CenterTimes

September 2021 | A Publication of The University of Texas Southwestern Medical Center | Campus Edition

UT Southwestern prepares for new School of Public Health

Celette Sugg Skinner, Ph.D., Interim Dean, School of Public Health

By Carol Marie Cropper

Prior to the COVID-19 pandemic, North Texas faced many long-standing public health challenges, including high rates of various common chronic illnesses, such as obesity and heart disease, disparities in access to care, and the impact of socioeconomic determinants on health in our communities. The pandemic, as the latest in many challenges to public health, has underscored the need to develop science-based interventions, as well as an expanded public health workforce in Texas. In response to these issues, UT Southwestern is establishing a School of Public Health.

As the University's newest school in more than 50 years, the School of Public Health will join UTSW's Medical School, School of Health Professions, and Graduate School of Biomedical Sciences and will initially be located in renovated space on South Campus.

"Beyond the need to address public health issues through research and innovation, as the COVID-19 pandemic has shown, there is also an urgent need for additional public health resources in our communities, including professionals trained in preventive interventions, epidemiologic crisis response, disease surveillance, contact tracing, and public health outreach," said Daniel K. Podolsky, M.D., President of UT Southwestern.

Dr. Podolsky noted that 200 of Texas' 254 counties lack sufficient resources in terms of the number of public health professionals trained in such specialties.

"The UT Southwestern School of Public Health will be dedicated to producing a new generation of public health leaders skilled in data sciences, epidemiology, health policy, health care delivery research, implementation science, and other disciplines," said Dr. Podolsky. "The new school will build upon our strengths in basic and clinical sciences, and the expertise we have developed in fields such as population and data sciences, bioinformatics, and computational biology."

The school, which expects to welcome its first class of Master of Public Health students in the fall of 2023, followed by classes for Ph.D. students in the fall of 2024, will also leverage assets in Dallas-Fort Worth – one of the most diverse and fastest-growing regions in the United States – by partnering with multiple community organizations, regional health systems, and universities, including partners Parkland Health & Hospital System, Children's Health, and UT Dallas.

In February, plans for the new School of Public Health were approved by the UT System Board of Regents; then the Texas Legislature endorsed the new initiative by appropriating $10 million in seed funding for the coming biennial.

Those funds, combined with

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UT Southwestern planning for new state psychiatric hospital in DFW

Texas Legislature approves initial $45 million in state funding for facility

By Carol Marie Cropper

In response to a statewide need for more psychiatric beds and with financial support from the Texas Legislature, UT Southwestern has begun planning DFW's first state-funded psychiatric hospital.

Once completed – perhaps as early as 2025 – Dallas will join other major cities such as Houston, San Antonio, and Austin in what is currently a 10-facility network of state psychiatric hospitals across Texas. Now, the closest such hospital is in Terrell, more than 30 miles to the east.

"As a public institution, this commitment to help build the first state psychiatric facility in the Dallas-Fort Worth metroplex represents a critical step in efforts to address the acute and growing need for inpatient mental health services," said Daniel K. Podolsky, M.D., President of UT Southwestern. "We are grateful for the trust and confidence that the Texas Health and Human Services Commission and state of Texas have placed in us to help develop and operate this new hospital. Our faculty, researchers, and staff are looking forward to working with the region's stakeholders to leverage the state's investment in order to increase the availability of mental health care, advance the research needed to develop the next generation of treatments, and expand the mental health workforce."

Although details may change during planning, the hospital is currently envisioned as a 200-bed facility on or near the UT Southwestern campus. It will serve adults with serious, acute mental health problems as well as people being evaluated or treated under the state's criminal justice system, said Hicham Ibrahim, M.D., Professor of Psychiatry and Associate Vice President and Chief Medical Officer, Ambulatory Services.

In May, the Texas Legislature approved $44.8 million for planning, designing, and acquiring land for the new hospital. Another appropriation will be required to build the hospital, with a related funding request planned for a special legislative session expected later this year. If additional appropriations are made, construction on the new facility could begin in the fall of 2022, possibly funded with federal Coronavirus Relief Fund dollars given to the state. The project would be delayed

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UTSW scientists closing in on map of the mammalian immune system

Bruce Beutler, M.D., Director of the Center for the Genetics of Host Defense

By Deborah Wormser

Using artificial intelligence, UT Southwestern scientists have identified thousands of genetic mutations likely to affect the immune system in mice. The work is part of one Nobel Laureate's quest to find virtually all such variations in mammals.

"This study identifies 101 novel gene candidates with greater than 95% chance of being required for immunity," said Bruce Beutler, M.D., Director of the Center for the Genetics of Host Defense (CGHD) and corresponding author of the study in *PNAS*. "Many of these candidates we have already verified by re-creating the mutations or knocking out the genes."

Lead author Darui Xu, Ph.D., a computational biologist at CGHD, wrote the software.

"We've developed software called Candidate Explorer (CE) that uses a machine-learning algorithm to identify chemically induced mutations likely to cause traits related to immunity. The software determines the probability that any mutation we've induced will be verified as causative after further testing," Dr. Beutler said. His discovery of an important family of receptors that allow mammals to quickly sense infection and trigger an inflammatory response led to the 2011 Nobel Prize in Physiology or Medicine.

The purpose of CE is to help researchers predict whether a mutation associated with a phenotype (trait or function) is a truly causative mutation, he said.

"CE has already helped us to identify hundreds of genes with novel functions in immunity. This will improve our understanding of the immune

Please see IMMUNITY on page 4

Novel microscopy method provides a peek into the future of cell biology

By Deborah Wormser

What if a microscope could explore the 3D microcosm of blood vessels, nerves, and cancer cells instantaneously in virtual reality, provide views from multiple directions in real time without physically moving the specimen, and work up to 100 times faster than current technology?

UT Southwestern scientists believe they have achieved just that, collaborating with colleagues in England and Australia to build and test a novel optical device that converts commonly used microscopes into multiangle projection imaging systems. The invention, described in an article in *Nature Methods*, could open new avenues in advanced microscopy, the researchers said.

"It is a completely new technology, although the theoretical foundations for it can be found in old computer science literature," said corresponding author Reto Fiolka, Ph.D. Both he and co-author Kevin Dean, Ph.D., are Assistant Professors of Cell Biology and in the Lyda Hill Department of Bioinformatics.

"It is as if you are holding the biological specimen with your hand, rotating it, and inspecting it, which is an incredibly intuitive way to interact with a sample. By rapidly imaging the sample from two different perspectives, we can interactively visualize the sample in virtual reality on the fly," said Dr. Dean, Director of the UTSW Microscopy Innovation Laboratory, which collaborates with researchers across campus to develop custom instruments that leverage advances in light microscopy.

Currently, acquiring 3D-image information from a microscope requires a

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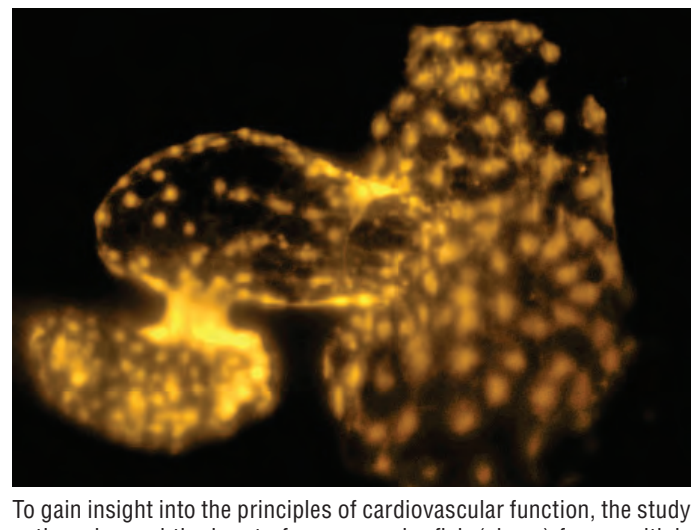

To gain insight into the principles of cardiovascular function, the study authors imaged the heart of a young zebrafish (above) from multiple angles.

INSIDE THIS ISSUE

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IN MEMORIAM

Jere Mitchell, M.D.: Cardiologist's research laid foundations of exercise physiology, changed bed rest practice

From Staff Reports

Jere Mitchell, M.D., former Director of the Harry S. Moss Heart Center and an internationally recognized exercise physiologist whose seminal findings on maximal oxygen uptake changed conventional medical practice on bed rest and laid the foundation for central command physiology, died July 17. He was 92.

"Dr. Mitchell provided groundbreaking understanding of the impact of exercise on cardiovascular function and the role of muscles in stimulating the cardiovascular system that have repeatedly overturned traditional thinking and medical practice," said Daniel K. Podolsky, M.D., President of UT Southwestern. "His findings helped lay the foundations for central command physiology and neural controlled circulation and are among the most cited research on the subject, leaving us a lasting legacy in the field of exercise physiology that continues to fuel insight."

Dr. Mitchell, Professor of Internal Medicine and Physiology and a UT Southwestern alumnus, conducted research on maximal oxygen uptake that became the foundation of the landmark Dallas Bed Rest and Training Study, which in 1968 found that prolonged bed rest dramatically reduced the heart's ability to pump blood effectively. The findings, which evolved from initial investigations into oxygen transport during exercise, overturned the common practice at the time of prolonged bed rest after heart attack and instead demonstrated the need to resume activity quickly. They were later applied to recovery after surgery and childbirth and led to head-down bed rest tilt studies and research on the effect of zero gravity on cardiovascular function, which helped establish the field of space physiology.

While working at the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH), Dr. Mitchell conducted research that overturned traditional thinking on differences between mean left atrial pressure and left ventricular end diastolic pressure, which revealed the transport function of the atrium. For this accomplishment, he received the first Young Investigator Award from the American College of Cardiology (ACC). Later at Oxford University, he conducted research on the role of muscles in stimulating the cardiovascular system. This identified what became known as the exercise pressor reflex which, along with research that revealed central command physiology, laid the foundations of neural controlled circulation. In conjunction with this research, Dr. Mitchell oversaw one of the longest running NIH program project grants, covering more than four decades.

In addition to the ACC's Young Investigator Award, Dr. Mitchell received the ACC's Distinguished Scientist Award – the only investigator to receive both awards. He also was recognized with the Carl J. Wiggers Award from the American Physiological Society, the Paton Prize from The Physiological Society, the Award of Merit from the American Heart Association, the Honor Award from the American College of Sports, a Career Development Award from the U.S. Public Health Service, the Albert Nelson Marquis Lifetime Achievement Award from Marquis Who's Who, and is listed as a Distinguished Humanitarian by Marquis Who's Who.

Jere Mitchell, M.D.

Dr. Mitchell was born in 1928 in Longview, Texas, and graduated with honors in 1950 from Virginia Military Institute before receiving his medical degree from UT Southwestern in 1954. He served his residency and a fellowship at UT Southwestern, along with a fellowship with the Laboratory of Cardiac Energetics for the National Heart, Lung, and Blood Institute in Bethesda, Maryland.

