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ORIGINAL ARTICLE

San Antonio Nathan Shock Center: your one-stop shop for aging research

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Abstract With evolving cores, enrichment and training programs, and supported research projects, the San Antonio (SA) Nathan Shock Center has for 26 years provided critical support to investigators locally, nationally, and abroad. With its existing and growing intellectual capital, the SA Nathan Shock Center provides to local and external investigators an enhanced platform to conduct horizontally integrated (lifespan, healthspan, pathology, pharmacology) transformative research in the biology of aging, and serves as a springboard for advanced educational and training activities in aging research. The SA Nathan Shock Center consists of six cores: Administrative/Program Enrichment Core, Research Development Core, Aging Animal Models and Longevity Assessment Core, Pathology Core, Analytical Pharmacology

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and Drug Evaluation Core, and Integrated Physiology of Aging Core. The overarching goal of the SA Nathan Shock Center is to advance knowledge in the basic biology of aging and to identify molecular and cellular mechanisms that will facilitate the development of pharmacologic interventions and other strategies to extend healthy lifespan. In pursuit of this goal, we provide an innovative "one-stop shop" venue to accelerate transformative research in the biology of aging through our integrated research cores. Moreover, we aim to foster and promote career development of early-stage investigators in aging biology through our research development programs, to serve as a resource and partner to investigators from other Shock Centers, and to disseminate scientific knowledge and enhanced awareness about aging research. Overall, the SA Nathan Shock Center aims to be a leader in research that advances our understanding of the biology of aging and development of approaches to improve longevity and healthy aging.

Keywords Biostatistics · Longevity · Pharmacology · Physiology · Pathology · Pilot grants

Introduction

Over the last few decades, experimental evidence in animal models has provided strong support for the idea that there exist common pathways involved in the aging process that regulate longevity, the progression of age-related pathologies, and the maintenance of the functional period of disease-free healthy aging. Moreover, there is strong evidence that these mechanisms, and aging itself, can be targeted therapeutically through dietary, pharmacological, and genetic approaches. Together, these ideas form the basis for the Geroscience hypothesis, which aims to understand and delineate how aging drives diseases and to exploit that knowledge to slow development and progression of age-related diseases [1]. Rigorous experimentation in appropriate research models to identify such pathways and interventions that target them is of high significance and may result in healthier aging, an increase in the years of active life, and perhaps reductions in healthcare costs associated with long-term chronic diseases. Thus, the aging field is at an important inflection point. With this in mind, the Geroscience hypothesis aligns with the overarching goals of the San Antonio (SA) Nathan Shock Center, which are to advance knowledge in the basic biology of aging and to identify molecular and cellular mechanisms that will facilitate the development of pharmacologic interventions and other strategies to extend healthy lifespan.

In pursuit of these goals, the SA Shock Center provides to the community with what we view as an enhanced platform to serve investigators in pursuit of conducting horizontally integrated transformative research in the biology of aging, as well as a springboard for advanced educational and training activities towards career development in the field. The SA Nathan Shock Center aims to be a leader in research that advances our understanding of the biology of aging and to provide a "one-stop shop" venue to accelerate transformative research in the biology of aging (Fig. 1). Importantly, this includes fostering and promoting the career development of early-stage investigators in aging biology through education and pilot project programs. We have leveraged and streamlined our resources and strengths to provide to the community six interrelated cores focused on achieving these objectives. These cores, discussed below, include (1) Administrative/Program Enrichment Core; (2) Research Development (RD) Core; (3) Aging Animal Models and Longevity Assessment Core; (4) Integrative Physiology of Aging Core (IPAC); (5) Pathology Core; and (6) the Analytical Pharmacology and Drug Evaluation Core (Table 1). Together, these cores provide an integrated venue to conduct and facilitate carefully phenotyped and well-integrated aging studies in (primarily) mammalian animal models. That is, we envision the ability to serve the community from conception and design of aging studies through the physiological assessment of aging phenotypes, including longevity, healthspan or healthy aging, pharmacology, and pathology. Moreover, our core structures provide the ability to be nimble and adapt to requests and changes in focus throughout individual studies or as a core overall.

Using our core structure, we have proven capable of applying genetic, dietary, biochemical, and pharmacologic methodologies to studies using several vertebrate animal models including rodents (mice and rats, including those genetically modified, and naturally long-lived naked mole-rats and Damaraland mole-rats) and non-human primates (common marmosets). Based on our past experiences and

