The future of medicine, today
Cover: A microscopic cross-sectional image of the cerebellum, showing nerve cells within the cerebellar cortex (blue) and connecting fibers (yellow). The cerebellum is a region in the back of the brain that is critical for coordination of the body’s muscle movements. Under the aegis of the Peter O’Donnell Jr. Brain Institute, UT Southwestern faculty are coordinating their efforts to identify the basic mechanisms of brain function and the underlying causes of brain diseases, as well as the means to promote repair and functional recovery.

VOLUME 27 / FEBRUARY 2018

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President's Message

Accelerating Brain Research to Improve Treatment

Scientists and clinicians at the Peter O’Donnell Jr. Brain Institute improved care for patients with neurodegenerative diseases and injuries this past year through innovative research in areas such as regenerative medicine, biomarker identification, and personalized therapy.

Making Inroads Against Cancer

Armed with the latest technology, UT Southwestern oncologists and scientists are taking aim at cancer by using the world’s best radiation oncology machinery, developing innovative nanoparticle-based immunotherapies, and investigating new diagnostic tools based on bioinformatics.

Achieving Breakthroughs in Heart, Transplant Medicine

Heart and transplant medicine specialists are pushing the envelope to achieve new breakthroughs in patient care, from investigating ways to potentially one day regenerate heart muscle in humans to tackling the toughest surgical cases by using innovative, challenging techniques.

Positioning UT Southwestern for the Future

UT Southwestern continued to expand this past year, breaking ground on an addition to the William P. Clements Jr. University Hospital as part of an $875 million facilities improvement project, while also increasing the size and scope of its clinical, educational, and research programs.

Advancing Science and Medicine

Exceptional scientific achievements this past year included discovery of a link between obesity and nonalcoholic fatty liver disease, identification of a gene that limits the desire to drink alcohol, and solution of 3-D protein structures using advanced microscopy.

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Dear Friends,

As we celebrate the milestone of UT Southwestern’s 75th anniversary in 2018, we are deeply grateful for your support, which has been essential to the accomplishments of our faculty in advancing biomedical research, educating and training the next generations of scientists and physicians, and providing innovative and compassionate patient care.

Comparatively speaking, UT Southwestern is a young institution, especially for the stature it has achieved as a nationally pre-eminent academic medical center, internationally renowned for the quality of its research. Founded as Southwestern Medical College by visionary and philanthropic members of the Dallas community in May 1943, UT Southwestern’s development over the years has been integrally connected to – and generously supported by – the Dallas community, as well as the State of Texas. Without this support, UT Southwestern would not be the expansive, thriving Medical Center it is today.

As a snapshot of current priorities and programs, I am pleased to send you this Annual Review of the 2016-17 academic year. As you will see, also included is a supplement that notes highlights of the past 75 years and identifies opportunities we see ahead.

As a society, we face especially compelling challenges in brain disease, cancer, and heart disease, as well as in the overall cost and delivery of health care. This 2017 Annual Review is dedicated to illuminating these issues and to informing you about the cutting-edge science, education, and patient care going on at UT Southwestern to address these challenges, as well as innovative approaches we are taking to health care delivery.

The brain in its mysterious functions and many illnesses may be medicine’s ultimate frontier, driving the scientific work and clinical care advancing under the overall aegis of UT Southwestern’s Peter O’Donnell Jr. Brain Institute. Our scientists are using the most sophisticated equipment and techniques available to advance knowledge about the fundamental mechanisms of brain functioning – and are also providing the very best in innovative clinical care possible today to patients and families faced with devastating brain diseases.

As you will find in this issue, UT Southwestern faculty are making especially important scientific contributions in areas such as regenerative medicine, which holds great hope for those who have suffered from spinal cord injuries, and in the genetics of sleep, which furthers understanding of issues related to memory and information processing. And at the same time, our physicians are caring for patients suffering from problems such as depression, Alzheimer’s disease, epilepsy, concussion, and brain cancer.

The opening of the William P. Clements Jr. University Hospital – Harold C. Simmons Comprehensive Cancer Center Radiation Oncology building in April 2017 further advanced our commitment to provide the very best in care for those suffering from cancer. It is the largest and most comprehensive radiation oncology facility in North Texas.

And in Simmons Cancer Center laboratories, UT Southwestern cancer biologists are working on the cutting-edge area of immunotherapy. Their efforts have resulted in a nanoparticle vaccine immunotherapy that targets several different cancer types in experimental models. Another important area is approaching the diagnosis and treatment of lung cancer through the analysis of massive data sets by faculty in the Lyda Hill Department of Bioinformatics; this work can lead to sophisticated predictions of risks faced by individual patients and to the development of treatments tailored to their specific situations.

We are proud of the transformative work being done by UT Southwestern scientists and physicians in heart disease. The Annual Review features an article about a patient whose life was saved by a UT Southwestern cardiac surgeon who is one of the very few experts in the country whose specialty is a rare, minimally invasive procedure for valve replacement that reduces the trauma of heart surgery.

We are looking forward to opening next summer the first of what will ultimately be a complex of five buildings on our West Campus site. This first building, on the site of the former St. Paul University Hospital, will provide multidisciplinary clinical space, faculty offices, and a state-of-the-art Simulation Center.

I am also pleased to report that we have begun construction on an expansion of William P. Clements Jr. University Hospital, several years ahead of original expectations. The expansion will include a third tower with nearly 300 beds. We are also planning a new building for the North Campus that will house both expanded services of the Simmons Cancer Center and laboratories for the O’Donnell Brain Institute.

I hope you share my pleasure and pride in UT Southwestern, and I also hope you will plan to join us for events in 2018 to celebrate UT Southwestern’s 75th anniversary. On behalf of the entire campus community, I thank you for your generous support and for all that you have done to enable UT Southwestern to discover and deliver the future of medicine, today.

Sincerely,

Daniel K. Podolsky, M.D.
President, UT Southwestern Medical Center
The Peter O’Donnell Jr. Brain Institute brings together UT Southwestern’s premier scientists and physicians on a mission – to reduce the devastating impact of brain diseases. Hope for the future can be seen through innovative research aimed at understanding the fundamental mechanisms of the brain and related diseases to provide cutting-edge clinical care for those in need.

**Accelerating brain research to improve treatment**

Model of neurons surrounded by dendrite extensions. In one study, UT Southwestern scientists successfully boosted the regeneration of mature nerve cells in the spinal cords of adult mammals by tenfold.
Welcome to the future of brain science

Everything depends on the brain. It makes us who we are and helps us build bridges to others. The Peter O’Donnell Jr. Brain Institute focuses on maintaining those cognitive functions – and treating diseases and disorders that disrupt them.

As the field of neuroscience enters a new age of innovation, work at the O’Donnell Brain Institute supports UT Southwestern’s aspiration to accelerate research breakthroughs into treatment advances.

The O’Donnell Brain Institute brings together premier scientists and physicians to use the most sophisticated equipment and techniques to uncover preventive options, improve diagnosis, and enhance clinical care for patients touched by a neurodegenerative injury or disorder. Already, these tools are being used to further our understanding of the fundamental mechanisms of the brain and causes of brain disease to help some of the estimated 50 million people in this country living with a brain disease.

Established in 2015 with a $36 million gift from the O’Donnell Foundation, the Institute continues to develop, strengthened by the generosity of a growing number of philanthropic partners and state and federal support. The goal, to benefit patients today and for generations to come, is to reinforce and expand the national leadership of UT Southwestern in neuroscience research and treatment.

This past year, some of the most innovative research developments have been in regenerative medicine, sleep science, biomarkers for treatment of depression, individualized therapies for rare brain diseases, study of sports-related concussion, and advanced technology to improve diagnosis and treatment for those with epilepsy.

The O’Donnell Brain Institute brings together premier scientists and physicians to use the most sophisticated equipment and techniques to enhance care.
Dr. Joseph Takahashi’s study identified two genes that regulate deeper stages of sleep, a finding that could aid in treatment of sleep disorders. To view a video of this story go to utsouthwestern.edu/sleep-gene.

Uneasy sleep: genes that may be at fault

Salt-Inducible Kinase 3 (Sik3) – Mutations in this gene caused mice that researchers labeled “Sleepy” to have 50 percent more non-REM sleep, the stage characterized by deep sleep.

Sodium Leak Channel Non-selective (Nalcn) – Mutations in this gene caused mice that researchers labeled “Dreamless” to be severely deficient in the amount of REM sleep, a stage of rest characterized in humans by rapid eye movements and vivid dreams.

The discovery of these two genes provides an entry point to help scientists understand sleep, which in turn could lead to new treatments for the millions of people unable to get a good night’s rest.

“This research is just the beginning. We believe that these two genes are the first of many that regulate sleep,” said Dr. Takahashi, Chairman of Neuroscience within the O’Donnell Brain Institute, a Howard Hughes Medical Institute (HHMI) Investigator, and co-senior author of a study on the findings published in Nature.

The work required an exhaustive forward-genetic approach that screened 8,000 mice with individually applied electroencephalography (EEG) monitors to search for brain waves indicative of sleep disorders.

The new study is closely tied to the forward genetics work Dr. Takahashi employed two decades ago in his landmark discovery of the Clock gene that regulates the body’s circadian rhythm. That finding led his laboratory to uncover a network of more than 20 other genes related to the body’s biological clock of physical and behavioral patterns that follow a roughly 24-hour cycle, mostly in response to environmental cues such as light and darkness.

Although previous research identified genes that regulate the switch between wakefulness and sleep, the mechanisms controlling the need for non-REM and REM sleep proved elusive until this latest discovery. The UT Southwestern researchers found two striking mutations: mice they called “Sleepy” that had 50 percent more non-REM sleep than wild-type mice, caused by a mutation in the Salt-Inducible Kinase 3 (Sik3) gene that showed clear dominant inheritance; and mice researchers called “Dreamless” that were severely deficient in the amount of REM sleep, a stage of rest characterized in humans by rapid eye movements and vivid dreams.

When the researchers introduced the same mutations into wild-type mice, their sleep patterns mirrored those of the “Sleepy” and “Dreamless” mice, confirming each gene as the sole cause of its respective trait.

“This study opens up future possibilities to create new sleep-regulating drugs, but doing so will occur in the distant future,” said co-senior author Dr. Masashi Yanagisawa, Professor of Molecular Genetics. He now directs the International Institute for Integrative Sleep Medicine at the University of Tsukuba in Japan, where most of the mice were screened.

Many scientists agree that the REM sleep stage is involved in the formation of emotional memories and coping with negative experiences. Hence, there is a possibility that manipulation of REM sleep could aid in treatment of conditions such as post-traumatic stress disorder.