He joined the UT Southwestern faculty in 1962 and was named Director of the Pauline and Adolph Weinberger Laboratory for Cardiopulmonary Research in 1966 before becoming Director of the Harry S. Moss Heart Center in 1976. He also helped establish the Human Performance Center, at the time a joint venture between UT Southwestern and the former St. Paul Medical Center; served on the science advisory board of the U.S. Air Force; was national Vice President of the American Heart Association; served as a Percy Russo lecturer and Professor at the Cumberland College of Health Sciences at The University of Sydney in Australia; and received an honorary Doctor of Philosophy from the University of Copenhagen in Denmark.

Dr. Mitchell had recently donated funds to establish a new distinguished chair approved by the UT System to be known as the Jere H. Mitchell, M.D. Distinguished Chair in Cardiovascular Science. In addition, the S. Roger and Carolyn P. Horchow Chair in Cardiac Research, in Honor of Jere H. Mitchell, M.D., which he held, and the Jere H. Mitchell, M.D. Distinguished Professorship in Clinical Research were created in recognition of his contributions to the field.

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Dr. Podolsky holds the Philip O'Bryan Montgomery, Jr., M.D. Distinguished Presidential Chair in Academic Administration, and the Doris and Bryan Wildenthal Distinguished Chair in Medical Science.

More online: Read the full story in the newsroom at **utsouthwestern.edu/newsroom**.

IN MEMORIAM

Peggy Joyce Whalley, M.D.: Pioneered work in maternal-fetal medicine and high-risk pregnancies

By Patrick Wascovich

Peggy Joyce Whalley, M.D., a Professor Emeritus of Obstetrics and Gynecology whose work in maternal-fetal medicine with high-risk pregnancies saved thousands of expectant mothers and their offspring during a 32-year career at UT Southwestern, died July 6 in Austin. The alumna of UT Southwestern Medical School was 94.

"She was truly a giant in academic obstetrics but was far from an egotistical person despite her many accomplishments," said Gary Cunningham, M.D., Professor of Obstetrics and Gynecology and Chair Emeritus who led the Department from 1983 to 2004. "She was regarded as a 'team player' and contributed to all aspects of departmental assignments."

Believing that confinement would improve the outcome for women suffering from complications of pregnancy, the then-junior faculty member convinced UTSW leadership in 1971 to establish one of the world's first high-risk antenatal units at the old Woodlawn Hospital. There, expectant mothers who were suffering from problems like diabetes, high blood pressure, or premature ruptured membranes received the focused care they needed. Under Dr. Whalley's direction, the perinatal mortality of women cared for in this five-bed unit dropped from 180 per 1,000 deliveries to 19 per 1,000 by 1974. The facility was later expanded and relocated to Parkland Memorial Hospital.


Peggy Joyce Whalley, M.D.

"Following the successes of the high-risk unit, Dr. Whalley began to get transfers of high-risk pregnant women to the unit for care, and eventually the other major hospitals in the area began to develop their own units," Dr. Cunningham said.

Recognizing the impact of this unit on mortality, Dr. Whalley received the Laurel Award in 1976 for her community service from the Dallas Branch of the American Association of University Women. Dubbed Peggy's Palace, the facility at Parkland was officially dedicated in 1988.

Her work at the high-risk unit continued a pattern of Dr. Whalley breaking ground for others to follow. After graduating from the Medical School in 1956, she completed her internship in internal medicine under the late Donald Seldin, M.D., Chairman Emeritus of Internal Medicine, and her residency in obstetrics and gynecology under the late Jack Pritchard, M.D., Professor Emeritus of Obstetrics and Gynecology. Dr. Whalley was the first female Ob/Gyn resident at Parkland and the first to serve as chief resident her senior year. She then completed a one-year fellowship in medicine under the direction of Dr. Seldin before joining the faculty in 1961.

Inspired by Dr. Pritchard's research, Dr. Whalley became interested in the hematologic changes occurring during pregnancy. She studied sickle cell disease, the impact of folic acid and iron deficiencies on the fetus, and the management of pregnancies complicated by diseases like diabetes, hypertension, renal and urinary tract infections, and hyperparathyroidism. Early in her career, she observed that asymptomatic pregnant women with bacteria in their urine (bacteriuria) often had inflammation of the kidney and pelvic linings (pyelonephritis). Acute pyelonephritis is a serious infection that poses hazards to both mother and fetus, including an increased risk of preterm birth.

"Dr. Whalley was an impeccable researcher and did much of the seminal work concerning urinary tract infections in pregnant women," said Dr. Cunningham. "And from experiences gained from the high-risk unit, the care of women with early onset preeclampsia was radically changed, from immediate delivery to domiciliary care that allowed in many cases valuable time for fetal maturation and mitigation of preterm deliveries."

In recognition of her dedication to teaching, research, and patient care, Dr. Whalley in 1975 was named the first Jack A. Pritchard Professor in Obstetrics and Gynecology. A year later, she became the first Director of the new Maternal-Fetal Medicine Fellowship – a position she held from 1976 to 1986. Upon retirement in 1992, Dr. Whalley became the second faculty member, and the first woman, to be named Professor Emeritus of Obstetrics and Gynecology at UTSW.

More online: Read the full story on *Center Times Plus* at **utsouthwestern.edu/ctplus.**

School Continued from page 1

money UTSW hopes to raise through community support, will go toward planning curriculum and hiring faculty, as well as redesigning existing UT Southwestern space to accommodate the new school, said Celette Sugg Skinner, Ph.D., Chair of the Department of Population and Data Sciences and Interim Dean of the UT Southwestern School of Public Health. Additional funding will be needed in the future as the program grows and requires construction of a dedicated building on campus, Dr. Skinner said.

UT Southwestern already plays a leading role in addressing public health needs in the region and conducts research on health care disparities and innovative interventions.

For example, as the region continues to battle COVID-19 infections, UT Southwestern's data scientists and epidemiologists produce a biweekly forecasting model that public health officials, as well as the general public, utilize to gauge whether the spread of the disease is rising or falling and what social behaviors are additional risk factors for exposure.

Beyond COVID-19 and continuously throughout the pandemic, UT Southwestern has also persisted in its efforts to provide basic and preventive care using a variety of outreach programs. Through the Fort Worth affiliate of its Harold C. Simmons Comprehensive Cancer Center – the Moncrief Cancer Institute – and alongside local cancer screening providers throughout North Texas, UT Southwestern has increased screening for breast, colorectal, and lung cancer in 35 regional counties. Additional efforts have also supported vaccinations for adolescents to protect against HPV, a common virus that can lead to several types of cancers later in life.

"This new school will be research-intensive and will generate evidence about what works with large groups of patients, develop professionals to expand the work, and learn more regarding what can be implemented on a large scale across systems that benefit the citizens of Dallas, the U.S., and the world," Dr. Skinner said.

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See the endowed titles held by Dr. Podolsky above.

Dr. Skinner holds the Parkland Community Medicine Professorship.

CenterTimes

Center Times is published by the Office of Communications, Marketing, and Public Affairs at UT Southwestern Medical Center. UT Southwestern is an Affirmative Action/Equal Opportunity Employer. Women, minorities, veterans, and individuals with disabilities are encouraged to apply.

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Researchers find immune component to rare neurodegenerative disease

Niemann-Pick disease Type C may eventually be treated with immune inhibitors

By Christen Brownlee

UT Southwestern researchers have identified an immune protein tied to the rare neurodegenerative condition known as Niemann-Pick disease Type C. The finding, made in mouse models and published in *Nature*, could offer a powerful new therapeutic target for this condition that was identified more than a century ago but still lacks effective treatments.

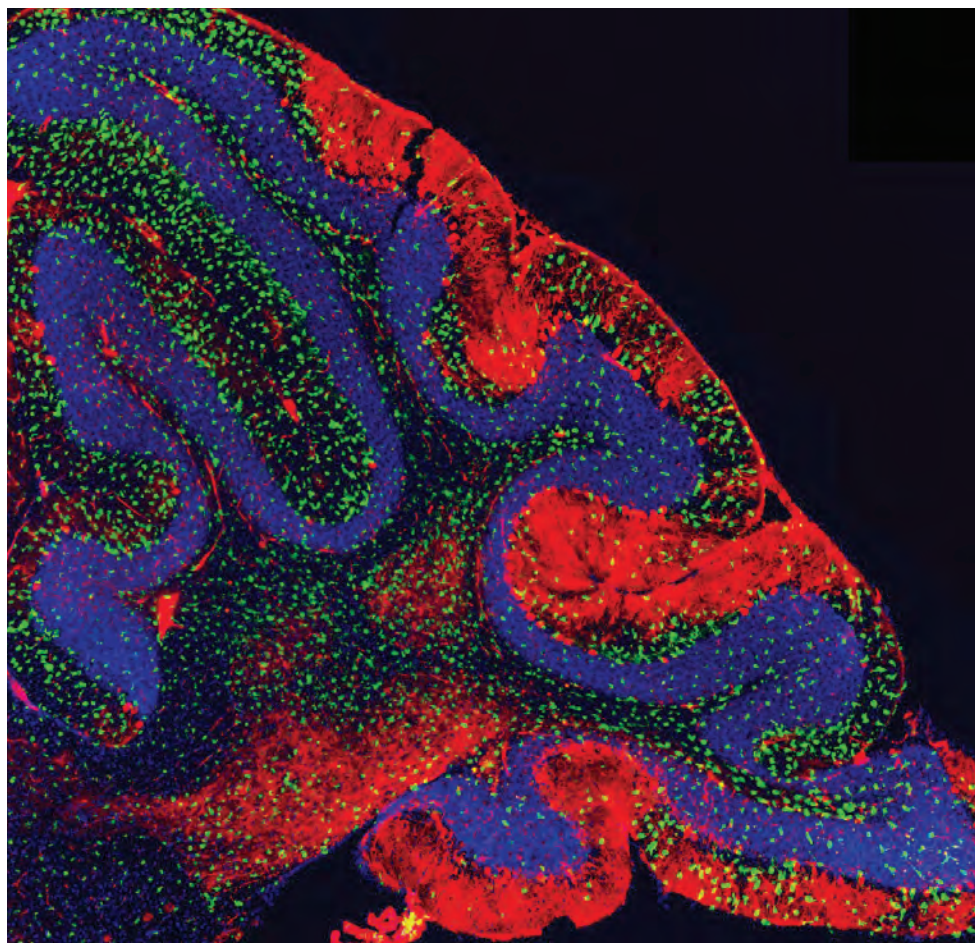
"Niemann-Pick disease has never been considered an immune disorder," said study leader Nan Yan, Ph.D., Professor of Immunology and Microbiology. "These findings put it in a whole new light."

Niemann-Pick disease Type C, which affects

Nan Yan, Ph.D.

about 1 in every 150,000 people worldwide, has long been considered a disease of cholesterol metabolism and distribution, a topic well-studied at UT Southwestern, where faculty members Michael Brown, M.D., and Joseph Goldstein, M.D., won the Nobel Prize in 1985 for their discovery of low-density lipoprotein (LDL) receptors that led to the development of statin drugs.