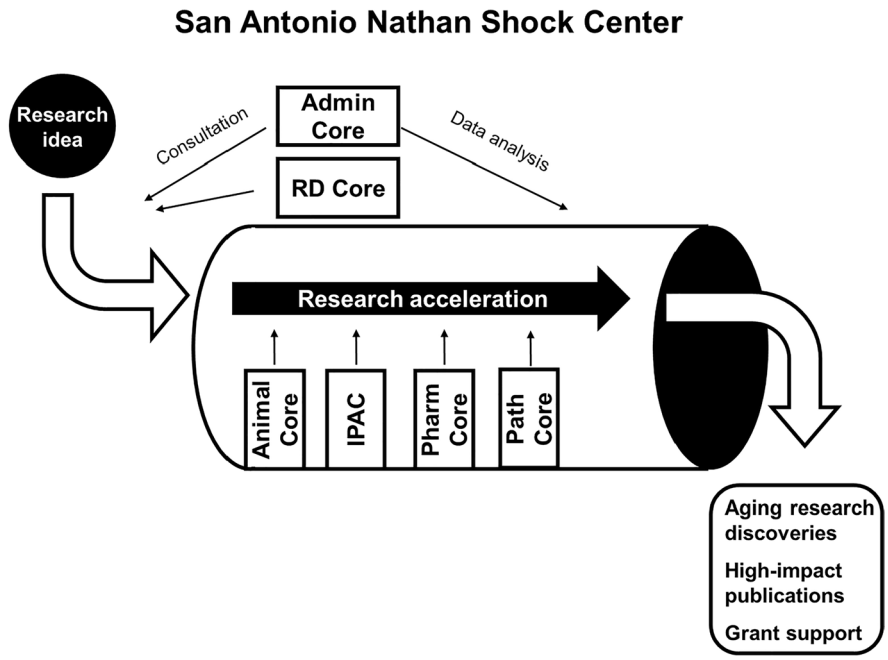

Fig. 1 Conceptualized goal of the San Antonio Nathan Shock Center to assist researchers in accelerating development of their research ideas to making significant discoveries in aging research

Table 1 Research cores and leadership of San Antonio Nathan Shock Center

Core	Leadership	Overall goal
Administrative	Randy Strong Peter Hornsby Adam Salmon	Provide continuous leadership and infrastructure that catalyzes scientific discoveries, promotes education and research career development, and partners with other scientists and the community
Research Development	Peter Hornsby James Lechleiter	Provide support for research career development of junior faculty and for more senior investigators who wish to apply their expertise in related research areas to basic aging research
Aging Animal Models and Longevity Assessment	James Nelson Adam Salmon	Provide investigators with animal resources, including mice, rats, mole-rats and marmosets, required to better understand integration of lifespan, pathology, physiological and molecular aging phenotypes
Pathology	Yuji Ikeno Gene Hubbard	Provide investigators with detailed pathological analyses and training regarding age-related lesions in mice, rats, and other animal models, e.g., non-human primates
Analytical Pharmacology and Drug Evaluation	Martin Javors Brett Ginsburg Marisa Lopez-Cruzan	Provide resources required for the application of existing and novel drugs to studies of aging and age-related diseases
Integrated Physiology of Aging	Nicholas Musi Veronica Galvan Elizabeth Fernandez	Provide intellectual and technical services on the selection, design, and conduct of functional assays in rodents and marmosets at the molecular, tissue/organ, and whole-organism levels

successes, we fully anticipate that our enhanced platform and training activities, partnering with internal and external investigators, will continue to greatly facilitate the identification of molecular and cellular mechanisms that influence aging. We believe that this holistic approach will ultimately result in novel

strategies and the identification of (pharmacologic) targets to extend healthy life expectancy.

As with all Nathan Shock Centers, we also serve as a resource and partner to investigators from other Shock Centers and as a nucleus for the dissemination of scientific knowledge and enhancing awareness about aging research. To us, this includes developing the potential to take innovative findings in the basic biology of aging research towards eventual clinical application. While not the immediate goal of the Nathan Shock Centers, this is the essence of the long-term view for geroscience. In this regard, the SA Nathan Shock Center is built on a unique foundation in aging research provided by our home institution, University of Texas Health San Antonio (UTHSA). These exceptional and tightly integrated resources in our research community include the San Antonio Claude D. Pepper Older Americans Independence Center (OAIC), a site of the NIA-funded Interventions Testing Program (ITP), a T32 Training Grant on Geroscience, and a Geriatric Research, Education and Clinical Center (GRECC) in our affiliated Veteran's Administration Healthcare System, all of which are integrated within the Barshop Institute for Longevity and Aging Studies which unites aging research at UTHSA. As part of this larger group, the SA Nathan Shock Center then serves as a central pillar in our internal aging program and a beacon to serve external investigators in pursuit of geroscience research.

Research cores of the San Antonio Nathan Shock Center

As mentioned above, the SA Nathan Shock Center is composed of six independent but interrelated cores. Also discussed above, we view that a strength of these cores is the ability to serve investigators from concept and design through successful completion of mammalian aging studies, all within the center. However, each core provides key individual services to internal and external investigators, either as a part of this process or independently through research projects, career development, or support. Key features and leaders of each core are described below. Greater detail on services provided by each core, contact information, and pricing structures can be found at our SA Nathan Shock Center website (https://nathanshock.barshop.uthscsa.edu/).

1. Administrative/Program Enrichment Core. Core Leaders, **Randy Strong Ph.D.** (strong@uthscsa.edu), **Peter Hornsby, Ph.D.** (hornsby@uthscsa.edu), **Adam Salmon, Ph.D.** (salmona@uthscsa.edu); Statistics Leader, **Jonathan Gelfond, M.D., Ph.D.** (gelfondjal@uthscsa.edu).

The Administrative/Program Enrichment Core (Administrative Core) is the organizational unit responsible for facilitating research in the basic biology of aging throughout the San Antonio (SA) Nathan Shock Center. The primary goal of the Administrative Core is to provide continuous leadership and infrastructure that catalyzes scientific discoveries, promotes education and research career development, and partners with other scientists and the community at large. Within our SA Nathan Shock Center framework, the Administrative Core serves as a central unit to foster and promote transformative geroscience research through integration of studies studying longevity (lifespan), integrated physiology (healthspan), pathology, pharmacology, and molecular phenotypes. These studies will drive discovery of molecular and cellular mechanisms that influence aging and the development of novel strategies (including the identification of pharmacologic targets) to promote healthy lifespan.

