JOE R. & TERESA LOZANO LONG SCHOOL OF MEDICINE

# FUTURE

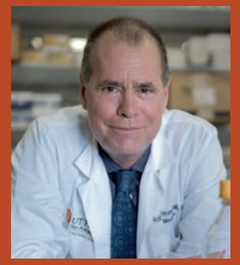
SPECIAL RESEARCH EDITION

## Reversing the impacts of aging:

The science of longevity

UT Health San Antonio

The University of Texas Health Science Center at San Antonio



# Advances in the fight for a longer health span

FUTURE

The one thing life guarantees is that it ends. But what about the diseases that come with aging, such as obesity, muscle wasting, cancer and dementia? Must we simply accept those as inevitable, too?

Here at the Joe R. and Teresa Lozano Long School of Medicine, decades of geroscience research has uncovered a far greater understanding of the role of aging in the development of chronic disease and how to reduce our risk for disabling diseases as we get older. This research has led to interventions that increase health span, the amount of time we have as an active and healthy adult.

While we can't reverse or slow our chronological age, researchers here have found that slowing our biological age is possible. For instance, our scientists have discovered that the drug rapamycin can extend health span. And in response to the decreased organ function that often comes from senescent cells, investigators here have developed a novel senolytic drug that degrades BCL-XL, which keeps these senescent cells alive. These drugs, in combination with the cumulative benefits of lifestyle interventions, can help maintain functional vitality for the duration of one's life.

This is critically important because, much like other graying populations across the globe, the United States has an aging problem. Many older adults have lost mobility and independence, and they often develop some form of dementia. Aging populations also face increased diagnoses of cancer, cardiovascular disease and diabetes. Living for longer durations with these chronic diseases not only robs us and our loved ones of years of meaningful interaction, but it also comes with a financial burden on our families, harms workforce productivity and increases the portion of the economy devoted to caring for the chronic diseases of aging.

Keeping our independence and enjoying our lives as we age should be motivating factors for all of us to make lifestyle choices that drive healthy longevity. The capacity to decrease rates of dementia, sarcopenia, obesity and steatohepatitis, diabetes, cancer, heart disease and other chronic conditions already exists, but capitalizing on this capacity requires consistent lifestyle changes combined with early treatment of these conditions.

We know that exercising at least three times a week, following a healthy eating plan such as the Mediterranean diet and getting eight hours sleep every night — along with daily social engagement and early treatment of chronic conditions like hypertension and hyperglycemia — are controllable factors that can increase health span. For those genetically predisposed to age-related diseases, these interventions are that much more important.

The articles in this issue of *Future* magazine delve into the science of aging, exploring what our research is unlocking with new treatments we are testing that can markedly reduce the diseases of aging and increase health span. These essential discoveries point to how we can address the specific health care needs of our current aging population and provide instruction for our younger generations on how to chart a healthier future.

Robert Hromas

Robert Hromas, MD, FACP
Dean, Joe R. and Teresa Lozano
Long School of Medicine

**HEAR MORE ABOUT INCREASING HEALTH SPAN**

***For more on the topic of living healthier longer,*** *scan the QR code to listen to an extended conversation with the directors of the university's Barshop Institute for Longevity and Aging Studies and its Biggs Institute for Alzheimer's and Neurodegenerative Diseases.*

IN THIS ISSUE




**ON THE COVER**

Researchers are unlocking the mysteries of aging at every stage of investigation, from basic science to clinical trials. This study participant provides invaluable data into the role of exercise in combating age-related disease for a national study being conducted at The University of Texas Health Science Center at San Antonio.

# MEASURES OF SUCCESS

## JOE R. AND TERESA LOZANO LONG SCHOOL OF MEDICINE

BEST GRAD SCHOOLS U.S.News & WORLD REPORT MEDICAL PRIMARY CARE 2023-2024

**#36**
IN PRIMARY CARE

BEST GRAD SCHOOLS U.S.News & WORLD REPORT MEDICAL RESEARCH 2023-2024

**#47**
IN RESEARCH

## 2023 RESEARCH FUNDING

NATIONAL INSTITUTES OF HEALTH
**$126.5M**

TOTAL ORGANIZED RESEARCH FUNDING
**$169.3M**

TOTAL SPONSORED PROGRAMS FUNDING
**$269.6M**

U.S. DEPARTMENT OF DEFENSE
**$8.8M**

ALL FEDERAL FUNDING
**$216.2M**

## TOP 40 DEPARTMENTAL BLUE RIDGE RANKINGS

**#27** OBSTETRICS & GYNECOLOGY

**#28** BIOCHEMISTRY & STRUCTURAL BIOLOGY

**#29** GENETICS (MOLECULAR MEDICINE)

**#29** PHYSIOLOGY (CELLULAR & INTEGRATIVE PHYSIOLOGY)

**#30** PHARMACOLOGY

**#30** UROLOGY

**#31** POPULATION HEALTH SCIENCE

**#36** ANATOMY/CELL BIOLOGY (CELL SYSTEMS & ANATOMY)

**#37** MICROBIOLOGY (MICROBIOLOGY, IMMUNOLOGY & MOLECULAR GENETICS)

**#38** NEUROLOGY



## Sam and Ann Barshop Institute for Longevity and Aging Studies

Research at the Sam and Ann Barshop Institute for Longevity and Aging Studies aims to bring fundamental discoveries in the basic biology of aging into clinical practice.

The Barshop Institute holds the unique distinction of being the recipient of three centers funded by the National Institute on Aging, including the Nathan Shock Center, the Claude D. Pepper Older Americans Independence Center and the Interventions Testing Program. It is the only institute in the nation to have these three centers, which are the foundation of the Barshop Institute's mission to understand the basic biology of aging and discover therapies to treat and cure debilitating aging-related diseases.

The Nathan Shock Center provides core services to enhance research of the fundamental biological questions of aging, promoting investigation into the molecular and cellular mechanisms that control the aging process and its role in the development of chronic disease and disability.

The Claude D. Pepper Older Americans Independence Center is furthering research efforts toward clinical care. The designation enables the translation of research into practical applications in the lives of older Americans and aims to develop better ways of restoring independence in senior adults.

The Interventions Testing Program supports research to test potential drugs and evaluate treatment strategies that could prevent or delay adverse age-dependent changes in cells and tissues, working to diminish the burden of disease in older populations.

MEMBERS
**25**

GRANTS
**67**

PUBLISHED PAPERS
**104**

### BIGGS INSTITUTE FOR ALZHEIMER'S AND NEURODEGENERATIVE DISEASES

The Glenn Biggs Institute for Alzheimer's and Neuro-degenerative Diseases is one of 33 National Institute on Aging-designated Alzheimer's Disease Research Centers and the only one in Texas.

The Biggs Institute provides a comprehensive network of clinical care for patients and their families, with access to the most advanced treatment in clinical trials. Working closely with the university's Barshop Institute, researchers at the Biggs Institute investigate the underlying causes of neurodegenerative diseases to find new therapies for both treatment and prevention.

## CENTERS AND INSTITUTES

Scan here to see the full list of centers and institutes at the Joe R. and Teresa Lozano Long School of Medicine.

# Living longer and staying stronger

*By Jessica Binkley Lain*

Breakthroughs in research on aging at the Sam and Ann Barshop Institute for Longevity and Aging Studies are pushing the field of geroscience forward. Here, investigators are gaining an understanding of why getting older is the biggest risk factor for so many chronic diseases.

Why do our bodies become frail as we age? For Elena Volpi, MD, PhD, FGSA, this question drives her career. As the recently appointed director of the Barshop Institute at UT Health Science Center San Antonio, she aims to uncover the fundamental mechanisms behind aging that cause the wide range of age-related diseases that can lead to disablement and death. Her goal is to keep older patients independent and active.

"The Barshop Institute is at the forefront of geroscience," Volpi said. "We study the basic mechanisms of aging, starting from cell systems, through animal models and, finally, translating them to humans."

Volpi has focused her research largely on sarcopenia, or the involuntary loss of muscle that occurs in older adults, and on finding novel methods to prevent it by targeting its underlying mechanisms.

"As we age, skeletal muscle becomes resistant to the normal anabolic action of nutrients, insulin and resistance exercise. This condition is called anabolic resistance," Volpi said. "Inactivity, such as bed rest, worsens anabolic resistance and sarcopenia."

Anabolic resistance leads to a reduced capacity of the blood vessels in our muscles to vasodilate, or widen to increase blood flow, in response to eating and insulin. With blood vessels unable to properly vasodilate, muscle tissue is not sufficiently exposed to the dietary nutrients that enter the bloodstream from the gut during a meal, a malfunction known as endothelial dysfunction. It also limits the availability of insulin to the muscle, further reducing the overall anabolic efficacy of the two crucial stimuli required for muscle growth after food intake, Volpi explained.

Anabolic resistance also causes reduced strengthening of muscle by dietary amino acids and resistance exercise. This loss of muscle strength comes from reduced signaling through the mTORC1 pathway within the muscle cells. Volpi's research found that improving endothelial function using vasodilatory drugs (antihypertensives) or aerobic exercise could restore normal mTORC1 signaling and anabolic effect of nutrients and insulin on the muscle of older adults.

"We also found that by increasing the amount of dietary amino acids or protein contained in a meal, we could improve the overall muscle protein anabolism that occurs after the meal. These studies have led us to testing amino acid/protein supplementation, aerobic exercise, intensive physical therapy or a combination of these treatments in clinical trials in healthy older adults and in geriatric patients recovering from an acute illness."

> Regular aerobic and resistance exercise and eating the optimal amount of protein can go a long way toward maintaining muscle, physical function and independence as people age.

## Maintaining muscle maintains independence

So far, Volpi's research suggests that taking adequate preventive measures, like regular aerobic and resistance exercise and eating the optimal amount of protein, can go a long way toward maintaining muscle, physical function and independence as people age.

"Based on our studies, balancing protein across all three meals and aiming for an intake of 25–30 grams of protein per meal could help stave off sarcopenia," she said.

Exercise is also fundamental in preventing anabolic resistance. A recommended exercise routine includes at least three days of moderate exercise such as walking, jogging, swimming or cycling, and resistance exercise such as weightlifting twice a week.

"When appropriate, use of drugs such as anabolic hormones [e.g., testosterone] to recover from illnesses or injuries can also help," Volpi added. While these hormones should only be used under supervision of a physician, they can help an elderly patient recover from chronic illness more rapidly.

"In the future, I would like to focus research on treatments that can specifically improve muscle growth and strength by targeting at

"I would like to focus research on treatments that can specifically improve muscle growth and strength by targeting at the same time endothelial function and the basic cellular mechanisms of muscle growth."

**Elena Volpi,** MD, PhD, FGSA, director of the Barshop Institute and professor in the Division of Geriatrics, Gerontology and Palliative Medicine

## AGING INTERVENTIONS

**Randy Strong,** PhD, director of the Interventions Testing Program at the Barshop Institute and professor in the Department of Pharmacology and Department of Cell Systems and Anatomy

When the National Institute on Aging's Biology of Aging Program established the Interventions Testing Program in 2003, UT Health Science Center San Antonio was one of only three sites in the nation to be awarded with a center to take part in the program. Investigators at these centers are tasked with testing treatment strategies and potential drug therapies that promote longevity.

Along with researchers from centers at the Jackson Laboratory in Maine and the University of Michigan, the three sites work cooperatively to perform testing in triplicate, providing instantaneous replication. Each site manages a colony of heterogeneous mice and a phenotyping core. To date, the program has found nine compounds that significantly increase median lifespan in mice: acarbose, aspirin, canagliflozin, captopril, glycine, nordihydroguaiaretic acid, Protandim, rapamycin and 17alpha-estradiol.

"Over time we'll get many more applications for these compounds. Something we've found is that any intervention that increases lifespan is likely to be useful for the treatment of a number of different diseases, not just one," said Randy Strong, PhD, professor of pharmacology in the Long School of Medicine and director of the Interventions Testing Program at the Barshop Institute.

the same time endothelial function and the basic cellular mechanisms of muscle growth using gerotherapeutics along with exercise and nutritional interventions."

