OFAS

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

Report of the Director

Dear Friends,

Founded in 1961, the Orentreich Foundation for the Advancement of Science, Inc. (OFAS) is now entering its seventh decade of investigating the causes of aging and factors influencing age-related diseases. In this Report you will find a timeline of our work, reflections from Foundation alumni who have gone on to become leaders in research, and summaries of our current research, including a link to videos of our latest Symposium.

One of the hallmarks of OFAS research is interaction: asking questions at all levels, from all members. Over the past 18 months we have renovated a building on the Cold Spring campus so that research staff can be located near each other in order to facilitate scientific interaction.

In December we hosted our fifth Symposium on Healthy Aging, held virtually for the first time. In July we supported a session at the AGE 2021 Annual Hybrid Meeting, where we awarded the Dr. Norman Orentreich Award for Young Investigator on Aging to Dr. Cristal Hill of the Pennington Biomedical Research Center. In addition, we will once again provide support for the Symposium on Aging and Neuroendocrinology (Bregenz, Austria).

Given the complexity of aging, our scientists collaborate with experts in their respective fields throughout the world. They are forging new partnerships to conduct clinical and epidemiological studies to test if their laboratory findings are translatable to humans. Looking forward, our scientists will continue to expand understanding of the biological basis of our signature finding, that sulfur amino acid restriction (SAAR) extends lifespan by delaying the onset of age-related disease. We are developing methods to implement this beneficial diet in humans, as well as investigating methods that can produce the beneficial effects of SAAR without the need for life-long dietary restrictions.

We thank you for your continued support and wish you the best in 2022.

David S. Orentreich, MD, FAAD
Director

Six Decades of OFAS

1960s

1961	OFAS incorporated on March 9
1965–1976	Plasmapheresis in dogs and rats
1967	First OFAS publication: aging as a significant factor in nail growth rate

1970s

1972–1984	Research on *Nothobranchius guentheri*, first as an aging model, then as an aid in malaria control
1974	Reported on estrogen administration and breast cancer in transgender women
1975-1976	Analysis of George Washington's hair
1977	Review: aging of skin and its appendages

1980s

1980	Kaiser Permanente sera collection transferred to OFAS; verification of integrity of stored samples
1983	Improvement of animal model used for acne research
1985–1989	Developed mouse model for androgenetic alopecia
1986	Developed long-hair Syrian hamster model for hirsutism research
1987	Moved to Biomedical Research Station in Cold Spring, N.Y.
1988-1993	Testosterone & dihydrotestosterone metabolic studies

1990s

1991–2008	Serum Treasury research linking *H. pylori* infection & various cancers
1992–1994	Extraction of 5α-reductase inhibitor from saw palmetto berries
1992–1994	Use of liposomes as drug delivery aid
1993	Publication of first peer-reviewed article on methionine restriction
1993	Collaborative study with Stanford University on effects of age on dehydroepiandrosterone sulfate concentrations in wild baboons
1995–2005	Studies on percutaneous absorption of organic chemicals, vitamins, & hormones through mouse & rat skin
1997	Development of skin penetration enhancers
1997	Lovastatin studies on hair follicles
1997–2000	Metformin *in vitro* & *in vivo* studies
1998	Studies of hypergastrinemia & risk of colorectal cancer

2000s

2000–2003	Identification of prostate cancer serum markers
2001–2003	Correlation between BMI, IGF-1, & binding proteins as risk factors for breast cancer
2001–2002	Association between TNFα & its receptors as risk factors for breast cancer
2002	Use of IGF-1 as a biomarker in epidemiologic studies
2004	Nanobacteria as cardiovascular risk factor
2004	Alzheimer's study—serum markers
2005–2006	Studies on prostate cancer risk factors in Blacks & whites
2006	Study of effects of methionine restriction on adiposity & insulin sensitivity
2006	Dr. David Orentreich joins Dr. Norman Orentreich as Co-Director of the Foundation
2007	Studies on effect of blueberry consumption on hearing & cognition
2008	Collaboration with Oxford University on methionine restriction effects on adiposity and implications of cysteine supplementation

