UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO
Claude D. Pepper Older Americans Independence Center

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CENTER DESCRIPTION

A core tenet of the geroscience concept is that multiple human diseases arise from aging itself. Thus, the central theme of the San Antonio (SA) Claude D. Pepper Older Americans Independence Center (OAIC) is translational geroscience – moving research on the basic biology of aging from the laboratory bench to the clinic, with the overarching goal of promoting healthy aging and developing desperately needed treatments, mainly pharmacological, for aging-related diseases. This goal is achieved through the following Aims:

1) Expand the knowledge base in translational geroscience by catalyzing transformative research;

2) Create a cadre of multidisciplinary early-stage investigators with customized expertise in translational geroscience;

3) Serve as a resource and partner to investigators from other OAICs and institutions;

4) Provide intellectual leadership, disseminate knowledge, and stimulate discussion on translational geroscience-related themes.

CORES

Leadership and Administrative Core (LAC)

Leader 1: Elena Volpi, MD, PhD volpi@uthscsa.edu
Leader 2: Randy Strong, PhD strong@uthscsa.edu

The Leadership and Administrative Core (LAC) fosters integration of aging-related basic and clinical sciences, catalyzes scientific discoveries, promotes education and mentorship, and partners with other scientists and the community at large to develop novel interventions to improve the health, quality of life, and independence of older Americans. The LAC monitors, stimulates, sustains, evaluates, and reports progress toward our OAIC's goal through the following Specific Aims:

1. Provide logistical support and promote operational cohesiveness to the SA OAIC.
2. Promote research protocol adherence and maintain regulatory compliance with university and governmental policies for the responsible and ethical conduct of OAIC-supported research.
3. Disseminate the scientific innovation accomplished by OAIC investigators, inside and outside our institution, regarding the latest knowledge on geroscience and promotion of healthy life extension.
4. Stimulate and facilitate interdisciplinary collaboration among OAIC investigators, cores, committees, and projects, to advance basic science in aging biology from the bench to the clinic.
5. Select and monitor pilot and exploratory studies and progress of Scholars aligned with the OAIC theme.
6. Monitor and evaluate OAIC progress, foster institutional collaborations, and leverage resources.
7. Provide programmatic and scientific guidance to training programs, pilot studies, and resource cores (RCs).
8. Participate actively in the national OAIC network to help advance its mission of promoting independence in older Americans.

Research Education Component (REC)

Leader 1: Robert Clark clarkra@uthscsa.edu
Leader 2: Peter Hornsby, PhD hornsby@uthscsa.edu
Leader 3: Blake Rasmussen, PhD rasmussenb@uthscsa.edu

The REC promotes the Aims of the San Antonio Older Americans Independence Center (OAIC) by supporting career development, mentoring, and research training for early-stage investigators to transition to independent research careers. The Aims of our REC are:

Aim1: Oversee the recruitment, selection, monitoring, and evaluation of a highly qualified, dedicated and diverse group of early-career REC Scholars; assisting with their development into clinical and translational scientists in geroscience who can effectively lead and contribute to interdisciplinary research teams.

Aim 2: Provide active multidisciplinary supervising (mentoring) teams that regularly monitor, evaluate, and guide the progress of each REC Scholar through their research and career development programs; Scholars and their mentors will develop individualized structured research education plans with clearly defined responsibilities and milestones based on their investigative needs and focused on cross-training in translational sciences.

Aim 3: Recruit and advance the careers of a diverse cadre of Scholars across multiple dimensions, including women, underrepresented minorities and active-duty military and veterans representative of our patient population to build a geroscience workforce with expertise in medicine, nursing, psychology, pharmacy and other health care disciplines necessary for advancing geriatric care in a team science environment.

Aim 4: Promote cross-fertilization and assure integration of the REC participants' career development and activities with a) all San Antonio OAIC programs and b) the national OAIC network.