The role of the Administrative Core of the SA Nathan Shock Center is to monitor, stimulate, sustain, evaluate, and report progress toward our goals. As with all Nathan Shock Centers, the Administrative Core provides the administrative, budgetary, and regulatory management support for the overall center which is directed by the leadership and Executive Committee. Regarding the research and development trajectory of the SA Nathan Shock Center, the Administrative Core plays a key role in fostering an environment that stimulates collaborative efforts and synergies among research resource cores and promotes education and research career development of early-career investigators. Normal oversight of the SA Nathan Shock Center is coordinated by the Administrative Core, including integration of the research cores of the center through monthly meetings and a Web-based project integration system. The Administrative Core also conducts continuous internal and external evaluations of the center at multiple levels, including Shock Center-funded projects, awardees, and cores to ensure accountability, improve efficiency,

assess outcomes, determine needs, and facilitate strategic planning to meet those needs.

The Administrative Core supports four significant outreach events designed to enhance the local and external aging research environment. These include the annual Barshop Symposium on Aging held at the Mayan Dude Ranch in Bandera, TX, a weekly seminar series on aging research held at UTHSA, biannual workshops held jointly with the San Antonio OAIC, and an annual student day for aging research held at UTHSA. During the pandemic, these outreach mechanisms have been held virtually, with great success, and we envision continuing to use a hybrid approach moving forward as conditions permit. In addition, the Administrative Core is developing webinars to explain and promote core services that are to be run by core leaders in the SA Nathan Shock Center as part of the educational and training goals of the center.

The Administrative Core also seeks to promote interactions in aging research through the sharing of core services with investigators at other institutions and building collaborations with other Nathan Shock Centers. The Administrative Core is the conduit of central contact to other Nathan Shock Centers and the Coordinating Center. Part of the collaborative effort exists in career development of junior investigators across the Nathan Shock Centers, in developing novel approaches to study aging research and supporting the Nathan Shock Centers' Symposia.

The Administrative Core of the SA Nathan Shock Center also directly supports research projects by providing biostatistical support to all core users, and data management and project tracking for each of the resource cores. Aging involves a complex set of phenotypes, and diverse types of measures from many investigators require coordinated data collection, complex preprocessing, merging, and integrated analyses. Statistical services provided through the Administrative Core aim to support investigators through the SA Nathan Shock Center through assistance in study design, analyses of experimental data generated by research cores, and development of novel statistical methodology and software for analyzing complex outcomes and phenotypes relevant to aging research [2, 3]. As with our research cores, statistical support can be requested by investigators for their individual research questions or as part of a comprehensive package to study aging that is serviced through multiple research cores of the SA Nathan Shock Center.

Overall, the Administrative Core is an important leader in the aging scientific community and contributes to three kinds of progress in aging research. First, it fosters a cooperative research environment within UTHSA that will attract investigators to aging research via specific educational programs (i.e., seminars, faculty and student retreats, and symposia that focus on various aspects of aging). Second, it fosters external collaborative efforts with other Nathan Shock Centers and external resources. Third, it assists with development and expansion of aging research at other institutions with fewer resources for biology of aging research than those in the existing infrastructure at UTHSA.

2. Research Development Core. Core Leaders, **Peter Hornsby, Ph.D.** (hornsby@uthscsa.edu), **James Lechleiter, Ph.D.** (lechleiter@uthscsa.edu).

The Nathan Shock Centers provide a network of resources to the community of researchers in the basic biology of aging across the country. This network involves both services provided by individual centers as well as activities that span multiple centers. The Research Development (RD) Core serves as the resource at the San Antonio (SA) Nathan Shock Center that connects investigators across the country with cores at our center that can assist them with their research programs.

The RD Core aims to assist investigators working in the basic biology of aging by offering grants that promote their research and provide discounted or supported service through our research cores (Fig. 2). Through the now 26-year existence of the SA Nathan Shock Center, the RD Core has established an excellent track record of bringing both junior and senior faculty into aging research. The resulting increase in the scope of aging research both locally at UTHSA and through outreach to other institutions within the San Antonio community and nationally has served to greatly enhance the research environment and promote the productivity of investigators involved in aging research.

The RD Core provides service to aging research through four main mechanisms. The first is through an Access to Core Services program (External Pilots). At the 2017 annual Shock Centers directors' meeting, the existing 6 Shock Centers at that time were

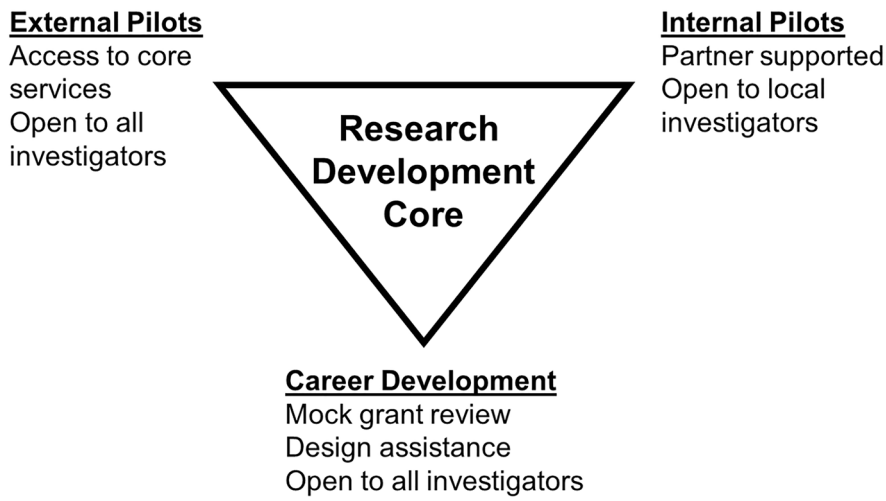

Fig. 2 Generalized conception of the supporting roles of the Research Development Core

in agreement that all core services among the Centers would be made available to any researcher at any institution via competitive pilot project awards. From this, the RD core developed the SA Nathan Shock Center External Pilots to facilitate research in the basic biology of aging across the country by providing funding that makes the core services of our center available to all qualified investigators on a competitive basis. With a yearly call for proposals, we provide a means for any investigator at any institution to use the services of any of the cores (Administrative, Animal, Pathology, Pharmacology, and Integrative Physiology of Aging) for their innovative research in geroscience. This program then enables scientists anywhere in the aging research community to leverage the unique resources available at the SA Shock Center.