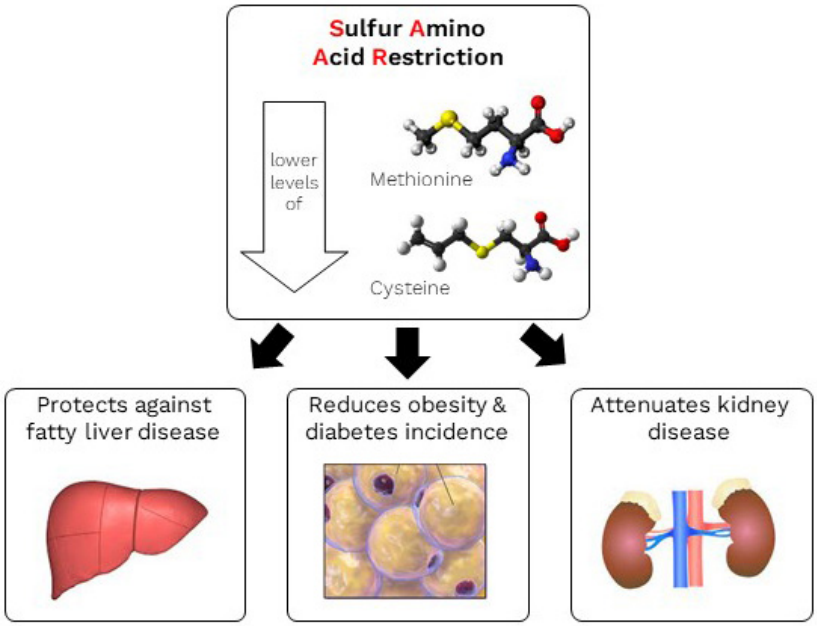
2010s

2010	Studies on methionine restriction & mitochondrial function
2010–2019	Collaboration with Penn State University to develop methionine-restricted diet studies for humans
2011	Angiopoietin-2 as a biomarker of incident acute myocardial infarction independent of traditional risk factors
2011	Dietary methionine restriction increases fat oxidation in obese adults with metabolic syndrome X
2013	Hosted first Symposium
2015–2018	Epigenetic mechanisms' crucial role in SAAR-induced health benefits
2017–2021	Identification of compounds that confer MR-like health benefits to mice, without dietary restriction
2018	SAAR diet protection against chronic kidney disease in mouse models
2018	Autophagic recycling of mitochondria & mitochondrial metabolism are indispensable to MR-dependent lifespan extension
2020	Age-at-onset determines the magnitude and type of SAAR-induced health benefits in animal models

Ables Laboratory

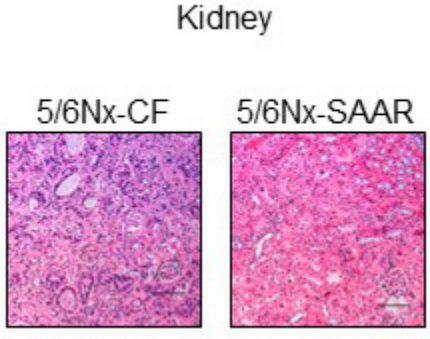
Dr. Ables uses mouse models to study the effects of dietary sulfur amino acid restriction (SAAR) (Figure 1). His early work at OFAS demonstrated that even a high-fat SAA-restricted diet can prevent the development of diabetes, obesity, and fatty liver disease (Ables et al., *PLoS One* 2012, 7: e51357). Later work showed that not only does a high-fat SAA-restricted diet prevent metabolic syndrome, but it can promote weight loss in obese mice (Cooke et al., *Obesity* 2020, 28: 1075). By looking at hyperhomocysteinemia, a marker for cardiovascular disease, his group found that SAAR does not affect cardiac function in mice (Ables et al., *Sci Rep* 2015, 5: 8886). As SAAR-fed mice are smaller than their control counterparts, the group studied bone strength. They found that although SAAR-fed mice have more fragile bones compared to controls, their bone composition was similar and, in fact, appropriate to their smaller body size (Ouattara et al., *Bone Rep* 2016, 5: 33). Because renal disease is an age-related disease in both mice and humans, they looked at SAAR in a mouse model of chronic kidney disease, finding that SAAR attenuates renal deterioration (Cooke et al., *FASEB J* 2018, 32: 693).

Figure 1. Protective effects of sulfur amino acid restriction in liver, fat tissue, and kidneys



To address the molecular mechanisms by which a SAA-restricted diet confers protection, the Ables lab uses gene studies to look at the tissue of animal models. In one such study, they found that protection against fatty liver disease in mice that were fed a high-fat SAA-restricted diet is associated with upregulated glucose-sensitizing hepatic *Pparg* and *Fgf21* genes and downregulated *Scd1* gene (Ables et al., *PLoS One* 2012, 7: e51357). Kidney cells from SAAR-fed mice (Figure 2) show downregulation of genes involved in inflammation and fibrosis (Cooke et al., *FASEB J* 2018, 32: 693). Dysregulation of autophagy, a method by which a cell degrades and recycles its proteins, worsens many age-related diseases. For this reason, the group looked at adipose tissue in obese mice that lost weight on a

Figure 2. SAAR attenuates kidney injury in 5/6Nx mice, a chronic kidney disease mouse model

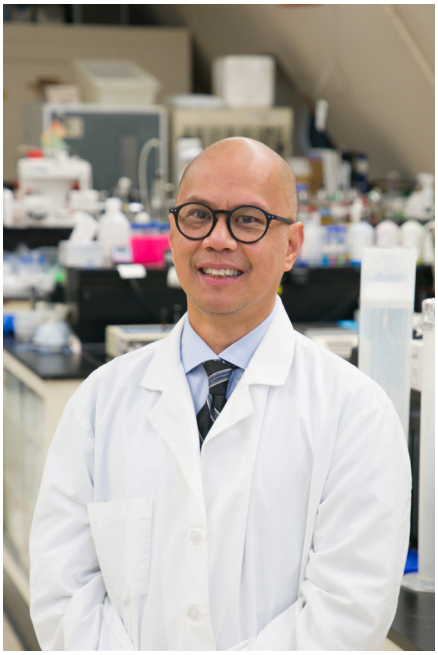


Representative images of kidney sections from 5/6Nx-CF and 5/6Nx-SAAR mice stained with H&E. Blue stained cells suggest infiltration of inflammatory cells. Source: *FASEB J* 32, 693. doi: 10.1096/fj.201700419R.

high-fat SAA-restricted diet (Figure 3). They found autophagy-related protein signaling in adipose tissue of the SAAR group to be upregulated when compared to the control-fed group (*Obesity* 2020, 28: 1075).

