two proteins affect so many aspects of health.

Given the potential of this sulfur amino acid-restricted (SAAR) diet to increase both healthspan and lifespan, it is vital to provide the public with accurate and timely information for incorporating the diet into their lives. To meet this need, we are working with Penn State College of Medicine to develop an app that will include information and dietary tools with up-to-date, evidence-based information to guide them in adopting a SAAR diet, which limits intake of foods high in methionine or cysteine.

It is worthy to note that a SAAR diet, consisting largely of plant-based foods, greatly reduces the environmental impact of food production. A SAAR diet could not only promote our own health and longevity, but the health and longevity of the planet.

In addition to our research, OFAS has continued to support the International Symposium on Neurobiology and Neuroendocrinology of Aging in Bregenz, Austria, and at this year's symposium, we awarded the first Norman Orentreich Award for Young Investigator on Aging. OFAS also hosted a session on Nutrition and Longevity during the Annual AGE meeting in Philadelphia. Our own biennial Symposium on Healthy Aging will take place in October 2019.

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 2019 and look forward to connecting with you through the Healthspan blog at www.orentreich.org.

Norman Orentreich, MD, FACP
Founder and Co-Director

David S Orentreich, MD
Co-Director

Healthspan Extension

Dr. Ables' research in the past year examined the role of the transsulfuration pathway, specifically cystathionine gamma-lyase enzyme (CGL), during methionine restriction (MR) in mice.

Recent studies show that hydrogen sulfide (H_2S) plays an important role in the lifespan extension benefits of MR. H_2S is a gasotransmitter, a gas synthesized in our bodies to perform a biochemical function. H_2S influences processes including blood flow, neurotransmission, inflammation, and bone remodeling. Enzymatic production of H_2S is made in part by CGL. The H_2S/CGL system protects against cellular aging, renal ischemia/reperfusion injury, and gastric cancer cell proliferation. Interestingly, an MR diet has also been shown to attenuate kidney injury and to delay cancer progression, as well as extend lifespan in rodent models. We hypothesize that the H_2S/CGL system is involved in the metabolic benefits on healthspan during MR. In addition, Dr. Ables, working with OFAS consultants Dr. Mark Horowitz (Yale University) and Dr. Arthur Cooper (New York Medical College), aims to develop a protocol to measure hydrogen sulfide using mass spectrometry from experimental samples.

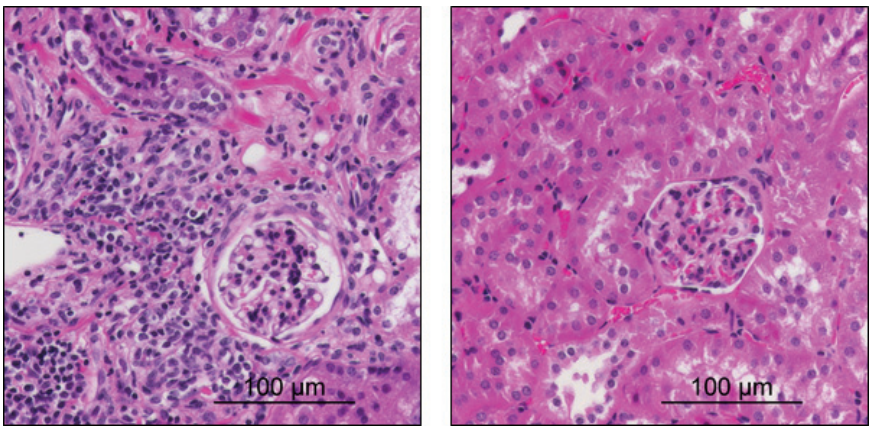
To test our hypothesis, Dr. Rui Wang (Vice President for Research, Laurentian University, Canada) provided CGL-deficient mice and wild-type littermates. After feeding the mice a diet high in fat and low in sulfur amino acid concentration (SAAR), they observed changes in adipose tissue homeostasis and glucose metabolism that may involve the CGL enzyme, which would translate to an improved overall health outcome.

Ongoing research includes studying the roles of FGF21 and adiponectin during MR. FGF21 attenuates obesity and insulin resistance, and adiponectin increases insulin sensitivity, so the increased levels of both seen with MR are thought to contribute to MR's effects on improved glucose metabolism. Preliminary results in MR mice suggest another yet to be discovered mechanism by which MR induces its beneficial effects.

