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:

In 2025, scientists at the Orentreich Foundation for the Advancement of Science (OFAS) continued to make significant progress toward fulfilling our founder Norman Orentreich's objective: to delay or prevent the onset of age-related decline, rather than solely focusing on treating diseases after they appear. Our research concentrates on expanding our understanding of our groundbreaking discovery that reducing sulfur amino acid consumption (SAAR) extends lifespan and healthspan in animal models, suggesting a comparable benefit in human populations.

Adhering to a continuous SAAR diet (cSAAR) presents significant challenges for humans. Even the most beneficial diet becomes ineffective if its maintenance is overly burdensome. Therefore, we explored alternative approaches that emulate the effects of cSAAR without the daily commitment to the SAAR diet. One such option is intermittent SAAR (iSAAR) which holds great promise for its ease of adherence compared to cSAAR. In an intermittent version, dietary restriction is implemented only three days per week, resulting in comparable benefits in animals and, we anticipate, in human populations. Our scientists have also been exploring dietary supplements which can mimic the benefits of SAAR diets. These mimetic agents hold promise for those who might have difficulty following a SAAR diet.

For several years, OFAS has sponsored biennial symposia that bring together leading scientists to engage in discussions on the intricate interplay between dietary factors, metabolic health, and the aging process. In 2025, we deviated from our traditional format by hosting a retreat where our scientists engaged in informal interactions with active and recent collaborators. This relaxed atmosphere generated novel ideas for future collaborative endeavors.

This very active year at OFAS would not have been possible without your continued support and faith in our mission. We are sincerely grateful for your continued support.

David S. Orentreich, MD, FAAD
CEO

Science Retreat

This year, OFAS hosted a novel retreat that brought together our scientific collaborators from around the country with our entire research staff. The rustic setting at the Edith Macy Conference Center (Briarcliff Manor, NY) provided the backdrop for informal discussions of current shared research and ideas for new avenues of investigation.

The intimate atmosphere allowed us to examine the possible future of SAAR and related interventions, as well as the opportunity to engage in team building experiences. Finally, we presented a beta version of a smartphone app designed to guide those who wish to follow an iSAAR diet.

A list of the presentations delivered at the retreat appears opposite.

Front Row, L-R: Gene Ables, Diana Cooke, Annaminh Mansour, David Orentreich, Dwight Mattocks. Second Row, L-R: Virginia Malloy, Itsaso Garcia-Arcos, Jay Zimmerman. Third Row, L-R: Mark Horowitz, Shyni Leela, Matthew Yousefzadeh. Fourth Row, L-R: Nath Nichenametla, Andrey Parkhitko, Brad Johnson, Tracy Anthony, Jason Plummer, Neal Fedarko, Derek Huffman, Chris Hine, Michael MacArthur, Jay Johnson.

Science Retreat

Pulmonary lipid metabolism in health, disease, and aging. **Itsaso Garcia-Arcos, Ph.D.**, Department of Medicine, SUNY Downstate Health Sciences University

Targeting age-related metabolic dysfunction to extend healthspan. **Andrey A. Parkhitko, Ph.D.**, Aging Institute, University of Pittsburgh

The role of immune cells in driving systemic aging. **Matthew Yousefzadeh, Ph.D.**, Columbia Center for Translational Immunology, Vagelos College of Physicians & Surgeons

R-loop mediated neurodegeneration in ALS4. **Shyni Gangadharan Leela, Ph.D.**, OFAS

Can we target GNMT to delay aging? **Derek M. Huffman, Ph.D.**, Institute for Aging Research, Albert Einstein College of Medicine

Growing research & investigators in uncertain times. **Neal S. Fedarko, Ph.D.**, Johns Hopkins School of Medicine

Mechanisms of metabolic homeostasis in young and aged mice. **Michael R. MacArthur, Ph.D.**, Lewis-Sigler Institute for Integrative Genomics, Princeton University

Amino acid insufficiency and circadian rhythms in metabolism. **Tracy G. Anthony, Ph.D.**, Department of Nutrition, Rutgers University

Sulfide metabolism as a central target for longevity and tumor suppression. **Christopher Hine, Ph.D.**, Cleveland Clinic Lerner Research Institute

New Staff

Shyni Gangadharan Leela joined OFAS as a postdoctoral associate in the Nichenametla Lab. Dr. Leela received her Ph.D. in biochemistry from the Faculty of Science of the University of Kerala (Kerala, India). Her doctoral thesis examined the anti-inflammatory effect of Jeevaneeya Rasayana (an herbal ayurvedic formulation) on experimentally induced rheumatoid arthritis. After completing her Ph.D., she worked as a Postdoctoral Fellow and Young Scientist at the CSIR–National Institute for Interdisciplinary Science and Technology (NIIST) in Trivandrum, Kerala, India, focusing on metabolic disorders.

