Report of the Director 2020

OFAS

Orentreich Foundation for the Advancement of Science, Inc.

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

Dear Friends,

As with every other institution, OFAS's 2020 has been greatly affected by the COVID-19 pandemic. One-hundred percent compliance with State directives and CDC advice has enabled our laboratories to operate safely throughout the worst of the pandemic in our area.

In February, I appointed Jay Zimmerman, Ph.D., as our Deputy Director of Research. Dr. Zimmerman has a decades-long history with us, and we are pleased to have him assume this new position. Also, we are renovating a building in order to provide centrally-located offices for our senior staff.

Beyond our walls, however, the pandemic's effects have been more deeply felt. The International Symposium on Neurobiology and Neuroendocrinology of Aging in Bregenz, Austria, which we have long supported, was canceled due to the pandemic. Our own Symposium on Healthy Aging, originally scheduled to be held next year, has been converted to an online conference. We will return to our live format in 2022.

On behalf of the dedicated staff at OFAS, thank you for your continued support and faith in our mission. We wish you the best in 2021.

David S Orentreich, MD, FAAD
Director

Deputy Director of Research Appointed

Dr. David Orentreich invited long-time OFAS consultant Jay Zimmerman, Ph.D., to assume the new position of Deputy Director of Research, responsible for overseeing scientific activity at OFAS.

Dr. Zimmerman first met OFAS founder, Dr. Norman Orentreich, in 1979. Recognizing their common research goals, Dr. Zimmerman became a consultant to OFAS, helping guide Foundation research during the following forty-three years. Notably, Dr. Zimmerman was a co-author of OFAS's seminal paper "Low methionine ingestion by rats extends life span" (Orentreich et al, *J Nutrition* 123; 269 (1993)).

Jay Zimmerman, Deputy Director of Research

Dr. Zimmerman has had a long career in both scientific research and administration. He received his BA in Biology from Franklin & Marshall College, and his Ph.D. in Zoology (endocrinology) from Rutgers University. Following receipt of his Ph.D., he conducted advanced postdoctoral studies in aging at the Masonic Medical Research Laboratory in Utica, N.Y.

After his postdoctoral studies, Dr. Zimmerman joined the faculty at St. John's University in Queens, N.Y. During his forty-five year career there he conducted studies of cardiac metabolism in aging, age dependent carcinogenesis, and lifespan extension by dietary manipulation. During this time, he managed over twelve million dollars in federal research and training grants, served as chairman of the Department of Biological Sciences for twelve years, and received awards as the "Best Graduate Teacher" (1998) and "Most Outstanding Researcher" (2002).

Scientific Advisory Board

We are pleased to announce the 2021 Scientific Advisory Board:

Jay A. Zimmerman, PhD, Deputy Director of Research, OFAS (Chair)

Herbert Burack, RPh, Pharmacist, Orentreich Medical Group

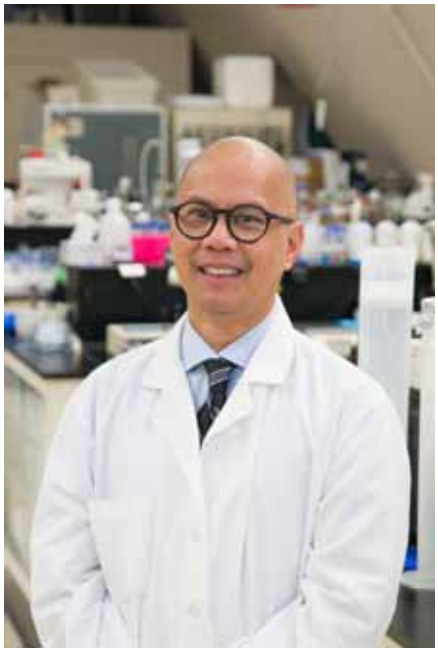
Arthur J.L. Cooper, PhD, Professor of Biochemistry and Molecular Biology, New York Medical College

Mark Horowitz, PhD, Professor of Orthopaedics and Rehabilitation; Vice Chair for Research Education & Training, Yale University School of Medicine