When the *Npc1* gene is mutated, cholesterol is not sent where it is needed in cells, causing



Immunofluorescent staining of *Npc1*-deficient mouse cerebellum, with Purkinje neurons in red, activated microglia in green, and nucleus in blue. Massive microglia infiltration and loss of Purkinje neurons cause severe neurological disease in Niemann-Pick disease type C. Credit: Ting-Ting Chu

the progressive decline in motor and intellectual abilities that characterize Niemann-Pick. Dr. Yan's lab team made its discovery by chance while researching the immune protein STING, short for stimulator of interferon genes.

STING is a critical part of the body's defense against viruses, typically relying on another protein known as cyclic GMP-AMP synthase (cGAS) to sense DNA and turn on immune genes to fight off viral invaders. The cGAS enzyme was identified at UT Southwestern.

STING journeys to different organelles to perform various tasks before it ends up in lysosomes, which serve as cellular garbage dumps. Disposal of STING is critical for an appropriate immune response, explained Dr. Yan; research has shown that when STING isn't properly discarded, it continues to signal immune cells, leading to a variety of autoimmune conditions.

To determine what proteins interact with STING, researchers used proximity labeling, which causes other proteins around a protein of interest to glow. After analyzing their data, Dr. Yan's team was surprised to find that STING interacts with a protein that's located on the surface of lysosomes and is produced by the *Npc1* gene.

Because STING had never been implicated in Niemann-Pick disease Type C, Dr. Yan investigated further. The researchers removed the gene for STING from mice in which the *Npc1* gene had also been deleted. Deleting *Npc1* typically causes progressive problems in motor function, but animals with both the *Npc1* and STING genes deleted remained healthy.

Further research suggested that the protein produced by *Npc1* has a binding site for STING that allows it to enter lysosomes for disposal. When the protein produced by *Npc1* is missing, STING remains in cells, propagating Niemann-Pick disease Type C. When researchers analyzed cells from human Niemann-Pick disease Type C patients, they found that several immune-stimulating genes were overactive, as would be expected if STING disposal was defective.

In addition, Dr. Yan found that STING signaling is activated independently of cGAS in Niemann-Pick disease. This expands STING biology beyond its conventional role in host defense against infection.

Dr. Yan said that his lab and others are investigating the use of experimental drugs that inhibit STING to treat various autoimmune conditions. These compounds may also be useful for Niemann-Pick disease Type C.

"If we can demonstrate that these compounds are effective in our animal models," Dr. Yan said, "we may be able to offer an effective therapy to Niemann-Pick disease patients."

■

Dr. Brown is the Director of the Erik Jonsson Center for Research in Molecular Genetics and Human Disease at UT Southwestern. He is a Regental Professor and holds The W.A. (Monty) Moncrief Distinguished Chair in Cholesterol and Arteriosclerosis Research, and the Paul J. Thomas Chair in Medicine.

Dr. Goldstein, Professor and Chair of Molecular Genetics, is a Regental Professor and holds the Julie and Louis A. Beecherl, Jr. Distinguished Chair in Biomedical Research, and the Paul J. Thomas Chair in Medicine.

Dr. Yan is a Rita C. and William P. Clements, Jr. Scholar in Medical Research.

More online: Read the full story in the newsroom at **utsouthwestern.edu/newsroom**.

Hope for patients with a rare bone-destroying condition

Research uncovers one cause of, and potential treatment for, Gorham-Stout disease

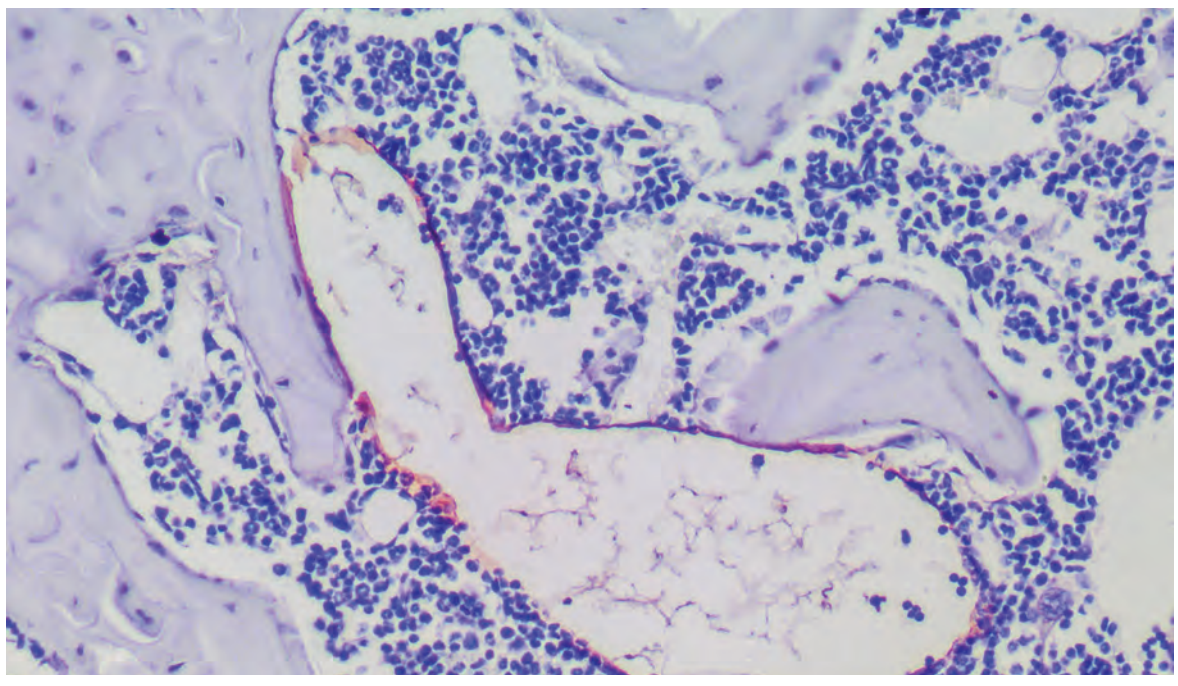
By Carol Marie Cropper

An international research team led by a UT Southwestern scientist has identified a cause of and a possible treatment for Gorham-Stout disease, a painful, disfiguring, and life-threatening condition that destroys bone and can cause respiratory failure. The disease typically strikes children or young adults, leading to damage of affected bones as they are invaded and taken over by lymphatic vessels. Bones in the skull, jaw, shoulder, rib cage, and pelvis are the most commonly affected.

In a study published recently in *JCI Insight*, the researchers identified a mutation in the *KRAS* gene in bone samples taken from a patient who later died of Gorham-Stout disease. When mice were engineered to have a similar *KRAS* mutation, they developed symptoms of Gorham-Stout disease, the study reported, indicating such mutations may be one cause of the disorder – a breakthrough for a disease whose origins have remained unknown.

In a second finding that holds particular promise for treatment, when researchers gave the young mice trametinib – a drug approved by the FDA to treat cancers linked to *KRAS* mutations – the mice showed fewer of the characteristic Gorham-Stout disease lymphatic vessel abnormalities.

"This finding has the potential to make a big huge impact on this disease and the treatment of patients," said Michael Dellinger, Ph.D., senior author of the study and Associate Professor of Surgery, Molecular Biology, and in the Hamon Center for Therapeutic



Brain staining shows lymphatic invasion in a mouse bone model of Gorham-Stout disease.

Oncology Research.

"Our work suggests that trametinib could be an effective treatment for Gorham-Stout disease and supports the testing of such MEK inhibitors," he added, referring to drugs like trametinib that can inhibit so-called MEK (mitogen-activated protein kinase kinase) enzymes involved in the cell proliferation associated with some *KRAS* mutations.

Clinicians have already told him they will try trametinib when patients don't respond to the current first-line treatment rapamycin, another cancer drug, Dr. Dellinger said. Such an off-label use would be allowed since the drug has already been approved by the FDA for another use.

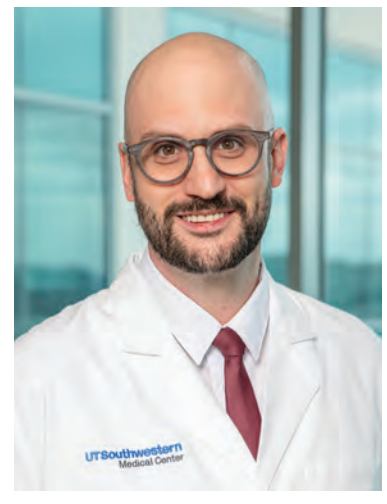
In 2018, Dr. Dellinger developed the first mouse model used to study Gorham-Stout disease. The creation of the new mouse model with *KRAS* mutations linked to the disease will make possible further studies by more researchers – many of whom do not have access to human patients or samples.

It is uncertain exactly how many people around the world currently have Gorham-Stout disease, although the number is typically placed in the hundreds.

Besides damage to bones, another problem that often arises in Gorham-Stout disease is lymphatic vessels designed to carry away excess fluid and waste fail to operate properly due to a reduction in the number of valves inside the vessels, Dr. Dellinger said. "Lymphatic vessels are the body's sewer system. They pick up fluid and carry it away, dumping it into blood vessels."

In Gorham-Stout disease, the fluid instead can build up around the lungs, causing respiratory failure. This is the most common cause of death in such patients.

Dr. Dellinger has received half of a $2 million shared Department of Defense grant to continue his research into the benefit of trametinib for treating Gorham-Stout disease and also to screen for other drugs to use in combination with trametinib.



Michael Dellinger, Ph.D.

Research support for this study came from the NIH, Fonds de la Recherche Scientifique, Walloon Excellence in Lifesciences and Biotechnology, Lymphatic Malformation Institute USA, Télévie, the National Lottery in Belgium, and the Belgium Foundation against Cancer. Anna L. McCarter, M.S., a UTSW research assistant, participated in the study, as did researchers at the Catholic University of Louvain and the European Reference Network on Rare Multisystemic Vascular Diseases, both in Brussels.