Most recently, Dr. Leela was a postdoctoral research associate at the University of Missouri (Columbia, Mo.), where her research focused on molecular mechanisms of neurodegeneration.

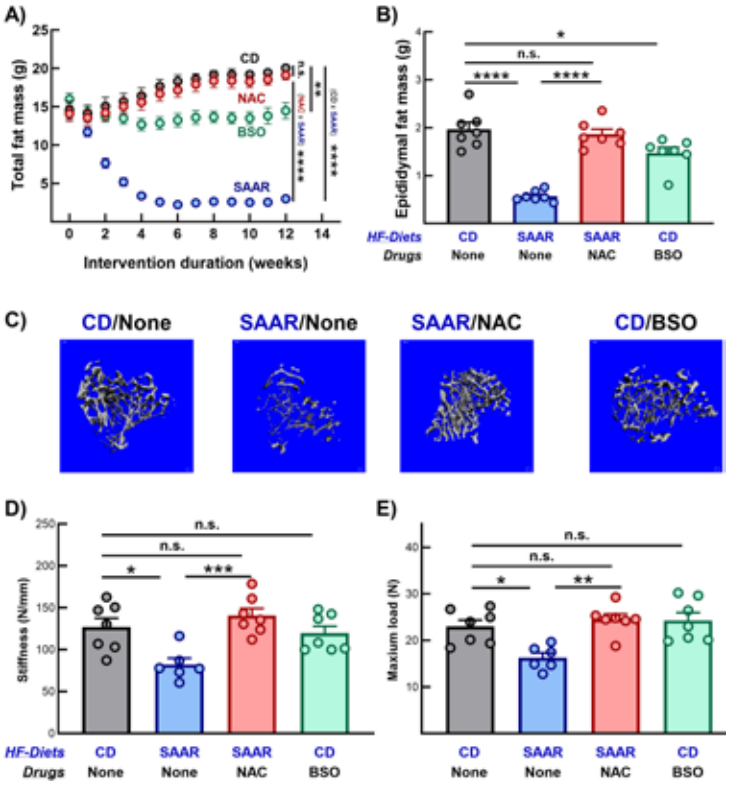
Nichenametla Laboratory

Discovery Points to a Simpler Path toward Combating Obesity and Diabetes

Dr. Nichenametla, along with Dwight Mattocks and Dr. Naidu Ommi, are pursuing the means to obtain the benefits of a SAAR diet without the difficulty of actual restrictions. Their research is opening a novel avenue for addressing obesity and diabetes—two conditions that affect millions of lives every year.

Amino acids are the building blocks of protein, and scientists have known for years that limiting specific dietary amino acids—sulfur-containing methionine and cysteine—can improve metabolic health and extend lifespan in animals. This approach helps laboratory animals stay lean, maintain stable blood sugar, and resist age-related diseases.

Dr. Nichenametla's group has turned its attention to a compound called DL-buthionine-(S, R)-sulfoximine, or BSO. This compound lowers the level of a cellular molecule called glutathione, which is also lowered when animals follow a SAAR diet. This led to asking the question: can BSO mimic the beneficial effects of an iSAAR diet?



In laboratory studies, mice feeding on a high-fat diet and treated with BSO avoided fat accumulation, had healthier livers, and maintained better blood sugar control.

Sailendra Nichenametla, Ph.D.
Senior Scientist

In a separate study, researchers tested BSO in a mouse model of a genetic form of diabetes characterized by an insulin synthesis defect. BSO treatment significantly decreased blood sugar levels and improved glucose control.

Thus far, the experiments have been conducted in male mice. The next phase will test BSO in female mice and determine the dosage that achieves comparable benefits.

If successful, this research could transform how the most common metabolic diseases are managed, making it possible to deliver the benefits of a complicated diet through a practical, science-based solution.