### New treatments from an enduring intervention

In addition to finding interventions for sarcopenia and maintaining muscle, investigators at the Barshop Institute are at the forefront of discovering the mechanisms behind longevity and investigating treatments that could extend healthy lifespan, or what is known as health span.

Some new treatments on the horizon include existing drugs that are being repurposed to target the hallmarks of aging. For instance, canagliflozin is a glucose-lowering drug that targets many cellular processes linked to aging, and rapamycin is an immunosuppressant that at low doses has been shown to extend lifespan in animals, Volpi said.

Adam Salmon, PhD, professor of molecular medicine and associate director of the Barshop Institute, studies the life-extending effects of rapamycin by examining its effects on mTOR, or the mechanistic target of rapamycin, which is the same pathway Volpi examined in her studies of anabolic resistance.

"The mTOR-signaling pathway has been shown to have a central regulatory role in aging and age-related disease," Salmon said. "It regulates growth signals to tell the cell when it's OK to divide and grow. Or, when nutrients are low, it reduces growth signals to tell the cell to go into survival mode."

In 2009, health science center researchers administered rapamycin to genetically heterogeneous mice and found that inhibiting mTOR extended median and maximal lifespan. Today, Salmon and his team continue to study the lifespan-extending effects of rapamycin in

"Based on our studies, balancing protein across all three meals and aiming for an intake of 25–30 grams of protein per meal could help stave off sarcopenia."

**Elena Volpi,** MD, PhD, FGSA, director of the Barshop Institute and professor in the Division of Geriatrics, Gerontology and Palliative Medicine

marmosets, a non-human primate used for preclinical translation studies.

Rapamycin, as well as other lifespan-extending drugs studied at the Barshop Institute, may work on the same mechanistic principles as a long-standing, well-established intervention to increase longevity: caloric restriction.

"This intervention has been known scientifically for around 100 years," Salmon said, though a proven explanation as to why it works remains unknown.

"We know this intervention affects many different pathways and many different physiologies. The mechanisms for aging aren't a single pathway, so the reason why caloric restriction extends lifespan is likewise probably working through its effects on multiple pathways."

After seeing the lifespan-increasing effect of inhibiting mTOR, Salmon conjectures that calorie restriction might reduce signals through mTOR because there are fewer nutrients available.

In any case, researchers have established that rapamycin increases longevity in mice. But does it work in humans?

"We've been using non-human primates to bridge the gap. Mice are the workhorses of much of research, but primates have more similar physiology and genetics to humans, they live much longer than

**Adam Salmon,** PhD, associate director of the Barshop Institute and professor in the Department of Molecular Medicine

mice and they develop many of the same things that people develop with age like cardiovascular disease," Salmon explained.

While marmosets are not a perfect human model, this animal study, which is currently in its seventh year, will provide a much better understanding of rapamycin's potential for increasing lifespan and healthy aging in humans, Salmon said.

## Finding the off-and-on switch for obesity

Other investigators at the Barshop Institute are focusing on metabolic homeostasis and how aging disrupts the intricate balance of metabolism of fat.

"As individuals age, the body tends to accumulate excess energy, attributed to decreased energy expenditure from inactivity and increased energy storage resulting from overeating," said Masahiro Morita, PhD, assistant professor of molecular medicine and investigator in the Barshop Institute.

"This metabolic shift leads to an elevated risk of metabolic syndromes, such as obesity and diabetes, which, in turn, heightens susceptibility to cancer and neurological diseases."

Research in Morita's lab has made significant strides in unraveling the pivotal role of the mRNA-degrading enzyme complex called CCR4-NOT, which functions as a switch for secretory protein expression. By degrading the mRNA's encoding secretory proteins, the CCR4-NOT complex effectively turns off their production once an external stimulus like feeding or exercise subsides.

"Notably, we have observed an elevated function of the CCR4-NOT complex in the obese state, leading to the excessive degradation of target mRNAs and subsequent downregulation of secretory protein expression. Our findings demonstrate that suppressing the function of the CCR4-NOT complex can alleviate metabolic syndromes caused by overeating," said Morita.

In a study published in April 2022 in *Cell Metabolism*, Morita's lab demonstrated the effects of suppressing

## PREVENTING FALLS

After prolonged illness or hospitalization, older adults are at greater risk of falls and subsequent injuries that may increase their loss of physical independence. Here are recommended steps from Elena Volpi, MD, PhD, FGSA, to help prevent falls before they happen.

**Talk to your primary care doctor** to determine if physical therapy is right for you. Determine the benefits of strength and balance training, as well as a nutritional evaluation by a dietitian. This is particularly important for those with diabetes, kidney disease or those who are involuntarily losing weight.

**Increase protein intake** with every meal. Protein-rich foods include meats, cheese, dairy and eggs, and plant-based options like legumes, nuts and seeds. Protein supplementation may also be recommended to facilitate muscle regrowth.

**Seek evaluation** for testosterone deficiency for men, which can be treated. In some cases, testosterone may also be replaced in women on a short-term basis to accelerate functional recovery.

**Carefully review with your doctor** and adjust medications and over-the-counter drugs or supplements, if necessary, as many medications can increase the risk of falling. Blood pressure medications, diuretics, sleep aids, certain antidepressants and neuropathy drugs can induce dizziness and drowsiness and possibly lead to falls. Talk with a doctor to determine if dose adjustment is necessary.

**Consider problems** like reduced vision, hearing loss, balance issues and foot deformity, which can also increase risks of falling and should be discussed with a primary care doctor.

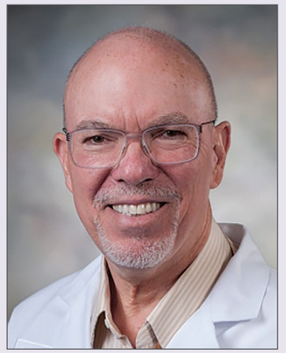
**Be aware of external factors** like footwear, loose rugs or electrical cords around the house, a lack of safety handles in the bathroom, the presence of steps and stairs or a family pet that likes to be underfoot. When appropriate, home health agencies can perform a home evaluation for fall risk and provide recommendations.


the CCR4-NOT complex in the liver. The study identified a novel compound named iD1, or inhibitor of deadenylase 1, that when administered to mice, stimulated the secretion of proteins GDF15 and FGF21, effectively suppressing appetite and boosting energy expenditure.

"These exciting results provide compelling evidence for the therapeutic potential of CCR4-NOT inhibition in combating metabolic imbalances associated with aging," Morita said. "We believe that iD1 holds tremendous potential in ameliorating age-related metabolic syndrome, offering a promising avenue for combating health issues associated with aging."



## WHY FEMALES LIVE LONGER THAN MALES



**James Nelson,** PhD, co-director of the Interventions Testing Program at the Barshop Institute and professor in the Department of Cellular and Integrative Physiology

Evidence shows that females of most animal species typically outlive their male counterparts. But why? This is an enduring question in the field of aging research, but recent studies at the Barshop Institute have shed some light on this mystery.

When it comes to anything sex-determined, investigators must first pinpoint where the sex difference originates. Does the distinction come from chromosomal differences, XX or XY, or is the difference determined by gonadal sex hormones from the testes or ovaries?

"We've discovered that most drugs that extend lifespan do so in a sex-specific way," said James Nelson, PhD, professor in the Department of Cellular and Integrative Physiology and co-director of the Interventions Testing Program at the Barshop Institute. "Most of the drugs only extend lifespan or do so more in males than in females. And we found that most of these drugs aren't causing male mice to live longer than females but are simply equalizing the male lifespan to that of female lifespans."

Two graduate students in Nelson's lab have identified that lifespan differences between the sexes are in fact determined by hormones, not genes. They determined this by castrating prepubescent male mice and observing that their lifespan, as well as their resilience to stressors, increased to equal that of female mice. While the exact mechanism is unknown, it has now been established that testicular hormones are to blame for the shorter lifespans seen in male mice.

"Further," Nelson added, "many of the drugs we've found through the Interventions Testing Program are acting as a 'castration' mimetic for longevity and resilience benefits and may be doing so without the deleterious effects that castration has on male reproduction, libido or other behaviors."

# The role of cellular senescence in aging and disease

*By Michael Seringer*

The study of space radiation and naked mole rats has helped UT Health Science Center San Antonio researchers uncover mechanisms of human aging.

While working on a project for NASA a decade ago, Sandeep Burma, PhD, realized that cell senescence, a biological phenomenon characterized by irreversible arrest of cell division, might hold the key to the pathological effects of space radiation, including dementia and cancer.

Burma, professor of neurosurgery and of biochemistry and structural biology in the Long School of Medicine, was researching the cancer-causing effects of space radiation using mouse models of brain cancer. He found that these cancers were spurred by factors secreted by senescent brain cells caused by space radiation.

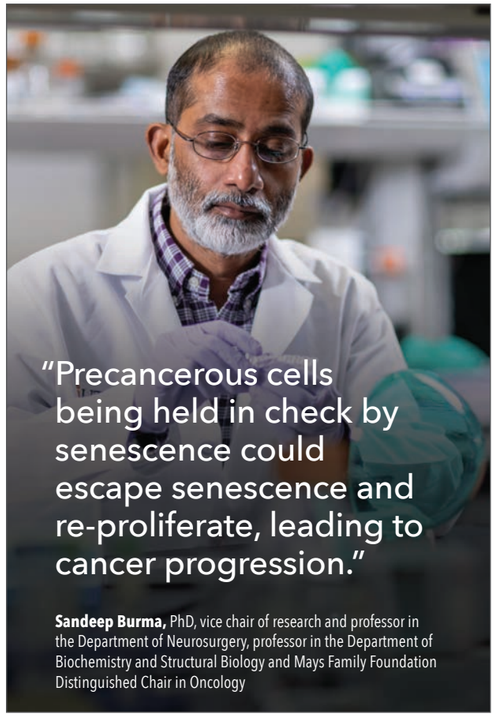
As cells divide over time, they accumulate damage to their DNA and other cellular components. Such damaged cells can enter a state of senescence in which they stop proliferating but remain active. While senescence prevents cancer in the short term, senescent cells promote aging and cancer in the long term. Investigators at UT Health Science Center San Antonio are working to uncover the mechanisms of cellular senescence and to design compounds to deplete these cells in order to potentially treat many age-related diseases and cancer.

“Cellular senescence is triggered by irreparable damage to DNA and cellular components, and shortening of the ends of chromosomes,” said Burma, who holds the Mays Family Foundation Distinguished Chair in Oncology.

“These damaged cells accumulate over time as cells divide or when they are subjected to stresses such as ionizing or UV radiation. Senescent cells generally exhibit large irregular shapes and cytoplasmic and nuclear changes and secrete factors that generate a senescence-associated secretory phenotype [SASP], which has an obvious role in the aging process.”

## The two faces of cellular senescence

Cellular senescence has been identified as a critical process in various physiological and pathological contexts, including embryonic development, wound healing, tissue repair, cancer prevention and aging. Once a cell is damaged or has a cancer-causing mutation, senescence halts its ability to divide, effectively preventing the formation of tumors.




Ironically, the cancer defense system provided by senescence also can promote cancer over time.

"Senescence is primarily an anti-cancer barrier as it prevents cells with damaged DNA or shortened telomeres from proliferating," Burma said. "However, senescent cells can paradoxically promote cancer via SASP factors, many of which can promote the proliferation, stemness, invasiveness or therapy resistance of cancer cells. SASP factors can also indirectly promote cancer development by suppressing anti-tumor immunity."

Burma's research has demonstrated that treating glioblastomas, a type of brain tumor, with radiation results in the senescence of astrocytes near the tumor. The SASP factors secreted by these astrocytes, which are resistant to cancer therapy, can promote tumor recurrence after treatment. They can cause the glioblastoma cells themselves to become senescent. These senescent tumor cells have a similar expression of SASP, which can promote tumor resistance to therapy and thus recurrence. Understanding how SASP's inflammatory and growth factors promote the proliferation and survival of cancer cells will lead to more effective cancer treatments with fewer side effects, he said.