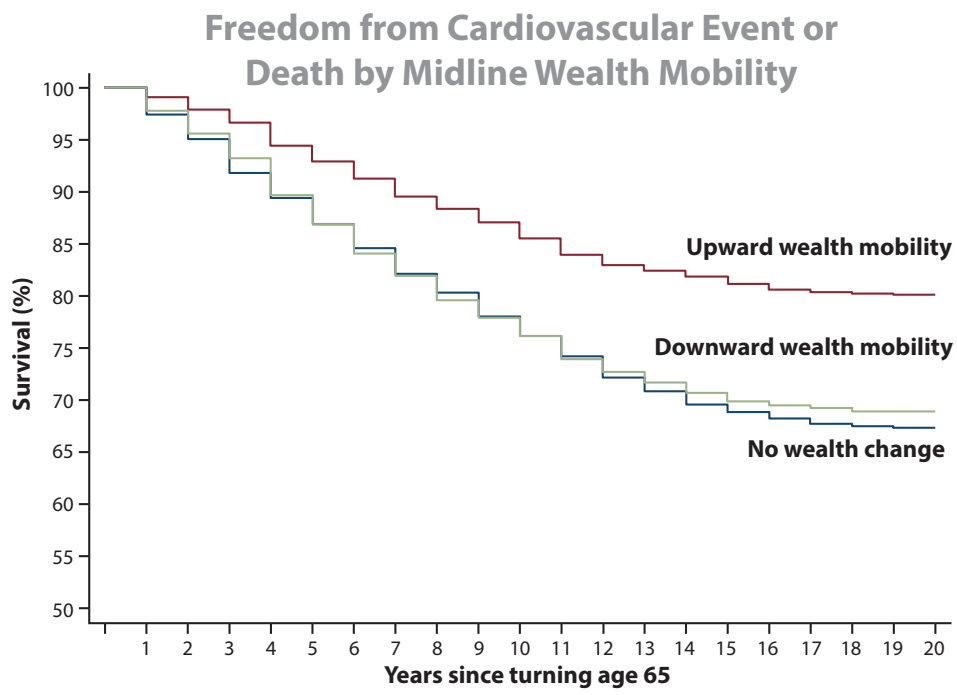
Study shows wealth mobility affects Americans' long-term cardio health

By Patrick Wascovich

In a recent study published in *JAMA Cardiology*, researchers found a correlation between a relative decline in wealth during midlife and an increased likelihood of a cardiac event or heart disease after age 65, while an increase in wealth between ages 50 and 64 was found to lower cardiovascular risk.

Although the association between socioeconomic status and cardiovascular outcomes is well established, little research has been done to determine whether longitudinal changes in wealth are associated with cardiovascular health. In the study, Andrew Sumarsono, M.D., Assistant Professor of Internal Medicine, along with colleagues from Harvard-affiliated Brigham and Women's Hospital Heart & Vascular Center and the London School of Economics, investigated the cardiovascular toll that changes in monetary health can have in the U.S., where there is a 10- to 15-year difference in life expectancy between the population's richest 1% and the poorest 1%.

Examining a cohort of more than 5,500 adults without cardiovascular disease, the study found that middle-aged participants who experienced upward wealth mobility – defined as relative increases in the total value of assets excluding primary residence – had lower cardiovascular risk after age 65 compared with peers of similar age. Conversely, participants who experienced downward wealth mobility in the latter parts of their careers had higher cardiovascular risk later in life. Cardiovascular events cited as outcomes include acute myocardial infarction, heart failure, cardiac arrhythmia, and stroke, or cardiac-related death.



"We already know that wealth relates to health, but we show that wealth trajectories also matter. This means that the cardiovascular risk associated with wealth is not permanent and can be influenced," said Dr. Sumarsono, a faculty member in the Division of Hospital Medicine.

The researchers estimate a 1% swing in cardiovascular risk for every $100,000 gained or lost by individuals. Notably, participants who started in the top 20% of wealth and experienced downward wealth mobility still had similar cardiovascular risk as those who remained fixed in the top quintile. However, those who started in the bottom fifth of wealth accumulation and experienced upward wealth mobility had lower cardiovascular risk than those fixed in the bottom quintile. These findings linking wealth change and downstream cardiovascular events were similar across all racial or ethnic subgroups.


Andrew Sumarsono, M.D.

"We found that irrespective of one's baseline wealth, upward wealth mobility relative to peers in late-middle age was associated with lower risk of a new cardiac event or death after age 65," Dr. Sumarsono said. "We also found the inverse was true – that people who experienced downward wealth mobility relative to one's peers faced a higher risk of a new cardiac event or death after 65, potentially offsetting some of the benefit associated with prior economic thriving."

More online: Read the full story in the newsroom at **utsouthwestern.edu/newsroom**.

Fighting off food poisoning depends on the time of day

Levels of natural antimicrobial molecule fluctuate on a circadian rhythm, study shows

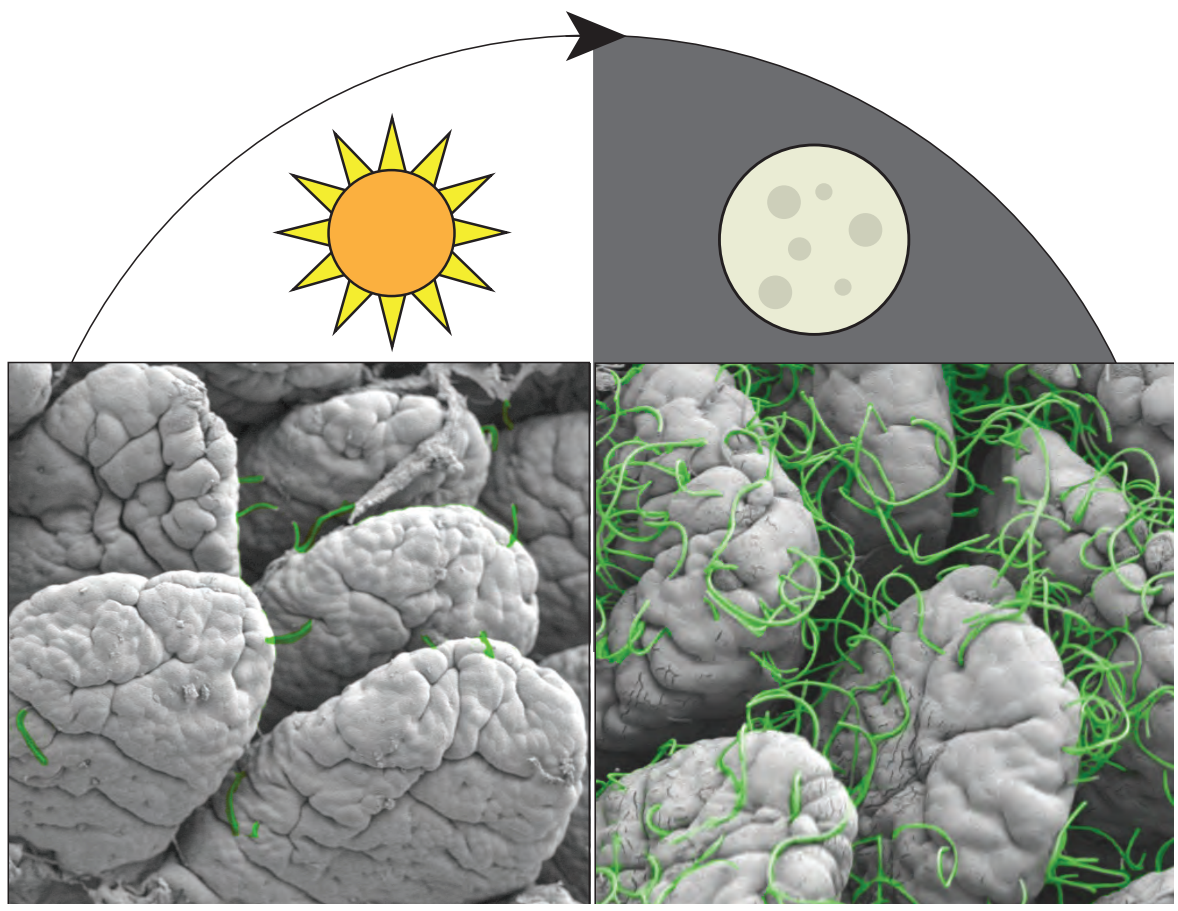
By Christen Brownlee

The body's ability to prevent food poisoning by producing a natural antimicrobial compound increases during the day, when exposure to noxious bacteria is most likely, a study by UT Southwestern scientists suggests. The findings, published in *Cell*, could eventually lead to timed therapies and vaccination regimens designed to maximize this immune response.

"This study shows that our immune systems are not turned on all the time, which is an unexpected result," said study leader John F. Brooks II, Ph.D., a postdoctoral fellow in the laboratory of Lora Hooper, Ph.D., study co-leader and Professor of Immunology and Microbiology. "Our findings suggest that there are peak times in which the body is more primed to fight infections."

Researchers have long known that virtually all animals follow circadian cycles tied to sunrise and sunset. Disrupting circadian rhythms can have serious health consequences; for example, chronic sleep disruption is related to increased intestinal infection in humans.

Drs. Brooks, Hooper, and their colleagues suspected that antibacterial immunity might change in the intestines on a circadian cycle. To investigate, the researchers looked for rhythms in the expression of natural antimicrobial agents produced in the guts of mice to fight foodborne illness. In normal lab mice, one of these antimicrobial molecules – known as regenerating islet-derived protein 3g (REG3G) – was more abundant at night, when these nocturnal animals are active, and less so during the day. However, in mice raised to have no gut bacteria, REG3G was essentially absent throughout the day and night.



A scanning electron micrograph shows segmented filamentous bacteria attaching to the intestinal surface of a mouse. More bacteria attach during the night than during the day. Credit: John F. Brooks II, Ph.D.

The researchers found that mice with cycling amounts of REG3G had large resident populations of segmented filamentous bacteria in their guts – microbes typically present in rodents, nonhuman primates, and humans – that attach to the intestinal lining and change their hosts' gene activity. Further experiments showed that these bacteria attached to the animals' intestinal lining during feeding, probably to siphon off nutrients. When they attached, REG3G production ramped up in the intestines.

This cycling had significant consequences for the ability of mice to fight off infection. When the researchers infected normal mice with bacteria, the animals had higher bacterial burdens and rates of death if they were exposed at sunset than at sunrise. Mice that can't make antimicrobial proteins, including REG3G, had similarly high rates of bacterial burden and death regardless of when they were infected.

If further research shows this phenomenon also occurs in humans, scientists may eventually be able to capitalize on it by timing the administration of synthetic antibiotics for intestinal infections and oral vaccines or finding new ways to avoid intestinal infections altogether.


John F. Brooks II, Ph.D.


Lora Hooper, Ph.D.

"These results make me think twice about waking up in the middle of the night and raiding the refrigerator," Dr. Hooper said. "It may be more dangerous to eat bacteria-laden potato salad when your gut defenses are lowest."

This work was supported by grants from the National Institutes of Health (R01 DK070855), The Welch Foundation (I-1874), and the Walter M. and Helen D. Bader Center for Research on Arthritis and Autoimmune Diseases. Dr. Brooks is a recipient of a highly competitive Howard Hughes Medical Institute Hanna H. Gray Fellowship.

■

Dr. Hooper holds the Jonathan W. Uhr, M.D. Distinguished Chair in Immunology and is a Nancy Cain and Jeffrey A. Marcus Scholar in Medical Research, in Honor of Dr. Bill S. Vowell.

More online: Read the full story in the newsroom at **utsouthwestern.edu/newsroom**.

Immunity

Continued from page 1

system so that we can find new ways to keep it robust, and also know the reason it sometimes falters," Dr. Beutler said.