Gene Ables, Associate Science Director

Future studies will examine the role of the satiety hormone leptin during MR using mouse models of leptin dysfunction. Dr. Ables will also examine sarcopenia, the progressive decline in muscle mass due to aging, and muscle integrity in aging mouse models.

To gain better understanding of the multiple and varied effects of MR, Dr. Ables has been working with several institutions. He is collaborating with Drs. Lucy Liaw and Rob Koza (Maine Medical Center Research Institute) on a project to identify novel vascular protective mechanisms in dietary-associated healthspan extension. He is also working with members of Dr. Matt Kaeberlein's lab (University of Washington, Seattle), studying the effects of MR during mitochondrial dysfunction with Dr. Alessandro Bitto and alveolar bone development with Dr. Jonathan An. And, he has utilized the expertise of Drs. Jonathan Wren and Holly Van Remmen (Nathan Shock Center for Aging at the Oklahoma Medical Research Foundation) for bioinformatics and redox biology in livers of mice undergoing MR.



These stained kidney sections from control-fed (standard diet) mice (left) and MR mice (right) suggest infiltration of inflammatory cells. Original magnification, 320. Scale bar, 100 mm. Adapted from FASEB Journal, *32, 693–702 (2018).*

Mechanisms of Lifespan Extension

Dr. Nichenametla's lab aims to understand the biological mechanisms that extend lifespan and to modulate these for the benefit of human health. Studies in his laboratory follow a two-pronged approach of basic and applied research. Utilizing rodents as primary experimental models, his lab seeks to delineate the biochemical pathways by which lifespan-extending interventions such as caloric restriction and methionine restriction (MR) work. While these dietary interventions serve as excellent tools to identify critical pathways for lifespan extension in laboratory models, findings are seldom *directly* applicable to human lifespan. However, the identified mechanisms may have applications in several human diseases. Considering the critical differences and similarities of the biochemical pathways between mice and humans, and based on findings in mice, his group seeks to devise new dietary or pharmaceutical formulations that are appropriate for specific diseases in humans.

Previous studies from his group demonstrate that MR improves two fundamental processes that regulate lifespan: 1) maintenance of structural and functional integrity of DNA, and 2) minimization of the synthesis of damaged and non-functional proteins during proteostasis (the complex process that regulates proteins from their origin to their breakdown). The presence or absence of methyl groups on DNA controls the flow of information as DNA carries out various processes in cells. Loss of these methyl groups results in various diseases such as cancer and is associated with aging. In recently published work from Dr. Nichenametla's lab (*Experimental Gerontology* 2017; 88, 1-8), MR prevented the loss of methyl groups, suggesting that this could be a crucial mechanism by which MR extends rodent lifespan. Since the loss of methyl groups also has implications for cancer, Dr. Nichenametla will, in collaboration with researchers from Penn State University, examine MR as adjuvant therapy in the prevention and treatment of breast cancer in humans.

Nath Nichenametla, Senior Scientist

While DNA can provide the necessary information for synthesis, proteins are functional only after they are folded into unique three-dimensional structures. A few of the 30,000 or more proteins a cell can synthesize are chaperone proteins, which are dedicated to imparting 3-D structure to the rest. Higher rates of protein synthesis without greater numbers of chaperone proteins result in more misfolded proteins, which can lead to diseases such as diabetes, cancer, and Alzheimer's disease. Dr. Nichenametla's group recently demonstrated that MR slows protein synthesis and increases the levels of chaperone proteins, suggesting that MR's lifespan extending effect is a result of improved proteostasis (*Annals of the New York Academy of Sciences* 2018; 1418, 80-94). In collaboration with researchers from the University of Michigan, he is currently investigating whether MR ameliorates human protein misfolding diseases in animal models of these diseases.

Other ongoing studies in his laboratory include a comparison of the biological mechanisms of the two most successful dietary paradigms that similarly increase lifespan despite their contrasting regimens: the familiar caloric restriction, which limits energy intake, and the unlimited caloric intake of the MR diet.