The second mechanism used by the RD Core is a Pilot Project Program for local investigators that aims to expand the scope of research in the basic biology of aging at UTHSA (Internal Pilots). The RD Core of the SA Shock Center has always played a key role in supporting promising early-stage investigators and assisting faculty at all levels to further their research in the basic biology of aging. The core continues to provide support for career development of junior faculty and for assisting more senior investigators who wish to apply their expertise in research areas related to basic aging research. In the past, we administered separate Internal Pilots for new junior faculty and for senior faculty wanting to do research on the basic biology of aging. In our current form, the RD Core Internal Pilots is open to both junior and senior investigators and is a cooperative program with our additional institutional funding support, which broadens our potential pool of applicants among the local research community.

The third mechanism used by the RD core is to assist new investigators in research career development and assist investigators at all levels to pursue novel ideas in aging research. The RD core provides a variety of forms of assistance with grant and project development, including mock grant reviews and design assistance, as well as aspects of career development. Mentoring is carried out by the core leadership in association with senior faculty of the Barshop Institute and is coordinated with mentoring activities of the awardees' departments and home institutions. These services are provided without fees and are developed in concert with investigators stated needs and goals. The RD Core provides research career development for both local junior faculty and for investigators at any institution. By these means, the core aims to assist in creating the next generation of researchers in geroscience.

Lastly, the RD Core takes a leadership role in evaluating the success of these programs by tracking grants and publications of awardees; recommending changes to our SA Nathan Shock Center Executive Committee when necessary. The overall metrics of the success of the core's activities are the awardees' success in publishing high-impact papers and obtaining sustained extramural grant support. In association with the Administrative Core, the RD Core maintains

continuing records of the success of awardees and makes recommendations for adjustment of the programs as needed. The RD Core also works closely with the Administrative Core with regard to generating well-publicized calls for proposals to each of our support mechanisms as well as disseminating results from our cores and investigators.

3. Aging Animal Models and Longevity Assessment Core. Core Leaders, **James F. Nelson Ph.D** (nelsonj@uthscsa.edu), **Adam Salmon, Ph.D.** (salmona@uthscsa.edu).

The Aging Animal Models and Longevity Assessment Core (Animal Core) provides investigators access to and technical support for maintaining and evaluating traditional mammalian aging models, as well as novel animal models of exceptional biogerontological interest. The Animal Core plays a key role in the SA Nathan Shock Center's overall aim to serve as a "one-stop shop" for comprehensive aging-related studies by generating, maintaining and monitoring rigorously characterized aging animals for investigators, which can, in turn, be referred to other cores in the SA Nathan Shock Center for integrated studies of mammalian aging. Moreover, the Animal Core can work with internal and external investigators, including any of the other Nathan Shock Centers, to provide reliable and repeatable aging animal models for research purposes.

The Animal Core has a long history of assisting investigators in their studies of aging mammals at every step of aging studies, from consultation and planning, through experimentation and technical assistance, and finally through data preparation and analysis. Services offered to investigators range from providing tissue or cell samples to conducting complete mouse or rat longevity studies. The Animal Core also provides dietary or pharmacologic interventions longitudinally to aging animals as a means towards mechanistic dissection of aging processes. Historically, the Animal Core has served investigators interested in such approaches using traditional mammalian animal models, i.e., mice and rats. In recent years, the Animal Core has leveraged Nathan Shock Center and institutional support to maintain and provide access to animals of biogerontological interest that are unique among the Nathan Shock Centers. The Animal Core provides access, including cells, tissues, and animals, to two species of extremely long-lived rodents, i.e., naked mole-rats and Damara mole-rats, and to a colony of common marmosets, a non-human primate of increasing interest for aging studies. New to the Animal Core in this cycle are genetically modified mouse models to probe the biological bases of sex differences in aging.

The first goal of the Animal Core is to breed and age new and established investigator-driven rodent models to elucidate mechanisms of aging. A significant barrier to aging research, particularly at institutions without large, research groups focused on aging, is access to aged animals and their tissues. The Animal Core assists investigators locally and nationwide by providing access to samples from four rodent species of interest to biogerontology, mice, rats, naked mole-rats, and Damara mole-rats, all maintained in facilities designed for aging rodent studies. Moreover, the Animal Core plays a vital role in rearing and maintaining mice and rats for investigators under interventions specified by investigators for their studies. These services include genetically modified rodents or rodents treated with interventions (nutritional and/or pharmacologic). Animal Core staff can provide complete animal care services to investigators, including breeding, weaning, animal identification, and genotyping, and implanting coded subcutaneous microchips (for animal ID) in animals for all aging studies. The Animal Core can coordinate with and perform additional services offered by other SA Shock Center Cores. Animals can be provided to investigators at any age requested, or sacrificed to collect tissues/samples for investigators. The Animal Core provides added value to requested aging studies by validating and characterizing rodents prior to investigator-led studies and, in the case of investigators from underserved institutions, can provide valuable, repeatable, and reputable animal husbandry that may not be available in their local vivarium. As part of this goal, the Animal Core also has previously banked tissues and primary cells from a variety of mammalian aging studies, including the five animal species that are central to the core and samples from intervention studies, all of which can be requested by investigators.