Dr. Takahashi, who holds the Loyd B. Sands Distinguished Chair in Neuroscience and received the 2016 Peter Farrell Prize in Sleep Medicine, said he had wanted to conduct such a genetic screen for sleep mutants for many years but had to overcome logistical issues. Most mouse studies involve no more than a few dozen animals and this one required thousands. Dr. Yanagisawa rapidly scaled up, optimizing his lab’s ability to screen large numbers of mice, accomplished initially at UT Southwestern and now at his institute in Japan.

“To be able to screen 8,000 mice is something that most people would say is too much work,” Dr. Takahashi said. “Technically, this project was very challenging.”
While normal sleep patterns include short durations of rapid eye movement (REM) sleep surrounded by longer stretches of non-REM sleep, a UT Southwestern study demonstrates how one gene can alter these patterns. Here’s a look at the stages of sleep:

**REM:** This phase, associated with vivid dreaming, starts about 90 minutes after falling asleep. Closed eyes scan rapidly from side to side. Brain waves are similar to those experienced during wakefulness. Heart and blood pressure increase, and breathing becomes faster. Muscles become transiently paralyzed, protecting the person from acting out dreams.

Many scientists agree this phase of sleep is involved in the formation of emotional memories and coping with negative experiences.

**Non-REM Stage 1:** This is the period between wakefulness and sleep. The heart rate begins to slow and breathing becomes regular. Dreaming is relatively rare. The person may be aware of sounds and may have quick body jerks. If awakened, the person will often believe they were not asleep.

**Non-REM Stage 2:** Muscle activity decreases and awareness of outside sounds recedes. Short bursts of brain activity protect the person’s sleeping state from outside disruptions and help with processing memory and other information. This stage occurs several times each night, usually accounting for about half the total sleep.

**Non-REM Stage 3:** Deep sleep. The person is completely removed from outside stimuli and will feel groggy if awakened. Heart rate, breathing, and blood pressure are at their lowest levels. Dreaming is more common at this stage, though not as common as during REM sleep. As in stage 2, memory and information processing occur during this stage. Sleepwalking or talking may also occur.

Regenerating hope for spinal cord injuries

In a stunning advance in the field of stem cell research, UT Southwestern scientists successfully boosted the regeneration of mature nerve cells in the spinal cords of adult mammals by tenfold.

“This research lays the groundwork for regenerative medicine for spinal cord injuries. We have uncovered critical molecular and cellular checkpoints in a pathway involved in the regeneration process that may be manipulated to boost nerve cell regeneration after a spinal injury,” said Dr. Chun-Li Zhang, Associate Professor of Molecular Biology, a member of the Hamon Center for Regenerative Science and Medicine, and a W.W. Caruth, Jr. Scholar in Biomedical Research.

Dr. Zhang, senior author of a study outlining the findings in *Cell Reports*, cautioned that this research in mice is still in the early experimental stage and is not ready for clinical translation.

A series of screens in living animals led to a two-step process that overcame the propensity of glial cells – the most common cells in the spinal cord – to form scar tissue following injury. Study lead author Dr. Lei-Lei Wang, a postdoctoral researcher in Dr. Zhang’s lab, led this effort.

The researchers first silenced parts of the p53-p21 protein pathway that acts as a roadblock to the reprogramming of glial cells into the more primitive, stem-like types of cells that have the potential to become nerve cells. In the second step, mice were screened for factors that could boost the number of stem-like cells that matured into adult neurons. Two growth factors – BDNF and Noggin – accomplished this goal.

This work built on earlier research at UT Southwestern in 2013 and 2014, when scientists in the Zhang lab created new nerve cells in the brains and spinal cords of mice by introducing transcription factors that promoted the transition of adult glial cells into more primitive, stem cell-like states, then coaxed them to mature into adult nerve cells.
In our study of more than 100 patients published in *Psychoneuroendocrinology*, we found that C-reactive protein (CRP) levels from a finger-prick blood test were associated with much higher remission rates if we matched patients with the right medication, Dr. Trivedi said. C-reactive protein is a well-known inflammatory marker linked to increased risk for heart disease.

For patients whose CRP levels were less than 1 milligram per liter of blood, the study showed, the drug escitalopram alone was more effective than the therapeutic bupro- pion. For patients with higher CRP levels, therapy with both drugs was more likely to work. This work and more in the Center for Depression Research and Clinical Care has been supported by $5 million gifts from both the Hersh Foundation and the W.W. Caruth, Jr. Foundation.

“These findings provide evidence that a biological test can immediately be used in clinical practice,” said Dr. Trivedi, a Professor of Psychiatry who holds the Betty Jo Hay Distinguished Chair in Mental Health and the Julie K. Hersh Chair for Depression Research and Clinical Care. UT Southwestern’s Center for Depression Research and Clinical Care was established with a gift from the Hersh Foundation to accelerate new discoveries into the causes and treatment of depression and mood disorders.

The next step is to conduct larger studies to verify CRP’s role with other antidepressants and find alternative markers where CRP does not prove effective.

“Currently, our selection of depression medications is not any more superior than flipping a coin, and yet that is what we do. It’s a lot of trial and error. Now, we have a simple biological test to guide treatment of depression.” – Dr. Madhukar Trivedi

The future of depression treatment – in a drop of blood

A groundbreaking advance in translational medicine from UT Southwestern that uses a drop of blood to measure an inflammatory protein promises a faster, more personalized path to effective treatment for depression.

Without a simple, data-based approach to diagnosing depression in the primary care setting, treatment is often delayed. A patient may try multiple therapies before seeing results in a process that can take months, or years.

“Currently, our selection of depression medications is not any more superior than flipping a coin, and yet that is what we do. It’s a lot of trial and error. Now, we have a simple biological test to guide treatment of depression,” said Dr. Madhukar Trivedi, Director of the Center for Depression Research and Clinical Care, a cornerstone of UT Southwestern’s Peter O'Donnell Jr. Brain Institute.

“Currently, our selection of depression medications is not any more superior than flipping a coin, and yet that is what we do. It’s a lot of trial and error. Now, we have a simple biological test to guide treatment of depression.” – Dr. Madhukar Trivedi

The study by Dr. Madhukar Trivedi (front) demonstrated that measuring a depressed patient’s C-reactive protein level can help physicians prescribe an antidepressant that is more likely to work.
The effects were dramatic: Ryan was again able to process complex information, he started remembering what he studied as a Dallas-area junior college student, he began earning A’s and B’s, and he improved enough to transfer to his dream school, the University of Louisville.

“We had only hoped to stop the neuro-cognitive decline, but as the enzyme worked to break down the proteins, Ryan got better. This stunning result is giving us a road map to how we can think about other diseases in the brain. Ryan’s journey will impact the lives of countless other children,” said Dr. Maher, who authored a study published last year that documents his cognitive recovery.

Ryan has lived long beyond the life expectancy of MPS 1 patients. He is one of the only four survivors of the 10 initial clinical trial participants. Ryan has a girlfriend. He is the Theodore H. Strauss Professorship in Neuro-Oncology.
Epilepsy facility enhances ability to diagnose, treat seizures

About one-third of people with epilepsy live with uncontrollable seizures because no treatment works for them. Determined to change that statistic, physicians and other caregivers at UT Southwestern now have a new treatment tool for these patients: a state-of-the-art epilepsy monitoring unit.

In May 2017, the Bruce Mickey, M.D. Epilepsy Monitoring Unit at Zale Lipshy University Hospital opened, made possible with a $1 million gift from Linda W. and Milledge “Mitch” A. Hart III.

The eight-bed unit specializes in care for adults with treatment-resistant epilepsy who require electroencephalogram (EEG) monitoring to locate the source of their seizures. In the unit, a team of epilepsy specialists monitors patients 24 hours a day, for up to two weeks, to pinpoint where in the brain seizures originate. Personalized treatment plans are created – which may include medication changes, neurostimulation, laser ablation, or surgical resection – in efforts to stop the seizures.

“There are thousands of patients with epilepsy in North Texas, including many with seizures that are unresponsive to medications,” said Dr. Ryan Hays, Associate Professor of Neurology and Neurotherapeutics and Medical Director of the Epilepsy Monitoring Unit (EMU). “We will now be able to increase the diagnostic and treatment options available on our campus.”

The UT Southwestern Epilepsy Program, part of the Peter O’Donnell Jr. Brain Institute, has tripled its number of epileptologists – experts who specialize in epilepsy diagnosis and treatments – since the fall of 2015. The Program has one of the nation’s largest epilepsy teams, with more than 35 multidisciplinary specialists. That group includes neurologists, neurosurgeons, neuroradiologists, and neuropsychologists, as well as advanced practice providers, nurses, and EEG technologists who treat both adult and pediatric patients.

The new EMU will help patients like Trevor Williams, who had brain surgery at UT Southwestern in 2016. Now 26 years old, Mr. Williams began having epileptic seizures at age 7, and the condition greatly affected his quality of life, he said. Mr. Williams hasn’t had a seizure since his surgery, although it’s too early yet to say if the procedure cured him. Nonetheless, his doctor notes that as time goes on, it becomes less and less likely that seizures will return.

a college graduate. And he’s looking forward to pursuing a career in sports administration, perhaps one day working in operations for a Major League Baseball team.

“It’s an incredible story that shows us there is so much recovery that can go on in the brain. Ryan will be forever my grounding to the idea that sometimes you must get out on the leading edge and push the boundaries,” Dr. Maher said.

Mark Dant, who still tears up when talking about his son’s battle to survive, watched Ryan walk across the stage to receive a college degree last year.

“Sarah [McNeil] could have said they don’t do experimental MPS treatments here. Dr. Maher could have said that it’s a really great story; they should go find someone to do that treatment,” he said. “But they gave it a shot, and look at where we’re at today. It was worth the try.”
“Trevor’s case represents the strength of our Program at UT Southwestern. The therapy we were able to give required integrating the effort of people from the neurology side, the radiology side, the EEG technicians, the surgical side, and more,” said his neurosurgeon, Dr. Bradley Lega, Assistant Professor of Neurological Surgery, Neurology and Neurotherapeutics, and Psychiatry.

UTSW leads groundbreaking effort to monitor youth concussions

The nation’s largest statewide effort to track concussions in youth athletes, led by UT Southwestern, has begun collecting data aimed at assessing the prevalence of brain injuries in high school sports. Launched in late 2016, the Concussion Network of North Texas (ConTex) registry is a partnership between the University Interscholastic League (UIL), which regulates athletics in public schools, and UT Southwestern.

The registry, which could be a key step in creating a nationwide database for concussions, fills a major gap in concussion research and may provide guidance as to whether certain rules or equipment changes are improving player safety.

“This is a groundbreaking initial step. I think we’re on the verge of a very impactful project that will inform the nation about the frequency of concussions,” said neuropsychologist Dr. Munro Cullum, Professor of Psychiatry, Neurological Surgery, Neurology and Neurotherapeutics, and Rehabilitation Counseling with the Peter O’Donnell Jr. Brain Institute. Dr. Cullum, the study’s principal investigator, holds the Pam Blumenthal Distinguished Professorship in Clinical Psychology.