Methionine Restriction Mimetics

The primary aim of Dr. Johnson's research is the identification of novel MR-like interventions that improve healthspan. For this purpose, Dr. Johnson's group makes use of multiple experimental model systems, ranging from baker's yeast to laboratory mice, in order to better understand the molecular mechanisms underlying the benefits of MR, in turn facilitating the identification of so-called MR mimetics. In previous studies, they demonstrated that dietary MR, genetic MR (impairment of the cell's methionine biosynthetic machinery), and enzymatic MR (enzymatic depletion of intracellular methionine) all significantly extend the lifespan of yeast.

In the past year, Dr. Johnson's group has explored how autophagy, a process whereby extraneous or damaged cellular components are beneficially recycled, contributes to MR-dependent cellular lifespan extension. Specifically, they found that the levels of multiple autophagy-related genes are increased by MR, likely resulting in an increased autophagic capacity in these cells. Consistent with this finding, they also observed that loss of any of several indispensable autophagy factors diminishes the extended lifespan observed for

Current Research

methionine-restricted cells. Strikingly, of the many known types of autophagy, Dr. Johnson's data clearly demonstrate that MR-mediated lifespan extension requires only the autophagic recycling of mitochondria (i.e., mitophagy). Indeed, his group found that not only is mitochondrial function enhanced by MR, but functional mitochondria are required for the full benefit of MR to cellular lifespan extension. Finally, they 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. Taken together, their data are consistent with MR producing changes in energy metabolism that, together with the oxidative metabolism of mitochondria, results in extended cellular lifespan.

Future studies in Dr. Johnson's laboratory will examine 1) to what extent metabolic alterations like those observed in yeast might be present in the tissues of methionine-restricted mammals, 2) whether such changes are causally related to MR-mediated improvements in mammalian healthspan, and 3) if the healthspan-extending alterations of MR could be produced in the context of an essentially normal, methionine-replete diet.

Jay Johnson, Senior Scientist

Other Projects

Sulfur Amino Acid Restriction App

Given the potentially beneficial clinical implications of sulfur amino acid restriction (SAAR), there likely will be significant public interest in this dietary intervention. As such, there is a need for information and dietary tools designed for the lay public as a means of increasing awareness, ensuring accuracy of information, and guiding the implementation of a SAAR diet. We are therefore designing both a mobile application and a website dashboard aimed at providing up-to-date, evidence-based information on SAAR.

In addition to information on the importance of sulfur amino acids (SAA) and health and SAAR's potential benefits developed during our preliminary clinical trials, users will have access to an interactive tool for assessing and designing diets based on SAA content. This will include a calculator to estimate an individual's SAA requirements based on age, gender, and body weight/type; a calculator to estimate daily SAA intake based on foods consumed; a listing of the SAA content of food items to provide details on foods both high or low in SAA; and an SAA smart list to provide comparisons between higher and lower SAA containing food choices.

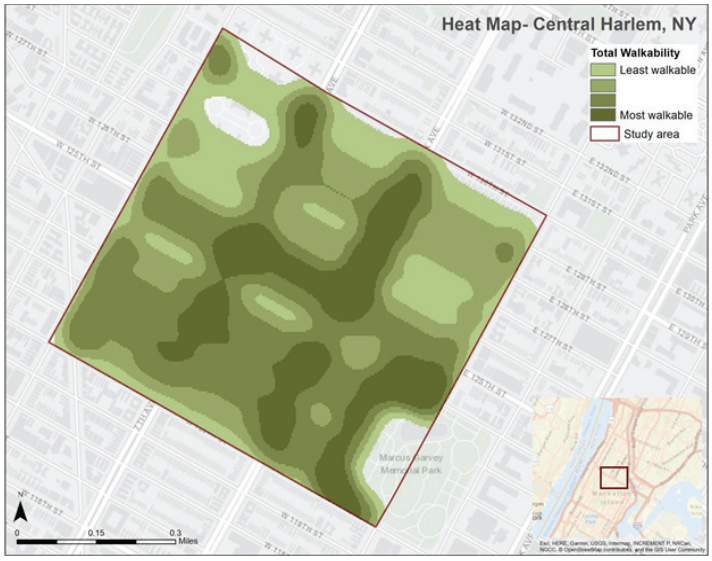
Zhen Dong, Doctor of Public Health Graduate Student, Penn State College of Medicine. Zhen will be developing content for the Sulfur Amino Acid Restriction App.