In addition to secreting the SASP factors, some cancer cells have demonstrated the capacity to break free of senescence after therapy. These escaped cells either develop mutations that counteract the signals driving senescence or develop alterations that allow the cells to ignore the changes associated with senescence. These once-senescent cancer cells can continue to divide and grow, leading to tumor progression.

"Precancerous cells being held in check by senescence could escape senescence and re-proliferate, aggressively leading to cancer progression," said Burma. "Similarly, tumor cells that have been rendered senescent by genotoxic therapy could escape after acquiring 'cancer stem cell' properties and give rise to an aggressive recurrence."

Understanding these escaped cells could lead to the development of a "one-two punch" in cancer therapy in which genotoxic treatments are followed by a drug that kills senescent cells, termed a senolytic. Such a two-step approach aimed at selectively eliminating senescent cells from the body after the initial cancer treatment is complete may provide far more benefit to glioblastoma therapy.

## SASP and the morbidities of aging

Senescent cell SASP factors are associated with multiple age-related diseases due to their role in promoting chronic inflammation and tissue dysfunction. The chronic inflammation caused by the SASP can contribute to the development and progression of various diseases including cardiovascular disease, diabetes, neurodegenerative disorders, osteoarthritis, autoimmune disorders and other conditions, said Daohong Zhou, MD, professor in the Department of Biochemistry and Structural Biology, director of the Center for Innovative Drug Discovery and associate director of drug development at the Mays Cancer Center at UT Health San Antonio.

The SASP is made up of secreted hormones, cytokines, chemokines and other molecules that induce inflammation. These SASP factors contribute to the development and progression of a range of diseases of aging. Likewise, SASP's influence on inflammation and tissue dysfunction can contribute


to the development and progression of various conditions associated with aging such as Alzheimer's and Parkinson's diseases, said Zhou.

By targeting specific proteins within cells, Zhou's research focuses on developing small molecules that can selectively kill senescent cells. The challenge in developing these small molecules, or senolytic therapies, is reducing the toxicity of compounds so that they remain therapeutic while minimizing side effects.

"The goal is a compound that patients can tolerate," Zhou said. "It has to be really safe with minimal toxicity so people will not suffer from side effects. This is important to improving the quality of life during the human lifespan."

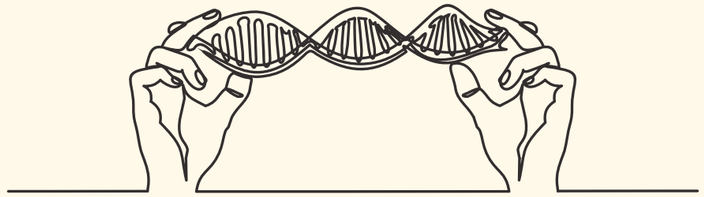
Zhou's research is taking advantage of small-molecule PROTACs (PROteolysis TArgeting Chimeras) to target and destroy specific proteins within cells, reducing the toxicity of potential therapies. PROTACs are a promising new tool in drug development allowing researchers to selectively eliminate disease-causing proteins that are challenging to target using traditional small molecules or antibodies.

Also at the forefront of research, Burma's lab is actively investigating the use of senolytic therapy for ameliorating the effects of aging and treating cancer. He is focused on developing compounds that are effective at clearing out senescent cells while leaving behind the healthy ones.

"Senolytics generally target anti-apoptotic or pro-survival mechanisms that senescent cells upregulate to survive," said Burma. "The basic premise here is that senolytics should clear out senescent cells but spare normal cells that do not upregulate these pathways."

Burma points to a recent paper that demonstrates how the naked mole rat may hold the key to

understanding the aging properties of cell senescence. These rodents are remarkable for their longevity compared to other small mammals of similar size. The naked mole rat, the longest living of all rodents, has a built-in mechanism for removing senescent cells. This ability to clear out senescence is responsible for the naked mole rat having an incredible 30-year average lifespan. The naked mole rat also demonstrates resistance to many age-related diseases, underscoring the potential of senolytic therapy for improving health and prolonging lifespan in humans.



## TARGETING TRANSPOSABLE ELEMENTS TO SLOW NEURODEGENERATIVE DISEASES

**Bess Frost,** PhD, associate professor in the Department of Cell Systems and Anatomy, Bartell Zachry Distinguished Professor for Research in Neurodegenerative Disorders, and investigator at the Barshop Institute and the Biggs Institute

Bess Frost, PhD, investigator for UT Health Science Center San Antonio's Sam and Ann Barshop Institute for Longevity and Aging Studies and its Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, is zeroing in on transposable elements to treat Alzheimer's and related diseases.

"Transposable elements are DNA sequences that make up about half of the human genome and are thought to have arisen from viral infections that occurred over the course of human evolution," Frost explained.

"While various mechanisms normally keep this viral-like DNA turned off, it becomes activated over the course of normal aging. This activation can cause the sequences to copy themselves and insert the new copy somewhere else in the genome, making a new mutation. It also causes the body to think there is a viral infection, which drives an inflammatory response."

Frost and her team studied fruit fly models of Alzheimer's disease and related "tauopathies," as well as mice and human brains. They discovered that aging activates these virus-like transposable elements, and these transposable elements then drive neuroinflammation in neurodegenerative conditions.

Because of the similarity of transposable elements to viruses, Frost is studying a repurposed antiviral medication, 3TC, in a phase 2 clinical trial for patients with Alzheimer's disease to see if the drug can reduce neurodegeneration and neuroinflammation. Studies in fruit flies, mice and human brain organoids suggest that 3TC can effectively suppress Alzheimer's-related neurodegeneration.



# Ending the silent suffering of urinary incontinence

*By Michael Seringer*

Increasing awareness about safe and effective interventions and dispelling myths about urinary incontinence are important first steps in significantly improving the quality of life for an aging population.

Urinary incontinence is common in both older women and men: Half of postmenopausal women and more than 25% of men over the age of 60 experience an overactive bladder. Despite its prevalence, urinary incontinence is not inevitable.

Sylvia Botros-Brey, MD, associate professor of urology and program director of the Female Pelvic Medicine and Reconstructive Surgery Fellowship at UT Health Science Center San Antonio, points to common misperceptions about urinary incontinence as the main reason many women with the condition fail to seek treatment. The belief that incontinence is a normal part of aging and the idea that it can be managed with over-the-counter products designed to disguise the problem prevent many women from seeking care, Botros-Brey said.

Older populations are particularly affected by urinary incontinence mythology and are often told to alter their lifestyle and to start budgeting for adult diapers or pads. This conventional thinking fails to consider the real costs of urinary incontinence and diminishes access to effective interventions, she said.

"There are too many myths about urinary incontinence, and it limits patients from wanting to go out and do things," Botros-Brey said. "Patients suffering from urinary incontinence limit their social interactions. They plan their interactions around bathroom visits. They are embarrassed to spend the night at friends' or family members' houses because they might leak in the bed. There are lots of ways these misperceptions contribute to debilitating social isolation among older populations."

Misperceptions about lifestyle and incontinence keep many patients and their physicians in a "just deal with the symptoms" mindset that dictates the trajectory of their treatment, she added. Lifestyle changes often fail to consider the patient's reality. For example, obese older adults suffering from urinary incontinence are told losing weight will

The belief that incontinence is a normal part of aging and the idea that it can be managed with over-the-counter products designed to disguise the problem prevent many women from seeking care.

**Sylvia Botros-Brey,** MD, associate professor in the Department of Urology and Department of Medical Education, and program director of the Female Pelvic Medicine and Reconstructive Surgery Fellowship

improve the condition. In reality, the threat of a leak prevents many people from increasing their activity, making the prospect of losing weight all the more challenging.

"The trick with losing weight first is that it is difficult to lose weight when leaking, and I have had patients who, once we treat the incontinence, can then go out and exercise to lose the weight," said Botros-Brey. "I try in my practice not to say, 'Oh, go lose weight and come back.' I realize if they could have lost weight, they probably would have."

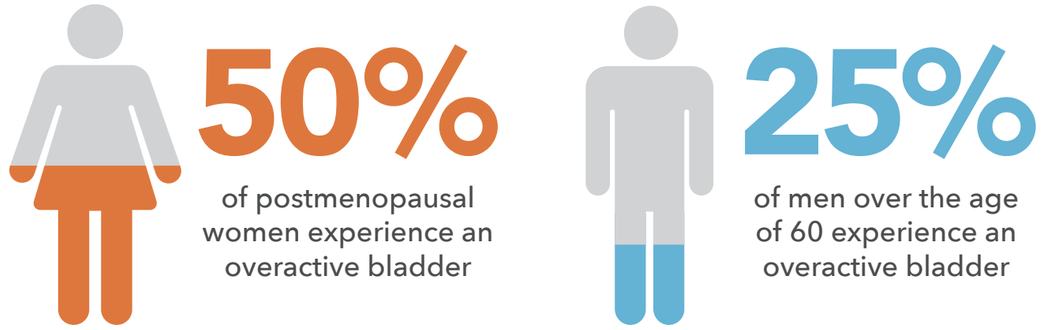
Botros-Brey combats misperceptions regarding urinary incontinence in her clinical practice as well as in her role supervising fellows who are focused on patient-centered medicine, in which shared decision-making between the patient and physician is part of a comprehensive care plan. This approach prioritizes listening to the patient to target therapies to the patient's needs while reducing barriers to care.

## Effective interventions for women

Two effective clinical interventions exist for women seeking treatment. Both the midurethral sling and Botox injections in the pelvic floor are procedures that are easily tolerated with proven results among women suffering from incontinence. The midurethral sling has a long history of being a safe and effective procedure for stress incontinence, while Botox injected in the bladder has become a game-changing treatment for urgency incontinence, Botros-Brey said. With each of these treatments, patients can go home the same day.

The midurethral sling acts like a hammock, helping to lift and support the urethra to prevent leakage during moments of increased pressure that cause stress incontinence. Stress incontinence happens when pressure is placed on the bladder muscles during activities such as sneezing or getting up from a seated position. By providing support to the urethra, the mesh sling improves bladder control. Midurethral slings have demonstrated effectiveness for years depending on contributing factors such as the type of sling used, patient comorbidities and age.

Botox (botulinum toxin) injections in the pelvic floor are an effective treatment for an overactive bladder or urge incontinence. Urge incontinence is characterized by a sudden and frequent need to urinate, often leading to involuntary leakage. By




temporarily relaxing the muscles in the bladder, Botox reduces the urge to urinate and provides effective relief for six to 12 months.

"Botox in the bladder has done for urgency incontinence what slings have done for stress incontinence," said Botros-Brey. "The treatment is reproducible; anybody can do it. It's an office procedure, so you don't have to go to the [operating room] to get it done. I have seen life-changing results with Botox."

## A masterclass in innovation for men

Urinary incontinence in men results primarily from benign prostatic hyperplasia (BPH), also known as prostate gland enlargement. A common condition that affects older men, BPH involves the noncancerous growth of the prostate gland, which can lead to urinary incontinence due to pressure on the urethra. As with women, many men with BPH don't learn about effective interventions for urinary incontinence and instead focus on hiding the symptoms instead of solving the cause of the problem.

BPH is the most common prostate problem for men older than age 50, affecting about 50% of men between the ages of 51 and 60 and up to 90% of men older than 80, said Ahmed Mansour, MD, assistant professor of urology and endowed professor of the Walsdorf Family Professorship in Urology at UT Health Science Center San Antonio. Many men simply learn to live with BPH-induced urinary incontinence because the symptoms are seen as an inevitable result of aging. Ignoring the lifestyle limitations and social isolation that occurs with urinary incontinence has a negative impact on men as they age, often leading to more serious problems.

"It is a hard thing when urination becomes the center of your day," said Mansour. "The urgent need to urinate frequently can often limit their ability to travel for long periods of time or attend long meetings because they must constantly be near a bathroom. The most bothersome symptom is patients' frequent need to get up at night to urinate, which disturbs their sleep. This can cause daytime fatigue, affect their daily activities and increases the risk of falling."

