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COMMENTARY



# A half-century history of aging research in San Antonio

Lisa C. Flores[a, #], Ganga Tandukar[a, #], Colton Allen[a], Yuji Ikeno[a, b, *]

[a] *Barshop Institute for Longevity and Aging Studies, San Antonio, TX, USA.*
[b] *Department of Pathology and Laboratory Medicine, The University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, USA.*

## Abstract

Since the biology of aging program started in 1975, the aging research group/Barshop Institute in San Antonio has been one of the front runners of aging research. Over the last half-century, aging research has rapidly advanced through examining the aging pathobiology and anti-aging effects of calorie restriction, genetic and pharmacological interventions, and translational and clinical studies. These developments and evolution of aging research are entering a new frontier aimed to uncover the complexity of aging processes and discover the anti-aging (preventive and/or therapeutic) measures for humans using cutting-edge technologies (multi-omics approaches and artificial intelligence/computational biology analyses).

The San Antonio aging research group and the Barshop Institute will continue to serve as one of the premier institutes for aging research under the strong leadership of the former and current directors to carry on Dr. Edward Masoro's legacy.

**Keywords:** Calorie restriction, genetic intervention, pharmacological intervention, translational research, aging

## Aging research in San Antonio—Barshop Institute for Longevity and Aging Studies

Aging research in San Antonio marked a half-century milestone in 2025 since Dr. Edward Masoro started the biology of aging program in 1975 after receiving the first funding support from the National Institute of Aging (NIA). Over the last 50 years, aging research has rapidly advanced by testing various theories of aging utilizing different intervention strategies, advanced technologies, and multiple experimental models and species, including humans.

Because of the growth of the aging research group and advancing scientific developments, the infrastructure supporting aging research has rapidly expanded. Until the mid-1990s, most members of the aging research group held academic appointments in the Department of Physiology at the University of Texas Health Science Center at San Antonio (UTHSCSA), where Dr. Masoro served as a Chairman, with a few members from other departments. Although aging research had been rapidly growing since mid-1970s in many universities, there was no department or institute dedicated exclusively for the research of aging. Dr. Masoro established the Aging Research and Education Center (AREC) after he stepped down from the Chairman's position in the mid-1990s to form a closely connected group of aging researchers and foster young scientists into the research of aging. In the mid-2000s, the seeds sowed began to grow and eventually blossomed. The heroic efforts by Dr. Arlan Richardson and the generous financial support by Mr. Sam Barshop and Mrs. Ann Barshop allowed us to build a research institute exclusively focused on the research of aging, *i.e.*, Sam and Ann Barshop Institute for Longevity and Aging Studies (Barshop Institute). The Barshop Institute is a very unique research facility where the investigators with various expertise and a broad spectrum of backgrounds (from basic scientists to physician/clinical researchers) physically work together in the same building, which allowed us to develop cohesive bonds and promoted active scientific interactions among the researchers.

Our aging research group/the Barshop Institute has continued to be one of the premier institutes for aging research because of the broad spectrum of research, rich academic

# Equal contribution for both authors
* Corresponding author: Yuji Ikeno
Mailing address: Barshop Institute for Longevity and Aging Studies and Department of Pathology, The University of Texas Health Science Center at San Antonio, 4939 Charles Katz Drive, San Antonio, TX 78229, USA.
Email: ikeno@uthscsa.edu
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environment, and strong leadership by the former and current directors.

## Birth and development of aging research—calorie restriction with Fischer 344 rats

Aging research in San Antonio was started by the former Chair of Department of Physiology, Dr. Masoro. After he accepted the Chairman's position in 1973, he attended a workshop on aging and learned that reduced food intake not only makes rats live longer, but also have less age-related diseases than *ad libitum* (AL) fed rats. This marked a turning point in his research, which led him to test the anti-aging effects of calorie restriction (CR) and seek the underlying mechanisms. The biology of aging program started after receiving funding support from the National Institute of Aging in 1975, which has further developed and evolved covering a broad spectrum of aging biology over the last 50 years [1].

A series of experiments to examine the pathophysiological changes of aging and the effects of CR were conducted by feeding Fischer 344 (F344) rats 40% less compared to the food intake of their control group fed AL. These experiments were conducted using a strict feeding protocol, precise calorie calculation and restriction, and ideal housing conditions for the aging studies developed by Dr. Masoro and his team: a) a semisynthetic diet that included the ingredients obtained from a defined macronutrient source; b) the CR diet was supplemented with vitamins and minerals for the CR animals to consume the same amount of vitamins and minerals as the AL control group (Masoro diet); c) animals were singly housed to accurately measure the amount of food consumption; and d) all rats were housed in a barrier facility with a strict protocol for sterilization. This established protocol and unique barrier facility allowed the investigators to obtain accurate data to seek the underlying mechanisms of aging and benefits of CR.

