JOE R. & TERESA LOZANO LONG SCHOOL OF MEDICINE

FUTURE

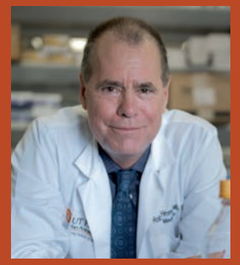
SPECIAL RESEARCH EDITION

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
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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.

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.

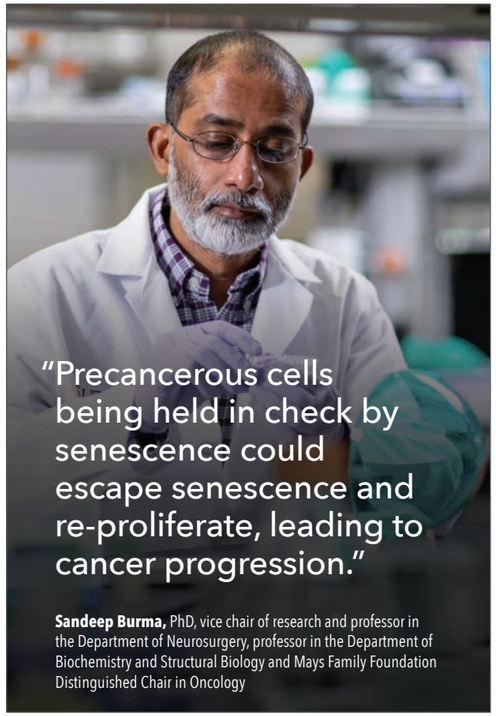
As cells divide over time, they accumulate damage to their DNA and other cellular components. Such damaged cells can enter a state of senescence in which they stop proliferating but remain active. While senescence prevents cancer in the short term, senescent cells promote aging and cancer in the long 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."

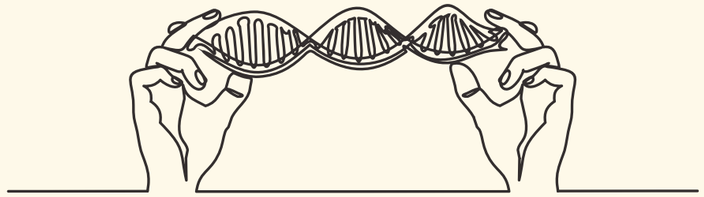
Zhou's research is taking advantage of small-molecule PROTACs (PROteolysis TArgeting Chimeras) to target and destroy specific proteins within cells, reducing the toxicity of potential therapies. PROTACs are a promising new tool in drug development allowing researchers to selectively eliminate disease-causing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