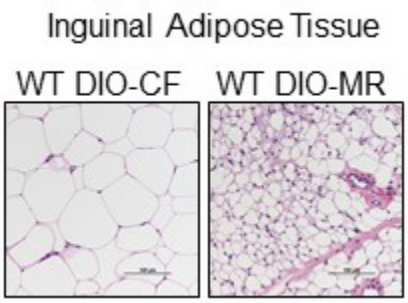
Dr. Ables's current research examines the effects of SAAR on neurodegenerative diseases, using mouse models of amyotrophic lateral sclerosis (ALS). His team is collaborating with Drs. Calvin Vary, Rob Koza, and Rea Anunciado-Koza (Maine Medical Center Research Institute, Scarborough, Me.) to identify biomarkers that are affected by SAAR. In conjunction with Drs. Mark Horowitz and Doug Rothman (Yale University, New Haven, Conn.), he is conducting a pilot study for using high resolution MRI to measure adipocyte depots in mice. Not only will these studies advance current understanding of SAAR, but they will also establish new techniques beneficial to aging research outside of animal models.

As data from genomic, transcriptomic, and metabolomic studies characterize new pathways and tissue-specific effects by which SAAR affects aging, more questions still need to be addressed. Does SAAR promote lengthening of the telomeres? Does SAAR delay cellular senescence? How does SAAR affect stem cells and regeneration? How will SAAR impact neurodegenerative disorders? Dr. Ables and his team look forward to exploring these and other questions in future studies.

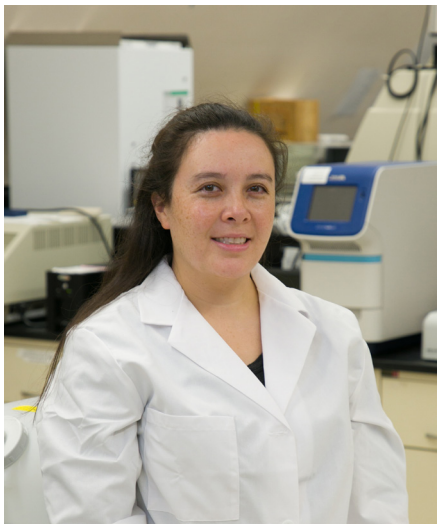


Gene Ables, Associate Research Scientist

Figure 3. Male obese WT mice lose weight after switching to an MR diet



More multilocular adipocytes appear in inguinal white adipose tissue of obese HFD-SAAR mice than in obese HFD-CF mice. This type of adipocyte is known to promote healthy metabolism. Source: *Obesity* 28, 1075. doi: 10.1002/oby.22763.



Diana Cooke, Senior Research Associate

A large body of work, including many studies from OFAS, has demonstrated that a sustained state of SAAR dramatically extends the healthspan of several model organisms; see Ables and Johnson, 2017 *Exp Gerontol* 94: 83. For example, continuously SAA-restricted rodents have less age-related pathology and are up to 45% longer-lived than control-fed littermates. Given that the vegan diet is low in both protein and free amino acids, eating a SAA-restricted diet is feasible for humans and, tantalizingly, preliminary studies suggest that SAA-restricted individuals may receive similar benefits to rodents. Unfortunately, long-term adherence to a SAA-restricted diet is likely to be challenging for some, and might be undesirable for others. Accordingly, a key goal of the aging field has been to develop simpler and/or more practicable interventions that still produce healthspan benefits similar to those engendered by SAAR.

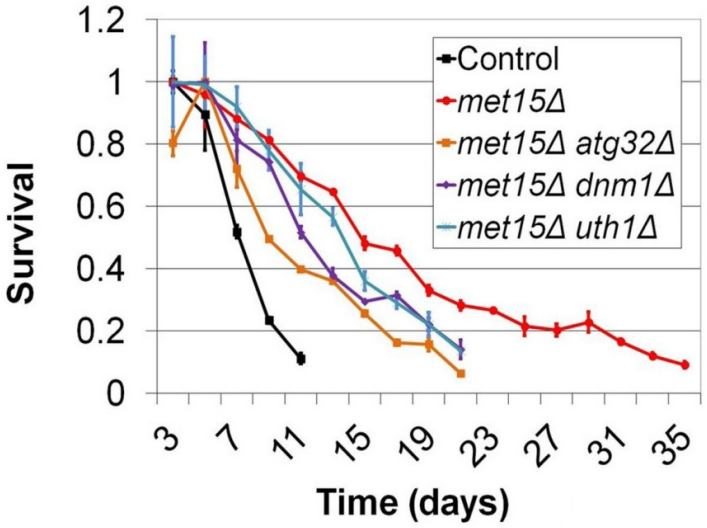
As a critical part of this effort, Dr. Johnson's research has focused on 1) characterization of the mechanisms underlying the benefits of SAAR, and 2) identification of novel SAAR-like interventions that improve mammalian healthspan. To achieve this, Dr. Johnson's group has made use of multiple experimental model systems, including baker's yeast, cultured mouse and human cells, and laboratory mice. Importantly, these experiments achieve SAAR by omitting the cysteine SAA entirely and instead manipulating the availability and/or synthesis of methionine. As a result, such interventions are referred to below as MR (methionine restriction).