## A life-changing procedure

Mansour stated that there is a non-pharmacological intervention that can effectively treat BPH and reduce incontinence called the Holmium Laser Enucleation of the Prostate (HoLEP) procedure. HoLEP provides an effective, less-invasive treatment for BPH that results in less bleeding, fewer blood transfusions, shorter time with a catheter in place and reduced hospital stays. While HoLEP does not cure all urinary incontinence, it can reduce symptoms in the lower urinary tract by shrinking the enlarged prostate.

"HoLEP is a procedure in which the prostate is approached internally [endoscopically], through the urethra, without any cuts on the skin. The laser is used to peel the enlarged part of the prostate


"Although considered as the new gold standard, HoLEP currently represents less than 5% of [benign prostatic hyperplasia] surgical procedures performed annually in the U.S."

**Ahmed Mansour,** MD, assistant professor in the Department of Urology and endowed professor of the Walsdorf Family Professorship in Urology

from its outer capsule, just like peeling an orange without cutting it into pieces," said Mansour. "This leads to maximal relief of prostate obstruction with less bleeding risk and less chances of recurrence of symptoms."

HoLEP is available in only a few medical institutions nationwide. Although HoLEP is a technology that has been around for more than 30 years, it has failed to catch on among urologists and represents only a small fraction of prostate interventions. The lack of HoLEP expertise and training leads to a lack of access to this noninvasive procedure and forces most men into the more traditional surgical interventions or simply altering their life to manage symptoms.

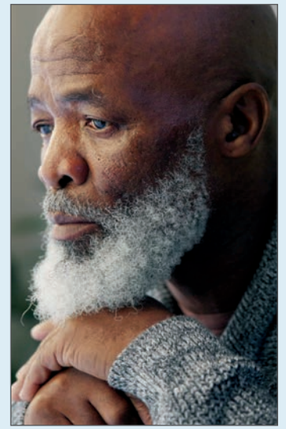
"Although considered as the new gold standard, HoLEP currently represents less than 5% of BPH surgical procedures performed annually in the U.S.," said Mansour. "It is performed mainly in limited centers of excellence nationwide, including UT Health Science Center San Antonio."

To increase access to HoLEP interventions, UT Health Science Center San Antonio incorporated HoLEP training into its residency program and created the inaugural "HoLEP Masterclass," a two-day, intensive training course for urologists across the globe. For the first time in the U.S., this training includes HoLEP training on cadavers. The intensive masterclass curriculum is popular among urologists and is an important first step in increasing access to HoLEP interventions for men suffering from BPH.

Because the HoLEP procedure is difficult to perform, requiring a high level of training, the class is critical to get urologists prepared to provide the intervention to their patient populations. UT Health Science Center San Antonio's HoLEP masterclass faculty work closely with urologists after the class ends to support their efforts to bring HoLEP to their health care organization, Mansour said.

Increasing awareness of interventions and dispelling myths about urinary incontinence are important steps in improving a patient's quality of life, from minimizing costs for absorbent pads to removing the resulting social isolation of a life largely controlled by proximity to a restroom, he said. Educating patients and physicians helps reduce the hidden costs and stigma of this condition. By promoting effective, non-invasive interventions, physicians at UT Health Science Center San Antonio are breaking the silence long associated with urinary incontinence.

## THE IMPACTS OF UNTREATED URINARY INCONTINENCE



### PHYSICAL:

**Skin problems**
Constant moisture from urinary leakage can lead to skin irritation, rashes and even skin infections.

**Urinary tract infections**
Incontinence can increase the risk of UTIs due to incomplete bladder emptying or constant moisture.

**Poor sleep**
Frequent trips to use the bathroom or bedwetting can disrupt sleep patterns, leading to fatigue and other health problems.

**Mobility issues**
Fear of leakage may cause individuals to limit their physical activities or outings, leading to reduced mobility and overall fitness.

### PSYCHOLOGICAL:

**Emotional distress**
Urinary incontinence can cause embarrassment, shame, frustration and anxiety about leakage occurring in a social setting.

**Depression and isolation**
The emotional toll of incontinence can lead to social withdrawal, isolation and even depression.

**Self-esteem issues**
Negative body image, feeling unclean and concerns about odor can contribute to low self-esteem and poor self-image resulting in increased anxiety.

**Lack of intimacy**
Incontinence can strain intimate relationships due to concerns about leakage during sexual activity and feelings of inadequacy.

### LIFESTYLE:

**Social limitations and isolation**
Fear of leakage or odor can lead to avoidance of social activities, gatherings or travel, impacting social engagement.

**Work performance**
Incontinence can affect work performance, productivity and interactions with colleagues, potentially leading to career challenges and stress.

**Financial stress**
The cost of managing incontinence, including purchasing protective products, can place financial strain on individuals and families.

**Quality of life**
The combination of physical discomfort, emotional distress and social limitations can significantly diminish overall quality of life.

# The promise of personalized diabetes care

*By Michael Seringer*


The work of UT Health Science Center San Antonio faculty has transformed the medical community's understanding of Type 2 diabetes, while helping usher in new therapies and improved protocols.

Type 2 diabetes is rampant in South Texas, and its rates are rapidly growing across the country as well.

According to a new analysis by the Centers for Disease Control and Prevention, one out of five U.S. adults will have diabetes by 2050. Today, close to 30% of the population on the Texas and Mexico border suffers from it. Currently, 12.4% of Texas has Type 2 diabetes — and more than 600,000 Texans don't even know they have the disease, according to a study by the American Diabetes Association.

Against the backdrop of these sobering numbers, the Texas Diabetes Institute is not only sounding the alarm, but is also making great strides in discovering the causes and potential treatments of this global health epidemic.

The Texas Diabetes Institute, an arm of University Health, the primary hospital partner of UT Health Science Center San Antonio, is located on San Antonio's West Side. It is at the leading edge of research and discovery in Type 2 diabetes. The institute's deputy director, Ralph DeFronzo, MD, professor of medicine and chief of the diabetes division at UT Health Science Center San Antonio, has transformed the medical community's understanding of Type 2 diabetes, while helping usher in new therapies and improved protocols.

"Our work completely revolutionized the understanding of the etiology of Type 2 diabetes by unequivocally demonstrating for the first time that insulin resistance was the earliest detectable disturbance present in individuals with Type 2," DeFronzo said. "The stress placed on the pancreatic beta cells to secrete insulin to overcome the insulin resistance, in combination with a genetic

predisposition for progressive beta cell failure, results in a relative deficiency of insulin and onset of diabetes."

## Diabetes in older adults

Most people experience the onset of diabetes between the ages of 40 and 50, and many suffer comorbidities that can place them as older adults in a precarious health situation. Comorbidities such as hypertension, cardiovascular disease, dyslipidemia, kidney disease, cancer, obesity, neuropathy and non-alcoholic fatty liver disease make diagnosing and treating diabetes a priority.

For instance, poorly controlled blood sugar levels are closely associated with cardiovascular disease among older adults due to the impact of diabetes on blood vessels. Elevated blood sugar levels can lead to the buildup of fatty deposits in the arteries, narrowing them and reducing blood flow to the heart. High blood pressure, stroke, peripheral artery disease, heart failure, arrhythmias, atherosclerosis, microvascular complications and inflammation are all cardiovascular risks that increase significantly with diabetes.

"Type 2 diabetes and atherosclerotic cardiovascular disease [ASCVD] are closely intertwined," DeFronzo said. "ASCVD represents the major cause of mortality in Type 2 diabetes. In a recent analysis of all major cardiovascular prevention trials by UT Health Science Center San Antonio, the unexplained cardiovascular conditions remain at about 50%. We have demonstrated that the molecular etiology of insulin resistance is a major factor that explains much of this unexplained cardiovascular risk."

Associate Professor Carolina Solis-Herrera, MD, chief of endocrinology and medical director of the Endocrinology, Diabetes, Obesity and Metabolic Health Clinics at the Long School of Medicine, suggests that according to national guidelines, it is recommended to use the newest classes of medications that have shown cardiovascular and renal protection in patients with diabetes. These drugs have different mechanisms of action that are complementary in providing cardiovascular and metabolic health to patients by decreasing complications and mortality.

"We currently have very novel and effective therapies to control diabetes that also provide cardiovascular protection to prevent patients with diabetes from heart attacks and strokes as well as to prevent or decrease the progression of diabetic renal disease," Solis-Herrera said. "These classes of drugs called glucagon-like peptide-1 receptor agonists [GLP-1 RA] and sodium-glucose cotransporter 2 [SGLT-2] inhibitors are available in the market and covered by most commercial insurance plans and Medicare. We widely prescribe them to our patients to keep their sugars controlled and provide them with cardiac and renal protection."

## Other concerning comorbidities

One common comorbidity among older diabetic adults is the increased rate of obesity.

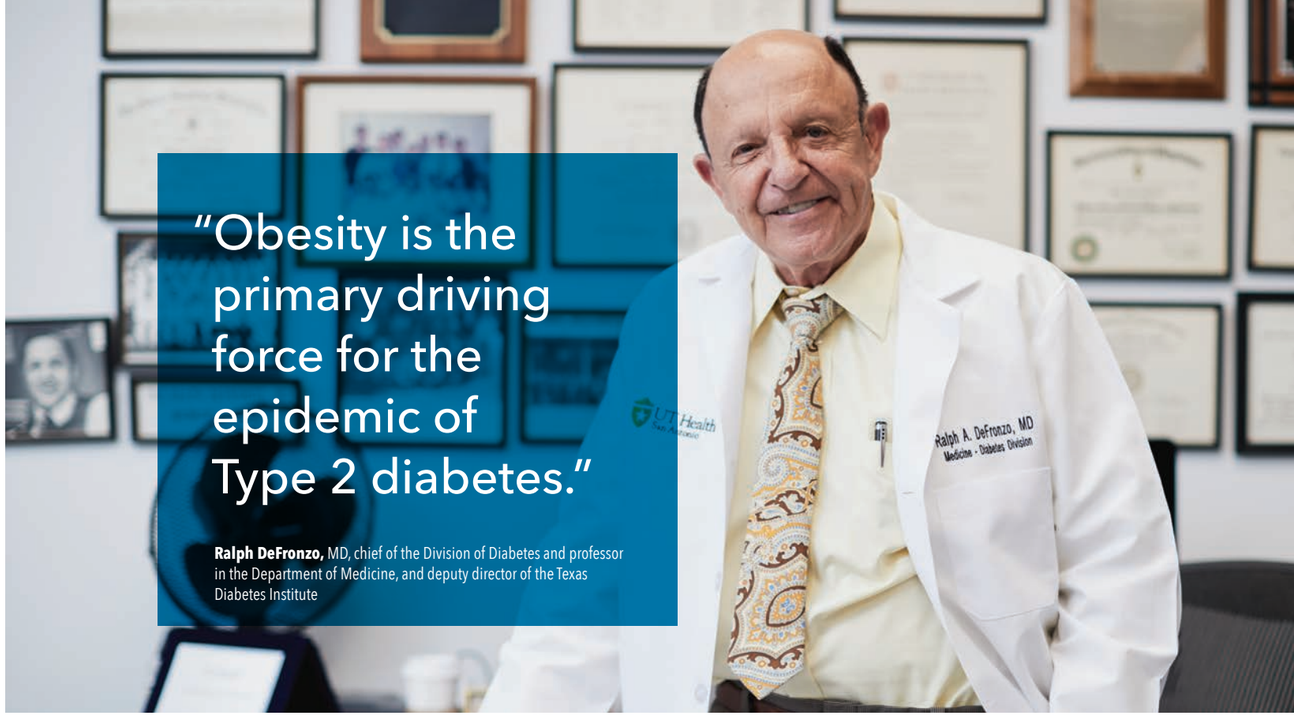
"Obesity is the primary driving force for the epidemic of Type 2 diabetes," DeFronzo said. Metabolism naturally slows down with age and, combined with a sedentary lifestyle and greater access to highly caloric foods, contributes significantly to weight gain among older adults.