“Children under age 15 account for the most traumatic brain injury visits to emergency rooms.

A large study of high school athletes participating in nine sports – baseball, football, and wrestling (for boys); softball and volleyball (for girls); and basketball and soccer (for boys and girls) – reported a combined 2.44 injuries per 1,000 exposures, defined as practices and/or games. Football, followed by wrestling, had the highest injury rates for boys, while soccer and basketball topped the girls’ rates.

Sources: UT Southwestern, Centers for Disease Control and Prevention, National Federation of State High School Associations

Dream into reality

A $1 million gift from Linda W. and Milledge “Mitch” A. Hart III (left) made the Bruce Mickey, M.D. Epilepsy Monitoring Unit possible. The couple celebrated the unit’s opening with Dr. Bruce Mickey and his wife, Dr. Barbara Schultz (right). For two decades, the Harts have supported many of UT Southwestern’s most important research and clinical programs. Both have participated in the President’s Research Council since 2002, and Ms. Hart serves on the President’s Advisory Board and its Executive Committee. Dr. Mickey, Professor of Neurological Surgery, Otolaryngology, and Radiation Oncology, holds the William Kemp Clark Chair of Neurological Surgery.
ConTex is administered by the Texas Institute for Brain Injury and Repair (TIBIR), a state-funded initiative to promote innovative research and education. With more than 800,000 students involved in high school sports in Texas, the registry has the potential to become the largest in the nation. The registry relies on middle and high school athletic trainers and school personnel to report all concussions that occur in UIL athletics. Data to be examined includes the cause of the injury, the player’s concussion history, the gender of the player, and more. Dr. Cullum said his research team will measure how often concussions occur in each sport and identify areas with low concussion rates. UT Southwestern also collects concussion incident information as part of the ongoing first phase of the study.

ConTex is modeled after a smaller, ongoing concussion study that Dr. Cullum helped launch in 2015 that assembles detailed information about concussions in the Dallas-Fort Worth area. That collaboration includes UT Southwestern, Children’s Medical Center Dallas, Texas Scottish Rite Hospital for Children, UT Dallas, and Texas Health Ben Hogan Sports Medicine. Dr. Cullum also led a first-of-its-kind study published that same year that found NFL players who lost consciousness due to concussion showed key differences in brain structure later in life.
Cancer – it’s no longer a death sentence. The disease may have a voracious appetite, but it has met its match at UT Southwestern, where top specialists in the nation are working nonstop to reduce cancer’s health care burden. Notable achievements include discovery of next-generation nanoparticle therapies, provision of the world’s best radiation oncology treatments, and development of a computer-based model to recommend optimal treatment of lung cancer.

Making inroads against cancer
Fighting cancer with the world’s best radiation oncology treatments

Patsy Whittenberg drove six hours from the Texas Panhandle for cancer treatment at UT Southwestern, the first place in Texas to offer the newest generation of Gamma Knife radiosurgery – a targeted radiation device that offers an alternative to invasive tumor removal surgery.

The Gamma Knife Icon, located at Zale Lipshy University Hospital, is one of several leading-edge radiation oncology technology systems available at UT Southwestern. Last year, treatment options for patients expanded with the opening of the new UT Southwestern William P. Clements Jr. University Hospital – Harold C. Simmons Comprehensive Cancer Center Radiation Oncology building, which at 63,000 square feet is the largest facility for radiation oncology in North Texas.

“What truly makes UT Southwestern special is the expertise and dedication of the people who work here, supported by the most advanced technology available and based on the latest research,” said Dr. Hak Choy, Chair of Radiation Oncology and holder of The Nancy B. and Jake L. Hamon Distinguished Chair in Therapeutic Oncology Research.

For Mrs. Whittenberg, the benefits of the Gamma Knife Icon far outweighed traditional treatment options – the newest generation of the machine offers better protection of surrounding brain tissue. It also allows for shorter treatment sessions and greater comfort, since it does not use the rigid head frame required by previous Gamma Knife radiosurgery system models.

“This machine was a blessing for me. I had my eyes closed and didn’t even know when I entered the machine,” said Mrs. Whittenberg, 77, whose sinus tumor was treated. “No pain, no side effects. The treatment was finished at noon, and we drove home that same day.”

Physicians from UT Southwestern’s Peter O’Donnell Jr. Brain Institute and the Simmons Cancer Center – the only National Cancer Institute-designated Comprehensive Cancer Center

Some of the most advanced radiation oncology technology in the world can be found at UT Southwestern, all aimed at helping patients better fight cancer.

Dr. Hak Choy (left) and Dr. Robert Timmerman with the latest CyberKnife M6 robotic radiosurgery system
It’s all in the numbers: Bioinformatics computer model predicts most aggressive forms of lung cancers

What does game-changing patient care of the future look like? It merges clinical innovation with sophisticated technology, solving problems such as how to determine which lung cancer patients have the best prognosis.

Using the tools of bioinformatics, a field that manages and analyzes extremely large sets of research data to solve scientific and clinical challenges, UT Southwestern evaluated more than 900 differences in the shape and structure of cancer cells and found that just 12 to 18 features could predict the risk.

“This computational approach should someday make it possible for doctors to tailor the treatment of individual patients based on risk predicted by computer algorithms – for instance, choosing to treat patients at higher risk more aggressively,” said Dr. Guanghua “Andy” Xiao, Associate Professor of Clinical Sciences and Bioinformatics whose research team developed this approach.

The Lyda Hill Department of Bioinformatics, under which this important work is taking place, was established in 2015 with an exceptional $25 million gift from Lyda Hill.

Convenience, and enhanced treatment and diagnostic options, are hallmarks of UT Southwestern’s radiation oncology services. In another example, six state-of-the-art linear accelerators in the new radiation oncology building produce patient-specific beams at speeds six times faster than conventional machines, leading to a substantial decrease of irradiation time for selected tumors.

Mrs. LeBlanc is a working woman, a mom, and a wife. She’s a great example of many women who will be impacted by this disease,” said Dr. Bruce Mickey, Professor of Neurological Surgery, Otolaryngology and Radiation Oncology, and Director of the Annette G. Strauss Center for Neuro-Oncology, part of the O’Donnell Brain Institute.

Dr. Mickey, who holds the William Kemp Clark Chair of Neurological Surgery, said the emphasis on brain protection is one of the founding principles of the O’Donnell Brain Institute. This principle drove the decision to upgrade to the sixth and newest model of the Gamma Knife system.

“Our new Gamma Knife Icon has been specifically designed to deliver a highly effective dose of radiation with the lowest possible radiation exposure to the surrounding normal brain tissue and cranial nerves,” said Dr. Mickey. Dr. Asal Rahimi, Assistant Professor of Radiation Oncology and Mrs. LeBlanc’s doctor. “We wanted to make this treatment more convenient for patients, because cancer is never convenient.”

Convenience, and enhanced treatment and diagnostic options, are hallmarks of UT Southwestern’s radiation oncology services. In another example, six state-of-the-art linear accelerators in the new radiation oncology building produce patient-specific beams at speeds six times faster than conventional machines, leading to a substantial decrease of irradiation time for selected tumors.

A - The Varian VitalBeam, one of six state-of-the-art linear accelerators

B - The Elekta Versa HD, another of the new linear accelerators

C - The next-generation Accuray CyberKnife, the M6

in North Texas – collaborate on Gamma Knife Icon treatments. The technology combines cone beam CT imaging to verify patient positioning before treatment and continuous monitoring during the procedure to ensure accuracy. With the Gamma Knife Icon, radiation treatments can be spread out in smaller doses, called fractionated treatments, or given as distributive treatments – in which multiple, separate targets are identified and only a subset are treated on any given day.

“Our new Gamma Knife Icon has been specifically designed to deliver a highly effective dose of radiation with the lowest possible radiation exposure to the surrounding...
In this study, researchers examined two subtypes of non-small cell lung cancer, the most common cause of lung cancer deaths. The UT Southwestern algorithms were developed based on scanned images in The Cancer Genome Atlas of routine cancer tissue slides used by pathologists to differentiate between malignant and benign tumors. After sorting through more than 3,000 slides for features such as cell size, shape, distribution, texture, and location of nuclei, the scientists were able to identify features to segregate cancers into aggressive and less-aggressive groups. Patients in the high-risk, aggressive group had more than twice the risk of death as those identified in the low-risk group.

“If we can someday use this clinically, we could provide patients in the high-risk group with more aggressive treatment, while patients in the low-risk group could receive effective treatments with fewer toxic side effects,” Dr. Xiao said.

Dr. Xiao, a member of the Quantitative Biomedical Research Center and the Harold C. Simmons Comprehensive Cancer Center, explained that pathologists routinely examine cancer tissue slides for lung cancer diagnosis and prognosis in a time-consuming, subjective process that relies on their highly trained memories, causing variation. In contrast, the computational approach augments the human touch. It needs only a pathological imaging scanner and a desktop computer.

The team is exploring the possibility of patenting the process. Before this computerized image analysis can be used clinically, however, it must be tested in a prospective study, Dr. Xiao said.
Illuminating cancer: New pH threshold sensor improves cancer surgery

The high acidity of cancer cells yielded the clue that led to the development of a tool that significantly improves surgeons’ abilities to remove cancerous tissues. The invention by UT Southwestern researchers is a transistor-like threshold sensor that hones in on high pH, literally lighting up cancerous cells.

Using mouse models, the UTSW team was able to demonstrate the nanosensor’s ability to light up a broad set of solid cancers, distinguishing them from healthy, normal cells. The study is published in *Nature Biomedical Engineering*.

“We synthesized an imaging probe that stays dark in normal tissues, but switches on like a lightbulb when it reaches solid tumors. The purpose is to allow surgeons to see tumors better during surgery,” said senior author Dr. Jinming Gao, Professor of Pharmacology and Otolaryngology with the Harold C. Simmons Comprehensive Cancer Center.

That’s important to the millions of patients facing cancer. According to the National Cancer Institute, there are 15.5 million cancer survivors in the U.S., representing 4.8 percent of the population. The number of cancer survivors is projected to increase by 31 percent, to 20.3 million, by 2026.

Used during surgery, the new nanosensor amplifies acidic pH signals in the tumor microenvironment to more accurately distinguish them from normal tissue.

“Cancer is a very diverse set of diseases, but it does have some universal features. Tumors do not have the same pH as normal tissue. Tumors are acidic, and they secrete acids into the surrounding tissue. It’s a very consistent difference,” said Dr. Baran Sumer, Associate Professor of Otolaryngology and co-senior author of the study.