With respect to the first aim described above, Dr. Johnson has 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; see Johnson and Johnson, *PLoS One* 2014, 9: e97729 and Plummer and Johnson, *Front Cell Dev Biol* 2019, 7: 301. Dr. Johnson's group has also found that mitophagy (a process that selectively recycles mitochondria) is indispensable for the benefits of MR to yeast (Figure 1). Furthermore, they have discovered that, similar to methionine-restricted animals, methionine-restricted yeast cells demonstrate a significantly altered pattern of metabolism as compared with controls.

With respect to the second aim, Dr. Johnson has recently developed a novel form of MR, intermittent MR (IMR), that is free from the disadvantages of the classical intervention (Plummer and Johnson, in review). IMR requires only 3 days per week of reduced methionine intake yet improves glucose metabolism and insulin sensitivity, prevents fatty liver disease, and completely protects mice against diet-induced obesity (Figure 2). Similar to continuous MR, IMR confers beneficial changes in the levels of multiple hormones implicated in the regulation of metabolism, health, and longevity. A key difference between the two interventions is that, in contrast to classical MR, the novel intervention results in little to no growth inhibition and does not negatively impact the development of lean body mass. In this respect, IMR is superior to MR.

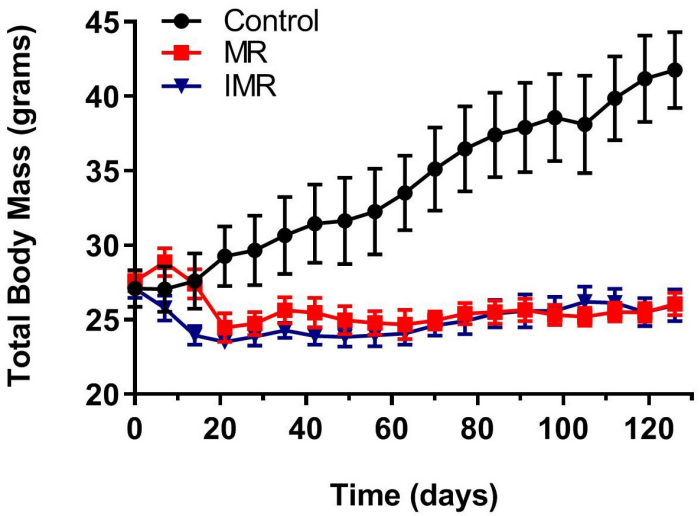
Relatedly, in a recently published study, Dr. Johnson demonstrated that administering certain selenium-containing compounds to mice produces the benefits associated with MR, even in the context of a normal (methionine-replete) diet. Similar to IMR, supplementation with these compounds protects mice against obesity (Figure 3) and confers several additional MR-associated healthspan benefits; see Plummer et al., *eLife* 2021, 10: e62483. In ongoing work, Dr. Johnson's group has also identified a number of additional compounds that do not contain selenium, but also act as mimetics of MR.

Figure 1. MR-dependent yeast lifespan extension requires mitophagy



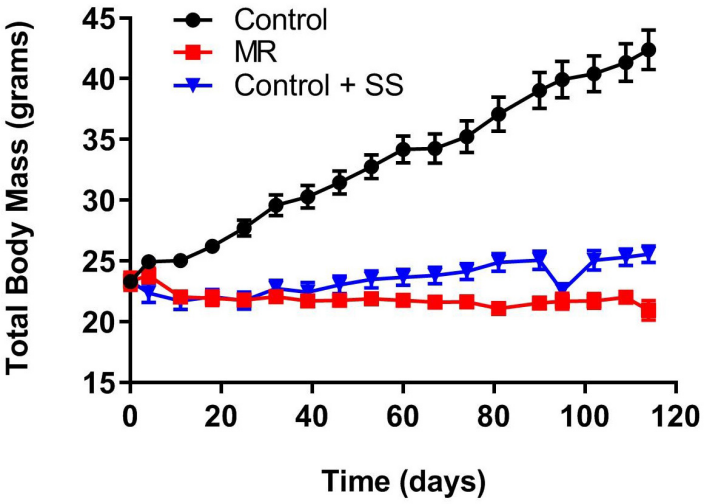
Full extension of yeast lifespan by genetic MR (met15Δ) requires Atg32, Dnm1, and Uth1, all factors involved in the autophagic recycling of mitochondria (i.e., mitophagy).