"The accumulation of excess weight can further exacerbate metabolic changes and increase the risk of additional chronic health conditions," Solis-Herrera said. "Obesity distinctively affects all aspects of physiology, thus shortening lifespan and health span through effects in multiple hallmarks of aging, such as cellular senescence."

University researchers continue to actively study the mechanism of action and efficacy of the newer, more potent GLP-1 RAs and are working on the development of novel, non-drug approaches to treat obesity, DeFronzo said.

Depression is another notable comorbidity linked to diabetes among older adults and is emerging as a significant factor that directly impacts quality of life. Biological factors such as chronic inflammation, insulin resistance and changes in neurotransmitter levels may contribute to the relationship between diabetes and depression, Solis-Herrera said.

Living with diabetes also takes a psychological toll on older adults who are expected to change their lifestyle and manage multiple medications as they confront declining physical health. Furthermore, some diabetes medications may contribute to mood disorders and depression. Undiagnosed depression can harm diabetics because they tend to exercise less and are prone to not adhere to their treatment plans.




"Patients may sometimes feel discouraged, worried, frustrated and tired of dealing with diabetes care daily," Solis-Herrera said. "People with diabetes are two to three times more likely to have depression than people without diabetes. Only 25% to 50% of people with diabetes who have depression get diagnosed and treated. Counseling and medication may be quite effective in helping patients handle the burden that having diabetes may cause in their lives."

## A patient-focused future

The treatment of diabetes among older adults once seemed bleak, but current innovations in care offer new hope. Novel research has provided a much greater understanding of the mechanisms behind the disease and yielded more effective treatments — reversing the trend of this epidemic.

Developments in genetics, metabolomics and artificial intelligence are paving the way for precise approaches to diabetes treatment. Tailoring treatments to an individual's genetic and metabolic profile could lead to more effective, personalized interventions, Solis-Herrera said.

"The convergence of artificial intelligence and precision medicine promises to revolutionize health care," Solis-Herrera said. "Precision medicine methods identify phenotypes of patients with less common responses to treatment or unique health care needs. Ideally, if we can identify specific phenotypes of diabetes, we could possibly tailor new targeted therapies to improve — or hopefully cure — diabetes."

The emergence of various Type 2 diabetes subclusters, each characterized by different clinical and physiological features, will also help direct more effective precision treatments. The identification of subclusters within Type 2 diabetes is an ongoing area of research and has been the subject of many publications authored by DeFronzo and others at UT Health Science Center San Antonio.

The genetic origins of Type 2 diabetes are important in uncovering subclusters as they reveal the interplay of multiple genetic factors that contribute to an individual's risk of developing the disease. Although lifestyle and environmental factors play a significant role in the development of diabetes, researchers are seeking to understand the genetic predisposition for the disease.

Some genetic variants associated with diabetes risk are more prevalent in specific populations, leading to differences in disease propensity. Understanding

the genetic mechanisms of diabetes is key to understanding how the disease disproportionately impacts Hispanic populations, Solis-Herrera said. Identifying the genes responsible for Type 2 diabetes within Hispanic populations is an active area of research at UT Health Science Center San Antonio and could potentially improve existing inequalities in health care.

"In the next decade, I expect that we will make major advances in elucidating the genetic etiology of Type 2 diabetes," DeFronzo said. Such advances include the development of novel insulin sensitizing and beta cell enhancing medications for the treatment of Type 2 diabetes and the introduction of novel combination peptide/hormones for the treatment of obesity that will stem the obesity epidemic, noted DeFronzo. "I also anticipate that identifying subclusters of Type 2 diabetes will allow a personalized approach to therapy."

### Reversing diabetes trends

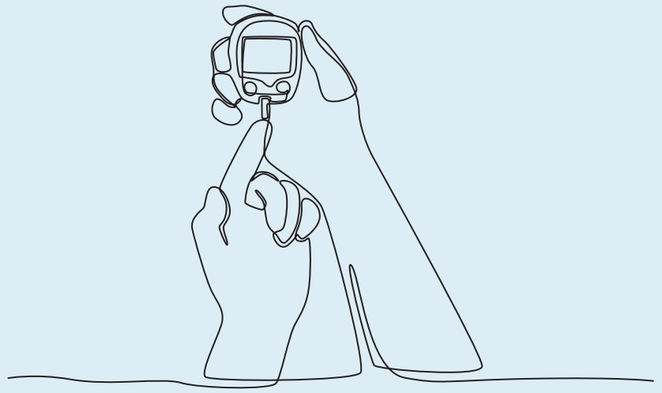
Should the diabetes rate projections noted earlier come to fruition, researchers warn that the volume of cases could overwhelm health care systems. However, even as these projections provide a window into the potential future of this epidemic, they fail to account for the impact of revolutionary discoveries occurring at institutions like UT Health Science Center San Antonio.

"We are the leading group worldwide in defining the etiology of prediabetes and developing therapeutic interventions for preventing the progression of prediabetes to diabetes," DeFronzo said.

With decades of research focused on the biomarkers of prediabetes, university investigators say they are well positioned to develop therapies designed to prevent prediabetes and to begin to reverse these disturbing diabetes trends.

Developments in genetics, metabolomics and artificial intelligence are paving the way for precise approaches to diabetes treatment.

**Carolina Solis-Herrera,** MD, medical director of the Endocrinology, Diabetes, Obesity and Metabolic Health Clinics, and associate professor and chief of the Division of Endocrinology



## THE ETIOLOGY OF TYPE 2 DIABETES

In his lecture titled, "From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus," DeFronzo organized the complicated nature of diabetes into eight distinct pathophysiologic defects.

The "triumvirate" DeFronzo referred to is the traditional three-pronged pathophysiological model of Type 2 diabetes, involving impaired insulin secretion, increased hepatic glucose production and reduced glucose uptake in peripheral tissues (muscle and fat cells). DeFronzo's "ominous octet" builds upon the triumvirate model by identifying eight key mechanisms that contribute to the hyperglycemia, or high blood sugar, in Type 2 diabetes. These mechanisms are insulin resistance in muscle, insulin resistance in the liver, increased hepatic glucose production, impaired insulin secretion, incretin effect (reduced GLP-1 response), increased lipolysis (fat breakdown), decreased muscle glucose uptake and defective regulation of hepatic glucose production.

"The ominous octet is now used by every national diabetes society in every country in the world to describe the etiology of Type 2 diabetes," DeFronzo said. "The identification of eight major pathophysiologic defects responsible for the development of Type 2 diabetes has revolutionized its treatment by causing a shift from the stepwise 'treat to fail approach' to the initiation of treatment with combination therapy."

# New therapies for keeping hearts healthy

*By Norma Rabago*

While aging itself increases the risk for developing cardiovascular disease, much can be done to prevent hypertension and reduce the odds of stroke or heart failure.

Open heart surgery is currently the only treatment for older adults with tricuspid valve disease. That can be changed, according to Allen Anderson, MD, FACC, FAHA, chief of the Division of Cardiology at the Long School of Medicine at UT Health Science Center San Antonio.

Anderson is investigating new, less-invasive therapies for tricuspid valve disease, a type of heart valve disease characterized by a leaky valve between the right ventricle and right atrium. When this valve doesn't work properly, the heart works harder to pump blood into the lungs and to the rest of the body. Severe leakage of this valve can lead to heart failure and kidney dysfunction if left untreated.

Anderson is part of a national team studying catheter-based therapies that can repair the leaking tricuspid valve without surgery. This would open treatment of damaged tricuspid valves to many more patients.

"Catheter-based therapies are sometimes the best option because the risks of open-heart surgery are very high or, in some instances, the patient is too sick or frail to undergo open heart surgery," Anderson said. "Not all valve disease has a catheter-based approach. New technologies are under development, and we will study the types of valve disease that can be treated less invasively."

## The high stakes of high blood pressure

Heart failure is the leading cause of hospitalization in those 65 and older, said Anderson.

"As the human organism ages, repair mechanisms don't work as well," he said. "Aging is associated with an increased risk for coronary artery disease and stroke."

Anderson's team is working to decrease the mortality from heart disease, which is the No. 1 killer of adults in Texas and often comes from common problems left untreated. One common cause of heart disease is poorly treated hypertension, said Anderson.

By age 60, about 60% of the population will have hypertension. By age 70, 65% of men and 75% of women will have developed hypertension.

"While it becomes more common with aging, hypertension is a disease that often starts in the third or fourth decade of life," Anderson said. "Left untreated, the complications of hypertension manifest in the 50s and beyond. Arterial wall stiffness, an adverse effect associated with aging, can lead to the development of hypertension."

In most patients, Anderson said, the cause of hypertension is unknown. For some, an unlucky roll of the genetics dice could be a cause. However, a diet high in salt, often associated with an American diet, obesity and sleep apnea are contributing factors to the development of the disease.

"Hypertension is both a problem of dysfunctional blood vessels and the result of damage to these vessels," said Anderson. "Particular areas are prone to damage from hypertension, such as the kidney, brain and aorta. The damage to kidneys and brain can be severe and lead to renal failure and stroke."

Leaving hypertension untreated not only impacts blood vessels, but also the brain, eventually leading to vascular dementia, said Anderson.

"Vascular dementia refers to the brain-damaging effects of hypertension on the brain circulation leading to small hemorrhage and impaired blood flow to parts of the brain," he said. Treatment of hypertension can lessen the likelihood of these vascular complications.

## Hypertension prevention

According to Anderson, the single worst thing an individual can do to damage their blood vessels, other than not treating hypertension, is to smoke.

"The lining of the blood vessels, called the endothelium, is affected, as are the deeper layers of the arteries," he said. "The result of damaging the blood vessel lining is the increased deposition of cholesterol, accelerating the process of


"The first thing any hypertension patient needs to do to treat their high blood pressure is to quit smoking. Sometimes, that alone is all that is needed."

**Allen Anderson,** MD, FACC, FAHA, director of the UT/UH Heart and Vascular Institute, professor and chief of the Janey and Dolph Briscoe Division of Cardiology, and the Janey Briscoe Distinguished University Chair in Cardiovascular Research

atherosclerosis. This occurs in many vascular beds including the brain, the heart and the peripheral arteries to the arms, legs and organs."

So, the first thing any hypertension patient needs to do to treat their high blood pressure is to quit smoking. Sometimes, that alone is all that is needed.

While coronary artery disease is a progressive disease that starts in young adulthood, for the aging population, it can become a clinically important problem causing coronary insufficiency or heart attack, Anderson said.

On the bright side, maintaining a healthy heart during aging is achievable. Some damage is even reversible, Anderson said. One way to reverse hypertension and heart damage is aerobic exercise, such as walking, running, swimming, biking or use of equipment like an elliptical, treadmill or stationary bike after consulting with a physician about the appropriate intensity. Aerobic exercise may be easier if a person joins a group to which they are accountable. This can provide extra motivation for maintaining an exercise schedule.

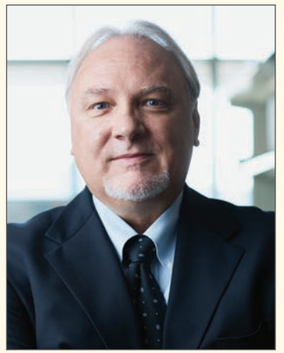
Another key to promoting a healthy heart by aerobic exercise is to realize that distance matters as much as speed. It is not how fast a person goes, but how far. Many individuals try to go too fast at first, then become discouraged when they are too exhausted to continue. A slower speed for a longer distance burns the same calories and is much easier to complete. A good exercise rate is not more than two-thirds of a person's maximum heart rate, which is 220 minus their age.

Of course, exercise does little good if a high-fat, high-salt diet is maintained at the same time. The good news is that exercise can suppress appetite.

Perhaps the single best intervention anyone can do to promote healthy aging is to regularly check their blood pressure and then comply with treatment if it is high.

The earlier a person begins to maintain a healthy heart the better, but it is never too late, Anderson said. The benefits of any of these positive actions begin to accrue almost immediately.