As a result of this work, the researchers founded a UTSW spinoff company, OncoNano Medicine Inc., which plans to launch the first-in-human, phase one clinical trial this year to evaluate safety and tolerability in patients with solid cancers. This trial will be followed by phase two efficacy studies in several cancer indications before going on to multicenter phase three clinical trials.

The researchers hope the improved surgical technology can eventually benefit cancer patients in multiple ways, including more accurate removal of tumors and greater preservation of functional normal tissue. These advantages can improve both survival and quality of life.

A new era for nuclear medicine and molecular imaging began in 2017 with the production and delivery of the first noncommercial radiotracer for human injection in North Texas. The radiotracer, carbon-11 acetate, is an investigational drug approved by the Food and Drug Administration. It was produced by the Cyclotron and Radiochemistry Program at UT Southwestern for clinical positron emission tomography (PET) imaging of brain tumors.

After injecting a dose of carbon-11 acetate into the bloodstream of a research participant, the scan at UTSW revealed a strikingly higher contrast in tumor masses than conventional PET scans performed with radiolabeled glucose.

“This success marks a major milestone of cancer research in the region and demonstrates the promising role of the cutting-edge imaging technology of PET in improving cancer patient care,” said Dr. Xiankai Sun, who leads the Department of Radiology-based Program.

UT Southwestern’s cyclotron – a 22-ton circular particle accelerator housed underground and secured behind 6-foot-thick concrete walls – produces short-lived positron-emitting radionuclides such as carbon-11 acetate – are difficult to transport and ideally should be produced where used. Producing such radiotracers on-site enables the cutting-edge imaging technologies of PET for patient care in North Texas and increases opportunities for expanded research efforts.

Carbon-11 acetate has previously been used in cardiology to evaluate oxygen consumption and blood flow in the heart, and in oncology to detect several tumor types, including prostate, kidney, bladder, and lung cancers. The researchers hope to further extend the imaging applications of this radiotracer to brain cancer diagnosis and prognosis, facilitating additional insights into cancer metabolism, said Dr. Sun, an Associate Professor of Radiology and a member of the Advanced Imaging Research Center who also holds the Dr. Jack Krohmer Professorship in Radiation Physics.
to more collaborations between immunologists and nanotechnologists,” Dr. Chen said.

“The partnerships are critical in propelling the rapid development of new generations of nanovaccines,” the researchers said.

The research was a collaboration between the laboratories of Dr. Gao and Dr. Zhijian “James” Chen, Professor of Molecular Biology and Director of the Center for Inflammation Research, established to study how the body senses infection and to develop approaches to use this knowledge to create new treatments for infection, immune disorders, and autoimmunity.

“For nanoparticle vaccines to work, they must deliver antigens to proper cellular compartments within specialized immune cells called antigen-presenting cells and stimulate innate immunity,” said Dr. Chen, also a Howard Hughes Medical Institute Investigator at UT Southwestern and holder of the George L. MacGregor Distinguished Chair in Biomedical Science. “Our nanovaccine did all of those things.”

With the emergence of new nanotechnology tools and increased understanding of polymeric drug delivery, Dr. Gao said, the field of nanoparticle vaccines has grown in the past decade and attracted intense interest from academia and industry.

“Recent advances in understanding innate and adaptive immunity have also led

Boosting immunity to fight cancer

UT Southwestern’s first-of-its-kind experimental nanoparticle vaccine targets the body’s immune cells to deliver proteins that stimulate the immune system. Here is how it works:

• The vaccine is administered, carrying tumor proteins to the lymph nodes.
• The vaccine activates an adaptor protein called STING, which in turn stimulates the body’s immune defense system.
• This action then spurs production of tumor-specific T-cells, which kill cancer cells.

Nanoparticle vaccine shows promise as cancer immunotherapy

A groundbreaking nanoparticle vaccine immunotherapy that targets several different cancer types has been developed by biomedical researchers at UT Southwestern.

The nanovaccine consists of tumor antigens – tumor proteins that can be recognized by the immune system – inside a synthetic polymer nanoparticle. Nanoparticle vaccines travel directly to the body’s lymph nodes to activate tumor-specific immune responses. Typical vaccines, on the other hand, require immune cells to pick up tumor antigens and then travel to the lymphoid organs for T-cell activation.

“What is unique about our design is the simplicity of the single-polymer composition that precisely delivers tumor antigens to immune cells while stimulating innate immunity. These actions result in safe and robust production of tumor-specific T-cells that kill cancer cells,” said Dr. Jinming Gao, Professor of Pharmacology and Otolaryngology in UT Southwestern’s Harold C. Simmons Comprehensive Cancer Center.

In this case, the experimental UTSW nanovaccine works by activating an adaptor protein called STING, which in turn stimulates the body’s immune defense system to ward off cancer.

A study published last year in Nature Nanotechnology outlining this research reported that the UTSW nanovaccine had anti-tumor efficacy in multiple tumor types in mice, including melanoma, colorectal cancer, and HPV-related cancers of the cervix, head, neck, and anogenital regions.

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(Left) Dr. Jinming Gao, Dr. Min Luo, and colleagues developed a promising nanoparticle vaccine for cancer immunotherapy that delivers tumor antigens to immune cells.
There are no lost causes, only challenges to achieve what others view as impossible. Like regenerate heart muscle cells in unique ways, such as exposure to a low-oxygen environment, aimed at helping patients recover from heart damage. Or to salvage the life of a patient through risky, minimally invasive heart valve replacement surgery. At UT Southwestern, heart and transplant medicine specialists are asking questions and taking chances, ultimately transforming lives.
A minimally traumatizing surgery for a maximum-risk heart

Seven percent. That’s the percentage of the blood in Tommy Lloyd’s heart that flowed through his aorta with each squeeze of his heart. For a healthy heart of someone in their 60s, that number should be about 70 percent.

While most people have a three-part aortic valve that opens and closes to send blood from the heart to the body, Mr. Lloyd was born with a two-part valve, which tends to stiffen and wear out earlier. By 2016, when Mr. Lloyd was 65, his heart condition had reached that critical point.

In January 2017, this medical problem led him to Dr. Neelan Doolabh, Associate Professor of Cardiovascular and Thoracic Surgery at UT Southwestern, who specializes in a rare minimally invasive procedure for valve replacement that reduces the trauma of heart surgery. Dr. Doolabh is one of only a handful of surgeons in the world who performs valve repairs, valve replacements, and other heart procedures without cutting into any bone – a departure from typical heart surgeries that require removal of the breastbone or ribs.

Dr. Doolabh was recruited to UT Southwestern because of his expertise in this specific surgery, which, performed through a small incision, is technically much more demanding and consequently difficult to teach and master. Patients have come from across Texas and the United States to UT Southwestern for this procedure; one patient even came from Saudi Arabia to see Dr. Doolabh.

Because there are so few surgeons trained in this specialized technique, it accounts for less than 1 percent of aortic valve replacement surgeries. For people like Mr. Lloyd, it’s a critical option to have. Fortunately for him, UT Southwestern had the resources he needed – and just a few hours from his home in Longview, Texas.

“I’m going to spell this out for you,” Dr. Doolabh told Mr. Lloyd. “We can replace the valve without problem, but your heart is so weak it’s going to be hard restarting your heart after removing you from the heart-lung machine.”
Heart valve replacement surgery: Benefits of an advanced approach

Less trauma to the body and shorter surgery and recovery times are significant benefits of the minimally invasive approach. But because the procedure is so technically demanding, only a few heart surgeons in the world perform this method routinely, and Dr. Neelan Doolabh is one of them. UT Southwestern is among a handful of major medical centers with the most experience in the procedure.

Rather than making the more traditional 10-inch vertical incision down the center of the chest to access the heart, Dr. Doolabh recommended the minimally invasive approach, which requires a less than 2-inch incision between the ribs. Almost all patients in need of a valve replacement are good candidates for the technique – which Dr. Doolabh has been performing for a decade – but it’s especially valuable for patients who are older, obese, or have multiple health issues.

TRADITIONAL OPEN-HEART SURGERY
- Incision: 10-inch vertical incision down the chest
- Surgery duration: 4-5 hours
- Recovery time: 6-8 weeks

MINIMALLY INVASIVE TECHNIQUE
- Incision: Less than 2-inch incision between ribs
- Surgery duration: 2 hours
- Recovery time: 10 days

Mr. Lloyd said he feels immense gratitude to Dr. Doolabh and the rest of the team, so much so that he felt inspired to make a gift to UT Southwestern for his excellent care. “When I was being discharged, Neelan [Doolabh] came by and we talked. I had tears in my eyes and I apologized for the tears,” Mr. Lloyd recalled. “He said, ‘it’s quite normal. You’ve been on the biggest roller coaster ride of your life.’”

Recovery for the traditional open-heart surgery approach can require six to eight weeks before patients can return to normal activities like driving. With the minimally invasive approach, people can often resume normal activities in about 10 days and – more importantly for Mr. Lloyd’s situation – the minimally invasive surgery is far less stressful on the body.

For Mr. Lloyd, who had always led an active life on his East Texas ranch, it meant doing many of the things that he hadn’t been able to do for quite a while before the valve replacement.

“Living on acreage, there’s always something to do. Building a fence. Taking down a pine tree and cutting it up to make a bonfire. Have I cut down any 90-foot trees lately? No, but that will be happening when it needs to be done,” he said.

“My goal was to turn my heart clock back 10 years, and that goal has been accomplished.”

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Researchers found significant sex-based differences in lipids, fat hormones, markers of inflammation and artery health, and indicators of muscle damage and kidney function.

UTSW study calls out differences in heart disease for women

Typically, women suffer heart attacks later in life than men. However, they are equally as likely as men to develop blockage in arteries to other parts of the body. The presentation of heart failure is also different: Women are less likely to have heart failure from a weak heart than from a stiff heart, meaning the heart muscle becomes stiff and unable to expand enough to fill up with blood.

These commonly observed variations in heart disease by sex are far more complex than just differences in hormones, however. Analysis by UT Southwestern researchers of these differences suggests new standards need to be developed for treatment of heart disease in women.

Those conclusions come from an analysis of data in the Dallas Heart Study, a large, multiethnic population study initiated at UT Southwestern in 2000.
Five simple medical tests are better indicators of who will develop heart disease than the standard strategies focused on blood pressure, cholesterol, diabetes, and smoking history, according to conclusions from a UT Southwestern study published last year from the journal Circulation.

“This set of tests is really powerful in identifying unexpected risk among individuals with few traditional risk factors,” said Dr. James de Lemos, Professor of Internal Medicine, who led the study with Dr. Amit Khera, Professor of Internal Medicine.