Figure 2. Intermittent MR 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. An intermittent variant of this intervention wherein mice alternate between the control diet and a low metionine diet (IMR) is just as effective as continuous MR in protecting against diet-induced obesity.

Figure 3. 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 an otherwise normal diet with sodium selenite (Control + SS) is just as effective as MR in protecting against diet-induced obesity.

Current studies are aimed at 1) understanding the mechanistic basis of these novel interventions and 2) assessing to what extent they reduce the rate of aging in mice. Future studies will determine whether IMR and supplementation with MR-mimetics are as effective for humans as they are for rodents. It is Dr. Johnson's hope that these interventions can be successfully translated to humans in order both to improve health and to reduce the burden of age-related disease.

Jay Johnson, Associate Research Scientist

Jason Plummer, Senior Research Associate

Nichenametla Laboratory

Dr. Nichenametla's lab aims to translate the healthspan benefits SAAR confers in animal models to humans. Toward this objective, he leads his team in investigating the mechanisms by which SAAR provides health benefits in rodents. In addition, he collaborates with several national and international research groups that investigate healthspan-improving effects of SAAR in humans.

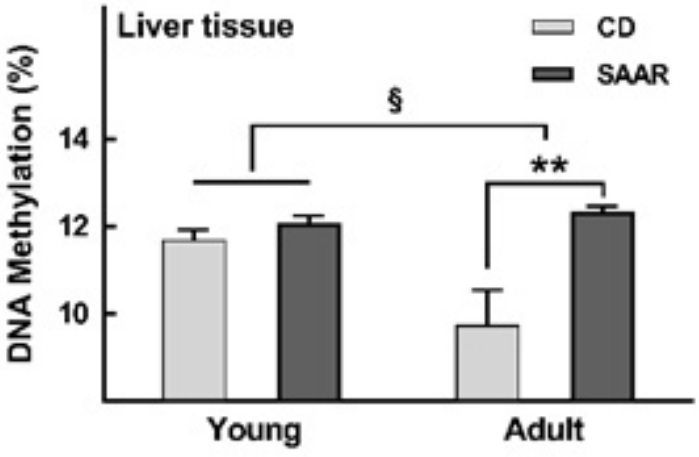
Sailendra Nichenametla, Associate Research Scientist

His early work at OFAS focused on the biological roles of the sulfur amino acids methionine and cysteine in healthy tissues. These include the role of methionine in regulating gene expression and protein synthesis rates, and the essential role of cysteine in the synthesis of glutathione, an antioxidant that prevents oxidative damage in cells. In his first project, he investigated whether the SAAR diet alters one of the basic mechanisms governing gene expression in cells. Gene expression from DNA is regulated by the presence or absence of methyl groups on DNA and histones. As animals age, the total number of methyl groups, and their specific location on DNA and histones, changes. Dr. Nichenametla discovered that SAAR prevents the loss of DNA methylation in liver cells of adult mice, which might be helpful in maintaining a youthful state of gene expression (Figure 1) (Mattocks et al., *Exp Gerontol* 2017, 88: 1). In collaboration with Dr. Jason Locasale at Duke University, he found that SAAR also changes the methylation status of histones (Mentch et al., *Cell Metab* 2015, 22: 861). These findings have implications in diseases in which gene expression goes awry, such as cancer.

In another investigation, Dr. Nichenametla focused on the effect of SAAR on the protein synthesis rate (the speed at which proteins are synthesized) and protein structure. Protein synthesis in normal cells is error prone: up to 30% of proteins are misfolded. When misfolded proteins accumulate, cells die. Cells do have a limited capacity to degrade misfolded proteins but cannot keep up with this job when the protein synthesis rate is high. Dr. Nichenametla's team observed a 33% decrease in the protein synthesis rate (Figure 2) and higher concentrations of chaperone proteins, PDI, and ERO1-α, which confer 3-dimensional structure to newly synthesized proteins in the endoplasmic reticulum (Nichenametla et al., *Ann NY Acad Sci* 2018, 1418: 44). SAAR might, therefore, limit protein misfolding. He is currently testing whether pharmaceutical interventions that induce changes similar to those seen in SAAR can treat protein misfolding diseases.