A second goal of the Animal Core is to conduct lifespan studies of genetically, nutritionally, or pharmacologically manipulated mice and rats. Since its inception, the Animal Core has conducted > 75

longevity studies in mice and rats, including calorie-restricted mice and rats, drug- and hormone-treated rodents, transgenic and knockout mice, and recombinant inbred strains. The Animal Core uses a set of standard operating procedures that ensures rigor and reproducibility; the median and the upper 10th percentile lifespan achieved by this Core usually match or exceed those elsewhere [4–7]. Prior to each study, the investigator meets with the Animal Core and Administrative Core to determine sample sizes required to meet minimum power requirements as well as to determine how best to analyze survivorship. As an example of the synergy of the SA Shock Center, the Animal Core can coordinate with other cores to assess physiological parameters (IPAC), pharmacokinetics and pharmacodynamics (Pharmacology Core), or pathological analysis (Pathology Core) as part of lifespan studies.

A third goal of the Animal Core is to provide aging marmosets to facilitate research testing the mechanisms of aging in non-human primates. We can assist and educate investigators in testing their novel findings from basic biology in the common marmoset (Callithrix jacchus) with a long-term view towards translation. The Animal Core can assist investigators with project design in studies on the marmoset, including project feasibility, proposed study procedures, and likely outcomes. The Animal Core can also provide in vivo data collection on basic physiological parameters (including body weight, composition, metabolic function, etc.) as well as dietary and pharmaceutical interventions. Again, the Animal Core can coordinate with the other research cores of the SA Nathan Shock Center to provide additional assessments in marmoset studies. The Animal Core can also provide banked samples, including blood, urine, feces, and tissue, from aged marmosets as well as fixed and frozen tissues collected from euthanized animals. These include samples from animals that had undergone interventions, such as administration of rapamycin, and their relevant controls. The Animal Core can also provide training to investigators regarding the use of marmosets as potential appropriate models for their own studies.

The training provided by leadership and staff of the Animal Core also contributes to the final goal of this Core, which is to educate and train investigators on the requirements for rigor and reproducibility in aging animal research. The Animal Core has a long history of training and consulting in experimental design and analysis of mammalian aging studies, and assisting in writing grant proposals involving aging rodents and marmosets. These activities add scientific rigor and reproducibility to aging animal studies; we can assist at multiple stages, including grant and manuscript preparation, experimental design, including sample sizes for longevity and cross-sectional studies, and appropriate models, and consultation on best practices for aging animal research.

Together, these goals highlight the role of the Animal Core in the SA Nathan Shock Center and how it can assist investigators in their aging research (Fig. 3). The Animal Core, in concert with the other cores, continues a long history of catalyzing biogerontological discovery, thereby fulfilling the SA Shock Center's overall mission to elucidate the molecular and cellular mechanisms that modulate aging, and thereby providing the basis for development of pharmacologic targets that extend healthy lifespan.

4. Pathology Core. Core Leaders, **Yuji Ikeno, M.D., Ph.D.** (ikeno@uthscsa.edu), **Gene Hubbard, D.V.M., M.S.** (hubbardg@uthscsa.edu).

Pathology increases exponentially with age and is a significant driver of age-related diseases. A major reason for lack of pathology data in many aging studies has been very limited access to pathologists with expertise in aging research. The overall goal of the Pathology Core is to assist investigators in determining whether experimental intervention on aging in mammalian models alters the development and progression of age-related pathological lesions. The pathological assessment of old animals helps investigators determine whether changes (functional, biochemical, molecular, etc.) are associated with, or independent of, underlying pathological conditions and histological changes and provide insights into potential biological/molecular mechanism(s) of action of aging interventions. In addition, pathological analysis of young animals can reveal how genetic, pharmacological, and other interventions affect early life development. Thus, it is essential to obtain accurate and thorough histopathological assessments of animals throughout the life course (i.e., young, middle, and old age).

The SA Nathan Shock Center Pathology Core [8–11] has an extensive history of service to

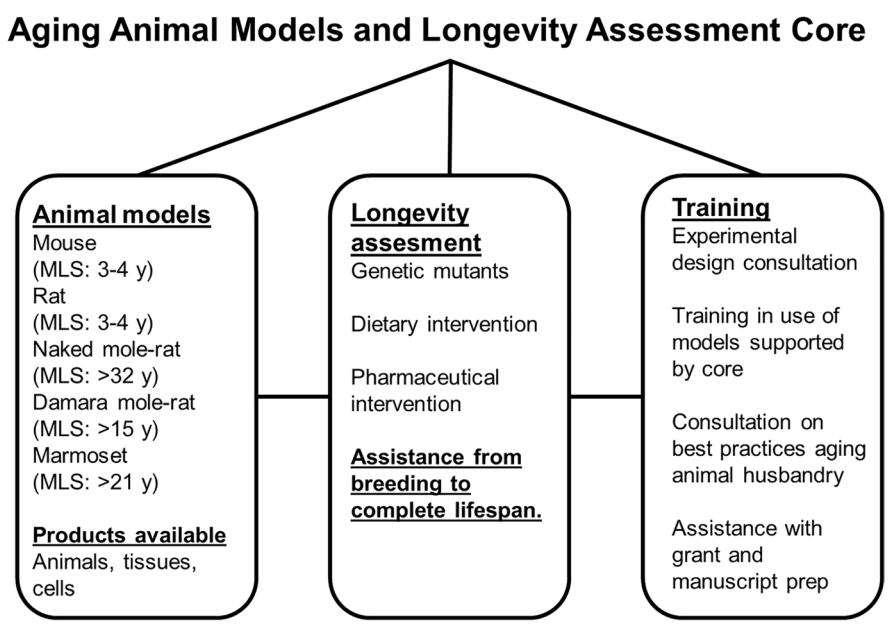

Fig. 3 Summary of services provided by the Aging Animal Models and Longevity Assessment Core