Figure 1. BSO prevents weight gain in obese mice on a high-fat diet without affecting the bone mineral density and bone strength.

BSO prevents weight gain in obese mice on a high-fat diet without affecting the bone mineral density and bone strength. Four groups of 18-week-old male mice (n=7/group) were fed high-fat (60% Kcal from fat) diets with either normal (CD) or low (SAAR) levels of sulfur amino acids, a combination of the SAAR diet with a glutathione precursor added in water (N-acetylcysteine, NAC), or a combination of the CD diet with a glutathione biosynthetic inhibitor added in water (DL-buthionine (S, R) sulfoximine, BSO). Compared to the CD, the BSO prevented overall weight gain (A) and decreased epididymal fat depots (B and C) without decreasing bone mineral density (D) or bone strength (E). The cSAAR diet, despite being better than BSO in decreasing total body fat (A) and epididymal fat (B and C), decreased bone stiffness (D) and bone strength (E). The detrimental effect was not seen in the BSO group.

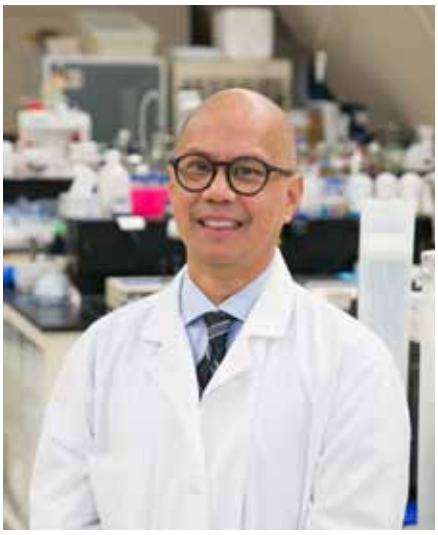
Parkinson's Disease

Using mice carrying a human gene mutation associated with Parkinson's disease, Dr. Ables and his associate, Diana Cooke, conducted a preliminary study to elucidate how SAAR affects the progression of neurodegenerative symptoms and brain pathology associated with Parkinson's disease. No significant differences in neurological symptoms were observed between the SAAR and control groups (both groups have the mutation), and there was some indication of altered gastrointestinal responses in the SAAR group. These findings suggest that SAAR may influence certain prodromal and non-motor features associated with Parkinson's disease.

Thyroid Hormone Signaling

Dr. Ables' Lab has initiated a two-year study on the metabolic effects of SAAR on thyroid hormone signaling. Deiodinase 2 (DIO2) is the gene that codes for an enzyme crucial for converting inactive thyroid hormone, T4, into its active form, T3. Hypothesizing that DIO2 is critical for metabolic processes during SAAR, the Lab is using DIO2-deficient mice in an attempt to clarify the DIO2's role in SAAR's benefits, particularly in brown adipose tissue thermogenesis, hepatic lipid metabolism, and skeletal muscle mitochondrial function. BAT thermogenesis is the process by which the body burns stored fat to regulate temperature and may instigate weight loss. Hepatic lipid metabolism is the process by which the liver breaks down dietary fats and converts them into energy or stores the excess for later use. Skeletal muscle mitochondrial function relates to how well the muscle cells produce energy for muscle function.

We expect this study to provide insights into how thyroid hormone metabolism interacts with SAAR. (Mice for this study were kindly donated by Dr. Arturo Hernandez's lab at MaineHealth Research Institute, Scarborough, Me.)



Gene Ables, Ph.D.
Associate Research Scientist

Collaborative Studies

Building on their 2024 study with Drs. Mark Horowitz, Basav Ganganna, and Doug Rothman (Yale University), evaluating Dr. Ables's study of the suitability of high-resolution MRI for measuring adipocyte depots in mice (Figure 2), the Ables Lab is now investigating how SAAR influences brain activity and immune cell composition. This should provide a better understanding of SAAR's effects on neural function and immune modulation. Additionally, they are continuing their collaboration with Dr. Andrey Parkhitko (University of Pittsburgh) to explore the broader metabolic and physiological impacts of SAAR. These joint efforts are helping to expand our understanding of how SAAR affects both the central nervous system and metabolic health.