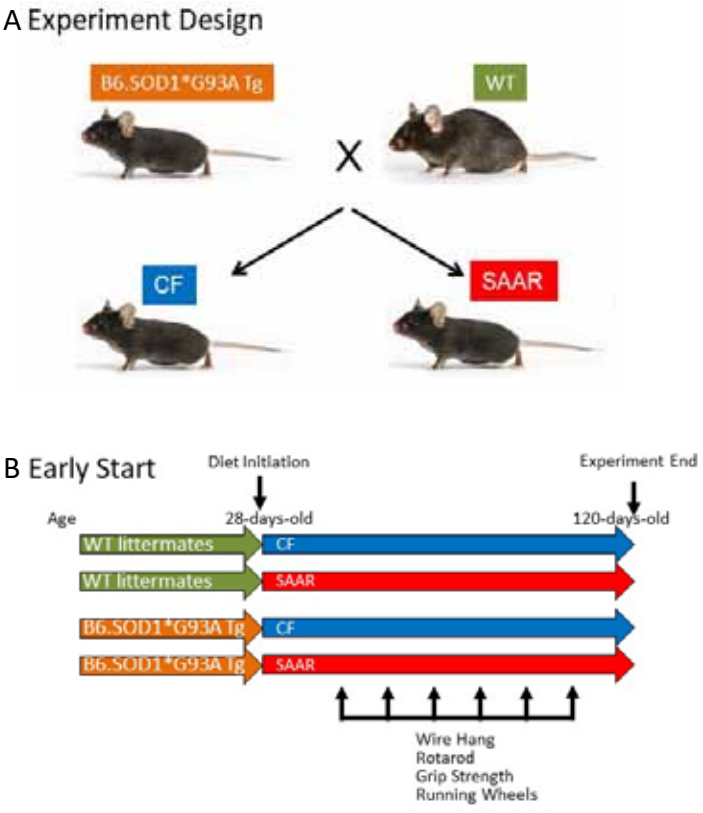
John P. Richie, PhD, Professor of Public Health Sciences & Pharmacology, Penn State University College of Medicine

Sulfur Amino Acid Restriction (SAAR) in Lou Gehrig's Disease

Dr. Ables continues to investigate the effects of sulfur amino acid restriction (SAAR) on neurodegenerative diseases using a mouse model for amyotrophic lateral sclerosis amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease. ALS is a progressive and fatal neuromuscular disease characterized by neuroinflammation progressing to neurodegeneration. No cure for ALS has yet been identified, and there is a dearth of proven useful therapeutic interventions. One of the causes of neuronal death in ALS is oxidative damage, something SAAR in rodents has shown to beneficially effect. However, the effect of SAAR on neurological systems using a mouse disease model such as ALS has not yet been examined. To investigate this, Dr. Ables's lab is conducting experiments on transgenic mice transfected with the ALS-associated G93A human superoxide dismutase 1 mutation, SOD1-G93A. They are in the process of analyzing data on the mechanisms by which SAAR effects the onset of disease, measured by various strength and agility tests. They are also analyzing whether SAAR suppresses disease progression by attenuation of inflammation and oxidative stress markers in neurons and muscle cells. Characterization of the effects of SAAR in SOD1-G93A mice is the first step that will direct future investigations of how SAAR may affect other neurological diseases.



Gene Ables, Associate Science Director



Experimental design for SAAR in SOD1 G93A mice. ***A.*** *B6.SOD1*G93A transgenic mice will be bred to wild type (WT) C57BL/6J mice. Transgenic and WT littermates will be fed either a control (CF) or a sulfur amino acid restricted (SAAR) diet.* ***B.*** *To test for disease progression, mice will be fed the diets before disease onset beginning at 28 days old while we study wire hang, rotarod, grip strength, and running wheel performance until 120 days of age.* ***C.*** *To test for attenuation of disease symptoms, mice will be fed the diets from 120 days old to 150 days old.*