investigators and contributions to seminal papers regarding the biology of aging. With the rapid expansion of aging biology research locally and across the country, there will be growing demand for greater understanding regarding the pathological mechanisms of aging, for which the Pathology Core can provide key assistance to investigators locally and worldwide. Services of the Pathology Core include detailed pathological analyses, including end-of-life and cross-section, of age-related lesions in mice, rats, and other animal models, e.g., non-human primates. End-of-life pathology data provide investigators with a profile of pathological lesions of animals in survival studies at the time of death, e.g., the prevalence and severity of both neoplastic and non-neoplastic diseases, the probable cause of death, comorbidities, and disease and tumor burden. Cross-sectional pathological analyses provide investigators with essential information about disease incidence, severity, and progression at the organ and whole-body levels. The Pathology Core also provides service to investigators in the form of histopathological, morphometric, immunohistochemical, and molecular analyses of specific lesions and tissues obtained from rodents and other animal models. These include neoplastic lesions, inflammation, senescent cell accumulation, glomerulonephritis, gliosis in the brain, and characteristics of adipose tissues (e.g., macrophage infiltration, senescent cell accumulation, and fat cell morphology) and are used to assist investigators in dissecting the pattern of pathological changes with age in their particular model system.

In addition to direct pathological analyses, the Pathology Core can also assist investigators in developing a comprehensive archive of histopathological data and images of histopathology slides as a resource for the following: (a) trend analyses by investigators; (b) basic pathological information for new studies; and (c) a tissue archive containing paraffin and frozen blocks, and frozen tissues. Depending on the preference of the investigator, these archives can remain private for investigator use only, or be deemed for public use by any interested investigator. The Pathology Core also maintains an independent archive of samples supported by the SA Nathan Shock Center that are available for use by all interested investigators and which contain samples prepared from normally aging rodents.

On a more basic level, the Pathology Core provides investigators with expert histological support for all studies, along with providing training to investigators

in both preparation of samples and data interpretation. Working with consulting investigators, the Pathology Core can prepare paraffin-embedded and frozen blocks, make tissue array slides and unstained paraffin or frozen sections, perform histological staining (including special staining), and perform laser-capture microdissection. The Pathology Core also works with faculty and trainees studying the biology of aging and pathogenesis of aging-related disease regarding technical aspects of these procedures, interpretation of data from pathological analyses in models of aging, and, perhaps most importantly, providing assistance with preparation of their data for their own grant applications and manuscripts.

Overall, the Pathology Core provides an important service to the greater aging research community and serves a critical role within the SA Nathan Shock Center's goal of one-stop shop service for mammalian aging studies in mice, rats, mole-rats, and non-human primates (Fig. 4). Moreover, by providing these resources and the resulting data widely to the scientific community, we believe the Pathology Core can assist in better understanding how geroscience can improve health.

5. The Analytical Pharmacology and Drug Evaluation Core. Core Leaders, **Martin Javors, Ph.D.** (javors@uthscsa.edu), **Brett Ginsburg, Ph.D.** (ginsburg@uthscsa.edu), **Marisa Lopez-Cruzan** (lopezcruzan@uthscsa.edu).

A major breakthrough in aging research has been the identification of key signaling pathways involved in the biology of aging that can be targeted by various compounds, including naturally derived products and pharmaceuticals. Examples of drugs that have been shown to have robust effects on lifespan and healthspan of rodents include mTOR inhibitors, senolytics/senomorphics, and inhibitors of gastrointestinal glucose absorption [8, 12, 13], among several others. These compounds provide powerful tools for research in the biology of aging and the pathophysiology of age-related disease.

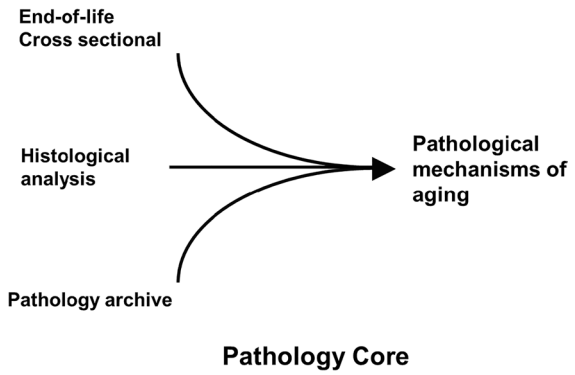

Fig. 4 Research and training roles supported by the Pathology Core

The Analytical Pharmacology and Drug Evaluation Core (Pharmacology Core) is a unique core among all Nathan Shock Centers and has an overall goal of promoting the application of existing and novel drugs to studies of aging and age-related diseases. The use of an approach to study aging that focuses on pharmacology offers several experimental advantages to investigators. First, pharmacology offers investigators the flexibility regarding the time course of treatment, i.e., an investigator can choose at which stage of life to begin, end, or cycle any particular pharmacological intervention. Second, a pharmacology-based approach offers the ability to combine a particular drug with other interventions, including dietary, genetic, or poly-pharmacy approaches. Third, pharmacological approaches can be used in any animal model and are not limited to conventional laboratory models. That is, pharmacology approaches can be tested in any of the species supported by the SA Nathan Shock Center or others of interest to investigators who request service from the Pharmacology Core [14, 15]. Furthermore, the potential to move a drug between laboratory animal models into human studies provides a solid basis of the translational relevance of the work. Consequently, the Pharmacology Core serves the increased demand to develop and test potential aging-modulating compounds that have grown over the last decade.