## EXERCISE IS MEDICINE



**Blake B. Rasmussen,** PhD, director of the Center for Metabolic Health and professor in the Department of Biochemistry and Structural Biology

There are remarkable biochemical and physiological adaptations that occur in the human body when muscles are put to work. From improved glucose tolerance, insulin sensitivity and oxygen utilization to lower blood pressure, better circulation and greater cardiac output, the list of benefits from regular exercise is long. Beyond boosting heart health, research also shows that regular exercise prevents dementia and osteoporosis.

Understanding the benefits of exercise at the molecular level is particularly important to understanding the aging process, said Blake B. Rasmussen, PhD, director of the Center for Metabolic Health at UT Health Science Center San Antonio. There is a vicious cycle in not exercising. Adults commonly lose muscle mass as they age, making them less active, which induces weight gain, making exercise even harder. Thus, lack of exercise is highly related to the development of obesity and Type 2 diabetes.

A loss of muscle mass in older adults also contributes to an increased likelihood of falls and hip fractures, further decreasing activity. A study published in the *Journal of Bone and Mineral Research* found that the one-year mortality rate following a hip fracture was approximately 14% for individuals aged 65 to 69 and increased to more than 48% for those aged 90 and above.

The major benefit of exercise is that it prevents many of the diseases of aging, Rasmussen said. He and others at the university's Center for Metabolic Health are leading a revolution in healthy aging through targeted exercise routines.

"Some specific advances from our work include new dietary recommendations for protein intake in older adults, targeted nutritional and exercise interventions to counter sarcopenia, and identifying the mechanism of how blood-flow restriction exercise in humans promotes muscle growth — a new technique that has been introduced to rehabilitation after knee surgeries," he said.

# Fighting dementia with precision interventions

*By Jessica Binkley Lain*

## Researchers at the Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases use a comprehensive approach to discover new targets for personalized and precise treatments of dementia.

Cognitive decline is one of the more distressing hallmarks of aging. Losing memory and the ability to control thoughts, emotions and behavior is a devastating loss for both patients and caregivers. The Biggs Institute at UT Health Science Center San Antonio is poised to make breakthroughs in dementia prevention and treatment as one of 33 centers in the nation recognized as a National Institute on Aging-designated Alzheimer's Disease Research Center.

"Dementia affects a person's memory and thinking, which is a core part of who we see ourselves as," said Sudha Seshadri, MD, founding director of the Biggs Institute. Seshadri has dedicated her career to studying the brain and identifying the genetic underpinnings of dementia, as well as caring for those suffering the loss of themselves.

"It's important to emphasize that dementia can happen in people with a lot of abilities," Seshadri said. "We don't want to just give this diagnosis and then say, 'go home and withdraw from society.' We want to help you live the best life you can. All of that is part of our responsibility."

### The dementia epidemic in South Texas

South Texas is home to a majority Hispanic population, a group of people who are 50% more likely to develop Alzheimer's disease than non-Hispanic whites and are projected to bear the


largest relative increase in Alzheimer's and related dementia cases by 2060, Seshadri explained. Factors such as poverty, inadequate access to health care, as well as the prevalence of diabetes and other vascular risk factors in this population all increase the risk.

This prevalence has a significant economic impact on the region, especially considering that each Alzheimer's patient has an average of three caregivers. For the 400,000 Texans who have Alzheimer's disease, there are 1.2 million Texans who are caregivers for them. Moreover, one in six of those caregivers is under the age of 35, holding them back during a time of major life milestones, such as pursuing additional education, starting families or starting new careers, Seshadri said.

However, dementia is inadequately studied in Hispanic patients, which is why many research efforts at the Biggs Institute focus on investigating dementia in people of Hispanic ancestry in all aspects of study, from genetics and environmental factors to inclusion in clinical trials.

This is important not just because Hispanics are the fastest-growing demographic in the country, but also because unraveling mysteries in one population can lead to breakthroughs that benefit everyone, Seshadri said.

"Typically, it is by studying populations that haven't yet been studied that we find answers," she said. Seshadri and her team are using genome sequencing, transcriptome sequencing, metabolomics and proteomics to identify why this population is prone to dementia. In addition, these studies will provide new targets to intervene in the progression of dementias.

## Precision therapies for patients

Clinical trials are crucial to find new treatments and improve existing ones, and to understand what combination of therapies can benefit patients for their specific disease. One of the major barriers to identifying new treatments for dementia is that it's not just one disease with one cause, but many diseases that can each have many etiologies.

"We know now that there are many contributions to dementia and with multiple types existing at once within a patient," Seshadri said. "We need to understand all of these and take a precision approach to the diagnosis and treatment. It won't be just one agent, but likely a combination of agents."

The most common and well-known cause of dementia is Alzheimer's, Seshadri explained, noting that 60% to 70% of dementia patients exhibit an Alzheimer's pathology, with plaques of beta-amyloid and tangles of tau. And the number of genetic variants associated with Alzheimer's is growing.

Seshadri is a founding principal investigator of the International Genomics of Alzheimer's Project, a National Institute of Aging-funded study established in 2009 that conducts genome-wide association studies.

"We've doubled the number of genes that we know are associated with Alzheimer's disease. We know now that there are around 90 genes," Seshadri said. "And each of these genetic variants is a route to understanding the biology and a potential target for treatment."

Moreover, there are other common causes of dementia beyond Alzheimer's that very often coexist, such as dementia with Lewy bodies, vascular dementia and other rarer causes. Researchers at the Biggs Institute study all of these, Seshadri said, which is why large clinical trials and observational studies are so important to sift through the many underlying causes and identify patterns that predispose people to Alzheimer's disease and related dementias.

"We have many trials and observational studies going on now, for all people at all different stages of dementia," Seshadri said. "We have trials for people at risk due to family history, even if they are completely asymptomatic, and then we have trials for people with mild cognitive dementia and for those with early dementia, as well as trials for people with specific, rare diseases."

## It's never too LATE for new discoveries

The study of one prominent and newly discovered underlying pathology, called Limbic-predominant Age-related TDP43 Encephalopathy, or LATE, has led to new insights about the complicated nature of multiple, coexisting pathology lesions in the brains of dementia patients.

Margaret Flanagan, MD, is an associate professor in the Department of Pathology and neuropathologist

## DEMENTIA RISK FACTORS AND PROTECTIVE MEASURES

**High blood pressure, obesity and diabetes** in midlife are known risk factors for developing Alzheimer's and related dementias later in life. Managing these chronic diseases earlier can help reduce the risk of developing dementia.

**Daily physical activity** is an essential protective factor against dementia. Incorporating movement into daily routines and maintaining an exercise regimen throughout life has significant benefits for both the body and the brain.

**Eating a healthy diet** incorporating many fresh fruits and vegetables and foods high in Omega-3 fatty acids, found readily in fish and plant-based sources such as chia seeds, hemp seeds and walnuts, can help to preserve brain health and enhance cognition.

**Developing a strong social support system**, engaging in hobbies and meeting new people and taking part in group activities are crucial to protecting against cognitive decline. Brain games such as crossword puzzles are great methods for building cognition and staying intellectually challenged throughout life.

**Adequate sleep** is crucial to brain health. Without it, the processes in the brain that clear away accumulations of pathogenic proteins cannot take place, increasing the risk of brain disease.

at the Biggs Institute. Her research investigates the role of the protein TDP43 in the development of different types of clinical dementia syndromes including LATE, which she contributed to naming.

LATE is an amnestic dementia syndrome similar to Alzheimer's disease, but it may stem from different underlying causes and disease mechanisms. At the time of brain autopsy examination, individuals with LATE have been found to have an accumulation of a pathologic form of the protein TDP43 in their brains, Flanagan explained. The discovery of TDP43 accumulation in one form of dementia raises the possibility that it could be targeted with a protein degrader or an antibody to decrease progression of LATE.

"Not only has the pathologic form of TDP43 protein been associated with the type of amnestic dementia that's very similar to Alzheimer's disease dementia, but, interestingly, the accumulation of the pathologic TDP43 in these individuals has also


been very strongly associated with atrophy in the hippocampus, also seen in association with the pathognomonic plaques and tangles of Alzheimer's disease," she said.

To make it more complicated, pathologic TDP43 also commonly coexists along with the plaques and tangles of Alzheimer's.

"We're finding more and more that multiple coexisting types of pathology lesions in the brain are much more common than having purely one type," she said. "It's the norm and not the exception."

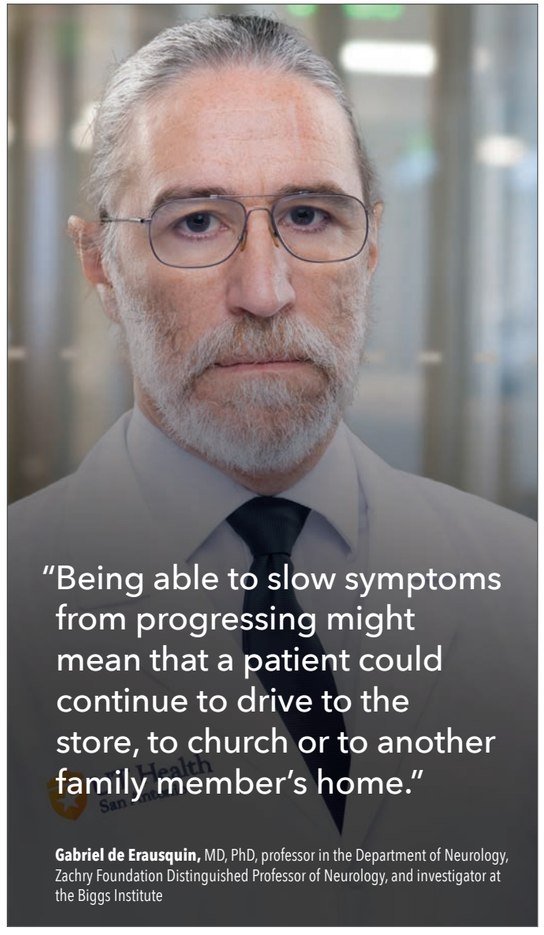
Thus, many forms of dementia overlap, with multiple distinct causes contributing to a given patient's cognitive decline, making it even more difficult to identify new therapies.

### Eye exams for early detection

Flanagan has worked with a new technology that has possibilities for early detection of specific combinations of pathology lesions and providing patients with personalized diagnostic protein profiles underlying their clinical dementia. Collaborating with researchers at the University of Minnesota and RetiSpec, a private company based in Toronto, Canada, Flanagan's work has helped validate a noninvasive retinal scanner that can take a picture of an individual's retina to identify each patient's unique hyperspectral signature based on the individual's distinctive combination of proteins accumulated in the back of the eye.

"These abnormal proteins appear to accumulate earlier in the eye than in the brain, and the hope is that routine eye exams using this noninvasive technology will ultimately reliably identify different combinations of coexisting pathology in the retina before symptoms develop in patients," Flanagan said. "Once the combination of coexisting pathology lesions is determined, then combination therapies specific to each patient's unique profile can be initiated before memory problems begin for effective, personalized dementia prevention."

This is especially important given that the new anti-amyloid antibodies for preventing cognitive decline in Alzheimer's disease are more successful when




given early in the course of dementia, she said.

### Stimulation to slow decline

A novel surgery to slow cognitive decline and memory loss from Alzheimer’s disease is being tested at UT Health Science Center San Antonio. The procedure, called deep brain stimulation, or DBS, is an established treatment for movement disorders such as Parkinson’s disease.

Gabriel de Erausquin, MD, PhD, professor of neurology in the Long School of Medicine and researcher at the Biggs Institute, has experience in overseeing more than 200 DBS cases for movement disorders.

De Erausquin has a long career treating both Alzheimer’s and Parkinson’s patients. Upon moving to the university, he began focusing on the application of deep brain stimulation and other neuromodulation techniques to combat memory loss. He currently serves as principal site investigator for a global study, across 27 sites worldwide, evaluating the effectiveness of DBS in treating patients with early, mild Alzheimer’s disease.

Deep brain stimulation for Alzheimer’s involves the placement of electrodes in the fornix, hippocampus and amygdala — areas of the brain associated with memory. The electrodes are connected to a battery-operated generator in the chest, similar to a pacemaker. A small impulse of electricity moves from the generator to the electrodes to stimulate specific areas of the brain. The surgery is minimally invasive for a quick recovery with the least amount of pain, blood loss and hospital time. The small electrical stimulus promotes memory retention in the brain, potentially preventing the decline of memory in most dementias.