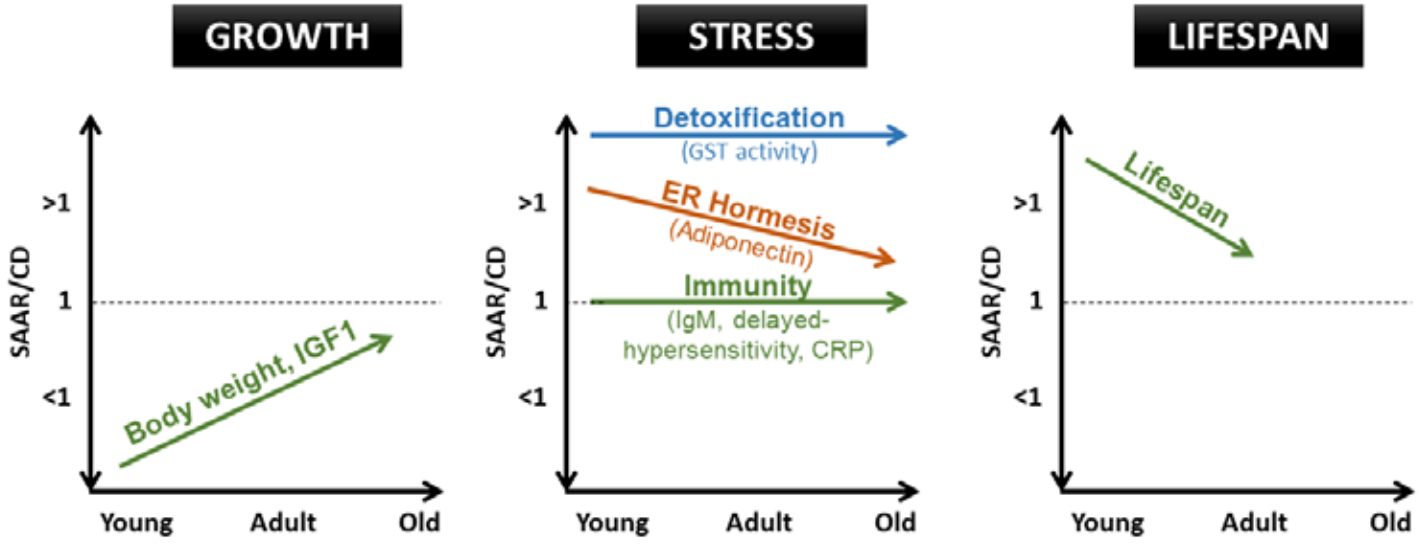
Age of Initiation of Sulfur Amino Acid Restriction (SAAR)

Dr. Nichenmetla's work addresses translating SAAR from the lab model to daily life in humans. An important challenge in translating SAAR from animal models is that while beginning SAAR in young animals in research models shows reduction in various undesirable effects and increases lifespan, it is accompanied by reduced growth rates in young animals fed such a diet. This is undesirable in human children. Thus Dr. Nichenametla's lab is looking at SAAR when begun in post-growth phases, *i.e.*, among adults.

Nath Nichenametla, Senior Scientist

Dr. Nichenametla's lab fed SAAR diets to young, adult, and old rats. When challenged with stressors, regardless of the age of onset, SAAR did not compromise the animals' ability to mount an immune response, and it enhanced detoxification capacity (measured by activity level of GST, an enzyme which inactivates endogenous toxins).

The later the diet began, the less ability that SAAR had to decrease body weight and extend lifespan; however, the the ability of SAAR to increase detoxification capacity was independent of age at initiation. Dr. Nichenametla's studies suggest that the benefits of SAAR—enhanced detoxification in response to stress—can be obtained even by beginning the diet later in life. His group will continue to study the effect of SAAR in environments different from the standard lab model and closer to real-world examples.



Trade-offs between the life-history traits, growth, stress responses, and lifespan in sulfur amino acid restriction (SAAR). SAAR-induced lifespan extension trade-offs with growth but not stress responses. Note: Young, adult, and old represent onset of the intervention in 2-month-old, 10-month-old, and 20-month-old male F344 rats, respectively. SAAR—sulfur amino acid-restricted diet (0.17% methionine without cysteine), CD—control diet (0.86% methionine without cysteine). Reprinted from Aging Cell *19: e13177, 2020.*

Intermittent Methionine Restriction (MR) Prevents Obesity in Mice

The dual aims of Dr. Johnson's research are characterizing the cellular mechanisms underlying the benefits of methionine restriction (MR), and identification of novel MR-interventions that improve healthspan. Because many of the mechanisms that regulate mammalian longevity were first identified as mechanisms that promote longevity in yeast, Dr. Johnson's group uses yeast models as well as mammalian cells and laboratory mice in his multifaceted approach.