Over the next 20 years, the effects of CR have been examined: a) the magnitude of lifespan extension, attenuation of pathophysiological changes during aging, and its reproducibility of the 40% CR study; b) whether beneficial effects of CR were mainly due to restricting growth by comparing three survival groups: i) CR only during the period of rapid growth (6 weeks to 6 months); ii) CR started from near full growth (6 months) throughout the rest of life; and iii) CR started from after weaning (6 weeks) throughout the rest of life; c) whether restriction of protein only without CR was the contributing factor to the life-extending effects; d) if aging and age-related diseases could be changed by two protein sources (casein versus soy protein); e) the impact of other macronutrients on longevity by reducing fat or the mineral component to 60% of the control diet without changes in calorie; f) whether the changes in circadian rhythms by different feeding patterns could be one of the important factors to the extended longevity by CR; g) the effects of changes in energy expenditure by CR and/or voluntary exercise; and h) the effects of 10% CR on aging and age-related diseases (please see the detailed results in the references [2-11]). In addition to the effects of CR, our group has tested the potential benefits of natural compounds (Aloe Vera extracts: [12]) and hormones (melatonin) on age-related pathophysiological changes in F344 rats.

## Genetic and pharmacological interventions

The accumulation of the data and knowledge obtained during 20+ years of aging research with F344 rats and CR allowed us to uncover the underlying mechanisms involved in the aging process and the anti-aging effects by CR. Some of the notable potential mechanisms are: a) reduced GH/IGF-1 actions; b) enhanced insulin sensitivity and signaling; c) reduced oxidative stress and maintained cellular redox state; d) enhanced DNA repair; e) suppressed mTOR signaling pathway; f) enhanced hormesis; and g) reduced senescent cell accumulation, *etc*. Each of these possible underlying mechanisms of aging and the effects of CR requires identifying the approach that can target specific pathways involved in each potential mechanism. Because CR could affect various pathways simultaneously, it becomes more difficult to identify the "key pathways." In the mid-1990s, Dr. Arlan Richardson, the successor of Dr. Masoro as a director of the biology of aging program, launched large scale studies to directly test various potential mechanisms of aging using genetic and pharmacological interventions. Since we decided to use mice for these projects, we first conducted the CR study with C57BL/6 mice to validate that 40% CR under different housing conditions (singly or multiple housing) could show similar anti-aging effects to the CR experiments with F344 rats [13].

To study genetic interventions, first, Dr. Richardson and his team tested the putative underlying mechanisms of the anti-aging effect of CR: a) enhanced DNA repair; b) reduced glucocorticoid actions; and c) increased glucose metabolism efficiency and reduced plasma glucose levels using the transgenic and knockout (KO) mice as a continuation of the biology of aging program [14]. Another notable project launched by Dr. Richardson was to test the role of oxidative stress/damage in aging and age-related diseases. For this particular project, transgenic and KO mice were used that up-regulate or down-regulate the various antioxidant enzymes, *i.e*., Cu/Zn superoxide dismutase (SOD), MnSOD, glutathione peroxidase (GPx), catalase, and thioredoxin (Trx), *etc*. [15, 16].

In addition to the genetic interventions, our group has been actively conducting pharmacological interventions by testing various drugs and natural compounds. One of the most notable projects is the aging study using rapamycin. This project was proposed by Dr. Dave Sharp, one of the key members of our aging research group, and Intervention Testing Program (ITP) conducted the survival study. As it is well-recognized within the aging research community, rapamycin suppresses the mTOR pathway, extends the lifespan, and attenuates various age-related pathologies in genetically heterogeneric (four-way cross)

mice [17].

These genetic and pharmacological intervention projects were made possible due to: a) Dr. Arlan Richardson's foresight and strong leadership; b) the conceptual and technical innovations; and c) the support provided by two major aging research centers, the San Antonio Nathan Shock Center and the Intervention Testing Program, which were established and supported by NIA.

## Translational and clinical research

The success of the studies with rapamycin opened the door to advancing translational research and clinical applications in humans. Therefore, the putative underlying mechanisms discovered through CR studies have led to genetic interventions, been further verified by pharmacological interventions, and extended into translational and clinical research. In the early 2010s, Dr. Nicolas Musi became the director of the biology of aging program and expanded the research to translational and clinical projects with pharmacological interventions and physical exercise. First, Dr. Adam Salmon started testing the potential anti-aging effects of rapamycin in common marmoset, which was the first study to test the effects of rapamycin with non-human primates. Second, Dr. Sara Espinoza conducted the clinical research to test the effects of metformin on human aging. And third, Drs. Musi and Espinoza tested the potential benefits of physical exercise with humans as a part of the NIH program, The Molecular Transducers of Physical Activity Consortium (MoTrPAC). In addition, our group started utilizing cutting-edge omics analyses (single-cell RNA sequencing, spatial transcriptomics, and lipidomics) as a new approach for the aging research. Those translational and clinical research with technical innovation led us to expand into the new area and advance aging research to a higher level. Therefore, the Barshop Institute became one of the few institutions to conduct aging research using multiple experimental models and species (mice, rats, naked mole-rats, non-human primates, and humans) to test various interventions of aging, *e.g.*, dietary, genetic, pharmacological, physical activity, *etc.*, under the leadership by Drs. Musi and Espinoza, and the support provided by another major aging research center, the San Antonio Claude D. Pepper Older Americans Independence Center (Claude D. Pepper Center) from NIA.