The findings were based on analysis of two large population studies, including the Dallas Heart Study, a landmark UT Southwestern study that has led to more than 200 published scientific studies. The five tests are:

1. **12-lead EKG:** provides information about hypertrophy, or thickening of the heart muscle.
2. **Coronary calcium scan, or low-radiation imaging test:** identifies calcified plaque buildup in the arteries of the heart.
3. **Blood test for C-reactive protein:** indicates inflammation.
4. **Blood test for the hormone NT-proBNP:** indicates stress on the heart.
5. **Blood test for high-sensitivity troponin T:** indicates small amounts of heart muscle damage that can be detected in people without any symptoms or warning signs.

All five tests are currently available at UT Southwestern and elsewhere, Dr. de Lemos said.

“We recommend this and other similar testing panels be measured selectively rather than routinely, and are best considered for individuals who are interested in as much information as possible about their cardiac risk,” Dr. de Lemos added, stressing that the testing should be monitored by physicians with expertise in interpretation of the results.

Sources: Dr. de Lemos, who holds the Sweetheart Ball-Kern Wildenthal, M.D., Ph.D. Distinguished Chair in Cardiology; and Dr. Khera, who holds the Dallas Heart Ball Chair in Hypertension and Heart Disease.

In a study published in Circulation, UT Southwestern researchers examined sex differences among 30 biological markers in 3,439 individuals. They found significant sex-based differences in lipids, fat hormones, markers of inflammation and artery health, and indicators of muscle damage and kidney function.

Compared with men, women tend to have higher levels of fat hormones, clotting proteins, and certain markers of inflammation, the study found. Women also tend to have lower levels of proteins that reflect unhealthy arteries.

“It has long been known that men and women have remarkable differences in their manifestations of heart disease,” said Dr. James de Lemos, Professor of Internal Medicine and senior author of the study. “Our study suggests that there are sex-based differences in many different biological pathways contributing to heart disease.”

Large differences in the levels of many proteins found in men and women made Dr. de Lemos realize that using the same level to diagnose abnormalities universally might not be appropriate.

“It is likely that the normal ranges for these proteins should be different between men and women,” said Dr. de Lemos, who holds the Sweetheart Ball-Kern Wildenthal, M.D., Ph.D. Distinguished Chair in Cardiology.

Beyond obvious differences in hormonal status between men and women, UT Southwestern researchers point to differences in body composition – particularly fat distribution – as some of the most important drivers of the sex differences in heart disease.

Additional research is needed to better understand whether differences in responses to environmental and social stressors also play a role, Dr. de Lemos said.

“It is high time that we begin to understand what drives specific forms of heart disease in women and not automatically apply the same diagnostic and treatment algorithms to the two sexes,” he said.

**Mars vs. Venus: Sex differences in heart disease**

- Men are more likely to develop congestive heart failure at a young age (under 55), but more women develop heart failure overall.
- Women are more likely than men to develop the kind of heart failure in which the heart still pumps appropriately.
- Of men and women who suffer a heart attack, women are more likely to die.
- Women with atrial fibrillation (a heart rhythm irregularity) are more likely to have a stroke than men.
- Heart attacks and angina occur later in life in women.

Dr. James de Lemos

**Check out these tests – they may save your life**

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First heart-liver transplant at UTSW saves singer’s life

A genetic disorder dealt singer and songwriter Andrea Joyner a serious blow in 2004. She received a diagnosis of juvenile hemochromatosis, which can lead to multiorgan dysfunction before the age of 30. The clock was ticking, and by late 2016 she faced imminent death without a rare heart-liver transplant.

But thanks to the exceptional care of multiple UT Southwestern transplant teams, the 40-year-old musician is now back to writing songs and living life to its fullest. The surgery that saved her also marked a historic milestone as the first heart-liver transplant performed at UT Southwestern.

“She’s done very well considering how close to death she was – within hours, most likely,” said Dr. Malcolm MacConmara, who led the liver transplant team through the September 2016 surgery.

With the double transplant, UT Southwestern joins the ranks of only four other Texas medical centers – including affiliated hospital Children’s Medical Center Dallas – that have performed the complicated heart-liver surgery, in which a newly implanted heart must withstand the stress of a liver transplant and the toxins released from the donor organ.

In 2006, Children’s completed a heart-liver transplant on a girl whose family came from Miami for treatment. The treatment team for that case included Dr. Sarah Blumschein, Associate Professor of Pediatrics at UT Southwestern, and transplant surgeons Dr. Kristine Gulesarian and Dr. Jay Roden, former faculty members.

More than 200 such transplants have been done in the U.S. since Feb. 14, 1984, when a 6-year-old patient from UT Southwestern traveled to Children’s Hospital of Pittsburgh to receive the world’s first heart-liver transplant. That patient, Stormie Jones, lived six more years before her body rejected the transplanted heart.

Dual-transplant challenges

Heart-liver transplants are “quite complicated. They’re not offered by a lot of institutions,” explained Dr. Matthias Pelz, Associate Professor of Cardiovascular and Thoracic Surgery, who led the heart transplant team at Clements University Hospital.

“It requires having the expertise of both sets of surgeons, clinicians, nurses, perfusionists – everyone involved for each organ – working together,” said Dr. MacConmara, Assistant Professor of Surgery.

On Aug. 25, Miss Joyner went on waitlists for both organs. Within days, however, her condition deteriorated to the point where keeping her alive long enough to get any organ became the issue. By Sept. 4, her heart had weakened to the point that she required placement on an external heart-lung machine to stay alive.

Fortunately, on Sept. 5, a heart and a liver became available. The surgery was scheduled the next day, with the heart transplant completed first.

With her second chance, Miss Joyner said she plans to continue her music – and to speak out to educate people about her rare disease, which went undiagnosed for so long.

Miss Joyner also thinks a lot about the organ donor who died and the family that donated her left behind. She said she’d like to meet them one day. “I can’t thank them enough. They saved me.”

Stormie Jones became the world’s first heart-liver transplant recipient in 1984. Initially a patient at UT Southwestern, her case played a fundamental role in findings by Nobel Laureates Drs. Michael Brown and Joseph Goldstein that established the importance of the liver in regulating cholesterol.
Low oxygen: The potential key to heart regeneration

Normal, healthy heart muscle is well-supplied with oxygen-rich blood. But UT Southwestern cardiologists have found that depriving the heart of oxygen may repair hearts damaged by disease. In lab environments, they’ve been able to regenerate heart muscle by placing mice in an extremely low-oxygen environment.

“In theory, creating a low-oxygen environment could lead to repair not only of heart muscle, but of other organs as well,” said Dr. Hesham Sadek, Associate Professor of Internal Medicine and Associate Director of the Hamon Center for Regenerative Science and Medicine. “Although exposure to this level of hypoxia can result in complications, it is tolerated in humans when performed in a controlled setting.”

Heart disease is the leading cause of death in the U.S., according to the Centers for Disease Control and Prevention. An estimated 5.7 million people have heart failure, which is the inability of the heart to pump enough blood to keep up with the demands of the body. There are no current treatments to regenerate heart muscle.

In this study, researchers with the Hamon Center gradually lowered the oxygen level in the air breathed by mice until it was at 7 percent – about the concentration of oxygen at the top of Mount Everest. After two weeks in the low-oxygen environment, the heart muscle cells – called cardiomyocytes – divided and grew. Under normal circumstances, cardiomyocytes do not divide in adult mammals.

The findings, published in Nature, build upon years of work at UT Southwestern that began with the discovery that the hearts of newborn mammals have the ability to regenerate, similar to the way skin has the ability to repair itself after a cut. But this ability of heart muscle to regenerate is quickly lost in the following weeks as the animal ages and cardiomyocytes are bathed in the oxygen-rich environment of the beating heart, causing oxidative damage to the muscle cell DNA.

“The adult human heart is not capable of any meaningful repair following a heart attack, which is why heart attacks have such a devastating impact,” said Dr. Sadek, who holds the J. Fred Schoellkopf, Jr. Chair in Cardiology. “Though counterintuitive, we’ve shown that severely lowering oxygen exposure can sidestep damage to cells caused by oxygen and turn cell division back on, leading to heart regrowth.”

Over a period of weeks, researchers lowered the oxygen level from the normal 21 percent to 7 percent, then monitored the mass and function of the heart. They demonstrated that reduced oxygen leads to both an increase in cardiomyocytes and improved heart function.

The researchers had tried a 10 percent oxygen environment, but found no heart regrowth at that level. To avoid oxygen damage to cells, oxygen levels needed to be very low, a situation referred to as hypoxia.

“This work shows that hypoxia equivalent to the summit of Mount Everest can actually reverse heart disease, and that is extraordinary,” said Dr. Benjamin Levine, Professor of Internal Medicine, who holds the Distinguished Professorship in Exercise Sciences and directs the Institute for Exercise and Environmental Medicine at Texas Health Presbyterian Hospital Dallas, a joint program of UT Southwestern and Texas Health Resources.

Although too early to translate into new therapies for human heart patients, these findings hold promise for the future. Worldwide, regenerative medicine like this has become a significant area of scientific focus.
Might heart attack-damaged heart muscle be prompted to repair itself?

To find out, researchers with the Hamon Center for Regenerative Science and Medicine at UT Southwestern launched clinical trials to investigate whether a type of mechanical pump called a ventricular assist device (VAD) can create an environment that results in regeneration of heart cells.

“Research at UT Southwestern over the past five years was the first to show that the heart muscle in mammals can actually regrow in the early days of life,” said Dr. Hesham Sadek, Associate Professor of Internal Medicine and Associate Director of the Hamon Center, who holds the J. Fred Schoellkopf, Jr. Chair in Cardiology. “This ability stops, in part because of the workload that the heart has to do. We believe that taking away that load by using VADs would reactivate this regenerative ability of the heart.”

VADs are used to support heart function and blood flow in people who have weakened hearts. The device takes blood from a lower chamber of the heart and helps pump it to the body and vital organs, just as a healthy heart would.

UT Southwestern has played an integral role throughout the relatively short history of VAD therapy and in the device’s rapidly evolving technology. The Medical Center participated in the landmark clinical trial (REMATCH) that led to the Food and Drug Administration’s approval of the first left ventricular assist device for destination therapy and was the only North Texas center to participate in the HeartWare Bridge-to-Transplant trial, which was completed in 2012 and led to FDA approval of the device.

The clinical trials will be conducted through a new Ventricular Assist Device Program. The first trials will be conducted with patients who currently have or will be getting VADs implanted to treat heart failure. For more information on the clinical trials, email ingrid.kepinski@utsouthwestern.edu.

A cancer drug with unique heart regenerative potential

Every once in a while, the journey to drug discovery takes an unexpected detour. An example of this is a recent UT Southwestern effort, in which anti-cancer research may someday help patients recover after a heart attack.

An anti-cancer agent in development – specifically a porcupine (Porcn) enzyme inhibitor – has been found to promote regeneration of damaged heart muscle. Because of the heart’s inability to repair itself, damage caused by a heart attack leads to permanent scarring that frequently results in serious weakening of the heart, known as heart failure.