The software examines 67 features of the primary genetic mapping data to arrive at estimates related to a mutation's likelihood of causing a trait. For some mutations, causation is very clear; for others, less so. Over time, the program "learns" from experiments in which researchers re-create the mutation in a fresh pedigree and verify or exclude the hypothesis of causation.

All mutations are made available to the scientific community through a public repository, and the data supporting causation are viewable within the Candidate Explorer program on the CGHD website, Mutagenetix.

The team used CE to evaluate about 87,000 mutation/trait associations that passed the initial statistical threshold for candidacy. The traits examined were based on flow cytometry data collected on circulating immune cells of third-generation mutant mice. In this screen, Candidate Explorer ranked 2,336 mutations in 1,279 genes as good or excellent candidates for causation of traits.

This work is part of a research program that Dr. Beutler set out on nearly a decade ago to identify every mutation that may affect the mouse immune system.

"We've now worked through about 60% of the genome and have identified thousands of genes – hundreds of them novel – that participate in immunity in the mouse," he said. "The vast majority of these also contribute to human immunity."

The current study focused on changes in cells known to be tied to immunity, such as B cells, T cells, macrophages, and natural killer cells. The work received support from the National Institutes of Health (grants R01 AI125581 and U19 AI100627).

■

Dr. Beutler is a Regental Professor and holds the Raymond and Ellen Willie Distinguished Chair in Cancer Research, in Honor of Laverne and Raymond Willie, Sr.

Results of the study

The researchers developed Candidate Explorer (CE), software that uses a machine-learning algorithm to identify mutations causative of phenotypes (traits).

Using CE, more than 87,000 mutation-phenotype associations were identified by flow cytometry screening of circulating immune cells from mutagenized mice.

The study showed 1,279 genes representing 2,336 mutations were rated as good or excellent candidates for causation of phenotypes. Many of these genes were not previously implicated in immunity.

More online: Read the full story in the newsroom at **utsouthwestern.edu/newsroom**.

Artificial intelligence used to assess metastatic potential of skin cancers

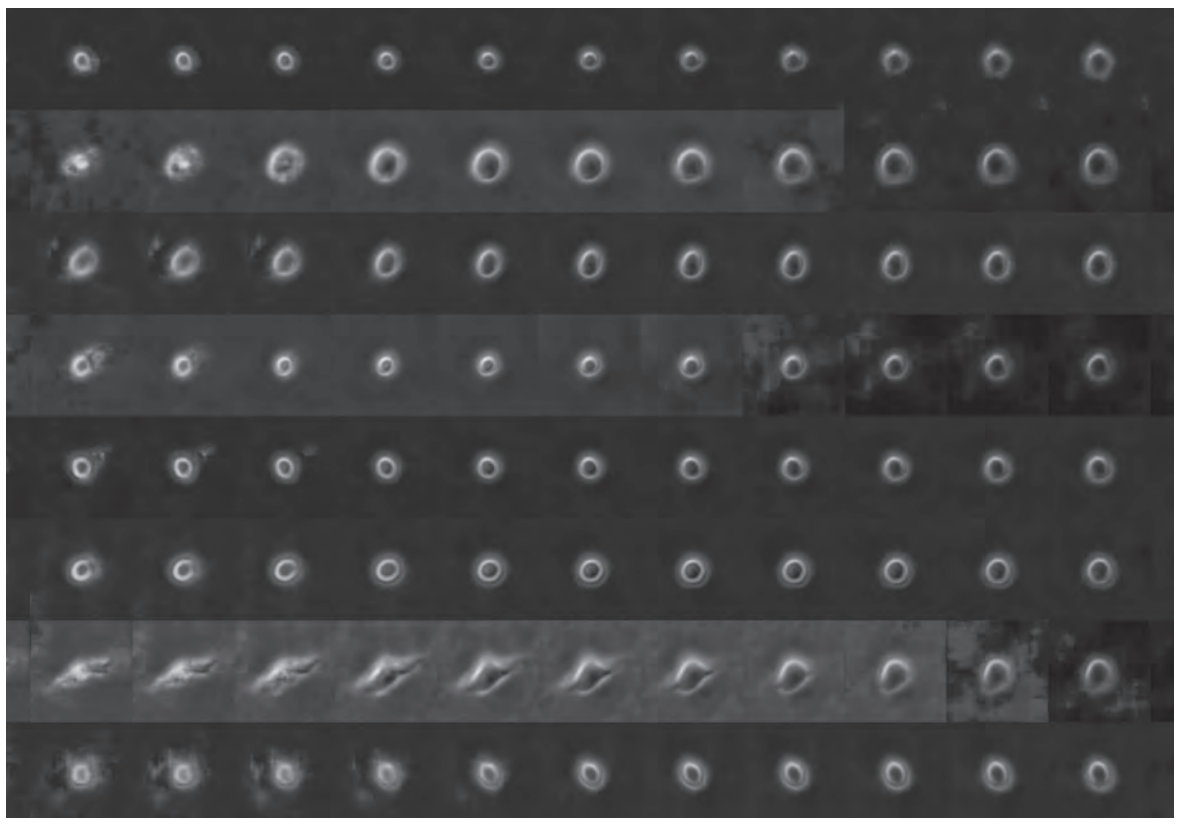
By Christen Brownlee

Using artificial intelligence (AI), researchers from UT Southwestern have developed a way to accurately predict which skin cancers are highly metastatic. The findings, published as the July cover article of *Cell Systems*, show the potential for AI-based tools to revolutionize pathology for cancer and other diseases.

"We now have a general framework that allows us to take tissue samples and predict mechanisms inside cells that drive disease, mechanisms that are currently inaccessible in any other way," said study leader Gaudenz Danuser, Ph.D., Chair of the Lyda Hill Department of Bioinformatics.

AI technology has significantly advanced, Dr. Danuser explained, with deep learning-based methods now able to distinguish minute differences in images invisible to the human eye. Researchers have proposed using this latent information to look for differences in disease characteristics that could offer insight on prognoses or guide treatments. However, he said, the differences distinguished by AI are generally not interpretable in terms of specific cellular characteristics – a drawback that has made AI a tough sell for clinical use.

To overcome this challenge, Dr. Danuser and his colleagues used AI to search for differences between images of melanoma cells with high and low metastatic potential and then reverse-engineered their findings to determine which features produced the variances. Using tumor samples from seven patients and information on their disease progression, including metastasis, the researchers took videos of about 12,000 random cells living in petri dishes, generating about 1.7 million raw images. The researchers then used an AI algorithm to pull 56 different abstract numerical features from these images.



Eight simulations of melanoma cell image traces converted with AI software show (from left) a state of highly metastatic potential to low metastatic potential. Highly metastatic cells tend to extend fingerlike protrusions (pseudopodia) and the cell body scatters more light, which relates to a rearrangement of cellular organelles. Credit: Andrew Jamieson

The research team found one feature able to accurately discriminate between cells with high and low metastatic potential. By manipulating this abstract numerical feature, they produced artificial images that exaggerated visible characteristics inherent to metastasis that human eyes cannot detect, he added. The highly metastatic cells produced slightly more pseudopodial extensions – a type of fingerlike projection – and had increased light scattering, an effect that may be due to subtle rearrangements of cellular organelles.

To prove the utility of the AI tool, the researchers classified the metastatic potential of cells from human melanomas that had been frozen for 30 years and then implanted them into mice. Those predicted to be highly metastatic formed tumors that readily spread throughout the animals, while those predicted to have low metastatic potential spread little or not at all.

Gaudenz Danuser, Ph.D.

Dr. Danuser noted that this method needs further study before it becomes part of clinical care. But eventually, he added, it may be possible to use AI to distinguish important features of cancers and other diseases.

■

Dr. Danuser holds the Patrick E. Haggerty Distinguished Chair in Basic Biomedical Science.

More online: Read the full story in the newsroom at **utsouthwestern.edu/newsroom**.

Nonsurgical treatment using valves provides relief for emphysema patients

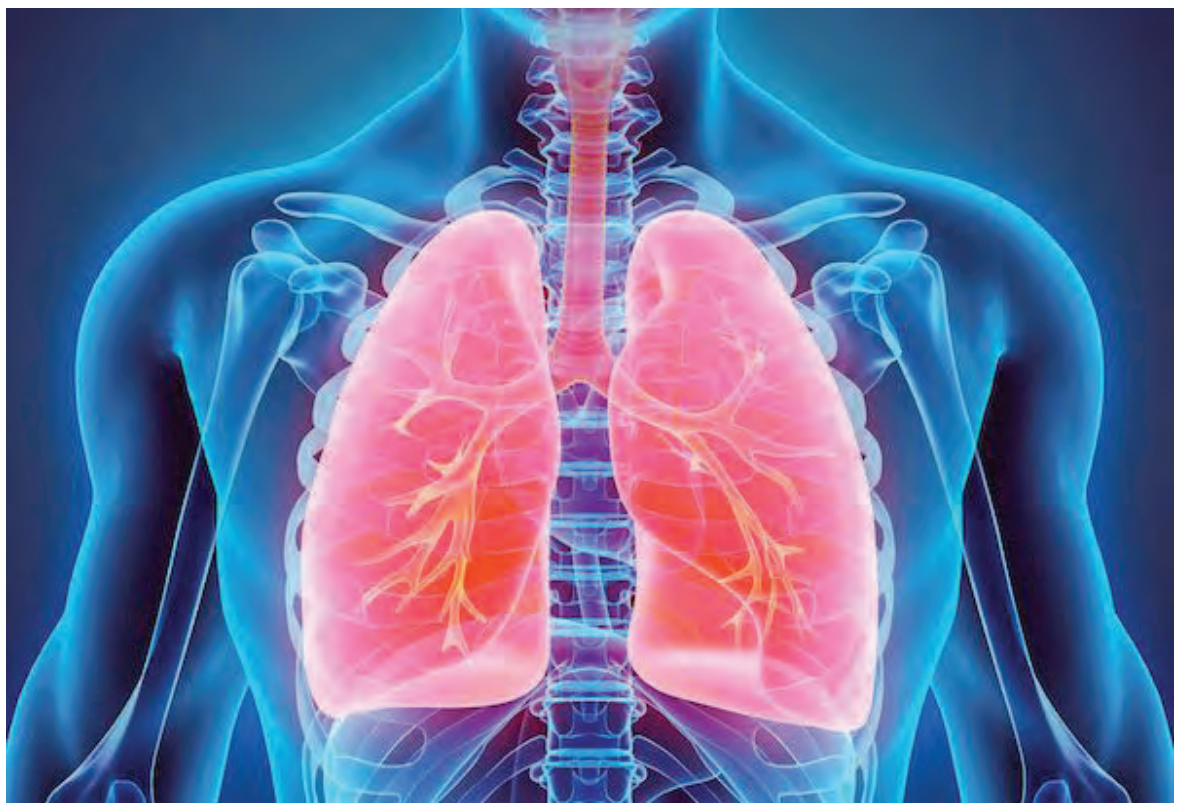
By Jan Jarvis

A nonsurgical procedure that uses innovative valve devices – both developed through multicenter clinical studies, including at UT Southwestern – is giving patients with severe emphysema a new treatment option that allows them to breathe easier.