Pilot and Exploratory Studies Core (PESC)

Leader 1:	Kelly Reveles, PharmD, PhD, BCPS	revelesk@uthscsa.edu
Leader 2:	Randy Strong, PhD	strong@uthscsa.edu

The PESC plays a key role in the San Antonio OAIC's central theme of translational geroscience by supporting projects that move research on the basic biology of aging from the laboratory bench to the bedside, in order to extend healthy life expectancy. The PESC will provide merit-based support for rigorously designed pilot studies that test both the efficacy and side effect profiles of promising pharmacologic, as well as nonpharmacologic cell-based and behavioral interventions, in pre-clinical marmoset models and early human clinical studies. The PESC will strive to achieve its objectives through the following specific aims:

Aim 1: To promote innovative, collaborative, multidisciplinary research to test interventions designed to extend healthy life expectancy, both in early human trials and in non-human primate marmoset models.
Aim 2: To work closely with the Resource Cores and Research Education Component to provide infrastructure, scientific support, and funding for innovative pilot proposals from mentored junior faculty investigators, as well as established researchers.
Aim 3: To encourage pilot studies that will develop and apply novel methods and technologies.
Aim 4: To sustain effective processes to solicit, review, and fund pilot projects, as well as ensure study completion, robust tracking of downstream impact, and optimal dissemination and implementation.

Preclinical Research Core (RC1)

Leader 1:	Adam Salmon, PhD	salmona@uthscsa.edu
Leader 2:	Cory Ross, PhD	cross@txbiomed.org

RC1 plays a central role in the SA OAIC by providing the knowledge, skills, and technical support to assist OAIC investigators in using the common marmoset (Callithrix jacchus) as a pre-clinical model for aging interventions (mainly pharmacological). RC1 achieves its mission through the following Specific Aims:

1) To provide OAIC investigators access to a unique colony of aging marmosets.

2) To provide resources required for studying effects of aging interventions on marmoset healthspan.

3) To provide and maintain a bank of tissues from marmosets across the age range.

4) To provide services to assess analytical pharmacology in marmosets.

5) To support the research training and dissemination missions of the OAIC.

Clinical Research Core (RC2)

Leader 1: Elena Volpi, MD, PhD volpi@uthscsa.edu

The overarching goal of RC2 is to offer comprehensive, centralized, clinical trial support for study design, regulatory compliance, recruitment, retention, assessment, procedures, pharmacology, and data management. RC2 achieves its mission through the following Aims:

1) Provide expertise and advice for investigators to plan and design innovative clinical studies to rigorously
test interventions to improve healthspan;
2) Enhance the SA OAIC support infrastructure to ensure successful subject recruitment and safe and ethical conduct of all OAIC-supported clinical studies;
3) Catalyze translational human studies and trials through provision of comprehensive core services;
4) Provide analytical and clinical pharmacology expertise supporting drug pharmacokinetic, and pharmacodynamic analyses as well as toxicity and safety assessment;
5) Disseminate to the lay public and scientific community the latest research on geroscience-related health promotion and the importance/relevance of translational geroscience research; and
6) Support training in translational geroscience for early-stage faculty and those new to clinical research.

Trial Design and Integrative Informatics Core (RC3)

Leader 1: Jonathan A. L. Gelfond, MD, PhD gelfondjal@uthscsa.edu
Leader 2: Meredith Zozus, PhD zozus@uthscsa.edu

The goals of RC3 are to provide biostatistical collaboration and expertise, as well as centralized research information services to ensure ready access to superior data quality for SA OAIC members. The Core will greatly facilitate data sharing and integrated analyses within the OAIC. Importantly, RC3 develops and implements unique services within UTHSCSA, capitalizing on its members' biostatistical and informatics expertise in aging-related research. RC3 brings these substantial resources to support the SA OAIC through these Specific Aims:

Aim 1: Trial design: Provide biostatistics and informatics support and expertise for the OAIC, including: study design, power analysis, and planning; protocol development; and EHR-based feasibility analysis.

Aim 2: Trial conduct, reporting, and integrated analysis: Provide OAIC clinical trials with advanced research informatics tools to support the conduct, analysis, and reporting of clinical studies.

Aim 3: Training and education: Provide expertise, education and hands-on training in the collection, management, and analysis of data in translational geroscience, and analytics mentoring for OAIC trainees.

Aim 4: Developmental projects (DPs) and novel informatics methodology: 4A. Create a database of geroscience-focused clinical trials to identify promising therapeutics and sensitive/specific aging-related biomarkers (DP4). 4B. Develop and validate predictive algorithms to identify cohorts within large databases that both meet trial criteria and are likely to enroll efficiently (DP5).

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications

None specified.