Obesity & Walkability

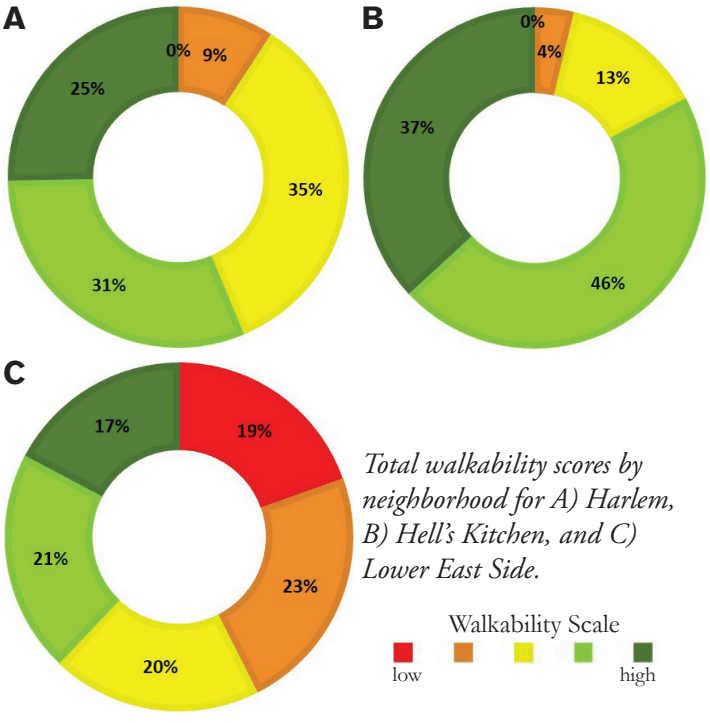
The annual health care cost of obesity-related illnesses is an astonishing $190 billion. Current U.S. trends predict a national obesity rate of approximately 44% by 2030, when there will be an estimated 78 million obese adults. If, however, obesity rates were to remain at 2010 levels, the projected savings to healthcare costs would be $549.5 billion (Finklestein, 2012). Recent studies reaffirm walking as an efficient, cost effective, and equitable preventive measure for obesity and related chronic illnesses. However, improvements toward a more walkable environment cannot be made without the proper understanding of the quality of the built environment and human perception of the walking experience. Expanding on previous research in Central Harlem, NY, where the combined obesity and overweight rate is 60%, Dr. Calinao's team studied human perception of the built environment to complement the microscale assessment previously completed. This data is key to the process of identifying opportunities for placemaking—a process that includes a community's physical, cultural, and social identity to create quality public spaces—that can encourage walking to improve health. Low comfort and safety walkability scores from the microscale assessment were confirmed in surveys conducted among residents. Placemaking solutions for the low-scoring areas include the introduction of street seating to provide additional comfort and, to increase safety, curb extensions to alter motorized traffic patterns, and proper barriers.

Older Adults & Walkability

Dr. Calinao and her team have started a second microscale walkability study focusing on the older adult population (ages 65 and older) in Manhattan, NY. The U.S. Department of Health and Human Services *Physical Activity Guidelines for Americans* (2nd ed, November 2018) advises older adults to aim for at least 150–300 minutes of moderate-intensity physical activity per week to maintain or improve overall health and to reduce the risk of chronic disease. Nationally, 24.2% of older adults engage in no leisure time physical activity (CDC, 2016). Active living communities for older adults are essential for fostering individual health and longevity. This study uses geographic information systems (GIS) to objectively measure walkability surrounding three older-adult living facilities and as a tool for planning and design of urban pedestrian environments. The goal for the upcoming year is to utilize GIS to distinguish and map the relationships among third places (social surroundings separate from the two usual social environments of home and the workplace), walkable areas, and soft edges (outdoor space adjacent to a residence), and to identify placemaking opportunities that would encourage older adults to incorporate walking as a preventive health measure. An older adult perception survey about their walking environment will likewise be conducted.



Heat map showing walkability for an area within Central Harlem, New York. Darker green represents the highest walkability, pale green the lowest.