The procedure, called bronchoscopic lung volume reduction, or BLVR, and the tiny endobronchial valve devices that redirect air to healthier portions of the lung were approved by the Food and Drug Administration in 2018. Soon after, UT Southwestern became the first hospital in Dallas to offer BLVR.

Muhanned Abu-Hijleh, M.D.

BLVR has now become a vital piece of UT Southwestern's nationally recognized pulmonary care for patients with chronic obstructive pulmonary disease, or COPD, said Muhanned Abu-Hijleh, M.D., Director of Interventional Pulmonology at UTSW, who was among the researchers to help develop the one-way valves and also served as Principal Investigator of the EMPROVE trial at UTSW, a multicenter clinical trial evaluating the valve system. Dr. Abu-Hijleh is also involved in multicenter trials testing new treatment options for patients with advanced COPD.



"We have performed more than 90 BLVR procedures since June 2019, and the results have been overwhelmingly positive," said Dr. Abu-Hijleh, Professor of Internal Medicine. "Our patients have reported less shortness of breath, better lung function, more tolerance of exercise, and improved overall quality of life."

Breathing is often a constant challenge for patients with severe COPD. Advanced emphysema typically damages lung tissue, causing loss of elasticity in the lung tissue and air sacs. This also leads to easy collapsibility of the small airways during exhalation and air-trapping in the lungs. A healthy adult takes about 10 to 16 breaths per minute – but patients with severe COPD, such as emphysema, usually breathe much faster. Patients often try inhalers, oxygen, medications, and pulmonary rehabilitation to breathe easier.

BLVR is a minimally invasive procedure that usually takes less than 30 minutes with a hospital stay of two to three days. The procedure uses tiny one-way valves to prevent air from entering the diseased areas of the lungs. The valves are placed inside the airways of a diseased lung to redirect air to healthier parts of the lung. The procedure is performed with a bronchoscope, a flexible tube that is inserted into the nose or mouth or through an anesthesia tube.

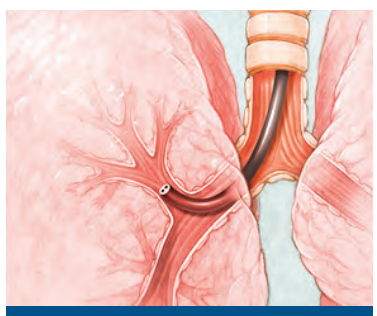
"On average, we insert two to five valves, which limit airflow into the diseased areas while still allowing trapped air and secretions to escape," Dr. Abu-Hijleh said. "By reducing the volume of diseased portions of the lungs and directing air to the healthier sections of the lung, patients will be able to breathe easier and enjoy better lung function."

The umbrella-shaped valves are placed inside the airways of a diseased lung to redirect air to healthier parts of the lung. Credit: Olympus America

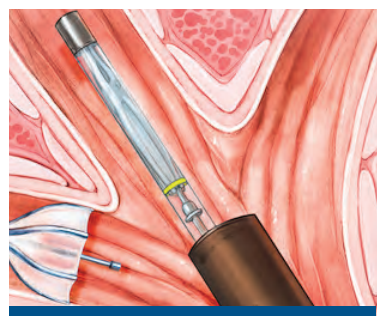
Not everyone qualifies for the procedure; severe emphysema patients must be on maximum medical therapy and inhalers, which reduce inflammation in their lungs and open the airways to ease symptoms. They also must be nonsmokers and participate in pulmonary rehabilitation.

For patients with severe lung disease, the procedure can be life-changing.

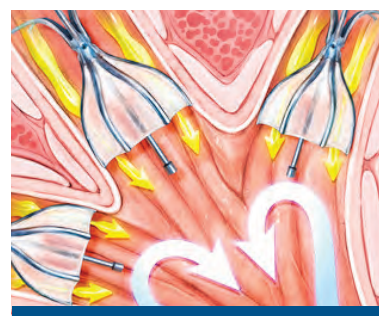
"BLVR doesn't just improve lung function for people with severe emphysema – it can give them a big psychological boost, as well, and a more positive outlook about their disease," Dr. Abu-Hijleh said. "Many of our patients have told us they were able to resume their daily routines, get out of the house more, and reclaim their lives because they feel better physically and mentally."



Using the scope



Placing the valves



Redirecting the air

Breathing easier

Cancer Biology Ph.D. student awarded HHMI Gilliam Fellowship

By Rachel Stowe Master

As an undergraduate studying chemistry at the University of Puerto Rico, Rio Piedras, Ester Álvarez Benedicto worked in an organic chemistry lab synthesizing compounds for anti-cancer properties.

"I quickly learned that delivery of drugs or biologics has been a difficult challenge and that often their untargeted delivery caused potent side effects," said Ms. Álvarez Benedicto, now a fourth-year Ph.D. candidate in the Cancer Biology Program and the Mechanisms of Disease and Translational Science Track at UT Southwestern. "This sparked an interest in me to work with drug delivery platforms such as lipid nanoparticles."

One of 50 recipients in the U.S. of a 2021 Gilliam Graduate Fellowship for Advanced Study, Ms. Álvarez Benedicto will use grant funding from the Howard Hughes Medical Institute (HHMI) to support her research to repurpose lipid nanoparticles (LNPs) for cancer treatment.

"It's an honor to be selected as a Gilliam Fellow and join countless other students and faculty invested in diversity, equity, and inclusion in science. Moreover, it's an opportunity to continue to aid UT Southwestern in its journey toward making our institution a place for everyone," Ms. Álvarez Benedicto said.

The Gilliam grant provides $50,000 annually for up to three years to pairs of dissertation advisers and their graduate students. Program goals are to ensure students from historically excluded and underrepresented groups in science are prepared to assume leadership roles, as well as to foster the development of a more inclusive academic scientific ecosystem by partnering with faculty and institutions committed to advancing diversity and inclusion in the sciences. This year, 296 applications were evaluated on the scientific and leadership promise of the students and their institutions' quality of and commitment to mentorship and the development of a more inclusive environment for all constituencies.

Ester Álvarez Benedicto

In the Siegwart lab, Ms. Álvarez Benedicto studies LNPs for nucleic acid delivery (RNA/DNA). LNPs have numerous applications – such as in the COVID-19 vaccine. "Both Pfizer and Moderna use LNPs to deliver the messenger RNA [ribonucleic acid] that codes for the spike protein. My project specifically intends to repurpose LNPs for gene delivery to immune cells. Our main goal is to target T cells to induce an immune response toward cancer cells," she said.

Current immunotherapies are expensive and difficult to access for patients with low socioeconomic backgrounds, and patients often relapse with a new tumor that no longer responds to the initial immunotherapy, she explained.

Daniel Siegwart, Ph.D.

"With our LNPs, we seek to make the manufacturing of immunotherapies easier and faster to treat the relapse of patients with resistant cancers and to make immunotherapies readily available, as the cost of manufacturing LNPs has proved to be cost-effective," she added.

"Ester is a dream student to work with – intelligent, creative, thoughtful, caring, and hardworking," said Daniel Siegwart, Ph.D., Associate Professor of Biochemistry and a member of the Harold C. Simmons Comprehensive Cancer Center.

"In addition to scientific research, I am especially looking forward to working with Ester on our planned diversity and inclusion initiatives. These will be supported by HHMI and target key gaps in representation and opportunities to support next-generation leaders."

When originally searching for a Ph.D. program, Ms. Álvarez Benedicto wanted an institution where she could work with nanotechnology and translational projects.

"UT Southwestern excels in both of the areas I was interested in for my research and also had an excellent community where I felt supported both as a Hispanic woman and as a scientist," she said.

About Gilliam Fellowships:

- 50 adviser-student pairs in 2021, the largest group to date
- 351 Fellows in the community since the program's inception
- $50,000 per year, per award
- Since 2016, the program has trained 199 mentors.

Gilliam mentor training:

- Creates inclusive environments for students in science by working with faculty to become aware of their own cultural identities; understand the critical role of listening; and feel comfortable engaging across cultures.
- Features a yearlong course in culturally aware mentorship.

Graduate student is first from UTSW to receive Soros Fellowship

By Jan Jarvis

Michael Trinh, the child of Vietnam War refugees, is the first graduate student from UT Southwestern to receive a Paul & Daisy Soros Fellowship for New Americans and one of 30 recipients nationwide. The fellowship will support his research on how cholesterol is transported inside human cells.

Recipients of Paul & Daisy Soros Fellowships for New Americans are immigrants or the children of immigrants and are selected based on graduate students' potential to make significant contributions to the United States; more than 3,400 students applied for the grants. Fellows receive up to $90,000 in funding to support their research.

"It is a great honor to be the first person from UT Southwestern to be selected," said Mr. Trinh, who is working toward an M.D./Ph.D. "This puts a spotlight on the work we are doing here."

"The Paul & Daisy Soros Fellows demonstrate the immense contributions that immigrants of all backgrounds make to the United States," said Craig Harwood, Fellowship Director. "Their stories and work fill me with a deep sense of hope for our nation's future."

The death of Mr. Trinh's grandfather from cancer solidified his desire to be a physician. He majored in biology at UT Dallas as part of the UT-PACT Program – a joint B.A./M.D. program that allowed him to matriculate at UT Southwestern after three years of college. As an undergraduate, Mr. Trinh worked in the UTSW laboratory of Michael Brown, M.D., and Joseph Goldstein, M.D., whose 1985 Nobel Prize-winning discoveries revealed new information about cholesterol metabolism. While Mr. Trinh knew he wanted to be a physician, working with Drs. Brown and Goldstein and seeing how their research made such a big difference in the world inspired him.

"It's really an honor to be trained by such rigorous physician-scientists," Mr. Trinh said. "I am so grateful to them for taking me under their wing."

During that time, Mr. Trinh studied the mechanism behind Niemann-Pick disease Type C, a rare disease often dubbed the "childhood Alzheimer's disease."

For his Ph.D. research in the Brown/Goldstein laboratory, he used CRISPR gene-editing technology to find genes required for cholesterol to move from one membrane to another in human cells. Genetic defects in this movement can cause fatal human diseases such as Niemann-Pick Type C. Mr. Trinh recently discovered that this movement requires another lipid named phosphatidylserine, a discovery with implications for membrane biology and cardiovascular science.

Michael Trinh

Last year, this work earned him the Merton Bernfield Memorial Award from the American Society of Cell Biology, and the William F. and Grace H. Kirkpatrick Award from the UT Southwestern Graduate School of Biomedical Sciences.

Mr. Trinh was born in Dallas after his parents fled Vietnam as children and met in the United States at a wedding. He was inspired to study medicine and science by his grandfather, whose commitment to being a lifelong learner motivated Mr. Trinh in his own educational journey.