For years, biomedical scientists in the Harold C. Simmons Comprehensive Cancer Center and the Hamon Center for Regenerative Science and Medicine have worked to develop a cancer drug targeting Wnt signaling molecules. These molecules, crucial for tissue regeneration, also frequently contribute to cancer. Essential to the production of Wnt proteins in humans is the porcupine enzyme, so named because fruit fly embryos lacking this gene resemble a porcupine.

In testing the porcupine inhibitor researchers developed, they noted a curiosity – that the number of dividing heart muscle cells was slightly increased, generating a new focus on whether such agents could be useful in regenerative medicine.

“Our lab has been studying heart repair for several years, and it was striking to see that administration of a Wnt inhibitor significantly improved heart function following a heart attack in mice,” said Dr. Rhonda Bassel-Duby, Professor of Molecular Biology and Associate Director of the Hamon Center, who collaborated on the investigation with Dr. Lawrence Lum, formerly an Associate Professor of Cell Biology and Associate Director of Basic Research at the Simmons Cancer Center.

Based on their results, the researchers induced heart attacks in mice and then treated them with a porcupine inhibitor. Their hearts’ ability to pump blood improved by nearly twofold compared with untreated rodents.

The study findings were published in Proceedings of the National Academy of Sciences. Importantly, in addition to the improved pumping ability of hearts in the mice, the researchers noticed a reduction in fibrosis, or scarring in the hearts. Collagen-laden scarring that occurs following a heart attack can cause the heart to inappropriately increase in size, which in turn can lead to heart failure.

Putting a mechanical pump to the regenerative test

For more information on suggested anti-cancer agent promotes regeneration of damaged heart muscle in mice.
What a difference three years can make. In late 2014, UT Southwestern opened the William P. Clements Jr. University Hospital, proud to unveil a new facility that raised the bar for patient care in North Texas. Now, unprecedented growth has led to the kickoff of a hospital addition, yet another indication of the Medical Center’s evolution on multiple fronts – an expanding clinical footprint, evolving partnerships, enhanced educational programs, and facility improvements.

**Positioning UT Southwestern for the future**

Architectural detail of Clements University Hospital. The hospital is scheduled to complete a 650,000-square-foot expansion in 2020.
Southwestern Health Resources evolves, joins ACO to offer next generation of coordinated, quality care

Southwestern Health Resources – the integrated health care network formed in 2015 by Texas Health Resources and UT Southwestern – continues to build on more than 50 years of collaboration between the two institutions. From preventive care to the most advanced interventions, the partnership blends the strengths of both entities to better serve North Texas residents.

One of the highlights for the partnership in 2017 was the selection of the UT Southwestern/Southwestern Health Resources Accountable Care Network by the Centers for Medicare & Medicaid Services (CMS) to participate in its Next Generation Accountable Care Organization (ACO) program, which aims to move away from a health care system that rewards the quantity of services to one that rewards the quality of health outcomes. This new model is designed for experienced ACO health care providers with a successful record of coordinating care while improving quality and efficiency. There are more than 600 ACOs in the U.S., but only 45 currently participate in the Next Generation (NextGen) program.

The goal of the Next Generation model is to test whether these incentives and tools to support better patient engagement and care management can improve health outcomes and lower expenditures for “Original Medicare” fee-for-service beneficiaries.

“Successful Medicare ACOs are on the cutting edge of health care reform,” said Danny Irland, Chief Financial Officer of the Accountable Care Network and Vice President for Market and Payer Relations, Southwestern Health Resources. “Networks like Southwestern Health are about creating efficiencies and quality enhancements that ultimately improve outcomes and help control costs.”

Suresh Gunasekaran leads Southwestern Health Resources’ new Population Health Services Company.

Population health turns lens on the continuum of care in North Texas

At UT Southwestern, providing excellent care to hospital and clinic patients has always been a priority. With the new Population Health Services Company – a component of Southwestern Health Resources, the integrated health care network formed in partnership with Texas Health Resources in 2015 – that mission has expanded to supporting patients outside of clinical settings.

Population health services is a concept based on addressing the health and comprehensive health needs of certain groups of high-risk patients — even when they are not directly in front of a doctor, explained Suresh Gunasekaran, Vice President for Health System Operations.

The traditional health care system relies on patients coordinating their own care with little formal support from the health care system. “What patients are doing when they’re away from us plays a tremendous role in determining whether they stay healthy or recover from surgery,” said Mr. Gunasekaran, who is also Senior Executive Officer of the Population Health Services Company (PHSC).

Population health includes better coordination between a patient’s primary and specialty care doctors, education on ways that patients can better take care of themselves, home-based care for those who cannot easily come to a clinic, and comparative analytics of patients with similar characteristics. All of this provides the services that patients need to achieve maximum health and recovery so they don’t need to return to the hospital and can function at the highest levels that their health allows. Moving to a more proactive process also helps decrease health care costs, Mr. Gunasekaran said. As of last fall, the Southwestern Health Resources PHSC employed 300 people, working with more than 100,000 patients.

The three key components of population health are:

Patient navigation — This supports patients in finding the right care at the right place at the right time, and helps them find providers and make their appointments.

Care management services — These services are geared toward patients with chronic conditions or who have recently had certain procedures. Those patients are assigned a clinician for a 30-, 60-, or 90-day period to help support their recovery needs.

Disease management — Physicians create unified care plans to ensure that patients with chronic conditions are following best-practice guidelines to manage their disease.

UT Southwestern had roughly 2.2 million patient visits in 2017. So how do clinicians determine which of those need population health? The answer lies in data and analytics, which the PHSC uses to identify various risk factors to predict which patients are most susceptible to complications and likely to need additional support.

“If you factor for things like age, previous health history, and length of hospital stay, you can determine a score to identify which patients are likely to need more help,” Mr. Gunasekaran said. “By focusing staff and resources on those who face a higher risk, such as patients who have multiple health conditions, we can keep them well rather than having to address their conditions at a more serious point.”
The UT Southwestern/Southwestern Health Resources Accountable Care Network (ACO) is part of a national initiative to reduce costs by coordinating and delivering better health care for Medicare patients. The ACO was among the country’s top-performing programs launched since 2014, according to CMS. Based on nearly $30 million in savings in 2015 alone, the accountable care network ranked eighth in the country overall and second in the state.

“We believe that our success has come from our clinically integrated program that draws in both physicians and patients and includes the ability to coordinate and manage care inside the high-performing network that is Southwestern Health Resources,” said Dr. John Warner, Vice President and Chief Executive Officer of UT Southwestern University Hospitals and Senior Executive Officer for Southwestern Health Resources Joint Operating Company.

“We continue to be very proud of our successes in achieving a reduction in the cost of care while delivering better quality and outcomes. Ultimately, these results demonstrate how Southwestern Health Resources will benefit patients, health care providers, and the general public,” added Dr. Warner, who holds the Jim and Norma Smith Distinguished Chair for Interventional Cardiology and the Nancy and Jeremy Halbreich, Susan and Theodore Strauss Professorship in Cardiology.

Southwestern Health Resources is comprised of a physician network, a 31-facility hospital network, and a population health services company that collectively provide higher value and easier access to all levels of care, from primary care to emerging therapies using the latest scientific discoveries. The network serves more than 7 million people across 16 counties in North Texas.

“We’ve proved that with the right analytics, data sharing through integrated electronic health records, the establishment of population health services, and the hiring of high-performing, talented physicians, we can address many of the issues facing the health care system,” said Suresh Gunasekaran, Vice President for Health System Operations and Senior Executive Officer of the SWHR Population Health Services Company.

Another milestone for the Southwestern Health Resources partnership last year came with the June opening of the UT Southwestern Family Medicine Residency Program and clinical practice at Texas Health Presbyterian Hospital Dallas. This marked an expansion of UT Southwestern’s geographic footprint in North Texas.

The nearly 10,000-square-foot clinic provides residents of the North Dallas community improved access to high-quality primary care physicians and health resources. The new Southwestern Health Resources residency track also provides exciting new opportunities for residents and physician faculty: Residents will be able to rotate through a variety of areas, from obstetrics to surgery, while both groups will be able to participate in training programs that embrace population health.

Clerkship phase gives medical students earlier patient care exposure

Becoming a doctor takes years of hard work and study. Because of that, medical students hunger for real-world patient care experiences. With the new curriculum that UT Southwestern began rolling out in 2015, second-year students are now getting that exposure to patient care six months earlier in their four-year program.

That experience comes in the form of core clerkships, which follow studies in integrated basic science and clinical topics during the pre-clerkship months.

In most medical school programs, students spend the first two years in a classroom (called pre-clerkship) before doing hands-on learning (clerkship) in a teaching hospital. In the new UT Southwestern Medical School curriculum – the second phase of which

The revised curriculum starts clerkships sooner, giving medical students the opportunity to explore more clinical fields before they select their specialties.
In September 2015, UT Southwestern Medical School launched an integrated, team-based curriculum to better train medical students to become knowledgeable, confident, and forward-looking clinicians and scientists. Following are some key milestones of the educational initiative and rollout:

**June 2013** – Planning to develop the new curriculum begins, led by the Dean and a five-member faculty committee.

**Summer/Fall 2013** – UT Southwestern’s Strategic Planning Committee for Curriculum Reform visits peer institutions nationwide to evaluate curricula.


**Fall 2014-Spring 2015** – Course content for the pre-clerkship phase is drafted and disseminated for peer faculty review.

**Summer 2015** – Pre-clerkship course content is finalized and construction of team-based learning space is completed.

**September 2015** – The Class of 2019 begins instruction under the new three-phase curriculum, initiating the pre-clerkship phase.

**January 2017** – Second-year students begin the clerkship phase.

**July 2018** – Fourth-year students begin post-clerkships, which include selecting individual interests.

**June 2019** – The first students to complete all four years of the new curriculum graduate.

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On Sept. 29, UT Southwestern President Dr. Daniel K. Podolsky and Vice President and Chief Executive Officer of University Hospitals Dr. John Warner (left and right at center) joined employees of William P. Clements Jr. University Hospital to celebrate the hospital’s expansion.

In September 2017, less than three years after Clements University Hospital was dedicated, UT Southwestern broke ground to start work on a third hospital tower, a significant expansion to the current two-tower building. The 30-month construction project will add a tower to house employees, patients, and services that are now delivered at Zale Lipshy University Hospital, making Clements the clinical site of neuroscience programs associated with the Peter O’Donnell Jr. Brain Institute.

Besides relocating all staff services currently provided at Zale Lipshy, the hospital expansion project will create a net addition of 144 beds campuswide. The planned renovation will also include an enlargement of the Emergency Department and add new operating rooms, interventional suites, and two parking structures.

Growth is coming to UT Southwestern’s William P. Clements Jr. University Hospital and its West Campus, and much sooner than expected.