The primary service provided by the Pharmacology Core is to assist investigators interested in pharmacological approaches to aging by developing dosage forms that effectively deliver drugs to specific mechanistic targets in animal models of aging. The services provided by the Pharmacology Core can be performed in studies using models supported by the SA Nathan Shock Center (e.g., mice, rats, mole-rats, marmosets) or others supported by other institutions. To reach this goal, the Pharmacology Core has a standard set of services to assist investigators.

For novel compounds or interventions, we can assist investigators with developing and validating bioanalytical assays for drugs and small molecules. Similarly, we can assist investigators in designing and creating usable, effective dosage forms. Included in this is working with investigators to ensure effective dosage forms in chosen form of intervention (i.e., incorporated in diet, solution, water, etc.) by measuring and confirming concentrations and stability of drugs in dosage forms. Lastly, the Pharmacology Core can assist investigators with quantifying and confirming drug concentrations in blood and tissues collected from experimental animals.

While each service of the Pharmacology Core can be requested independently, the Pharmacology Core also works as a key component of the overall goal of the SA Nathan Shock Center. The Pharmacology Core works in synchrony with the other research cores to assist investigators with best practices and approaches regarding the design and implementation of their research projects. For example, coordinated efforts among the cores can assist in developing methods to measure (Pharmacology Core), administer (Animal Core), and test the effects (IPAC, Pathology Core) of treatment with any compound. The Pharmacology Core has developed innovative modifications to the process of bioanalytical assay development and validation using HPLC/MS/MS, the design and manufacture of food pellets with homogeneous distribution and intended concentrations of drug, and the confirmed delivery of drug into mice with effective pharmacokinetic drug distribution, all of which have improved the efficiency of drug studies across the country [14, 16–18].

Importantly for the goals of the Nathan Shock Centers, the Pharmacology Core also serves to provide consultation and education regarding experimental design, data interpretation, and grant/manuscript writing for investigators using drugs in aging research. The areas of expertise include the particular research services described above as well as assistance with determination of dosage formulation, common and alternative pharmacologic approaches, such as level/timing of doses in studies, pharmacokinetic experimental design, and interpretation of data and preparation of papers and grants. These services are not only particularly important for pilot projects supported by the RD Core but also relevant to any investigator interested in pharmacological interventions

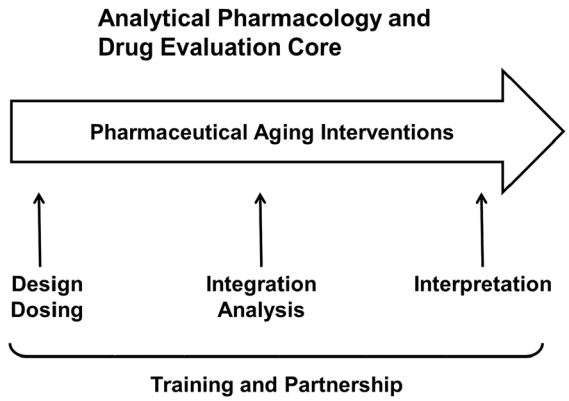

Fig. 5 Overall process of services provided by the Analytical Pharmacology and Drug Evaluation Core

to the aging process. Overall, the Pharmacology Core offers services and expertise that may be scarce at other universities (Fig. 5). Access can be especially important for early-stage investigators, where core services can provide preliminary data or cost-effective access to expertise. Core services can also be crucial to established investigators new to aging research, to overcome bottlenecks and encourage new areas of research.

6. The Integrative Physiology of Aging Core. **Nicolas Musi, M.D.** (musi@uthscsa.edu), **Veronica Galvan, Ph.D.** (galvanv@uthscsa.edu), **Elizabeth Fernandez, Ph.D.** (fernandeze@uthscsa.edu).

The Integrative Physiology of Aging Core (IPAC) was created in response to a shift in focus from study of cellular mechanisms of aging, realizing that maintaining physiological function (health span rather than lifespan) will have a robust positive impact on human health [19]. This shift resulted in a marked increase in demand from local and national investigators (most of whom were new to aging research) for tools to (a) assess functional outcomes in rodent models generated to examine basic molecular mechanisms of aging, and (b) conduct studies on effects of pharmacological interventions that target aging-modulating pathways. The IPAC has made major contributions to the expansion of knowledge in the biology of aging through activities involving the broad research community, providing services to internal and external