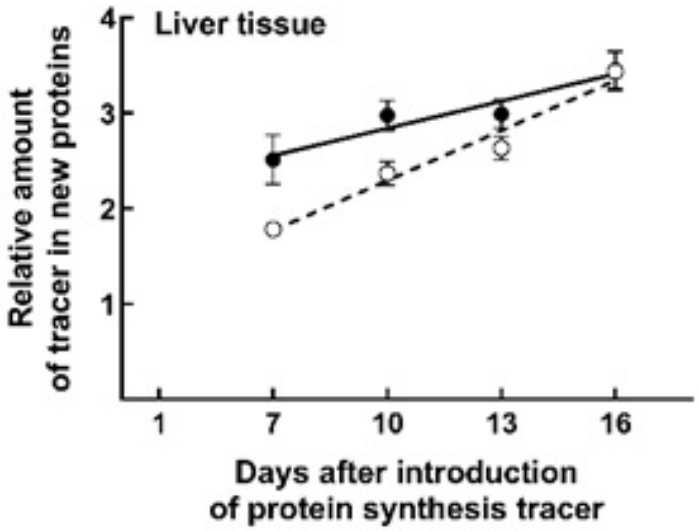
While multiple rodent studies show that SAAR induces health benefits and extends lifespan, the majority of these studies used young rodent models. Since the SAAR diet in humans is intended for adult consumption, it is critical to know whether it is effective in adult and old animals. Hence, Dr. Nichenametla and his team conducted a study initiating SAAR in rats at different ages: seven weeks (young), ten months (adult), and 20 months (old). They compared several changes that are typically induced by SAAR diets in the three age groups and concluded that some of the effects depended on

Figure 1. Effect of SAAR diet on global DNA methylation in the livers of young and adult mice



CD—control diet with 0.86% methionine; SAAR—sulfur amino acid-restricted diet with 0.21% methionine; ★ indicate statistically significant difference; § indicates interaction between dietary methionine concentration and age of onset of SAAR diet.

Figure 2. Effect of SAAR diet on protein synthesis rates in the livers of F344 rats

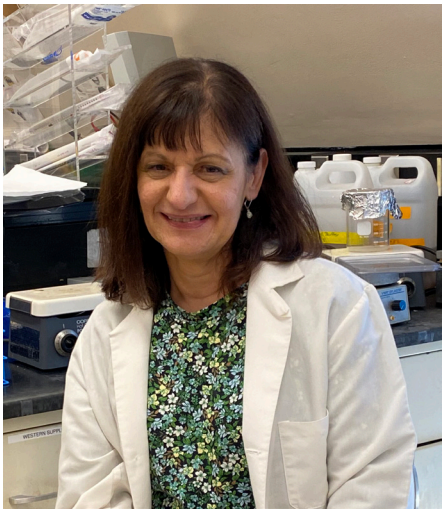


● indicate SAAR diet with 0.17% methionine; ○ indicate control diet with 0.86 % methionine; the slopes are significantly different ($p < 0.05$).

age-at-onset (maximal effects observed in young rats), while others did not (Nichenametla et al., *Aging Cell* 2020, 19: e13177). To complement these findings, Dr. Nichenametla's team conducted another experiment to show that, despite some weaker effects compared to young onsets, SAAR significantly extends lifespan in adult onsets. These findings highlight critical aspects in the formulation of SAAR diets for adult consumption. The degree of SAAR in young rats compared to their requirements is about 80% (0.86% in the control diet, which is the normal nutrient requirement, vs. 0.17% provided in the SAA-restricted diet). However, the SAA requirement of adult and old rats is much lower than 0.86%. Hence, some of the attenuated effects observed in these initial studies could be due to lower actual restriction in adult and old rats, i.e., less than 80%. Future studies will investigate whether a further reduction in SAA concentration in the SAAR diet (below 0.17%) would induce stronger changes in adult and old rats.

Few clinical SAAR studies in humans have been conducted. These studies have shown that SAAR's effects in humans are modest compared to its effects in rodents. However, SAAR diets in human and animal studies differ in one critical aspect: the presence of dietary cysteine. Animals and humans can make cysteine from methionine. Animal SAAR diets are formulated by decreasing the concentration of methionine and completely eliminating cysteine. Due to difficulties in the formulation of a SAAR diet for human consumption, human studies thus far have lower methionine concentration but do not eliminate cysteine. Thus, it remains unknown if the diet's milder effect in humans is due to the presence of cysteine. Indeed, several epidemiological studies indicate that obesity-related biomarkers correlate with circulating levels of cysteine and not methionine. In experimental models, decreased fat accretion is a hallmark of SAAR; however, the effect of SAAR on fat accretion is abolished when the animal's SAA-restricted diet was supplemented with cysteine. Dr. Nichenametla's ongoing research involves titrating both the methionine and cysteine levels in experimental SAAR diets, which allows him to distinguish SAAR-induced effects specific to low methionine and those due to low cysteine. These findings will help to determine whether we can improve the efficacy of human SAAR diets by controlling the levels of both methionine and cysteine.

Dwight Mattocks, Senior Research Associate



Virginia Malloy, Senior Research Associate

Dong Laboratory

Since the initial study (Orentreich et al., *J Nutr* 1993, 123: 269) demonstrating that lifelong feeding of a diet low in methionine as the sole SAA source increased maximum lifespan in rats, similar methionine restriction interventions have been shown to delay aging in a number of animal- and cell-based models. Further, SAAR diets have been associated with reductions in body weight, adiposity, and oxidative stress; improved glucose metabolism; and beneficial changes in the levels of a variety of blood biomarkers, including insulin, glucose, leptin, adiponectin, insulin-like grown factor-1, and fibroblast growth factor-21. Dr. Dong's research investigates the translational implications of SAAR diets on chronic disease prevention in humans from an epidemiological perspective. Dr. Dong's early studies analyzing a large national representative database found that a diet of higher SAA intake was associated with higher diabetes-related mortality and risks of cardiometabolic diseases. Other studies also suggest that dietary intake of SAAs is positively associated with Type 2 diabetes-related risk factors and biomarkers in humans, not only in populations in western countries, but also in eastern countries like China. This is of significant public health importance given the high rates of diabetes and high intake of SAAs in many developed countries.