Past Scholars
Mitzi Gonzales, Biggs Institute, UT Health Science Center San Antonio (2019-2021)
Jia Nie, Barshop Institute, UT Health Science Center San Antonio (2019-2021)
Rozmin Jiwani, School of Nursing, UT Health Science Center San Antonio (2019-2021)
Gustavo Almeida, UT Health San Antonio (2020-2022)
Christopher Shannon, Department of Medicine, UT Health San Antonio (2020-2022)
Jamie Walker, MD, UTHSCSA (2021-2023)
Juan Pablo Palavicini, PhD, UTHSCSA (2021-2023)
Tiffany Cortes, MD, UTHSCSA (2021-2023)

PILOT/EXPLORATORY PROJECTS (12 Pilot Projects Listed)

1. **Project Title:** **Effect of aging on hepatic steatosis in marmosets: A model of non-alcoholic fatty liver disease (NAFLD)**

   Leader: **Amrita Kamat, PhD**

   The objective of the proposed study is to investigate for the first time whether there are age-related changes in hepatic fat accumulation, a hallmark of NAFLD, in marmosets. We hypothesize an age-associated increase in hepatic steatosis and alterations in serum lipid profile in the marmoset model. To test our hypothesis, we propose the following Aims.

   Aim 1) To investigate whether hepatic fat accumulation increases with age in marmosets. In this aim, we will measure liver and abdominal fat in young and old male and female marmosets using magnetic resonance imaging (MRI) and spectroscopy (MRS). We will also utilize diffusion-weighted imaging (DWI) which is an emerging tool to evaluate liver fibrosis.

   Aim 2) To elucidate whether there are changes in serum lipid profile with age in marmosets. A serum lipidomic profile will be determined and evaluated to look for significant changes in the lipids with aging. To investigate associations between hepatic fat accumulation and cardiovascular health, blood pressure measurements will also be conducted.

2. **Project Title:** **Effect of SGLT2 inhibition on aging-related biomarkers in older obese adults with pre-diabetes**

   Leader: **Carolina Solis-Herrera, MD; Curtis Triplitt, PharmD.**

   Inhibitors of the sodium-glucose co-transporter (SGLT2) are FDA-approved for the treatment of type 2 diabetes (T2DM). Their mechanism of action involves lowering of blood glucose concentration secondary to increased glucose excretion of glucose by the kidney. These drugs also cause significant improvements in body weight, blood pressure and cardiac function. Based on these pleiotropic effects, including its calorie restriction-mimetic properties, we hypothesize that SGLT2 drugs will impact several markers related to aging, including reductions in oxidative damage to DNA and proteins, DNA methylation, advanced glycation end products-receptor for AGE (AGE-RAGE), cellular senescence, and improvements in mitochondrial function.

   Aim 1: To determine whether SGLT2 inhibitors improve biomarkers of aging in older obese adults with pre-diabetes
   Aim 2: To determine whether changes in aging-related biomarkers are linked to changes in glucose metabolism and healthspan.

3. **Project Title:** **Differential effect of glucose regulating drugs on the onset and progression of frailty: healthcare analytics meets aging research**

   Leader: **Tiffany Cortes, MD; Alex Bokov, PhD**

   The purpose of this proposal for the 2021 San Antonio Calude D. Pepper Older American Independence Center Pilot and Exploratory Studies Core Pilot application is to understand the factors that lead and the effect of anti-hyperglycemics on frailty progression and incidence in older adults with diabetes. Briefly, our specific aims are: (1) Examine predictors of frailty progression in older adults with Type 2 diabetes from our UT Health San Antonio/University

Hospital patient population. (2) Determine the effect of timing of metformin initiation and different classes of diabetes medication on frailty in older adults with Type 2 diabetes. Analyses will be conducted in older adults with well controlled diabetes who are either prescribed metformin alone or no drug treatment (Aim 2a) and in patients who have been prescribed at least one additional antihyperglycemic agent to manage their diabetes (Aim 2b). a. Compare the trajectories of frailty in older adults with well-controlled type 2 diabetes (HbA1c ?7.5%) on metformin monotherapy versus no anti-hyperglycemic agents in the UT Health San Antonio/University Hospital population over four years. b. Compare the trajectories of frailty among older adults with type 2 diabetes who are prescribed metformin monotherapy compared to those prescribed metformin plus a second line antihyperglycemic agent. We hypothesize that hyperglycemia, adiposity and increased inflammation will accelerate frailty progression in older adults with diabetes (Aim 1).