The number of patients the hospital serves has grown more rapidly than anyone could have foreseen—an indication of the trust that the community has in the excellent care that UT Southwestern University Hospitals deliver.

The core clerkships in ambulatory medicine, along with the specialized elective offerings, give students a personalized education to help them become successful clinicians or researchers— or, in some cases, both.

Dr. Arlene Sachs, Director of Student Academic Support Services and Assistant Professor of Psychiatry, and her team worked with the students on preparation for their United States Medical Licensing Examination Step 1 exam, the first of two required national board exams taken by all U.S. medical students.

“Previously, all second-year students prepared independently and all took the Step 1 at the same time,” Dr. Sachs said. “But, as part of the new curriculum, we developed a required six-week course to support students in their preparation for Step 1.

“We met individually with students to advise on best practices and to aid each student in developing a personalized study schedule. They reported on their progress with weekly surveys, which allowed us to reach out and help students stay on track for success.”

The ultimate measure of success for a student is to become an exceptional physician or researcher. The revised curriculum moves students toward that goal, arming them with the valuable skills and knowledge found at UT Southwestern, a leading academic medical center.

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When it is complete in 2020, the new tower will not only consolidate all UT Southwestern inpatient services in one facility, but will also allow the Medical Center to improve the quality of hospital care and services; lower the cost of care by eliminating redundancies in infrastructure, staffing, and inventory; position Clements as a destination, high-acuity hospital in the region; and prepare UT Southwestern for future referrals from growth of the Southwestern Health Resources network.

Dr. John Warner, Vice President and Chief Executive Officer, University Hospitals, is enthusiastic about the prospect of bringing together Clements and Zale Lipshy programs and staff under the same roof.

"Being in the same building is going to help make us even better," said Dr. Warner, who holds the Jim and Norma Smith Distinguished Chair for Interventional Cardiology, and the Nancy and Jeremy Halbreich, Susan and Theodore Strauss Professorship in Cardiology. "I look forward to us all being together. It will streamline and simplify many of our consultation services and it will strengthen and support our multidisciplinary care model."

Leaders are still exploring how the Zale Lipshy space will be used.

Clements University Hospital sits in the area of UT Southwestern known as West Campus – the former site of St. Paul University Hospital – which also is undergoing large-scale development.

The $875 million West Campus Facilities Master Plan will unfold in five phases over 20 years. Ultimately, the plan will add 1.1 million square feet of facility space.

Evidence of UT Southwestern’s commitment to excellence came last summer with its ranking by U.S. News & World Report as the No. 1 hospital in Dallas-Fort Worth, second in Texas, and among the top 50 programs nationally in six clinical areas – in recognition of the care provided at both William P. Clements Jr. University Hospital and Zale Lipshy University Hospital.

"UT Southwestern is committed to delivering excellence in all that we do. It is gratifying to see recognition of the quality of care our patients receive as a result of the dedication of our physicians, nurses, and entire staff," said Dr. Daniel K. Podolsky, President of UT Southwestern, who 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.

The six specialties in which U.S. News ranked UT Southwestern nationally are Urology, Geriatrics, Diabetes & Endocrinology, Neurology & Neurosurgery, Nephrology, and Ear, Nose & Throat. In addition, the publication ranked UT Southwestern high-performing in the areas of cancer, gastroenterology and GI surgery, orthopedics, and pulmonology, as well as in the treatment areas of heart failure, colon cancer surgery, lung cancer surgery, and chronic obstructive pulmonary disease.

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The first phase involves construction of a nine-story, 305,000-square-foot academic and clinical building that will house faculty offices, outpatient clinics, and a state-of-the-art simulation center, all estimated to be completed this year. The simulation center will include four mock operation, ICU, emergency, and obstetrical rooms; 20 mock patient exam rooms; and six advanced technology team training rooms. Clinical areas of the building will include 220 exam rooms and procedure rooms for multiple specialties. An 805-space parking garage also will be added in this phase.
UT Southwestern’s community-based care initiative grows

UT Southwestern’s expansion into areas beyond the core Dallas campus continued this past year with a groundbreaking held in August for the Medical Center’s sixth planned clinic, in Frisco.

In a partnership with Texas Health Resources (THR), the overall $270 million construction project will bring an acute care hospital of THR and multispecialty clinic complex to Frisco, a rapidly growing part of Collin County. Clinical services will commence by the end of 2019.

The 120,000-square-foot UT Southwestern Medical Center at Frisco multispecialty clinic (illustration above) will include an extension of the Peter O’Donnell Jr. Brain Institute, providing neurology, spine surgery, and a state-of-the-art concussion rehabilitation facility. The Harold C. Simmons Comprehensive Cancer Center will offer programs in breast and colon cancer screening and treatment. Pediatric specialty services will include ophthalmology, otolaryngology, gastroenterology, and dermatology. Other services will include physical medicine, rehabilitation, and therapy.

At several of UT Southwestern’s existing community-based satellite locations, program adjustments took place in 2017 to better serve patients’ needs. The UT Southwestern Medical Center at Las Colinas was transformed into a multispecialty center complete with imaging and lab services; UT Southwestern Medical Center at Park Cities added internal medicine; and UT Southwestern Medical Center at Richardson/Plano added new providers for multiple specialties.

Two new satellite locations opened last year: The UT Southwestern Monty and Tex Moncrief Medical Center at Fort Worth and UT Southwestern Family Medicine at Texas Health Dallas.
Innovation, personal touch hallmarks of new Radiation Oncology building

In April 2017, patients began walking through the doors of the uniquely designed UT Southwestern William P. Clements Jr. University Hospital – Harold C. Simmons Comprehensive Cancer Center Radiation Oncology building.

With 63,000 square feet of space on three floors, it is the second largest radiation oncology facility in Texas, but its large glass windows, bright modern art, and textured walls make it feel more like a combination of Google headquarters and a soothing spa.

“This building was designed to focus on patients – their outcomes, their safety, their entire healing experience here,” explained Dr. Hak Choy, Chair of Radiation Oncology. “We wanted to build a colorful, cheerful space for our patients and I believe this is probably the most patient-centric center you will see. From the very beginning, we wanted to put together a facility that’s not only state of the art but also modern and patient-friendly in design,” Dr. Choy added. “We were determined that it be structured in such a way that it would enhance the delivery of quality care, create efficient patient management, promote collaboration among caregivers, and ensure high levels of safety.”

Inside the building’s walls are some of the most technologically advanced pieces of equipment for treating cancer, including the next-generation CyberKnife robotic radiosurgery system, which delivers radiation with micro precision to preserve surrounding tissue. UT Southwestern has more experience with the CyberKnife than any other center in Texas, and the new model – the M6 – uses robotics and computer technology to check its accuracy while it’s treating patients.

The building features other innovations to enhance patient care, such as a real-time location tracking system that alerts if patients have been waiting too long or when someone is ready for the next procedure. Each major disease site – such as brain, breast, or gastrointestinal cancer – has its own dedicated area.

“That framework is consistent with how the Radiation Oncology Department treats cancer,” said Dr. Choy, who holds The Nancy B. and Jake L. Hamon Distinguished Chair in Therapeutic Oncology Research. “Each physician specializes in the treatment of a particular cancer type, enabling individual specialists to bring familiarity and expertise to each patient encounter.”

“This building was designed to focus on patients – their outcomes, their safety, their entire healing experience here.”

– Dr. Hak Choy
Never give up. That pioneering, no-holds-barred mentality of UT Southwestern scientists and physicians inspired significant advances in science and medicine this past year, from delineation of a link between obesity and nonalcoholic fatty liver disease to deciphering the 3-D structure of an Ebola virus protein.
A national effort to understand acute liver failure – two decades and 3,000 study participants later

A multicenter study on acute liver failure initiated by UT Southwestern 20 years ago and funded by the National Institutes of Health (NIH) has increased understanding of this sometimes-fatal condition, leading in turn to improved, lifesaving patient care.

The Acute Liver Failure Study Group, now active at 12 sites in the U.S. and Canada, including UT Southwestern, has recruited more than 3,000 participants to date. Information gathered from those patients over the years has given physicians a clearer picture of what acute liver failure (ALF) looks like and how best to treat it. The study group’s principal investigator, Dr. William M. Lee, Professor of Internal Medicine at UT Southwestern and a world-renowned liver disease expert, began the research effort in 1997 with an NIH grant. Funding support has continued, and is committed through at least 2020.

“ALF is extremely rare, with only about 2,000 cases in the U.S. each year,” said Dr. Lee, who holds the Meredith Mosle Chair in Liver Disease in his honor. “Because of its rarity, many physicians aren’t that familiar with this rapidly progressive and fatal liver disease and may not recognize it quickly.”

In 2002 and 2009, Dr. Lee testified before FDA Advisory Committees examining whether the maximum daily dose of acetaminophen should be lowered and whether acetaminophen should be removed entirely from prescription opioid/acetaminophen combinations and over-the-counter mixtures. Those studies prompted the FDA in 2011 to ask pharmaceutical companies to reduce, within three years, the maximum dose for acetaminophen in prescription (opioid) drugs to 325 milligrams per tablet, down from the previously permitted 750 milligrams.

The FDA also directed drugmakers to add warnings about mixing acetaminophen with alcohol – which some studies have shown increases the risk of ALF – as well as clearer warnings about the possibility of liver damage.

A national effort to understand acute liver failure – two decades and 3,000 study participants later

UT Southwestern’s Dr. William M. Lee has led a multicenter study on acute liver failure since 1997.

Unraveling the mysteries behind America’s No. 1 cause of acute liver failure

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variants that increase the risk of nonalcoholic fatty liver disease, or NAFLD.

NAFLD is a growing problem associated with obesity. The National Institutes of Health estimates that 3 to 12 percent of adults in the U.S. have nonalcoholic steatohepatitis, the most serious form of NAFLD that can lead to chronic liver disease and liver cancer.

Of the three gene variants, or alleles, examined in the *Nature Genetics* study published last year, the strongest genetic-environmental interactions were found in the *PNPLA3* gene variant, the first genetic cause of NAFLD ever identified. That variant was identified in the Dallas Heart Study, a longitudinal, multiethnic, population-based study directed by Dr. Helen Hobbs.

Obesity amplifies genetic risk of nonalcoholic fatty liver disease

The combination of genetics and obesity can sometimes lead to serious, life-threatening health conditions for the unsuspecting. Now, an international study based at UT Southwestern has revealed a new wrinkle in this genetic-environmental correlation: Obesity significantly amplifies the effects of three gene variants that increase the risk of nonalcoholic fatty liver disease, or NAFLD.