A limitation of these previous studies is that dietary intake was assessed only at a single point in time. No data was available on the impact of long-term SAA consumption on the incidence of diabetes; therefore, Dr. Dong is currently investigating ongoing dietary SAA intake and long-term risk for diabetes in two prospective cohorts of the Framingham Heart Study: the Offspring and Third-Generation cohorts.

Preliminary results indicate that higher cumulative consumption of SAAs would lead to higher risk of diabetes development in humans. These results, together with previous preclinical data, provide strong evidence for implementing a novel dietary approach for chronic disease prevention based on reduction of SAA intake.

Zhen Dong, Affiliated Assistant Scientist

Sulfur amino acids are an 'essential' dietary component, meaning the human body cannot make them. The Recommended Daily Allowance (the amount required for meeting the needs of 97%-98% of the population of healthy adults) is 19 mg/kg/day: 12.2 mg/kg/day for methionine and 6.6 mg/kg/day for cysteine. However, nationally representative studies in the US indicate that a majority of adults consume diets containing well in excess of this RDA. The finding that low-SAA diets are typically heavily reliant on plant-derived proteins suggests that SAA reduction may, in part, be responsible for health benefits associated with a plant-based diet.

In the future, Dr. Dong will continue exploring epidemiological associations between cumulative consumption of sulfur amino acids and risks of other chronic disease development, including cardiovascular diseases, neurodegenerative diseases, and others.

Table 1. Dietary SAA requirements and usual intake

Estimated Average Requirement	*15 mg/kg/day*
Recommended Dietary Allowance	*19 mg/kg/day*
Average American Intake	*40 mg/kg/day*

Dr. Norman Orentreich made major contributions to my early career in biogerontology. We were introduced in 1968 by Paul Glenn, a financier who had just established in 1965 the Glenn Foundation for Medical Research. Norman and Paul began to hold informal meetings in NYC, and heard of some grad student at Rockefeller University who was studying aging. I soon became a regular attendee of these stimulating meetings at OFAS, which often led to rollicking conversations at Patrissy's and other restaurants. I admired Norman's enormous curiosity and ability to uncover false assumptions and major gaps in thinking about aging. Norman and I began to meet privately after I received my Ph.D. in 1969, and he made me an astonishing suggestion to become an MD with his support and build a research institute together. Although I didn't see the need for an MD, Norman gave critical support to setting up my lab in 1970 at Cornell Medical College, my first academic job. Without OFAS's rental of a scintillation counter and ultracentrifuge, I couldn't have gotten key data needed to support my first grants from NSF and NIH. Aging was not a recognized field of legitimate research in 1970. Norman mentored me on how basic aging processes underlie age-related diseases manifested in skin and hair. Some of my colleagues wondered why I bothered to publish a study on aging and hair growth in the black mouse (*Journal of Gerontology*, 1973). After I left New York for USC in 1973, Norman and I continued to have long discussions as OFAS developed the methionine-restriction paradigm. I miss him deeply and am glad for the continued productivity of OFAS.

—Caleb E. Finch, Ph.D., ARCO/William F. Kieschnick Chair in the Neurobiology of Aging, University of Southern California School of Gerontology (OFAS Scientist, 1968-1973)

In 1995, I interviewed for a job with the *in vivo* group at OFAS. The approach to research at OFAS is one of complete collaboration. Our weekly meetings where we sat and discussed research with top doctors and scientists molded me into the scientist I am today. The passion to learn and find answers that Dr. O instilled in his team helps me every day as I develop and run my studies. I am eternally grateful for having had such a innovative and well-rounded introduction to scientific research. It was this experience that opened doors for me to be a key contributor to novel antibiotics and cancer treatments that are saving lives today.

—LuAnna J. Lemon, BS, Senior Associate Scientist, The Janssen Pharmaceutical Companies of Johnson & Johnson (OFAS Research Associate, 1995–2000)

Our involvement in research at OFAS, including work studying methionine restriction and aging, provided a strong foundation in our future healthcare career paths. After OFAS, we both returned to graduate school in Philadelphia; John earned an MS in Biomedical Engineering from Drexel and Meg a Masters in Physical Therapy from Hahnemann.

—John Kotes, MS, Technology Manager, GlaxoSmithKlein & Meg Randells Kotes, MS, Physical Therapist (OFAS Research Associates, 1991–1996)

During my 3-year tenure at OFAS, I learned the importance of putting the patient at the center of the scientific debate. I also learned that every question is worth considering as long as it raises a critical scientific issue, and OFAS was ready to invest in addressing it. The other valuable lesson I learned is that, no matter what position you had at OFAS, everyone was encouraged and expected to contribute to the scientific discussion, and their ideas were given the same level of consideration. This has really shaped my next career in the pharmaceutical industry and continues to guide my approach to every drug development program I am involved in, as well as my leadership style, encouraging my collaborators to think outside the box. Every time I am in a meeting I remind myself that I am not the smartest person in the room.