4. Project Title: Development of marmoset age-dependent iPSC line resources to determine single cell transcriptome and regulome atlas

Leader: Marcel Daadi, PhD

With a significant gap between preclinical success and clinical failure and the stagnant development of effective treatments for age-associated diseases, it is essential to develop relevant and reliable biological materials with information resources to guide the development of novel groundbreaking therapies. We propose to generate high quality validated induced pluripotent stem cell (iPSC) from marmosets at two ages, young adult and aged, to be used to conduct comprehensive characterization of the effect of donor age on these cells, at the single cell level. We will generate a single-cell transcriptome and regulome atlas of gene regulatory networks in marmosets that's age-specific. These studies will determine for the first time whether age of donor significantly affects outcomes, which will be invaluable for developing models of age-associated biological variations towards understanding age-associated disease pathogenesis and development of novel interventions. IPSCs offer powerful model systems, including standardized organ and cell-specific assays to understand organ-specific responses to aging and for screening drugs or vaccines. Looking forward, iPSCs have the potential to be powerful translational interventions to improve or reverse numerous age-related pathologies and diseases. This proposal will be the initial step in understanding what role age may play in development of potential iPSC-derived treatment options. In Aim 1 we will generate, in vitro characterize and authenticate iPSC lines from young adult marmosets 4-6 year old (3 males, 3 females) versus aged marmosets >10 year old (3 males, 3 females). We will compare age-related changes in the mitochondrial functions and cellular resilience in a fluorescent-based high throughput-screening assay. The iPSC lines will be generated from skin biopsies or blood from live animals and thus will require no animal euthanasia. In Aim 2 we will use high-resolution single-cell RNA sequencing and single-cell ATAC sequencing on the iPSC lines and iPSC-derived brain organoids to generate a single-cell transcriptome and regulome atlas of age-associated gene regulatory networks that will serve as a blueprint for novel discoveries and interventions relevant to human aging. When complete, these resources will for the first time uncover whether age of donor significantly alters iPSC in marmosets. As potential project extensions, these data will be used, in collaboration between Daadi's and Salmon's lab in high throughput screening assays for anti-aging small molecules. The proposed project will develop into broadly applicable and invaluable resources stimulating new collaborations to expedite translational research and discoveries of novel insights into the human aging, health and diseases.

5. Project Title: Direct measurement of high?energy phosphate compounds in breast cancer survivors in response to exercise ± creatine supplementation

Leader: Darpan Patel, PhD; Geoffrey Clarke, PhD

Individuals with breast cancer are at high risk for skeletal muscle wasting that may be exacerbated by chemotherapy or tumor-related factors. Given the implications of treatment toxicities in relation to muscle mass, identifying strategies to enhance muscle post treatment are required. Exercise after treatment has been found to be beneficial in rehabilitating breast cancer survivors post chemotherapy, helping improve muscle strength, physical function and quality of life. However, fatigue can impair adaptations to exercise. Fatigue in breast cancer survivors is hypothesized to be associated with reductions high energy phosphates leading to reduced intramuscular adenosine triphosphate. Creatine is one of the most widely studied supplements with research demonstrating its efficacy in augmenting training adaptations such as improved strength and physical function in a variety of healthy populations. In cancer-related physical impairments, supplementing creatine phosphate may promote muscle hypertrophy, strength and endurance; reversing the deleterious effects of chemotherapy observed in this population. No studies to date have been conducted in breast cancer patients. The primary objective of this proposal is to is to test the hypothesis that creatine phosphate supplementation will increase high energy phosphates in vivo and accelerate adaptations associated with exercise in breast cancer survivors that have recently completed chemotherapy. The secondary objectives are to (1) compare in vivo high energy phosphate concentrations in breast cancer survivors compared to age-matched controls; (2) determine if high energy phosphate concentrations are associated with muscle cross-sectional area, body composition or physical function; and (3) determine the effects of creatine phosphate supplements in modulating strength and physical function in cancer survivors. To test the primary objective's hypothesis, we will conduct an open-label, randomized controlled trial of exercise ± creatine phosphate supplementation, enrolling 15 breast cancer survivors into each arm of the study (30 breast cancer survivors in all). All participants will complete 12 weeks of exercise, 3 times per week, administered virtually via Zoom. Creatine phosphate supplementation will be administered at 20 grams per day for 7 days (loading phase), later reduced to 5 grams per day for the subsequent 11 weeks (maintenance phase). To complete the secondary objectives of this study, we will conduct a cross-sectional study comparing in vivo high energy phosphate concentrations, body composition and physical function in the 30 breast cancer survivors recruited for the clinical trial to 30 age-matched controls.