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At a glance: Key findings of Study Group

Since 1997, the Acute Liver Failure Study Group has published 94 studies on acute liver failure. Among significant findings:

- A 2009 study determined that the antidote N-acetylcysteine (NAC) can effectively treat acute liver failure (ALF) caused by drugs other than acetaminophen, if given in time.
- A 2016 study showed that ALF patients whose conditions were caused by acetaminophen poisoning were more likely to die within 48 hours than those with other causes of liver failure.
- Another 2016 study found that ALF patients overall are now more likely to survive and less likely to require a liver transplant than in earlier years.

The impetus for the study began in 1993, when Dr. Lee noticed that more than half of the patients treated at Dallas’ Parkland Memorial Hospital for acute liver failure had excess quantities of acetaminophen. His findings were reported in *The New England Journal of Medicine* (NEJM) that year. A follow-up study, published in *NEJM* four years later, found that almost a third of the Parkland ALF patients had accidentally poisoned themselves, simply trying to relieve pain. And, Dr. Lee’s research found, those accidental overdose patients were more likely to die.

Thanks to the study group’s efforts, gains have been made in the diagnosis and treatment of all forms of acute liver failure. Currently, the study group is evaluating a test developed at the University of Arkansas that rapidly detects the toxic byproducts of acetaminophen poisoning to identify an overdose patient quickly. If the test proves to be effective, it could be available in two to three years, Dr. Lee said.

A new medication to treat all forms of ALF is also under study by the group. Working with the North Carolina biopharmaceutical company Ocera Therapeutics Inc., the group has tested the safety and tolerability of this potential drug to treat brain edema before symptoms progress. Brain edema, or swelling, is a complicating factor of hepatic encephalopathy—a decline in brain function that occurs as a result of liver disease. In this condition, the liver cannot adequately remove toxins from the blood, leading to potential brain damage.

The New England Journal of Medicine (NEJM) is a weekly medical journal that was first published in 1843. It is one of the most highly regarded medical journals in the world. The journal covers all aspects of medicine and includes peer-reviewed, original research articles, reviews, and scholarly discussions of contemporary issues in medicine.
The UT Southwestern team had previously studied how β-Klotho and the liver hormone fibroblast growth factor 21 (FGF21) binds to the β-Klotho-FGF21 receptor complex.

This study of genetic influences on brain function affecting drinking behavior reflects the promise of pharmacogenetics, a field of precision medicine involving how genes affect responses to drugs, said Dr. Mangelsdorf, also Professor of Biochemistry, a Howard Hughes Medical Institute Investigator, and holder of the Alfred G. Gilman Distinguished Chair in Pharmacology, and the Raymond and Ellen Willie Distinguished Chair in Molecular Neuropharmacology in Honor of Harold B. Crasilneck, Ph.D.

In the largest study of its kind, UT Southwestern Medical Center scientists collaborated with researchers in Europe to identify a gene variant that suppresses the desire to drink alcohol.

“Zeroing in on a gene that limits the desire to drink alcohol”

“In comparing the genetics of more than 105,000 light and heavy social drinkers, we identified a variation in the β-Klotho gene linked to reduced alcohol consumption,” said Dr. David Mangelsdorf, Chair of Pharmacology. “The variant was seen in approximately 40 percent of the people in this study.”

The study’s findings may aid the development of drugs to regulate alcohol intake. Uncontrolled drinking is linked to two heart disease risk factors in particular: high blood pressure and obesity, according to the American Heart Association. Dr. Mangelsdorf and his lab partner, Dr. Steven Kliewer, were corresponding authors of the Proceedings of the National Academy of Sciences study. Both are members of the National Academy of Sciences, the highest American honor for scientists.

“Excessive alcohol consumption is a major public health problem worldwide, causing more than 3 million deaths per year,” said Dr. Kliewer, a Professor of Molecular Biology and Pharmacology who holds the Diana K. and Richard C. Strauss Distinguished Chair in Developmental Biology.
Using 3-D weapons of science to fight infectious diseases

Pathogens responsible for some of the world’s most deadly infectious diseases are being studied at the atomic level to find their weak points by UT Southwestern researchers and other colleagues.

A study published in December 2015 found that FGF21 works via the brain’s reward pathway to reduce cravings for sugar and that FGF21 needed β-Klotho to function in that signaling pathway. The current study indicates that FGF21 requires β-Klotho in the signaling pathway that suppresses alcohol consumption, Dr. Mangelsdorf said.

In 2014, they reported that FGF21 acts on the brain to cause weight loss. They also published two studies in 2013 reporting on FGF21’s ability to regulate metabolism, circadian (body clock) behavior, and female reproduction.

“This is a hormone with some remarkable pharmacologic effects,” Dr. Mangelsdorf said.

Drug discovery begins with an understanding and analysis of a protein’s microscopic structure. In particular, determining the 3-D atomic structure of proteins helps scientists identify where a pathogen might be vulnerable to assault by drugs or vaccines.

So how is a 3-D structure made? A protein must be cloned, turned on as a gene, and crystallized. Then X-ray diffraction data – defining the location of each of the hundreds or even thousands of atoms to generate 3-D models of the structures – are collected to be analyzed with graphics software.

UT Southwestern’s contribution to these efforts as part of the Center for Structural Genomics of Infectious Diseases involves managing the salvage pathway, meaning scientists design custom methods for determining structures of molecules that resist standard approaches and for which the high potential for drug or vaccine development justifies applying advanced efforts.

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the Ebola nuclear protein (NP) to form a complex that protects Ebola’s genetic material from digestion by the host’s enzymes. The structure revealing the interactions between the VP35 fragment and the NP protein provided the first glimpse into the protein complex’s role in viral replication. That work was reported as a *Cell Reports* cover story in 2015.

The 3-D atomic structure is among the 1,000 deposited by the consortium into the Worldwide Protein Data Bank, a shared scientific archive supported by the National Institutes of Health.

UT Southwestern’s contribution to the Ebola project began with a request to the consortium for help in structural studies of the Ebola protein VP35. UTSW researchers conducted detailed structural studies of a VP35 protein fragment that interacts with the Ebola nuclear protein (NP) to form a complex that protects Ebola’s genetic material from digestion by the host’s enzymes. The structure revealing the interactions between the VP35 fragment and the NP protein provided the first glimpse into the protein complex’s role in viral replication. That work was reported as a *Cell Reports* cover story in 2015.

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Structures solved with help from the UT Southwestern team include proteins involved in the replication of the Ebola virus – a pathogen notorious for its ability to evade the body’s immune system.
OTD's mission is to protect and license a full spectrum of UTSW discoveries, ideas, and inventions. That includes medical devices – ranging from surgical instruments to new smartphone apps. Some of the most successful examples of discoveries that have passed through the OTD include the development of Citracal, a supplement used worldwide for the prevention of osteoporosis, and the most widely prescribed version of tissue plasminogen activator, an effective clot-busting drug for stroke victims.

Mr. Grassler wants to identify such failures earlier so that capital and energy can be preserved for other promising programs at UTSW. OTD staff use their expertise in drug discovery and in development and training in medicinal and synthetic chemistry to leverage relationships with pharmaceutical companies to reduce costs – and perceived risks in the preclinical phase.

By assisting UT Southwestern researchers with planning and negotiating; advising and reviewing discoveries in their nascent stages; helping to advance experiments and projects that lead to discoveries; and devising strategy for UTSW drug development, Mr. Grassler’s goal is to work with researchers to ensure that discoveries are better prepared for late preclinical and clinical development and that their valuations are increased.
About technology development

UT Southwestern Medical Center has been protecting and licensing intellectual property for more than 40 years. In 1998, the Office for Technology Development (OTD) was created to manage UT Southwestern’s technology transfer activities and to facilitate the formation of biomedical companies based on UT Southwestern-developed technologies. The Office is organized within four divisions:

- **Technology Commercialization**
  Manages and markets intellectual property developed by University investigators/inventors. Identifies companies best suited for commercial development of intellectual property.

- **Cooperative and Sponsored Research**
  Drafts, negotiates, and executes all nonroyalty bearing-legal agreements governing intellectual property transferred into or off of UT Southwestern’s campus.

- **Venture Development**
  Researches technologies suitable for entrepreneurial development and assists in developing startup companies based on those technologies.

- **Financial Management**
  Manages the Office for Technology Development’s financial portfolio.
Based on that finding, Dr. Patel's lab collaborated with Regulus Therapeutics to test an anti-microRNA-17 drug. The test drug slowed the growth of kidney cysts in two mouse models and in cell cultures of human kidney cysts.

The test drug slowed the growth of kidney cysts in two mouse models and in cell cultures of human kidney cysts.

Polycystic kidney disease is an incurable genetic disease that often leads to end-stage kidney failure. The name carries the weight of a potential early death sentence for those diagnosed.

Dr. Vishal Patel, Assistant Professor of Internal Medicine at UT Southwestern, hopes to one day change that grim prognosis.

Polycystic kidney disease is a fatal, incurable kidney disease being developed.

“Amping up the nucleotide sequence of every known microRNA, all that is required is to prepare an anti-miR with a sequence that is exactly the opposite of the miRs,” he said.

For those reasons, anti-microRNA compounds are a major focus right now in drug development.

UT Southwestern's foundational basic-science work, coupled with advanced clinical treatment, makes it the perfect testing ground for new lifesaving drugs such as the one Dr. Patel is testing.

Researchers in Dr. Patel's lab focused on microRNA cluster 17–92 following identification of potential miR targets. They found that genetically deleting microRNA-17–92 slowed cyst growth and more than doubled the life spans of some mice tested.

In 2009, Dr. Patel began searching for microRNAs that might underlie the progression of ADPKD. MicroRNAs – or miRs for short – are tiny RNA fragments that interfere with normal gene expression. Proof of their presence in humans was first reported in 2000. Those discoveries led to a groundswell of interest in developing drugs to treat diseases caused by microRNAs, Dr. Patel said, in part because the process can be straightforward once the problem-causing fragment is identified.

“Because miRs are so small, drugs can easily be designed against them. And since we know the nucleotide sequence of every known microRNA, all that is required is to prepare an anti-miR with a sequence that is exactly the opposite of the miRs,” he said.

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In concert with a California biotech firm, his research team is currently testing a potential drug to treat the disease. Preclinical animal testing has been completed and an investigational new drug application has been filed by San Diego-based Regulus Therapeutics Inc. Early stage human clinical trials began in December 2017, Dr. Patel said.

Affecting about 600,000 people in the U.S., autosomal dominant polycystic kidney disease (ADPKD) causes numerous fluid-filled cysts to form in the kidney. An affected kidney, normally the size of a human fist, sometimes grows as large as a football. As their numbers and sizes increase, these cysts eventually interfere with the kidney's ability to filter blood and remove bodily waste. About half of those affected with ADPKD suffer kidney failure by age 60, according to the National Kidney Foundation.

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Based on that finding, Dr. Patel's lab collaborated with Regulus Therapeutics to test an anti-microRNA-17 drug. The test drug slowed the growth of kidney cysts in two mouse models and in cell cultures of human kidney cysts.