Total walkability scores by neighborhood for A) Harlem, B) Hell's Kitchen, and C) Lower East Side.

2019 Symposium on Healthy Aging

In 2013, as part of our commitment to promoting the exchange of knowledge and strengthening relationships in the scientific community, we inaugurated a series of symposia that would focus on issues concerning diet and aging. In the coming year, we will host the fourth biennial symposium.

The keynote address will be given by Dr. Ana Maria Cuervo, Co-Director, Institute for Aging Research and Professor of Developmental and Molecular Biology, Albert Einstein College of Medicine (Bronx, NY).

October 16–18, 2019

Mohonk Mountain House

New Paltz, NY

Meetings Supported

In addition to our own symposium, OFAS continues to to support other meetings as well. In 2018 we once again sponsored a session at the International Symposium of Neurobiology and Neuroendocrinology of Aging which was held in Bregenz, Austria July 15–20.

OFAS also hosted a session during the Annual AGE meeting in Philadelphia. The partnership was organized by Dr. Gene P. Ables (OFAS), Dr. Christian Sell (Drexel University; 2018 AGE President), and Ms. Catherine Hornsby (AGE meeting organizer). This panel on Nutrition and Longevity was moderated by Dr. Ables. The speakers and the topics they discussed were:

- Dr. Brian Kennedy (National University of Singapore): Conserved modulators of aging: Will they work in humans?
- Dr. John Newman (Buck Institute): Fasting and fasting-mimicking diets in health and lifespan
- Dr. Sebastian Brandhorst (University of Southern California): Ketone bodies in aging and cognition: Targeting metabolic signals for new therapies
- Dr. John Richie (Penn State University): Dietary sulfur amino acid restriction in healthy adults: a controlled feeding study

The Norman Orentreich Award for Young Investigator on Aging

OFAS presented the first Dr. Norman Orentreich Award for Young Investigator on Aging to Dr. Andrei Grești ă of the University of Medicine and Pharmacy of Craiova, Romania. The award was presented at the 14th International Symposium on Neurobiology and Neuroendocrinology of Aging in Bregenz, Austria. With this award, we hope to inspire young investigators to continue aging research and to acknowledge the potential of their work. Andrei was selected for his presentation: “Restore cell balance in the aged brain after stroke by direct in vivo reprogramming technology”. In addition to the $1,000 prize, Andrei was invited to present at the 2019 OFAS Symposium on Healthy Aging.

Publications

Cooke D, Ouattara A, Ables GP. Dietary methionine restriction modulates renal response and attenuates kidney injury in mice. *FASEB Journal*, 2018: 32: 693-702.

Dai Z, Mentch SJ, Gao X, Nichenametla SN, Locasale JW. Methionine metabolism influences genomic architecture and gene expression through H3K4me3 peak width. *Nature Communications*, 2018; 9: 1955.

Nichenametla SN, Mattocks DAL, Malloy VL, Pinto JT. Sulfur amino acid restriction-induced changes in redox-sensitive proteins are associated with slow protein synthesis rates. *Annals of the New York Academy of Sciences*, 2018; 1418: 80-94.

Tyler JK, Johnson JE. The role of autophagy in the regulation of yeast life span. *Annals of the New York Academy of Sciences*, 2018; 1418: 31-43.

Presentations & Posters

Nichenametla SN, Mattocks DAL, Malloy VL. Discrete effects of methionine and cysteine on biomarkers of sulfur amino acid restriction (poster). Nutrition 2018 (American Society of Nutrition), Boston, MA, USA.

Plummer JD, Johnson JE. Extension of cellular lifespan by methionine restriction involves alterations in central carbon metabolism and is mitophagy-dependent (oral presentation). Cold Spring Harbor Laboratories: Mechanisms of Aging Meeting, Cold Spring Harbor, NY, USA.

Cooke D, Jean K, Ruseskas J, Ables GP. Methionine restriction mitigates age-related functional decline and activates autophagy in skeletal muscle of aged mice (poster). Gordon Conference on Autophagy, Italy.

Cooke D, Jean K, Ruseskas J, Ables GP. The effects of methionine restriction in muscles of young and aged mice (poster). 2018 AGE Meeting, Philadelphia, PA, USA.

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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.

Information for Donors

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