6. Project Title: Mechanisms to Reduce Mental and Physical Fatigue Following Diet and Exercise Training in Older Adults

Leader: Monica Serra, PhD; Jason O'Connor, PhD

Fatigue is a strong predictor of negative health outcomes in older adults. Tryptophan, an essential amino acid, may play an integral role in fatigue progression. The accumulation of oxidative metabolites of tryptophan metabolism (i.e., kynurenines) is strongly associated with fatigue. Reductions in fatigue observed with exercise training appear to be mediated by skeletal muscle peroxisome proliferator-activated receptor-? co-activator-1? (PGC-1?), inducing a shift of kynurenine to kynurenic acid. This is catalyzed by kynurenine aminotransferase (KAT) enzymes, which precludes oxidative kynurenine metabolism and its. However, we find that subjects participating in exercise training often continue to report fatigue after the intervention,

suggesting a need to identify additional methods to maximize the fatigue response to exercise. In the past two decades, numerous studies have shown the advantageous effects of branched-chain amino acids (BCAAs) on exercise performance. Further, studies in animal models suggest that BCAAs decrease the transport of tryptophan and its metabolites into the CNS because BCAAs and tryptophan compete for the same carrier system. Thus, combining BCAA with exercise may synergize to divert metabolism away from formation of neurotoxic tryptophan metabolites with known deleterious effects on mental and physical fatigue. This randomized pilot examines the influence of systemic and skeletal muscle tryptophan metabolism on mental and physical fatigue following exercise training with and without BCAA supplementation in fatigued older adults. Our central hypothesis is that eight weeks of BCAA added to exercise will increase expression of KATs shifting kynurenine metabolism towards enhanced synthesis of kynurenic acid, thereby reducing fatigue. Aim 1) Evaluate the impact of EX+PLA vs. EX+BCAA on changes in mental fatigue, in association with changes in systemic and skeletal muscle tryptophan metabolism. We hypothesize that EX+BCAA will result in greater increases in PGC-1?, KATs, and kynurenic acid and decreases in kynurenine in plasma and skeletal muscle, leading to declines in mental fatigue measured by Brief Fatigue Inventory. Aim 2) Determine the effects of EX+PLA vs. EX+BCAA on changes in physical fatigue, in association with changes in systemic and skeletal muscle tryptophan metabolism. We hypothesize that EX+BCAA will result in greater changes in tryptophan metabolism (as outlined in Aim 1), leading to improvements in physical fatigue measured by aerobic capacity and strength. The discovery that kynurenine concentrations are associated with fatigue and are responsive to BCAA supplementation during exercise training could have important implications for the development of future interventions, both lifestyle and pharmacologic, to treat fatigue in older adults.

7. Project Title: **Improvement in vestibular function using mitochondrial antioxidant therapy**

Leader: **Brian Perry, MD**

This project proposes to determine if daily supplementation with alpha lipoic acid (ALA) and Co- Q 10 can improve or stabilize vestibular function in an elderly population as determined by rotational chair testing. Our hypothesis is that the use of dietary supplementation with alpha lipoic acid and Coenzyme Q10 (CoQ-10) will improve vestibular function in older adults. To test our hypothesis, we propose the following Aims. Aim 1. To determine if supplementation with known mitochondrial antioxidants (alpha lipoic acid and CoQ-10) will stabilize or improve vestibular function in older adults. Aim 2. To demonstrate that those individuals who are not provided supplementation with alpha lipoic acid and CoQ-10 will have a decline in vestibular function. Aim 3. To demonstrate a reduction in falls in the group provided with mitochondrial antioxidant therapy compared to the control group.

8. Project Title: **Nutritional optimization and bone health management for older adults undergoing hip fracture: a pilot study.**

Leader: **Boris Zelle, MD**

The overall objective of this pilot study is to examine the feasibility of a best practice protocol for optimization of nutrition and bone health in these patients. The rationale for our proposal is that implementing a feasible perioperative nutritional and bone health intervention will inform future clinical trials and request for extramural funding. We will pursue the following two specific aims: Aim 1. Test the feasibility of a perioperative nutritional and bone health intervention in aging patients undergoing hip fracture surgery. We hypothesize that a nutritional intervention is feasible within this patient population. Aim 2. Determine the primary efficacy of the perioperative intervention to improve surgical outcomes in aging patients undergoing hip fracture surgery. We will use the pilot data to calculate the estimated magnitude of potential impact on select surgical outcomes to be used for future clinical trials.