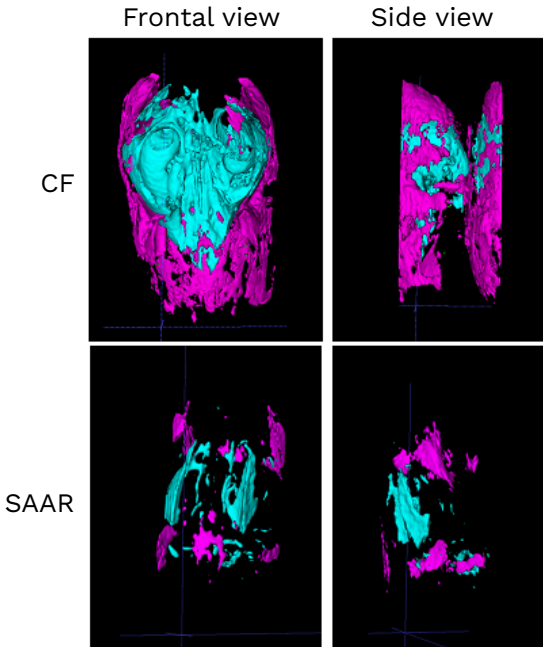


Figure 2. Regional fat distribution in SAAR and control-fed mice.

The scans show regional fat distribution in male C57BL/6J mice fed either a high-fat control (CF, top panels) or sulfur amino acid restricted (SAAR, bottom panels) diet. Blue indicates abdominal fat; pink represents subcutaneous fat. The 3D MRI provides a detailed visualization of fat deposition across different body regions in these mice. *High-resolution magnetic resonance imaging (MRI) was performed at the Yale University Magnetic Resonance Research Center in collaboration with Drs. Horowitz, Ganganna, and Rothman.*