In 2021, a San Antonio woman in her 70s underwent South Texas’s first DBS surgery for Alzheimer’s at University Hospital, clinical partner of UT Health Science Center San Antonio, with great success, De Erausquin said.

“The usual course of illness for people with early Alzheimer’s disease is a progressive loss of function that is very steady and doesn’t slow down,” De Erausquin said. And while DBS cannot reverse disease progression, “being able to slow symptoms from progressing might mean that a patient could continue to drive to the store, to church or to another family member’s home. That ability is quickly lost if symptoms advance.”

Trial testing for DBS surgery has now closed, but a second part of the trial testing multisensory neurostimulation is currently underway. This method stimulates the brain without surgical implants, using outside sources such as light and sound. The results aren’t yet in, but so far, De Erausquin has seen “promising results” in slowing disease progression using these techniques.

### An unwelcome opportunity for discovery

Another project De Erausquin leads is the Alzheimer’s Association Consortium on Chronic Neuropsychiatric Sequelae of SARS-CoV-2 infection, a World Health Organization initiative of research and clinical teams from around the world to track the long-term impact of COVID-19 on the brain.

“When the pandemic hit, this created a very unwelcome, but great scientific opportunity,” De Erausquin said. “We had a unique time-locked, very well-defined environmental challenge that we thought could be a risk factor for cognitive decline. One of the things that has become apparent from the cooperative work around the world is that COVID does, in fact, increase the risk of cognitive decline, particularly in older adults.”

Younger people suffering from long COVID tend to have difficulty maintaining attention and concentration and have some trouble with executive function, but their memory isn’t particularly affected, De Erausquin explained. Older adults over 60, however, seem to have much more prominent impairment to recent memory and language, failing at simple tasks, forgetting appointments and losing the ability to recall words — a profile that is “much more consistent with what you expect to see in somebody with Alzheimer’s,” he said.

“The link between Alzheimer’s disease and environmental factors has been discussed for the better part of the past 100 years,” De Erausquin explained. There is a definitive link between gum disease and Alzheimer’s, for example. This links the microbiome of the mouth to the function of the brain over time, opening a new area of potential intervention to prevent dementia. And it’s been found that if an individual has had to receive antiviral drugs administered intravenously at some time in their life, their risk of having Alzheimer’s disease later is decreased by half, he said.

“The exact nature of these infections in relation to the process of Alzheimer’s remains to be proven or studied, but that’s exactly what the pandemic gave us — a very specific opportunity to address an environmental trigger as a possible pathological process underlying Alzheimer’s disease.”

Study researchers are looking at large samples of whole genome sequencing data to understand if there is a particular genetic risk that makes someone more likely to have a cognitive decline following COVID and if that risk would also lead to developing Alzheimer’s disease later in life, De Erausquin said. So far, he reports that researchers have found that there is a definitive genetic component in the form of heritability, but which particular genes are to blame for this interaction remains unknown.

Seshadri, Flanagan and De Erausquin share a passion for making neurodegenerative disease a mere memory for South Texas. Together, they and their research colleagues at UT Health Science Center San Antonio are on the cusp of revolutionizing the prevention and treatment of dementia.

## THE RESEARCH VALUE OF BRAIN DONATION

Currently, the best method for understanding the molecular and pathological changes in the brain that cause the symptoms of dementia is examination of a patient’s donated brain at autopsy, studying the brain in detail using molecular methods. The Brain Bank at the Biggs Institute was established in 2020 with the aim of advancing discoveries that come from studying brain tissue. With more than 260 donations to date, the institute’s brain bank will remain pivotal in understanding and battling brain disorders for decades to come.

# Living your best life by sleeping better

*By Jessica Binkley Lain*

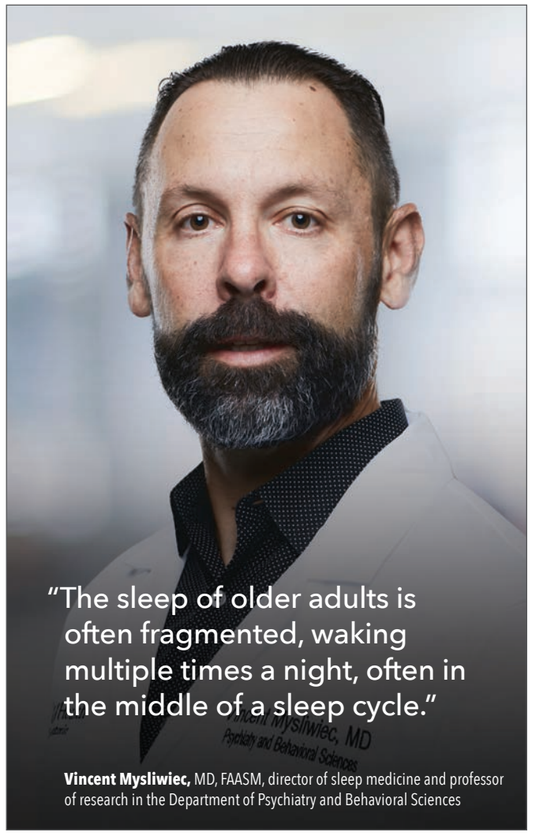
Inadequate sleep doesn't just cause sleepiness and poor concentration. It can also degrade the body over time and age us quicker.

We've all been told how essential sleep is to our health. But in our busy, often overworked lives, many feel it's worth the risk to scrimp on sleep. "I'll sleep when I'm dead" is an all-too-common response for many when asked about their sleep habits.

That mentality is dead wrong, explains Vincent Mysliwiec, MD, FAASM, a professor of research and director of sleep medicine at UT Health Science Center San Antonio. Sleep is a biological requirement that helps the body to recover physically and mentally, to process emotions and consolidate memories, Mysliwiec said. Without sleep, memory and emotions do not function properly, and health suffers. Worse, too little sleep can even lead to an early death.

"We have seen studies where individuals with a short sleep duration were shown to have higher rates of mortality," he said, noting that while it's not a direct cause-and-effect relationship, poor sleep causes hormonal imbalances that can lead to detrimental effects on health. Imbalances caused by insufficient sleep can lead to unintentional weight gain. This happens because poor sleep decreases production of the hormone leptin, which decreases appetite. Lack of sleep also increases ghrelin, the hormone that triggers the feeling of hunger, Mysliwiec said.

"When those two hormones are imbalanced, it can contribute to poor eating practices, which then,




**Vincent Mysliwiec,** MD, FAASM, director of sleep medicine and professor of research in the Department of Psychiatry and Behavioral Sciences

While it's not a direct cause-and-effect relationship, poor sleep causes hormonal imbalances that can lead to detrimental effects on health.

along with many other factors at play, can lead to obesity, hypertension or cardiovascular disease," he said.

There have also been substantial advances in understanding the critical role of sleep for brain health. During sleep, the toxic metabolic byproducts of the brain are cleared away through the glymphatic system, Mysliwiec stated. Similar to the body's lymphatic system, the glymphatic system is responsible for eliminating metabolic waste from the brain, helping to prevent the accumulation of tau and amyloid beta, which are linked to Alzheimer's disease. In other words, good sleep can help stave off dementia.

## Drilling down on a unique demographic

Mysliwiec's research has focused on sleep and sleep disorders in military personnel.

"We have learned that the rigors of military service, which include long duty days, frequent changes in sleep patterns, short sleep duration, sleeping in austere environments and periods of stress from deployments and leadership positions contribute to the development of sleep disorders," he said.

Mysliwiec's findings have established that the most prevalent sleep disorder in military personnel is the co-occurrence of insomnia and obstructive sleep apnea, also known as COMISA. Military personnel with COMISA have higher rates of mental health disorders such as anxiety, depression and PTSD.

"Sleep disorders are more common with age, and sleep apnea is typically diagnosed in middle-aged adults," Mysliwiec said. "The finding that these complex sleep disorders are present in younger military personnel supports that military service may be a distinct risk factor for sleep disorders, which may also be present earlier than expected."

The reason for earlier diagnosis in military personnel is, in part, due to short sleep duration, as military personnel typically sleep less than six hours per night, he said.

## Sleep cycles and stages

Sleep occurs in cycles of about 90–110 minutes, with four stages for each cycle. Dreaming can occur in each stage. In general, most people need five cycles per night to achieve the full benefits of sleep — hence the well-known recommendation for getting eight hours of sleep each night.

Because each stage of sleep does something helpful, uninterrupted sleep cycles are important to hit every stage. For example, the deepest sleep occurs in Stage 3, where the body can adjust hormones, metabolism and the immune system. Waking during this stage may lead to grogginess the next day.

The last stage of a sleep cycle, Stage 4, is called rapid eye movement, or REM sleep. It's in this stage that the brain processes new information and commits it to long-term memory.

## How aging impacts sleep

Sleep needs do shift slightly with age, with adults over 60 typically going to bed earlier and waking earlier, known as an advanced sleep phase, Mysliwiec explained. Their sleep cycles are slightly shorter in length, but no less important to complete. They still need a full night's rest to maintain good health and functionality. Older adults typically need about 30 minutes less sleep a night than younger and middle-aged adults because of these shorter sleep cycles. But very often, older people are not getting the sleep they need.

The reason for this is that the sleep of older adults is often fragmented, waking multiple times a night, often in the middle of a sleep cycle, Mysliwiec said. This can be due to sleep disorders as well as medical disorders such as nocturia, or using the restroom at night from prostate enlargement in men or incontinence in women.

Chronic pain also can wake a person in the middle of a sleep cycle and often make it difficult to fall back asleep. This loss of sleep can make chronic pain worse, implementing a vicious cycle. Pain control is essential for good sleep but should be achieved with as little opioid use as possible. That drug class interferes with the REM sleep cycle stage and can worsen pain.

Sleep disorders are seen at a much higher rate among older adults than in younger adults, with the two most prevalent disorders being insomnia and obstructive sleep apnea, said Mysliwiec. Insomnia is present in at least 25% of older adults, with a greater prevalence in women compared to men, and approximately 50% of older adults have obstructive sleep apnea, seen more frequently in men, he said.

However, there are challenges to studying sleep disorders for those of advanced age.

"The current standard for evaluating sleep stages and architecture is based on human scoring, which does not necessarily account for the changes that occur to the electroencephalography [EEG] pattern of older individuals," Mysliwiec said, noting that to better understand age-related changes in sleep, specific sleep characteristics need to be compared at the individual level to filter out masking variables, such as skull thickness.

More longitudinal studies to assess EEG-based changes over time are also needed to allow researchers to determine if changes in sleep patterns in older adults are in fact consistent with an underlying sleep or brain disorder or inherent to the normal aging process, he said.

Mysliwiec advised that early diagnosis, intervention and preventative measures can protect individuals from the degrading effects of insufficient sleep. Treating sleep disorders not only helps prevent dementia and obesity, but it also increases productive cognition during the day and decreases the risk of infection.

"There are healthy sleep habits we can adopt, as well as treatments and interventions available for sleep disorders to help someone get the good sleep they need," he said. "Getting the best sleep you can get earlier in life is going to pay dividends later in life."

## TIPS FOR GETTING A GOOD NIGHT'S SLEEP

1. Get the recommended eight hours of sleep on a nightly basis.
2. Ensure that you have a regular sleep-wake cycle, going to bed around the same time every night, even on weekends.
3. Avoid alcohol prior to sleep.
4. Keep the bedroom slightly cool.
5. Get regular exercise during the day, avoiding evening workouts too close to bedtime.
6. Avoid excess sugar and caffeine, especially right before bed.
7. Don't use phones or other bright screens one hour before going to bed.
8. Avoid working in bed. Associating your sleep space with work can contribute to stress and insomnia.
9. Get sunlight first thing upon waking. This helps cue your circadian rhythm to best align with falling asleep at night and awakening in the morning.
10. Seek a physician's evaluation if you must use a nightly sleep aid such as diphenhydramine or melatonin. This may be masking a sleep disorder. Sleep disorders, just like most medical disorders, worsen over time without the appropriate treatment.