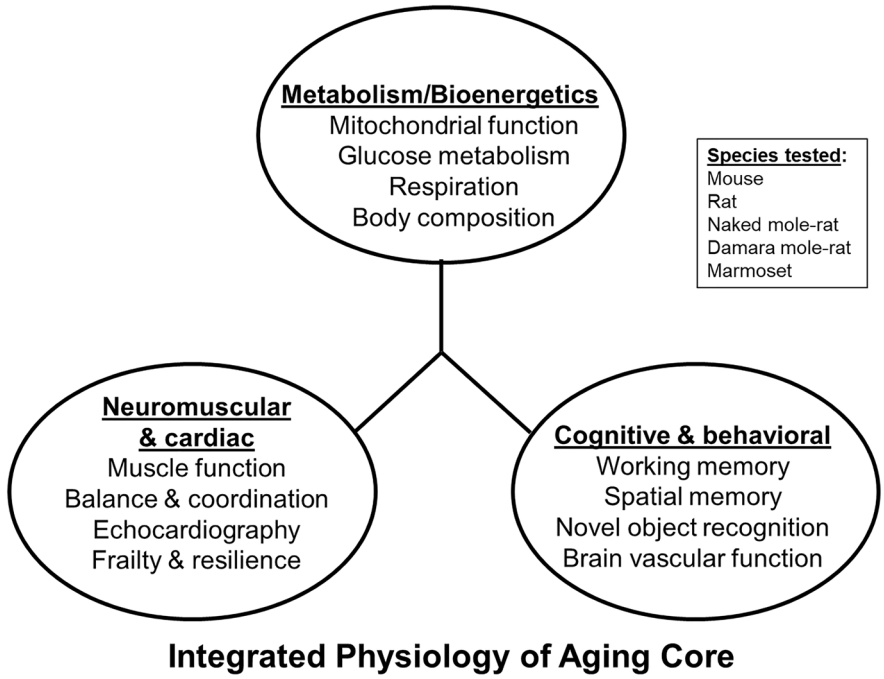

Fig. 6 Generalized services provided by the Integrative Physiology of Aging Core

investigators and training their laboratories to conduct functional assays relevant to aging [15, 18, 20–27]. This has included novel outcomes in all functional domains tested by the IPAC and in multiple animal models supported by the SA Nathan Shock Center.

To assess health span, the IPAC expands phenotypic assessment in rodents so that we can effectively model critical functions that decline with age in humans, but for which animal model counterparts are underdeveloped. The IPAC also advances the goal of performing effective functional assessment at the organismal level, using powerful longitudinal design and analysis tools to track multiple functional outcomes during aging in animal models, so that associations and mechanisms of cross-talk among different physiological systems can be identified. With the Animal Core, the IPAC also bridges a large translational gap between rodent and human studies by expanding functional assessment to models such as the marmoset monkey, a short-lived primate species eminently suitable for aging research, as well as by capitalizing on extreme rate of aging differences between closely related species, such as mice and naked mole-rats, to identify critical healthspan determinants and mechanisms.

The goals of the IPAC are to assist investigators with the design of experiments and the selection of tests to measure age-associated functional changes, to coordinate IPAC activities with other resources available at the SA Nathan Shock Center and our institution to maximize the impact of each individual project, to carry out integrative functional assessments from systemic to molecular targets, to analyze and interpret data, and to disseminate knowledge through hands-on training and education of researchers on concepts and tools used in the field. The IPAC builds on its successful record of accomplishment of providing services to advance basic and applied biology of aging research through the assessment of key age-relevant functional outcomes. The IPAC innovates through the incorporation of novel tools, such as functional tests of age-sensitive parameters, both in naked mole-rats and in marmosets, as well as single-cell studies and measures of frailty in mice and in marmosets.

The IPAC provides services on functional domains: (a) metabolism/bioenergetics; (b) neuromuscular and cardiac; and (c) cognitive and non-cognitive brain functions. A list of all services and their prices are provided on the website for the IPAC (https://nathanshock.barshop.uthscsa.edu/integrated-physiology-aging-core/). Services are also matrixed by level: molecular, tissue/organ, and whole organism. Depending on the project, the Core can perform

focused functional phenotyping within one or more domains and levels, or batteries of coordinated functional assessments that include measures from all three domains (Fig. 6). IPAC operations involve three phases: (1) consultation and planning; (2) experimentation; and (3) data analysis and interpretation. During the consultation and planning phase, IPAC Co-leaders work closely with investigators and the Administrative Core to design rigorous, adequately powered studies that best address their hypotheses in a cost-effective manner. In line with the NSC's goal to serve as a "one-stop shop" for comprehensive aging-related studies, leaders of other Cores are engaged during the planning phase to refine the design of the study and identify opportunities to engage other cores (e.g., Pathology, Pharmacology). During the experimentation phase, IPAC and investigators work together to monitor progress and collectively analyze data. Investigators often receive hands-on training on conduct of assays and data analysis, allowing them to incorporate key competencies into their laboratories and then train others (knowledge dissemination).

The IPAC advances the biology of aging and geroscience fields by employing emerging animal models of exceptional interest in aging. For example, a unique feature of the Core is the development of the common marmoset as a model of aging to help close the large translational gap between animal and human studies.

Other innovations at the IPAC include (1) measures of cellular, organ, and whole body resilience; (2) functional lipidomics to assess the role of lipid metabolism and signaling in aging; and (3) single-cell methodologies for rodents and marmosets. The IPAC is an essential pillar of the San Antonio NSC's overarching mission to function as a comprehensive platform that integrates physiological (healthspan), longevity (lifespan), pathological, and molecular phenotypes for the study of aging mechanisms.

Take home message from the SA Nathan Shock Center

The SA Nathan Shock Center is at the forefront of aging biology research and serves investigators nationwide through its resource cores and incorporation of continually evolving technologies and services. Thus, the SA Nathan Shock Center is well poised to continue to facilitate transformative research in aging biology through a comprehensive research platform that is unique in the aging research community. The SA Nathan Shock Center is able to longitudinally integrate longevity (lifespan), physiologic (healthspan), pathologic, pharmacologic, and molecular phenotypes using mammalian models of aging from concept to completion. We fully anticipate that by serving the scientific community with our enhanced platform, the SA Nathan Shock Center will continue to greatly facilitate the identification of new molecular and cellular mechanisms that influence aging, yielding novel strategies and therapeutic targets. Our emphasis on pharmacologic approaches to probe aging mechanisms is consistent with and supports the perceived need to discover, develop, and test therapeutic interventions to delay aging, with the long-term goal of translating these outcomes to extension of healthy life expectancy.

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