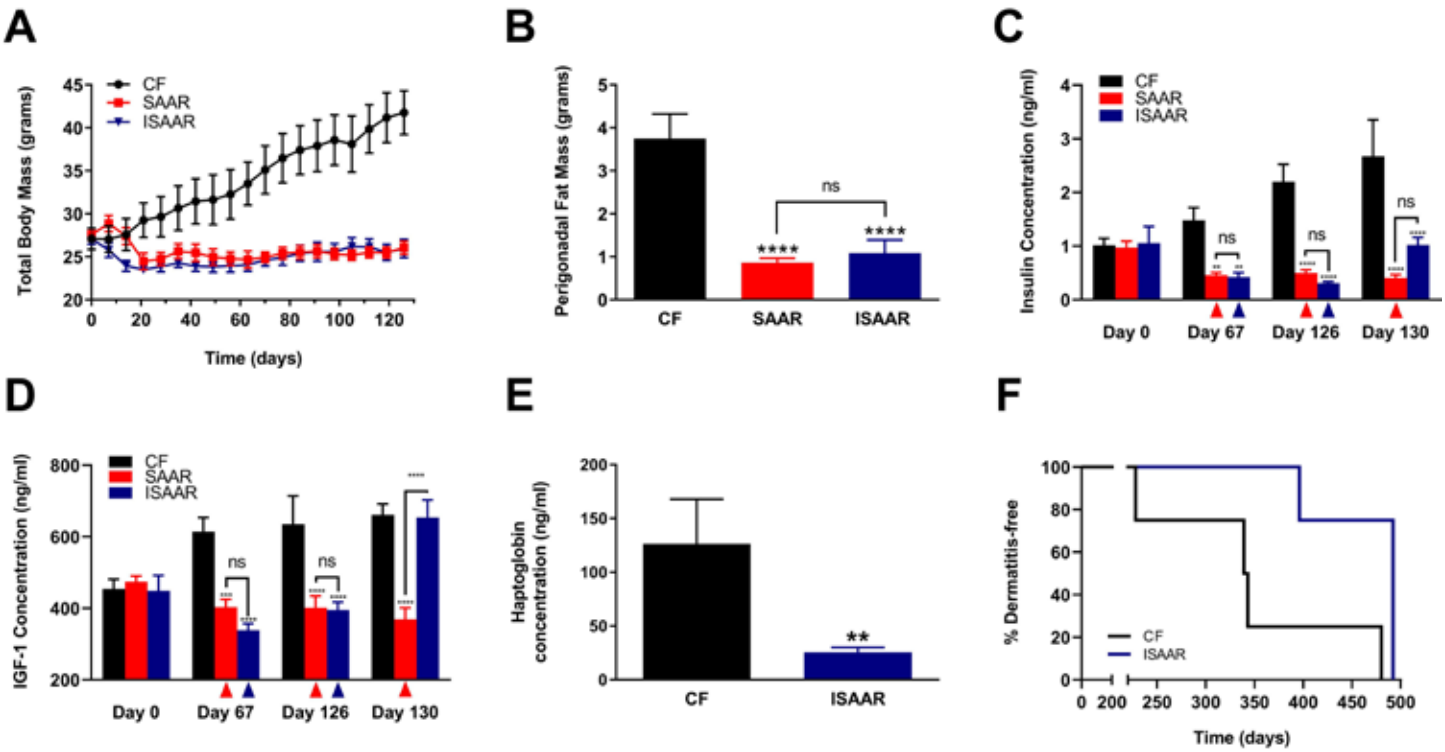
Johnson Laboratory

It is now well-known that a sustained state of SAAR produces multiple metabolic health benefits and extends the healthy lifespan of several model organisms, including rodents (Ables & Johnson, 2017 *Exp Gerontol* 94:83). For example, continuously SAA-restricted rats have less age-related pathology and are up to 45% longer-lived than their control-fed counterparts. Even though SAAR is feasible for humans, long-term adherence to such a diet is likely to be extremely challenging for many individuals. Another obstacle to the successful translation of this intervention to humans is the fact that several deleterious effects of cSAAR have been reported for both rodents and humans. These include the loss of musculoskeletal mass, increased bone marrow adipogenesis, and an increased incidence of bone fractures.

To address these issues, the Johnson Lab previously developed three novel dietary interventions that produce similar health benefits to cSAAR, yet are more practicable and free of deleterious side effects. The first is characterized by supplementation of an otherwise normal diet with selenium (Plummer et al., 2021 *ELife*

Jay Johnson, Ph.D.
Associate Research Scientist

Figure 3. The manifold health benefits of intermittent SAAR



(A) Comparisons over time of the average values of total body mass are shown for control-fed (CF; black circles) and continuously SAA-restricted (SAAR; red squares) female mice, as well as animals subjected to intermittent SAAR (ISAAR; blue triangles). (B) Average values at the conclusion of the experiment (~18 weeks on diet) for the mass of perigonadal fat pads surgically resected from the above animals. Longitudinal comparisons are given for the average blood concentrations of (C) insulin and (D) IGF-1 for animals undergoing the various dietary regimens. Colored triangles denote that sampling occurred following a period of SAAR. Also shown are (E) the average plasma levels of the inflammatory marker haptoglobin after 33 weeks on diet, as well as (F) the incidence of dermatitis for animals that were maintained on the control diet or intermittently SAA-restricted. For panels A-E, error bars represent standard error of the mean. For panels B-E, statistically significant differences are either indicated (**, p<0.01; ***, p<0.001; ****, p<0.0001) or absent (ns).

10:e62483). The second is an intermittent form of SAAR that requires only three days of reduced SAA intake per week (Plummer & Johnson, 2022 *Aging Cell* 21(6):e13629). The third intervention involves providing pyruvate to animals for four days per week.

The Johnson Lab has demonstrated that all three interventions protect against diet-induced obesity, maintain normal glucose metabolism (despite the challenge of an unhealthy diet), and produce beneficial changes in the levels of hormones involved in nutrient signaling and the regulation of longevity. Further, all three interventions prevent chronic inflammation, as well as the development of an inflammation-associated skin condition known as ulcerative dermatitis; (Plummer & Johnson, 2025 *J Inflamm* 22(1):24). Examples of such benefits are shown for iSAAR in Figure 3.

Given these effects, it is likely that one or more of these interventions may extend not only the healthy period of an animal's life (i.e., its healthspan), but also its overall survival. To test this hypothesis, the Johnson Lab has recently initiated a large-scale survival study aimed at determining whether iSAAR or intermittent pyruvate supplementation can extend mouse lifespan. Should this prove to be the case, it is Dr. Johnson's hope that some (if not all) of these exciting new interventions might eventually be translated to humans in order to both improve public health and reduce the burden of age-related disease.

Publications

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