9. Project Title: **Exploring the effects of blood flow restriction training on neuroplasticity in older adults.**

Leader: **Gustavo Almeida, PhD, PT**

A comprehensive examination of the primary motor cortex-mediated neural mechanisms underlying BFRT is crucial for optimizing therapeutic exercises to maximize CME and gains in neuromuscular performance. Yet, it is still unclear whether BFRT can improve neuromuscular performance by means of eliciting CME in older adults. Thus, the specific aims of our study are Aim 1: To determine the effects of BFRT on CME and neuromuscular performance in older adults. We hypothesize that older adults in the BFRT program (n=10) will show improved CME, gait speed, balance and quadriceps muscle power compared to the low resistance group (n=10). Aim 2: To explore associations between CME and neuromuscular performance in older adults. We hypothesize that change in CME parameters will be positively associated with change in gait speed, balance, and quadriceps muscle power only in the BFRT group.

10. Project Title: **Brain rejuvenation by replacement and enhancement of aged microglia in marmoset models.**

Leader: **Senlin Li, MD**

We hypothesize that the aged marmoset brain can be effectively rejuvenated/restored by replacement and enhancement of the aged microglia population. In this pilot project, we will use a pharmacological approach to test the hypothesis. Signaling through CSF1R is essential for microglia survival. Rapid depletion of microglia can be achieved in adult mice through oral administration of CSF1R inhibitors, without inducing notable compensatory mechanisms or overt phenotypic health abnormalities. A small molecular CSF1R inhibitor PLX3397 (pexidartinib) has been granted US FDA approval as treatment for tenosynovial giant cell tumors, making it advantageous to study translation of CSF1R inhibition toward broader clinical applications. Furthermore, a newer generation CSF1R inhibitor, PLX5622, exhibits both a higher specificity for CSF1R and improved brain penetrance. It is thus conceivable that eliminating age-associated primed microglia and resetting/repopulating the system through CSF1R inhibition could ameliorate age-related cognitive decline. Mouse studies using PLX5622 support this idea. To translate these exciting findings in rodents toward human trials, we propose this pilot study in marmosets with two specific aims. Aim 1: Find an effective dose of PLX5622 in marmosets through pharmacokinetic (PK) study. PK data of PLX5622 in preclinical species (mouse, rat, dog, and monkey) have been well documented in the literature. However, the conversion charts for larger primates (old world monkeys) are not particularly applicable to marmosets (new world monkeys) likely because of their anatomical differences.

Therefore, we propose to obtain the marmoset specific data through a simplified PK study. Aim 2: Evaluate the effects of PLX5622 therapy on the cognitive abilities of aged marmosets.

11. Project Title: **mTOR inhibition: A novel therapy for reducing age-associated endothelial dysfunction in older subjects**

Leader: **Ellen Kraig, PhD; Dean Kellogg, MD**

With aging, systemic inflammation increases and likely contributes to the development of age-associated pathologies including cardiovascular diseases (CVDs). CVDs are not only cardiac diseases, but also the arterial system and are associated with reduced large artery compliance and reduced endothelial function. Recent work in old (30mo) mice showed that both large vessel compliance and nitric oxide (NO) dependent endothelial function improved with 6-8 weeks of RAPA treatment (3). This application requests funds to determine whether RAPA is similarly able to reverse age-associated endothelial dysfunction in humans. Aim I. Test whether RAPA treatment improves endothelial function in elderly subjects. Plasma from the human RAPA clinical trial (17 RAPA-treated subjects and 14 placebo subjects) will be tested in Dr. Doug Seals' ex vivo assay for endothelial function. The pre-treatment values will be compared to values obtained for the 6-8 week treatment time point in order to detect any change in endothelial function associated with mTOR inhibition. Aim II. Correlate changes in endothelial function with the other general, immune, physical, epigenetic, and cognitive measures already available. To gain insight into the underlying mechanisms regulating RAPA's pleiotropic effects, we will perform a correlation analysis to assess which of the parameters previously measured are coordinately regulated and associated with any detected RAPA-induced change in endothelial function.