## Current challenges and the future of aging research

Multiple studies demonstrated that the intervention of a single pathway showed anti-aging effects, which provided us with hope to attenuate aging processes in humans by altering those signaling pathways using mainly dietary and/or pharmacological interventions. However, there are several considerations and hurdles to clear and extra-steps are required before the clinical applications because the aging process in humans seems to be far more complex than our initial assessment. The effects of interventions could be different between the laboratory animals and humans because humans have more diverse: a) genetic backgrounds; b) calorie intake and dietary compositions; c) age-related diseases; d) physical activities and lifestyle; e) socio-economical backgrounds, and other factors than the controlled living conditions of experimental animals.

For example, the optimal conditions of dietary interventions, including the levels of calorie restriction, may vary: a) in different stages of life, *i.e.*, young, middle age; and old; b) in tissues/organs; c) in various functions and diseases; d) in males and females; e) based on genetic background; and in any combinations of these. In addition, the optimal dose and biological effects of pharmacological interventions need to be carefully monitored by: a) drug concentration; b) metabolic rates; c) biological changes, *e.g.*, signaling pathways and functions in cells/tissues/organs as pharmacokinetics and pharmacodynamics could be changed with age. Therefore, it is essential to address the complexity of the mechanisms of aging before we test the effects of aging interventions in humans.

Since 2023, the translational and clinical research has further expanded, and to address the potential challenges of the studies with humans described above, special efforts have been made to collect and archive the tissues/specimens from mice, rats, naked-mole rats, non-human primates, and humans (participants of multiple clinical studies) to establish a biobank. Our current aging research group is conducting multi-omics analyses (single-cell RNA sequencing, spatial transcriptomics, lipidomics, proteomics, and metabolomics, *etc.*) with the archived tissues/specimens from various species including humans. The large data sets obtained from the multi-omics approaches will be analyzed and the integrations of the multi-omics layers will be further conducted by artificial intelligence/computational biology. These experiments will allow us to discover the common pathways of aging across the species. Furthermore, our group has been conducting the experiments to examine age-related changes in pharmacokinetics and pharmacodynamics with non-human primates and humans led by Dr. Adam Salmon (non-human primates), and Drs. Dean Kellogg, Brett C. Ginsburg, and Elena Volpi (humans). These expanded translational and clinical research are conducted under the current leadership by Drs. Volpi, Salmon, and Blake Rasmussen, and the continued support provided by the San Antonio Claude D. Pepper Center and Nathan Shock Center supported by NIA.

These new projects utilizing the revolutionized approaches/technologies will provide valuable information: a) for further understanding of mammalian aging including humans; b) allow us to develop new preventive/therapeutic methods to attenuate aging processes; and c) for development of precision medicine that could tailor health care to individuals.

## Conclusions

The aging research in San Antonio marked a half-century

milestone since Dr. Edward Masoro started the biology of aging program in 1975. The research uncovering the underlying mechanisms of aging and the discovery of effective interventions of human aging are urgently needed as the elderly population (65 years and older) has been rapidly growing in the U.S. and other countries. The aging research in San Antonio started with CR projects, developed with genetic and pharmacological interventions, evolved to translational and clinical research, and is currently seeking the underlying pathways in the aging processes utilizing various intervention methods, cutting-edge technologies, and multiple experimental models and species, including humans.

The long history of continued aging research was possible because of: a) very strong leadership by the former and current directors of the biology aging program/Barshop Institute; b) strong institutional and community support; and c) active and dynamic scientific interactions among the researchers, including basic, clinical, and physician scientists. In this rich research/academic environment, our team will continue to: a) explore new frontiers; b) undertake new challenges; and c) conduct experiments with conceptual and technical innovations.

Our aging research group and the Barshop Institute will continue to be one of the premier institutes for aging research carrying forward Dr. Masoro's legacy.

"In academic science, you ask a question, and you are totally in control of being able to answer it. How many walks of life give you that kind of freedom?"—Edward Joseph Masoro (1924–2020).

## Declarations

**Availability of data and materials:** Not applicable.

**Conflict of interest statement:** Yuji Ikeno is a member of the editorial board of *Aging Pathobiology and Therapeutics*. The authors declare that they have no conflicts of interest or involvement in the journal's review process or editorial decision regarding the publication of this manuscript.

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