# Seeking participants for a healthier future

*By Jessica Binkley Lain*

Investigators are working to eliminate the barriers of recruiting older adults for clinical research to increase the pipeline of anti-aging interventions.


"When a study is seeking 'healthier older adults,' that often means the exclusion of a lot of people who would probably have the most to benefit."

**Tiffany Cortes,** MD, assistant professor in the Division of Endocrinology, Metabolism and Diabetes and investigator at the Barshop Institute

The primary health challenges that emerge with aging, such as preventing dementia, cancer and heart disease, remain unsolved. Often, the only way to solve these is by testing new anti-aging compounds in volunteers.

Clinical trials are only as good as their participants, and when it comes to studying an aging population, there are many challenges to recruit and retain study participants.

**Kimberly Summers,** PharmD, associate vice president for research operations at the UT Health Science Center San Antonio

"Clinical research into aging at UT Health Science Center San Antonio is moving science forward," said Kimberly Summers, PharmD, associate vice president for research operations. "The more we understand about the interactions between genetic, behavioral, social and environmental factors involved in the aging process, the closer we get to early interventions that prevent age-related diseases and degenerative decline."

UT Health Science Center San Antonio conducts around 40 active clinical studies focused on aging research, Summers said. Approximately 20% of those active studies are interventional, where a new drug is tested, and the remaining are longitudinal studies that follow subjects in real time to gain insight into cause-and-effect relationships for aging, she said.

Summers explained that the major barriers to the recruitment of older participants include substantial health issues that could exclude them from the trial, social and cultural barriers, and occasionally an impaired capacity to provide effective informed consent.

"Our investigators and study staff have expertise that goes beyond the informed consent document and often engages family members and caretakers

as part of the process," Summers said, adding that flexibility in time and location of visits and the use of virtual visits are offered to increase the ability of the elderly to participate in a trial.

### Accounting for comorbidities

Another major challenge facing clinical research on aging is when the study calls for healthy older adults as participants. Older patients often have other diseases in addition to the one being studied, which can complicate the study and may prevent participation.

"It's tough because we want to control as many variables as possible. If a study is testing a drug for diabetes, you want your participant to have diabetes, but then you want any other comorbidities to be stable or controlled so you can see the effects of the intervention," said Tiffany Cortes, MD, assistant professor of medicine in the Division of Endocrinology, Metabolism and Diabetes and researcher at the university's Sam and Ann Barshop Institute for Longevity and Aging Studies. "But the challenge in targeting older populations is, as you get older, you're more likely to have many other comorbidities. Trying to get somebody who is 75 without cardiovascular or metabolic disease, for example, can be very difficult."

Cortes leads an ongoing clinical trial studying the effect of GLP-1 receptor agonists like semaglutide on physical strength, body fat versus muscle composition, and biomarkers of aging in older adults with prediabetes or diabetes.

"When a study is seeking 'healthier older adults,' that often means the exclusion of a lot of people who would probably have the most to benefit," Cortes said.

Cortes studies the effects of semaglutide — a U.S. Food and Drug Administration-approved medication commonly prescribed for Type 2 diabetes and weight management — on the body composition in adults 65 and older, analyzing measures of lean body mass, fat mass and changes in physical activity. Cortes is also examining changes on the cellular level, looking for biomarkers of aging, such as signs of inflammation and cellular senescence.

"Looking at both the physical function and cellular level changes together, we can determine

## MULTI-OMIC APPROACHES TO UNDERSTANDING AGING

While the health effects of regular exercise are well understood, its impact at the genetic and molecular level is not. These unresolved questions drove UT Health Science Center San Antonio researchers to co-lead the National Institutes of Health clinical exercise trial called MoTrPAC.

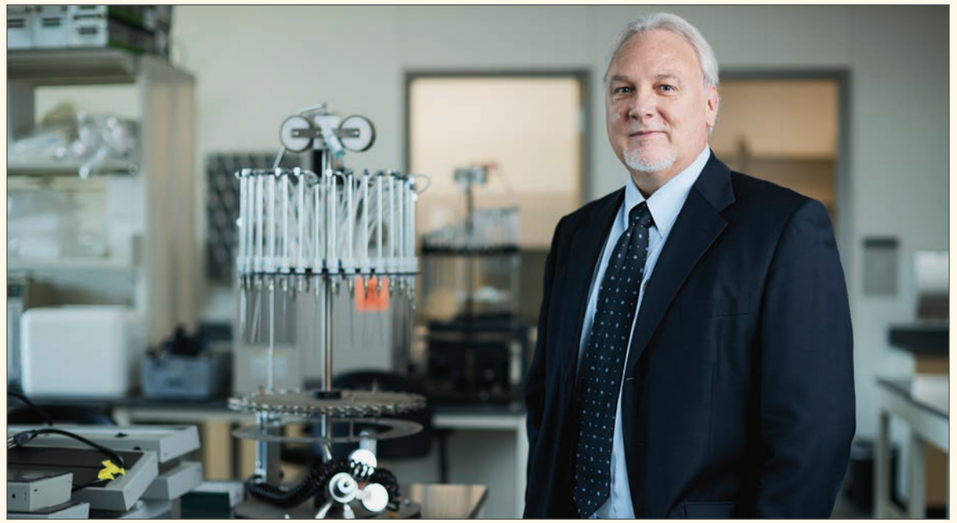
The Molecular Transducers of Physical Activity Consortium is a far-reaching clinical trial that brings together a collaborative national network of researchers from an array of scientific disciplines. MoTrPAC attempts to determine the molecular mechanisms underlying the effects of physical activity on the human body. Data integration and sharing allows researchers to gain insights into how various molecular components interact and influence each other in complex biological systems. A multi-omics study design gives investigators a more complete understanding of biological processes by analyzing multiple omics datasets simultaneously.

"For the past seven years, I have been one of the principal investigators for the largest investment the NIH has made on the role of exercise in human health," said Blake B. Rasmussen, PhD, director of the Center for Metabolic Health at UT Health Science Center San Antonio. "It combines transcriptomics, proteomics, metabolomics, lipidomics from blood and tissues collected from humans before and after three months of exercise training."

Rasmussen believes MoTrPAC's multi-omics approach will yield many answers to important metabolic questions.

### Why is it so hard to gain muscle as you age?

The MoTrPAC team at UT Health Science Center San Antonio has demonstrated that it is more difficult to maintain muscle mass with age, let alone increase muscle mass. Data from younger and older adults who completed a three-month weight training program showed



**Blake B. Rasmussen,** PhD, director of the Center for Metabolic Health and professor in the Department of Biochemistry and Structural Biology

that younger adults put on about 7–8 pounds of muscle after three months, compared to 1–2 pounds for older participants, Rasmussen said.

"Older adults don't respond as well to nutrition or exercise as compared to younger adults," he said. "Nutrition and exercise are key components to maintaining muscle function and size. As we age, older adults tend to have a little bit more difficulty in using the anabolic components of nutrition, such as protein, to help build and restore their muscles."

By using genomics, transcriptomics, proteomics, metabolomics and epigenomics, the MoTrPAC clinical trial is designed for further discovery on why older adults cannot use protein to build muscle as well as younger adults. Investigators are currently developing novel nutritional, small molecule, mechanical and exercise therapies to help older adults maintain their muscle function into advanced age, Rasmussen said.

Senescent cells in the muscles of older adults may decrease the ability to use protein to build muscle after exercise. Thus, small molecular senolytic drugs targeting muscle senescent cells are being tested to assess whether they help older adults gain more muscle after exercise.

### Essential biomarkers

As the MoTrPAC trial studies the molecular responses to exercise, it will identify biomarkers that could provide indicators of an individual's response to exercise, leading to personalized exercise recommendations and improved health outcomes for older adults.

"We may learn what types of exercises are the best for older adults," Rasmussen said. "We may learn how much rest is required between exercise bouts when trying to improve muscle size and function. We may discover what foods should be prescribed for older adults. We may identify particular pathways at the molecular level that may lead to the discovery of new drugs or nutraceuticals."

The MoTrPAC clinical trial, combined with this breadth of established metabolic scholarship, is poised to lead discovery on the mechanisms of aging — research that could yield new strategies for disease prevention and treatment and life-changing therapies for older adults.


"We need to go into the community to explain why research is important and take the time to really establish that connection."

**Claudia Satizabal,** PhD, associate professor in the Department of Population Health Sciences and investigator at the Biggs Institute

if semaglutide has not only glycemic and weight-control benefits, but also aging-focused benefits for older adults," Cortes said. She also explained that there are some concerns to consider for this older age group about retaining muscle mass while taking a drug that aids in weight loss, because some of this weight loss may come from muscle. All participants in the study are provided lifestyle counseling with expert dietitians and exercise physiologists.

## Reciprocal research

"Something I love about doing this research is the impact of our studies on our participants," Cortes said. "I get to see the joy our patients have in being able to give back to their community and advance scientific knowledge. Frequently they are eager to learn about other trials and ways they can contribute."

When participants can become active again in their community, it garners not only interest in a study, but also more trust in science and medicine, she explained. It's also important for researchers to give back to the participants who are in aging studies that do not test an intervention against aging, but rather, where the natural history of aging itself is followed.

"It should be a reciprocal interaction. It's important to offer them something meaningful," said Claudia Satizabal, PhD, associate professor in the Department of Population Health Sciences and investigator at the Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases at UT Health Science Center San Antonio.

Satizabal leads the San Antonio Heart and Mind Study, a longitudinal study that revisits the San Antonio Heart Study, conducted at the university between 1979 and 2006. For this current study, which was awarded a five-year, $15.5 million grant from the National Institute on Aging, Satizabal is investigating why older Mexican Americans in the San Antonio region experience a higher rate of dementia than older non-Hispanic white adults.

While the original study focused on diabetes and heart disease in participants between 25 and 64 years old, the new study will utilize MRI and positron emission tomography to measure amyloid and tau buildup in the brains of those same participants, who are now in their 60s and older.

Beyond monetary compensation, Satizabal emphasizes the importance of providing education and meaning for participants, especially in older and underrepresented populations.

## Building community connection and trust

"We need to go into the community to explain why research is important and take the time to really establish that connection," Satizabal said. "It takes time to do this, but it has a high payoff because once you establish that relationship with the community, they know they're contributing to something that is beneficial for everyone, and you also are able understand their concerns."

This is especially important for observational studies, such as the Heart and Mind Study, in which participants aren't given an opportunity to try a new drug or treatment as an incentive.

"It's important to explain how their contributions matter and are helping to shape research and health policy. Because without the participants, we wouldn't be able to do what we do," Satizabal said.

In addition, participants in Satizabal's study are informed of their lab results and any findings pertaining to their personal health, she said. This provides a free, complete health checkup regularly, to which some study participants may not have access. Medical concerns are discussed with primary care providers, and recommendations or referrals for further care or counseling are also offered. In addition, all study materials are offered in English and Spanish to be as inclusive as possible. Transportation services and caregiving programs are also provided for participants who need them.

"We're trying to be as comprehensive as possible to have a system that accommodates all types of situations so that the participant is not burdened by their involvement in the study," she said.

Ultimately, understanding the community, building trust and establishing a partnership with enrolled participants is crucial to recruiting and retaining older participants. Thus, the aging research teams at UT Health Science Center San Antonio often partner with local churches, gyms, nursing homes, rehabilitation centers, libraries and recreation centers to identify older study participants. Past study participants are also often the best recruiters of new study recruits, which underscores the importance of establishing trust within the local community.

With well-informed, enthusiastic study participants, investigators at UT Health Science Center San Antonio will continue to make clinical discoveries that prevent physiological and cognitive degeneration and chronic illness in aging populations in South Texas and far beyond.

### LEARN MORE ABOUT CLINICAL TRIALS

**Barshop Institute:** Want to be a part of advancing medical knowledge to treat or prevent various age-related diseases? Scan the QR code to learn about current clinical trials at the Barshop Institute.

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