—Ed Tamer, Ph.D., Associate VP Nonclinical Development, Reata Pharmaceuticals (OFAS Director of Cell Culture Lab, 2002–2005)

I could not have had a better scientific foundation than what I received at OFAS. I also gained solid friendships to see me through my early years.

—George Hristopoulous, MS, Senior Scientist, Bioanalytics, Vir Biotechnology, Inc. (OFAS Research Associate, 2000–2007)

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.

This year, we hosted our first virtual symposium. Speakers discussed a range of topics, from *in vitro* studies to clinical interventions in humans. A short summary of their presented work appears on page 13. Recordings of most presentations and panel discussions are available on the OFAS website at www.orentreich.org/symposia/2021-symposium/videos/.

Invited Speakers

Alessandro Bitto, Ph.D.
University of Washington, Seattle, Wash.
Acarbose suppresses symptoms of mitochondrial disease in a mouse model of Leigh syndrome

Zhen Dong, Dr.P.H.
OFAS, Cold Spring, N.Y.
Cumulative consumption of sulfur amino acid intake and incidence of diabetes

Max Guo, Ph.D.
National Institute on Aging, NIH, Bethesda, Md.
Aging biology research supported by the National Institute on Aging

Cristal Hill, Ph.D.
Pennington Biomedical Research Center, Baton Rouge, La.
Linking brain FGF21 signaling to improvements in health and lifespan during dietary protein restriction

Jay E. Johnson, Ph.D.
OFAS, Cold Spring, N.Y.
Dietary supplementation with compounds that produce methionine restriction-like benefits, including inhibition of insulin/IGF-1 signaling and improved healthspan

Sailendra Nichenametla, Ph.D.
OFAS, Cold Spring, N.Y.
Discrete effects of methionine and cysteine on sulfur amino acid restriction-induced changes in adipose metabolism

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An evolving role for the long non-coding RNA H19 in aging and senescence

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Metabolic regulation of the senescence program through methionine restriction and mTOR inhibition

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Sulfur amino acids and metabolic outcomes: Preliminary data, challenges, and experiences from human clinical intervention studies

Highlights

Alessandro Bitto His study provides the first evidence that the microbiome may rescue severe mitochondrial disease and provides a proof of principle that biological aging and mitochondrial disorders are driven by common mechanisms.

Zhen Dong Higher long-term sulfur amino acid intake was associated with higher risk for Type 2 diabetes in humans, suggesting that dietary patterns with low sulfur amino acid intake are protective against its development.

Cristal Hill Collective data from her research demonstrate that FGF21 signaling in the brain is required for dietary protein restriction-induced improvements in metabolism and that FGF21 is required for dietary protein restriction to defend against age-related metabolic and physical impairment, and in turn, to extend lifespan.

Jay Johnson His findings reveal four novel dietary interventions that produce the same short-term healthspan benefits as methionine restriction, but in a methionine-replete context.

Sailendra Nichenametla His findings indicate that methionine restriction and cysteine restriction exert discrete effects on several sulfur amino acid restriction (SAAR) phenotypes, and that SAAR-induced changes in adipose metabolism are specifically due to cysteine restriction.

Thomas Olsen & Kathrine Vinknes Findings from their pilot studies indicate that it is feasible to design SAA-restricted diets for human consumption in a domestic setting and that some of the changes induced by SAA-restricted diets in animal models are also induced in humans. Preliminary data showed that intermediates in sulfur metabolism distal to methionine and cysteine differed between normal-weight and overweight individuals. In addition, short-term SAAR induced changes in several less commonly assayed sulfur analytes in plasma and urine.

Manali Potnis Results from her work indicate an essential role for the long non-coding RNA H19 in cell cycle progression, chromatin structure, and possibly proper mitotic cell division.

Christian Sell His team has identified specific metabolic changes in the cell that link fatty acid oxidation to one carbon metabolism and histone modifications. These changes provide a mechanism allowing metabolic regulation of cell fate decisions such as entry into senescence and cell differentiation.

Norman Orentreich Award for Young Investigator on Aging

OFAS presented the second Dr. Norman Orentreich Award for Young Investigator on Aging to Dr. Cristal Hill of the Pennington Biomedical Research Center (Baton Rouge, La.). The award was presented at the AGE 2021 Annual Hybrid Meeting Event, Madison, Wisc. With this award, we hope to inspire young investigators to continue aging research and to acknowledge the potential of their work. Dr. Hill investigates the role of fibroblast growth factor 21 on the regulation of nutrient selection, metabolism, and energy expenditure. She was selected for her presentation "Age-related neuroprotection by dietary restriction requires OXR1-mediated retromer function". In addition to the $1,000 prize, Cristal was invited to present at the 2021 OFAS Symposium on Healthy Aging.

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