12. Project Title: **Aging Biology of Salivary Glands in a Non-human Primate Model**

Leader: **Chih-Ko Yeh, BDS, PhD**

In addition to clinical observations showing that human salivary flow rates decrease with advancing age, histological studies have shown that the secretory units (i.e., acini) in the SG are replaced by non-functional fibrotic and fatty tissues during human aging. Our study of the histomorphological, cellular, and transcriptomic changes that occur in the marmoset SG during aging is critical to our understanding of this NHP's oral gerontology. We hypothesize that the marmoset SG is similar to that of humans and thus represents an appropriate NHP model for studying human SG aging biology. To test our hypothesis, we have developed two Specific Aims: Aim 1. To determine aging-related histological changes in major SGs of the marmoset. Rationale: To establish the relevance of marmosets as a NHP model of human oral gerontology, it is critical to determine if histological changes and loss of acinar cells in the marmoset SG parallel that of humans. Aim 2. To determine how the transcriptome of key SG structures change during marmoset aging. Rationale: Both clinical studies and pre-clinical rodent models indicate that SG progenitors, involved in homeostasis and the injury response, are dysregulated during aging9,10. However, changes in the cell composition and microenvironment of SG tissues during aging have scarcely been investigated. To address this gap, our first aim will identify histomorphological changes occurring in the acinar compartment and within SG regions responsible for maintaining homeostasis or response to injury. The second aim will utilize state-of-the-art single-cell spatial transcriptomics to map and quantify age-related changes in the genome-wide transcriptional profiles of SG

structures11,12 identified by histology in the first aim.

DEVELOPMENT PROJECTS (5 Development Projects Listed)

1. **Project Title:** **Comparative assessment of the role of mTOR in cardiac aging**
   Leader: **Marc Feldman, MD and Yuji Ikeno, MD, PhD**
   Core(s): Preclinical Research Core (RC1)
   Clinical Research Core (RC2)
   Trial Design and Integrative Informatics Core (RC3)

   Study Question: Does rapamycin improve age-related changes in cardiac compliance and reduce fibrosis/collagen?

   Preliminary RC2-supported studies using cardiovascular magnetic resonance imaging (CMR) suggest that rapamycin treatment improves diastolic function in healthy older adults (see RC2). Now, this DP will use CMR with late gadolinium enhancement (LGE) to evaluate the effects of 2 months of rapamycin (vs. placebo) on parameters related to cardiovascular aging in 20 healthy adults over 70 years old. CMR data will include measurements of global and regional ventricular systolic and diastolic function, and LGE measurements of myocardial extracellular volume to assess fibrosis. RC1 will conduct parallel studies in marmosets; from an ongoing study, Dr. Ikeno will quantify collagen and elastin in banked aorta and heart samples from young (

2. **Project Title:** **Comparative lipidomics of aging**
   Leader: **Xianlin Han, PhD,**
   Core(s): Preclinical Research Core (RC1)
   Clinical Research Core (RC2)
   Trial Design and Integrative Informatics Core (RC3)

   Study Question: Can changes in the circulating lipidome be developed as a cross-species biomarker of aging, age-related disease, and functional decline?

   Diverse lipid signaling pathways can modulate the aging process and systematic analyses of the total lipid structure – the lipidome – in clinically relevant samples can reveal novel mechanisms in aging biology, biomarkers for diagnosis, and targets for therapeutics. As an initial step, using samples provided from generally healthy marmosets (RC1) and humans (RC2) across the normal age range for both species, this DP will assess the effects of age on the plasma lipidome. RC1 will provide plasma from ~20 each young (2-5 yrs.), middle-aged (6-9 yrs.) and old (10+ yrs.) naturally aging marmosets. All animals will be phenotyped by our common battery and resilience assessment. RC3 will assist with statistical comparisons of effects of age on changes and test the extent to which the lipidome reflects health and functional status. Identification of similarities in the aging lipidome across species may elucidate important biomarker targets for geroscience. Reflecting the growing interest in this topic, NIA recently released RFA-AG-20-039, “Lipid Signaling in Healthspan and Longevity Regulation”.

3. **Project Title:** **Development of senescence biomarkers for clinical trials**
   Leader: **Paul Hasty, PhD**
   Core(s): Clinical Research Core (RC2)
   Trial Design and Integrative Informatics Core (RC3)

Senolytic/senomorphic drugs hold promise for aging and aging-related diseases. However, clinical trials to evaluate these drugs will require sensitive and specific senescence biomarkers. The goal of this project is to lay the foundation for the development and evaluation of non-invasive measures of cellular senescence. The ongoing repository (STARR) will be leveraged to (i) link known markers of senescence [p16 in CD3+ cells, senescence associated secretory phenotype (SASP) gene expression, and b-gal staining] obtained from tissues (blood, skin, fat) with healthspan outcomes; and to (ii) identify novel senescence biomarkers. This DP will also leverage ongoing and future trials on drugs/interventions with senolytic/senomorphic activity (e.g. dasatinib, polyphenols, metformin, mTOR inhibitors, exercise, weight loss) to determine which biomarkers change with the intervention and can predict functional outcome measures. In the future, this DP will conduct earlyphase precision medicine research on senolytics. For example, it will evaluate whether transcriptomic profiling (by RC3) of adipose tissue obtained in vivo can be used to determine which senolytics are most effective in clearing senescent cells and reducing SASP using in vitro cell functional assays. We could then test if molecular profiling predicts in vitro and in vivo clearance of senescent cells and whether their clearance is linked with changes in putative peripheral (non-invasive) senescence biomarkers and healthspan-related outcomes.