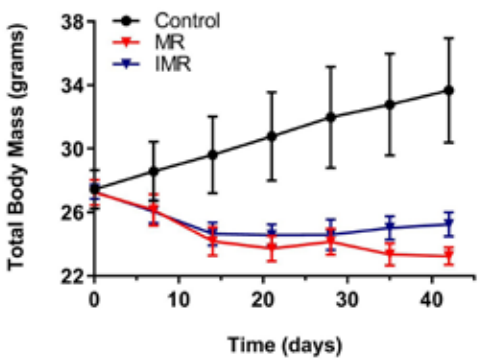
In two published studies, Dr. Johnson demonstrated that regardless of how methionine was restricted—dietary MR, genetic MR (*i.e.*, impairment of the cell's methionine biosynthetic machinery), or enzymatic MR (*i.e.*, enzymatic depletion of intracellular methionine)—restricting methionine significantly extended the lifespan of a yeast model; see Johnson and Johnson, "Methionine restriction activates the retrograde response and confers both stress tolerance and lifespan extension to yeast, mouse, and human cells." *PLoS One* 9: e97729 (2014) and Plummer and Johnson, "Extension of cellular lifespan by methionine restriction involves alterations in central carbon metabolism and is mitophagy-dependent." *Frontiers in Cell & Developmental Biology* 7: 301 (2019).

Jay Johnson, Senior Scientist

In addressing why MR causes increased lifespan, Dr. Johnson's group found that mitophagy, a process whereby damaged mitochondria are digested and recycled by a cell, is indispensable for the benefits of MR to yeast. In yeast cells fed an MR diet, damaged mitochondria continue to be successfully recycled. Without MR, this housecleaning process of removing damaged mitochondria decreased with age. This is a significant alteration from the metabolism of untreated cells.

The Johnson lab also produced two novel interventions that confer MR-like benefits to yeast: (1) supplementation with a selenium source, and (2) treatment with various methionine-like amino acids. Dr. Johnson tested both these interventions in mouse models and found that, like MR, they protect against diet-induced obesity. Usefully, these interventions are able to offset obesity in the context of a normal, methionine-replete diet.

Along with these two additive interventions, Dr. Johnson is studying an intermittent variant of dietary MR. Current results show intermittent MR (IMR) is just as effective as continuous MR in protecting mice against diet-induced obesity (see figure). Further studies by Dr. Johnson are aimed at understanding the mechanistic basis of these three novel interventions, and assessing to what extent they reduce the rate of aging 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-methionine diet (IMR) is just as effective as continuous MR in protecting against diet-induced obesity.

Current Research

Sulfur Amino Acid Consumption in Humans

In the past year, Dr. Dong researched and investigated the association between consumption of sulfur amino acids (SAAs) and chronic diseases, especially diabetes, in humans.

The beneficial impacts of SAA-restricted (SAAR) diets have been researched since the 1993 publication of OFAS's groundbreaking paper describing the lifespan-extending effects of a low-methionine diet. However, in the United States, the average person consumes SAAs at levels far in excess of the Estimated Average Requirement of 15 mg/kg/day. Animal studies have suggested that consumption of diets that are high in SAAs may result in negative health outcomes, including potential increased risk for cardiovascular, brain, and liver diseases. Favorable effects of SAAR in animal models include healthy lifespan extension, reduction in body weight and adiposity, reduced insulin resistance, and positive changes in blood biomarkers including insulin, glucose, leptin, and adiponectin. However, data on the possible associations between intake of SAA and health outcomes in humans are limited. Therefore, Dr. Dong, working with Dr. Ables and OFAS consultant Dr. John Richie (Pennsylvania State University), is developing a protocol to examine if there is an association between consumption of SAA and human health status using data from the Framingham Heart Study Cohort.

Zhen Dong, Scientist

Dr. Dong's research addresses three different diseases known to be affected by SAAR in animal models: diabetes, heart disease, and cancer. She will assess over time the reported intake of SAA versus diabetes morbidity rates, and any changes in relevant biomarkers; reported intake of SAA versus heart disease mortality and morbidity rates and changes in relevant biomarkers; and reported intake of SAA with cancer mortality and morbidity rates and changes in relevant biomarkers.

To better understand the multiple and varied epidemiological effects, Dr. Dong has been working with several experts including Drs. Xiang Gao and Raghu Sinha (Pennsylvania State University, Hershey, Pa.).