Now, with support from the Soros Fellowship, Mr. Trinh can continue his own research, advancing the legacy of learning that his grandfather instilled in him. He said the Soros Fellowships are a great recognition of what immigrants have to offer this country.

"These are people from all different parts of the world who are working to make it a better place," he said.

■

Dr. Brown is the Director of the Erik Jonsson Center for Research in Molecular Genetics and Human Disease at UT Southwestern. He is a Regental Professor and holds The W.A. (Monty) Moncrief Distinguished Chair in Cholesterol and Arteriosclerosis Research, and the Paul J. Thomas Chair in Medicine.

Dr. Goldstein, Professor and Chair of Molecular Genetics, is a Regental Professor and holds the Julie and Louis A. Beecherl, Jr. Distinguished Chair in Biomedical Research, and the Paul J. Thomas Chair in Medicine.

Hospital Continued from page 1

1½ to 2 years if the funding request is not approved until the 2023 regular session, Dr. Ibrahim said.

"This will be the only hospital in Dallas that specializes in the care of the seriously mentally ill and will help fill a growing gap in hospital beds available for such individuals," said Carol A. Tamminga, M.D., Chair of Psychiatry. People in need of care now sometimes wait days or even weeks for a bed to open, remaining in an emergency department or nonspecialty health facility without receiving the comprehensive specialized care they need, Dr. Tamminga explained.

UT Southwestern, ranked the No. 1 hospital in Dallas-Fort Worth by *U.S. News & World Report* for the last five years, will operate the hospital for the Texas Health and Human Services Commission (HHSC) and, Dr. Tamminga said, "We'll want to provide inpatient care with the highest level of quality."

Beyond the exceptional care that psychiatric patients will receive at UT Southwestern, the Medical Center's involvement provides other important benefits. The hospital will bring researchers at UTSW access to a large patient population base for studies to understand and find cures for mental health diseases that are, for the most part, only treated symptomatically.

"That's why these diseases are so deadly," said Dr. Tamminga. "They start early in life and last a whole lifetime."

In addition, UTSW researchers will examine current treatments to develop best-in-class protocols and share those guidelines with other mental health facilities in Texas, she said.

The hospital, in partnership with UT Southwestern Medical School, will enable more future psychiatrists to be trained, promoting workforce development in Texas and lessening a statewide shortage.

Hicham Ibrahim, M.D.

Carol A. Tamminga, M.D.

Since 2016, UT Southwestern has worked with HHSC and the Legislature to obtain funding for the hospital, Dr. Ibrahim said. A 2014 HHSC-commissioned study identified a shortage of available psychiatric beds statewide and recommended renovating or replacing aging hospitals, as well as building some new ones. The Waco/Dallas/Arlington region was cited as one area of need.

Since that study, the Legislature has appropriated more than $1 billion to renovate, expand, or replace existing state hospitals and build new ones. An early estimate for the cost of planning and building a 200-bed hospital in Dallas came in at $255 million, but that number is likely to be different now, said Dr. Ibrahim.

As planning for the new hospital moves forward, UT Southwestern will reach out to the community for input from behavioral health care centers, the criminal justice system, patient advocacy groups, and other stakeholders, Dr. Ibrahim said.

"This is going to be a game changer for the community," Dr. Ibrahim said of the hospital. "This community has needed the hospital – has needed those beds – for a long time."

■

Dr. Podolsky holds the Philip O'Bryan Montgomery, Jr., M.D. Distinguished Presidential Chair in Academic Administration, and the Doris and Bryan Wildenthal Distinguished Chair in Medical Science.

Dr. Tamminga holds the Stanton Sharp Distinguished Chair in Psychiatry.

Longtime UTSW faculty members appointed Professors Emeritus

James McCulley, M.D.: Led as Chair of Ophthalmology for more than four decades

By Carol Marie Cropper

James McCulley, M.D., who as Chair grew UT Southwestern's Department of Ophthalmology into a major comprehensive care and training center while also producing internationally recognized research on topics such as eyelid inflammation and a blindness-causing parasite that can affect contact lens wearers, has been named Professor Emeritus at UTSW.

Under Dr. McCulley's leadership spanning 40 years, the Department expanded from nine faculty to more than 50 by the time he stepped down June 30. He put the Department on firm financial footing and nurtured a program that now has the subspecialty depth to treat a wide array of eye diseases and conditions and that boasts one of the leading ophthalmology residency programs in the nation.

Along the way, he published more than 300 peer-reviewed articles, becoming an internationally recognized researcher on an eyelid inflammation condition called blepharitis that causes dry eye, as well as sounding an early alarm to contact lens wearers on the risk of blindness from acanthamoeba, a parasite found in fresh water, tap water, and sometimes even in contact lens solution. Dr. McCulley's blepharitis research received National Institutes of Health funding for 28 years.

However, he said, "What I'm most proud of is the strength of the Department of Ophthalmology that was created during my tenure as Chair."

"Dr. McCulley has served as an excellent clinician, is an accomplished researcher, and has trained and mentored scores of ophthalmology clinicians and investigators," said Dwain L. Thiele, M.D., Vice Provost and Senior Associate Dean for Faculty Affairs and Initiatives. "He is best known for his leadership that has guided the development of UT Southwestern's Ophthalmology Department into one of the most outstanding departments of ophthalmology in the United States."

Dr. McCulley joined UT Southwestern in 1980 as an Associate Professor of Ophthalmology and was named Chair the following year. He was appointed by Kern Wildenthal, M.D., Ph.D., UT Southwestern's second President, who is now President Emeritus and Professor Emeritus.

"Dean Wildenthal's comment to me was that my success would depend on how effectively I hired, and that has proved to be the case," Dr. McCulley said.

Dr. McCulley became the second Chair of Ophthalmology at UT Southwestern – the Department had earlier been a Division. In his clinical practice, he focused on the ophthalmological subspecialties of corneal and external diseases of the eye and surgeries to correct vision, such as LASIK and other keratorefractive surgeries. Some of his best-known research examined the safety and effectiveness of such procedures. He also led the way in culturing corneal cells in vitro so they could be transplanted as a thin tissue to avoid patients needing a full-thickness corneal transplant.

James McCulley, M.D.

Prior to joining UTSW, Dr. McCulley served as Assistant Professor of Surgery (Ophthalmology) at Stanford University School of Medicine. Earlier experience included serving as a Lieutenant Commander in the Medical Corps of the United States Naval Reserve and a Staff Ophthalmologist at the National Naval Medical Center in Bethesda, Maryland. A native of Fort Worth, he attended Texas Christian University, then graduated from Washington University School of Medicine in St. Louis. He completed his internship, residency, and a fellowship at Harvard Medical School-affiliated institutions.

Dr. McCulley received the prestigious Castroviejo Medalist Award in 2012, as well as the American Academy of Ophthalmology's Life Achievement Honor Award in 2014.

For the future, he plans to continue teaching and attending conferences but will phase out his clinical practice by the end of the year.

■

Dr. Thiele holds the Jan and Henri Bromberg Chair in Internal Medicine.

Julio Pérez Fontán, M.D.: Former Chair of Pediatrics recognized for innovation

Julio Pérez Fontán, M.D.

By Jan Jarvis

Julio Pérez Fontán, M.D., who led UT Southwestern's Department of Pediatrics as Chair for more than a decade, has been appointed Professor Emeritus of Pediatrics in honor of his contributions. Dr. Pérez Fontán, who retired in August, also served as Physician-in-Chief at Children's Health until Sept. 1.

Soon after he joined UT Southwestern in 2004, Dr. Pérez Fontán became known for his dedication and innovation.

"Dr. Pérez Fontán was a 'model' Chair who led his Department with wisdom, vision, equity, and an unwavering commitment to the institution's mission," said David Johnson, M.D., former Chair of Internal Medicine. "Under his leadership, the Department of Pediatrics excelled in scholarly output, clinical care, and educational achievement."

Stephen Skapek, M.D., Interim Chair of Pediatrics, added that Dr. Pérez Fontán set and executed clear goals for the Department.

"The health of our educational programs and the integrity of our faculty practice were always paramount as he guided the Department through a period of tremendous growth," Dr. Skapek said.

Although Dr. Pérez Fontán found it gratifying to treat critically ill children, he was just as committed to building a strong set of pediatric programs at UT Southwestern and Children's Health. During the past 16 years, he worked to develop an infrastructure that would lead to improved pediatric care in Dallas. Bringing a top-notch team to UT Southwestern was one of his goals.

In the laboratory, his research focused on factors that define the biomechanical interdependence between airways and the surrounding lung parenchyma. His work was funded by the National Institutes of Health and resulted in multiple publications and reviews in the medical literature.

Growing up in Spain, Dr. Pérez Fontán chose a discipline – pediatrics – that not only promised enormous personal rewards but also the opportunity to understand more about the why and how of developmental disorders. For 40 years, Dr. Pérez Fontán has not only answered his calling to care for sick children, but he has strived to improve health care by advancing research and education.

"When we teach others, we not only have a multiplier effect, but also establish a foundation on which others can advance and improve on what we did ourselves," he said.

Dr. Pérez Fontán came from a family of physicians. He received his undergraduate and graduate degrees – both summa cum laude – from the University of Santiago de Compostela in Spain. He completed a residency in pediatrics at the Children's Hospital of the Autonomous University of Barcelona.

He served on the faculty of the Department of Pediatrics and the Cardiovascular Research Institute at the University of California, San Francisco, until 1985, when he was recruited to the Department of Pediatrics at Yale University School of Medicine. In 1992, he was recruited as the founding Director of the Division of Pediatric Critical Care Medicine at Washington University School of Medicine and the St. Louis Children's Hospital.

Dr. Pérez Fontán, who plans to divide his time between Westport, Connecticut, and the Atlantic coast of Northern Spain, said leaving UT Southwestern will be difficult.

"I am very appreciative of the opportunities I was given here," he said. "This is a wonderful institution. I look forward to remaining part of it as an Emeritus Professor and to take pride in the accomplishments of the many colleagues and friends that I leave behind."

■

Dr. Johnson holds the R. Ellwood Jones, M.D. Distinguished Professorship in Clinical Education.

Dr. Skapek holds the Distinguished Chair in Pediatric Oncology Research.

NEWS

MAKERS

Ortigoza honored for neonatal research

Investigation of the best approach to feeding premature babies to improve their health has led to recognition for **Eric Ortigoza, M.D.**, Assistant Professor of Pediatrics. For his research, Dr. Ortigoza received the Society for Pediatric Research's 2021 Award to Enhance Diversity in the Research Workforce.

"This award is encouraging to me as an early career investigator with interest in nutrition and feeding-related research," Dr. Ortigoza said. "The ability to feed preterm babies safely without increasing the risk of gastrointestinal complications has the potential to change neonatal intensive care, improving the quality of life of future preterm infants."