4. Project Title: **Aging trial meta-analytic database (ATMDb)**
Leader: **Joel Michalek, PhD**
Core(s): Clinical Research Core (RC2)
Trial Design and Integrative Informatics Core (RC3)

RC3 is focused on designing aging-related trials that are rigorous, efficient, feasible, and based on solid preliminary data. This can be challenging because 1) trials with multimorbidity endpoints are novel; 2) biomarkers related to these endpoints are in development; and 3) treatment effect sizes are unknown.

Goal: Through this DP, we will create a database of aging-related clinical trials involving drug classes related to aging, multimorbidity endpoints, and aging-specific biomarkers. The database and research publication will include trials' primary clinical endpoints, anticipated/realized effect sizes, sample sizes, inclusion/exclusion criteria, durations of treatments, classes of compounds, secondary endpoints and related effect sizes.

Methods: RC3 will formally examine translational geroscience-focused trials (completed and in-progress) through a systematic review of the literature and clinicaltrials.gov. This online database of multimorbidity and disease-agnostic healthspan-extending trials will be freely available to all OAICs. The initial trial searches will focus on SA OAIC priority agents such as rapamycin, metformin, senolytics, and other compounds under study by OAIC investigators. This database will also include a meta-analytic perspective on the sensitivity to intervention of the assessed aging biomarkers so that investigators will be informed by empirical evidence in selecting cost-effective assays to measure treatment effects. Initial biomarker searches will focus on SA OAIC priority outcomes, namely frailty, epigenomic aging assays, and senescence markers. Article search criteria will be aided by a research librarian (funded by RC3). Abstraction will be done by Dr. Michalek (Project Lead) and Dr. Gelfond, with quality control and abstraction done in coordination with RC2 lead Dr. Espinoza. RC3 will record trial design consultations and note those consultations that use the meta-analytic database. The web-accessible database will allow for crowdsourcing feedback to evaluate accuracy and adapt

search criteria. Reporting will comply with Preferred Reporting Items for Systemic Reviews and Meta-Analyses guidelines. This systematic review and meta-analysis will inform power calculations and primary/secondary outcome selection in future studies supported by RC3 of the SA OAIC as well as other scientists in the field.

5. Project Title: **Adaptive cohort identification (ACI)**

Leader: **Meredith Zozus, PhD**

Core(s): Trial Design and Integrative Informatics Core (RC3)

Rationale: To help with recruitment of OAIC studies during the current grant cycle, RC3 investigator Dr. Alex Bokov used the i2b2 application and data warehouse containing de-identified electronic medical record (EMR) data for 1.7 million patients to pull data from diverse sources (Epic Clarity, Sunrise, IDX, etc.), seeking potential participants who meet trial inclusion/exclusion criteria. While this uncovered participants who met highly specific criteria, subjects were not always efficiently enrolled. Goal: This DP will use machine-learning methods to leverage information within the EMR and clinical trial operational databases to more efficiently identify eligible participants who are more likely to enroll in the trial. Methods: Dr. Zozus (Project Lead) and Dr. Gelfond will use machine learning to adaptively model the full i2b2 patient profiles to match participant characteristics with those associated with successful trial enrollment. Using machine-learning tools (KNN, SVM, LASSO, etc.), subjects more similar to enrolled participants will be prioritized for screening. The effectiveness of this algorithm will be measured by a changepoint analysis that compares the enrollment rate (proportion who successfully enroll) before and after project implementation and examines the accrual rates in specific randomization strata to minimize sampling bias. Efficiency will also be measured by in-person screenings per enrolled subjects. We hypothesize that adaptive cohort identification will enhance accrual rates. If our hypothesis is supported, this algorithm will be made available to other scientists in the OAIC network and broad scientific community.

RESEARCH (0 Projects Listed)

PUBLICATIONS

2024

2023

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RECOGNITION AND AWARDS (2023-2024)

Recognition and Awards not specified.

MINORITY RESEARCH

General Brief Description of Minority Activities:
Not defined.

Minority Trainee(s):

- Nothing to report, Nothing to report
  Nothing to report

No minority grant information specified.