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 2021, we will host our first virtual symposium. We will return to our live format in 2022.

Publications & Presentations

Nichenametla SN, Mattocks DAL, Midya V, Shneyder J. Differential effects of sulfur amino acid-restricted and low-calorie diets on gut microbiome profile and bile acid composition in male C57BL6/J mice. *Journal of Gerontology: Biological Sciences*, in press.

Nichenametla SN, Mattocks DAL, Malloy VL. Age-at-onset-dependent effects of sulfur amino acid restriction on markers of growth and stress in male F344 rats. *Aging Cell*, 2020: 19: e13177.

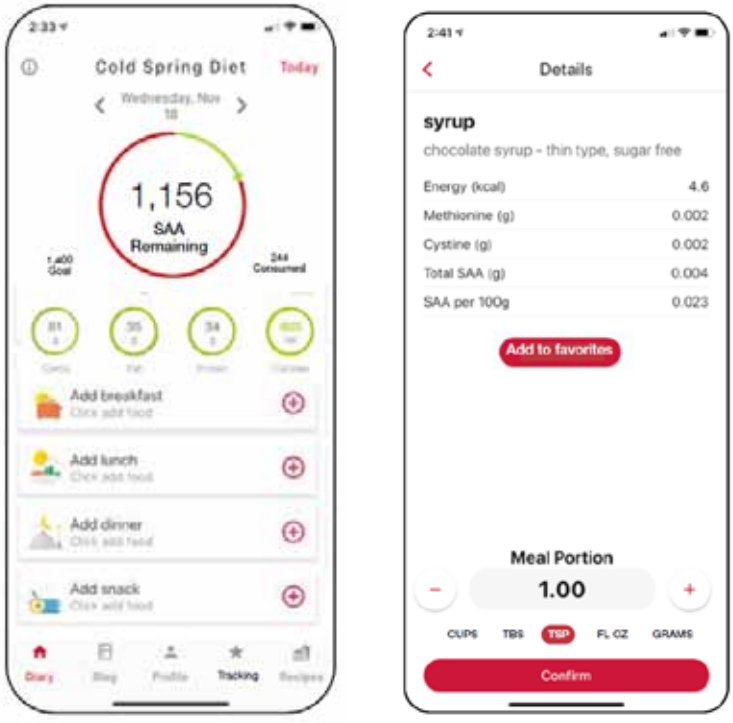
Cooke D, Mattocks DAL, Nichenametla SN, Anunciado-Koza RP, Koza RA, Ables GP. Weight loss and concomitant adipose autophagy in methionine-restricted obese mice is not dependent on adiponectin or FGF21. *Obesity*, 2020: 28: 1075-1085.

Komninou D, Malloy VL, Zimmerman JA, Sinha R, Richie JP. Methionine restriction delays aging-related urogenital diseases in male Fischer 344 rats. *GeroScience*, 2020: 42: 287-297.

Dong Z, Gao X, Chinchilli VM, Sinha R, Muscat J, Winkels RM, Richie JP. Association of sulfur amino acid consumption with cardiometabolic risk factors: Cross-sectional findings from NHANES III. *EClinicalMedicine*, 2020: 19: 100248.

Ables GP. The benefits of a sulfur amino acid-restricted diet. Annual Philippine-American Academy of Science and Engineering (PAASE) Meeting, August 2020 (virtual).

Sulfur Amino Acid Restriction App



The app helps users to search for foods, examine sulfur amino acid (SAA) content, and track their SAA intake.

Given the potentially beneficial clinical implications of sulfur amino acid restriction (SAAR) in humans, there likely will be significant public interest in this dietary intervention. To address this need for information and dietary tools designed for the lay public, we are designing an app aimed at tracking SAA consumption and providing up-to-date, evidence-based information on SAAR for users. The app's nutrients database is currently being upgraded.

Information for Donors

The Orentreich Foundation for the Advancement of Science, Inc., is a 501(c)(3) non-profit corporation (EIN 13-6154215) duly registered with the United States Internal Revenue Service as an Operating Private Foundation under Section 4942(j)(3).

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Orentreich Foundation for the Advancement of Science, Inc.
910 Fifth Avenue, New York, NY 10021
Research Laboratories: 855 Route 301, Cold Spring-on-Hudson, NY 10516

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