In a longitudinal, prospective cohort study of 57 preterm infants of different gestational ages, Dr. Ortigoza and his team used noninvasive electrogastrography (EGG) to measure electricity of the stomach and how it changes with gestational age. They also characterized the babies' gut microbiome.

"Using EGG, we measured a stomach dysrhythmia called tachygastria," he said. "We found that preterm infants spend 30%-50% of the time in tachygastria, but greater than 50% of the time in tachygastria was associated with a unique gut microbiome characterized by an expansion of *Proteobacteria* that preceded the development of surgical necrotizing enterocolitis (NEC), a serious gastrointestinal emergency than can lead to significant morbidity or death."

Next, Dr. Ortigoza and his research team will investigate whether EGG and other noninvasive technologies may be potential tools to differentiate between developmental feeding intolerance from gastrointestinal immaturity and pathologic feeding intolerance from gastrointestinal pathology, such as NEC.

Eric Ortigoza, M.D.

Pandey receives awards for heart research

Research led by **Ambarish Pandey, M.D.**, Assistant Professor of Internal Medicine and a Texas Health Resources Clinical Scholar, has been recognized for demonstrating the importance of frailty as a potentially modifiable risk factor for heart failure.

Ambarish Pandey, M.D.

Dr. Pandey received the 2021 Health in Aging Foundation New Investigator Award, which honors early career investigators whose research reflects new and relevant insights in geriatrics.

His work assessed frailty burden at baseline and at follow-up, including the risk of heart failure. Using data from the Look AHEAD (Action for Health in Diabetes) trial, the research team observed that higher burden of frailty was associated with higher risk of heart failure in those with Type 2 diabetes. They also found that the frailty-associated risk of heart failure was modifiable with changes in the frailty burden over time.

"These findings highlight the importance of assessing frailty in older patients with Type 2 diabetes as a strategy to identify those who may be at a higher risk of developing heart failure," he said.

In a separate honor, Dr. Pandey and his team were among five winners of the National Heart, Lung, and Blood Institute (NHLBI) Big Data Analysis Challenge: Creating New Paradigms for Heart Failure Research. The award includes a $50,000 prize.

"We developed a machine learning-based approach to predict patients – at the time of hospitalization – who may be less likely to respond to diuretics and, thus, may be diuretic-resistant," he said. "Early identification of these patients may allow us to implement more aggressive diuresis protocols early on and allow quicker resolution of patients' volume overload and symptoms of shortness of breath and congestion."

An estimated 6.5 million American adults live with heart failure, a chronic and progressive disorder. Through its competition, the NHLBI seeks to foster innovation and address the need for new, open-source disease models that can define subcategorizations of adult heart failure and ultimately support new research potentially leading to advancements in managing heart failure.

An Olympic undertaking

UTSW Medical School student plays on Nigerian team in this summer's Tokyo Games

By Carol Marie Cropper

Despite the rigors of medical school and a worldwide pandemic, Erica Ogwumike – a rising second-year student at UT Southwestern Medical School – has made another one of her dreams come true: playing basketball in the Olympics.

Ms. Ogwumike, the daughter of Nigerian immigrants who was born in the U.S. and has dual U.S.-Nigerian citizenship, was chosen as a member of the Nigerian women's national basketball team. The Houston-area native and her 12-member team played three games in Tokyo from July 27 to Aug. 1, competing against teams from the U.S., France, and Japan. The team's games finished just in time for Ms. Ogwumike to return to Dallas and start the upcoming medical school year.

She was a star player at Rice University, where she graduated in 2020 with a triple major in health science, policy studies, and Spanish. She was drafted to play professionally by the New York Liberty – and immediately traded to the Minnesota Lynx – but decided on medical school instead.

Ms. Ogwumike, wearing her Olympic team uniform

Ms. Ogwumike's Olympic selection hasn't changed her mind.

"I love medicine. This is what I want to do," she said, describing medicine as an altruistic profession focused on "helping patients reach their optimal level of health. … I feel like there's nothing that's more rewarding than that."

UTSW medical student Erica Ogwumike, a member of the Nigerian women's national basketball team, fulfilled a dream when she played at the Olympics.

Still, she is grateful for this extraordinary opportunity to participate in a sport where she shined and in which two of her older sisters now play professionally for the Los Angeles Sparks.

"Playing at the Olympics – playing on the Nigerian National Team – was something that I really wanted to do, so I tried to find a way to be able to do it without losing some of the experiences that I get in medical school."

The effort meant getting up at 5 a.m. this summer to review medical school coursework and do research on diversity inclusion for a professor before heading to practice with others in contention for the Nigerian team, followed by more research, a second practice, and then additional research going well into the night.

During the 2020-21 school year, COVID-19 restrictions meant Ms. Ogwumike couldn't practice with a team, so she did strength and conditioning exercises for two hours each morning before beginning her studies and trained once or twice a week with a professional who works with Women's National Basketball Association players.

"It required a lot of early mornings," she said.

One of the reasons she is drawn to medicine, she said, is that it demands the kind of drive, time management, and organizational skills she developed playing basketball.

Growing up the youngest of four sisters in a Houston suburb, Ms. Ogwumike said her parents lined up piano and dance lessons, as well as gymnastics, and – when they got too tall for gymnastics – basketball for the girls. Ms. Ogwumike is 5 feet, 9 inches tall, while two of her sisters top 6 feet and the third stands 5 feet, 11 inches.

Ms. Ogwumike and her team at the Olympic opening ceremony

In high school, Ms. Ogwumike excelled at more than sports; she was also president of her junior and senior classes and graduated class valedictorian.

Ms. Ogwumike said her first thought upon hearing she had made the Nigerian team after playing in a July 18 exhibition game in Las Vegas was that she needed to check with UT Southwestern to make sure her Olympics trip wouldn't interfere with her return to medical school in August. There was no need for concern.

Ms. Ogwumike, a second-year student, passed on a chance to play professional basketball to attend UT Southwestern Medical School.

"They're so supportive and they were just really excited," she said. "They told me to take a lot of selfies, and they're rooting for me."

"Erica Ogwumike is exactly the type of student we want at UT Southwestern," said Shawna Nesbitt, M.D., Associate Dean for Student Diversity and Inclusion. "She is bright, dedicated, and motivated to excellence. We are delighted to have her as a member of our student body and proud that she has reached the highest level of attainment in her sport – competing in the Olympics."

Ms. Ogwumike knows she is fortunate. But her success isn't the result of luck.

"If there are two things that you're truly passionate in, go 100% at both of them," she said. "I didn't have to sacrifice one dream at the expense of another."

More online: From Tokyo, Ms. Ogwumike shares more about her Olympic experience. Check out the video on *Center Times Plus* at **utsouthwestern.edu/ctplus.**

Sports medicine doctor serves as volunteer physician at Olympics

By Patrick McGee

UT Southwestern's medical expertise made its way to the Olympics in Tokyo with Stephanie Tow, M.D., providing her knowledge of sports medicine as a volunteer physician to the Games.

"A lot of sports medicine physicians strive to work at the Olympics at some point, so it was an honor to be asked and to be able to go so early in my career," said Dr. Tow, an Assistant Professor in the Department of Physical Medicine and Rehabilitation. "It's such a privilege to be able to work with international leaders on this side of sports medicine."

For two weeks, Dr. Tow served as a volunteer physician on the general medical staff. She was assigned to provide general medical support to those in the media center or at an isolation hotel designated for participants who tested positive for COVID-19 and were asymptomatic or had mild symptoms.

It was her first time back in Asia since living in Hong Kong on a Fulbright Scholarship from 2008-2009.

Dr. Tow's position as the head team physician for the U.S. Paralympics national swim team helped in her application to serve on the Olympics medical staff. She also has a wealth of experience in sports medicine event coverage, including serving as the Medical Director for the World Para Swimming World Series in Lewisville in 2021 and as a volunteer physician with multiple youth, high school, collegiate, and professional sports teams and events during her career.

She and all other participants completed two COVID-19 tests within 96 hours of their flight arrivals in Tokyo. After she landed, Dr. Tow underwent a comprehensive review process that included approval of documents and more screening, including another COVID-19 test, after which she and all Olympic Games participants had to perform daily COVID-19 testing during the duration of their trip.

Stephanie Tow, M.D.

"I took every protective measure I could," said Dr. Tow, who completed her residency at UTSW in 2017. "It was an exciting time to finally bring the world together and show off a lot of our athletes in the Olympic and Paralympic movements."

Microscopy Continued from page 1

data-intensive process, in which hundreds of 2D images of the specimen are assembled into a so-called image stack. To visualize the data, the image stack is then loaded into a graphics software program that performs computations to form two-dimensional projections from different viewing perspectives on a computer screen.

"Those two steps require a lot of time and may need a very powerful and expensive computer to interact with the data," Dr. Fiolka said.

The team realized it could form projections from multiple angles by optical means, bypassing the need to acquire image stacks and rendering them with a computer. This is achieved by a simple and cost-effective unit consisting of two rotating mirrors that is inserted in front of the camera of the microscope system.

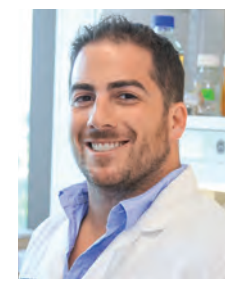
"As a result, we can do all this in real time, without any noticeable delay. Surprisingly, we can look from different angles 'live' at our samples without rotating the samples or the microscope," Dr. Fiolka said. "We believe this invention may represent a new paradigm for acquiring 3D information via a fluorescence microscope."

It also promises incredibly fast imaging. While an entire 3D-image stack may require hundreds of camera frames, the new method requires only one camera exposure.

Initially, the researchers developed the system with two common light-sheet microscopes that require a post-processing step to make sense of the data. That step is called de-skewing and essentially means rearranging the individual images to remove some distortions of the 3D-image stack. The scientists originally sought to perform this de-skewing optically.

While experimenting with the optical de-skewing method, they realized that when they used an incorrect amount of "de-skew," the projected image seemed to rotate.

Reto Fiolka, Ph.D.



Kevin Dean, Ph.D.

"This was the aha! moment. We realized that this could be bigger than just an optical de-skewing method; that the system could work for other kinds of microscopes as well," said Dr. Fiolka, also a member of the Harold C. Simmons Comprehensive Cancer Center.

"This study confirms the concept is more general," Dr. Dean said. "We have now applied it to various microscopes, including light-sheet and spinning disk confocal microscopy."

Using the new microscope method, they imaged calcium ions carrying signals between nerve cells in a culture dish and looked at the vasculature of a zebrafish embryo. They also rapidly imaged cancer cells in motion and a beating zebrafish heart.

The research received support from the Cancer Prevention and Research Institute of Texas (RR160057) and the National Institutes of Health (T32CA080621, F32GM117793, K25CA204526, R33CA235254, and R35GM133522). Dr. Fiolka has filed a patent for the scan unit and its applications to microscopy. Additional disclosures are included in the paper.

More online: Read the full story in the newsroom at **utsouthwestern.edu/newsroom**.