accelerating the future of medicine
President’s Message 2

Connecting Brain Research to Better Care 4

At the Peter O’Donnell Jr. Brain Institute, UT Southwestern investigators and clinicians are pursuing better treatments, cures, and preventions for all types of brain and neurological disorders, using innovative tools and strategies such as gene editing and biomarker analysis.

Breaking New Ground in Research and Treatment 18

As a leader in biomedical discovery and patient care, UT Southwestern raised the bar this past year with efforts that included the opening of an advanced cryo-electron microscope facility, exploration of nanoparticle technology, and completion of the first lung-liver transplant in North Texas.

Preparing for the Next Generation of Medicine and Science 38

Evolution of the Medical Center, geared toward the future, includes growth through innovative clinical alliances, program and facility enhancements, and educational curriculum improvements.

Translating Genetic Data Into Personalized Medicine 52

Using genetic analysis, researchers at UT Southwestern are identifying more effective, individualized treatments and pinpointing biomarkers that can aid in disease diagnosis or prevention.

Building Upon Scientific Advances 62

The extraordinary, groundbreaking research of UT Southwestern scientists led to prestigious honors last year and receipt of a rare national grant to pursue more effective kidney cancer treatments.

2016 Annual Review 68

New Appointments and Major Gifts — 70
Financial Statement — 74
Gift Report — 78
Dear Friends,

With deep gratitude for your support, I am pleased to send you UT Southwestern Medical Center’s 2016 Annual Review. As you will see, UT Southwestern continues to flourish, and once again in 2015-16, our faculty have significantly contributed to accelerating the future of medicine through their path-breaking biomedical research; their exceptional patient care; and their dedicated and innovative approaches to medical education and training.

The cover of this year’s annual review highlights the brain, medicine’s ultimate frontier, to convey the priority we are placing on addressing the devastating toll of diseases of the brain through the Peter O’Donnell Jr. Brain Institute at UT Southwestern. Despite great progress in uncovering the underlying mechanisms of many diseases over the last several decades, modern medicine has just begun to understand the human brain, the body’s most complex system and medicine’s greatest mystery.

Brain disease in its various forms – whether developmental, traumatic, psychiatric, or degenerative – looms as one of the greatest challenges of our time. Despite the varying underlying causes and processes of brain injuries and disorders, the fundamental challenge is crosscutting – the need to identify the basic mechanisms of brain functions and the underlying causes of brain diseases, as well as the means to promote repair and functional recovery. UT Southwestern scientists and clinicians are committed to taking on this challenge, and as you will see in the articles that follow, they are actively using sophisticated techniques in gene editing, biomarker analysis, and other advanced technologies to better understand, treat, cure, and prevent a wide range of neurological and brain disorders.

Indeed, we are reaching new heights in scientific discovery and clinical care across many disciplines, bridging the gap between today’s medical challenges and tomorrow’s cures. UT Southwestern investigators are using pioneering technology, such as cryo-electron microscopy, DNA sequencing, and nanoparticle development, to solve puzzling scientific questions and achieve better treatments.

The opening in May 2016 of our new $17 million cryo-electron microscope facility represented a significant milestone in the use of advanced technology. With a unique collection of instruments, literally not found anywhere else in the world, our investigators can now view 3-D images of objects as tiny as an atom or an intact cell. This technology is expected to accelerate discoveries in basic research that answer fundamental scientific questions, as well as to contribute significantly to translational investigations that advance the development of drugs and other therapies to combat human disease.

Increasingly, medical care is shifting toward personalized, tailored treatments based on an individual’s genetics. UT Southwestern is active in this field as well, for example, using DNA sequencing to analyze a patient’s tumor sample to develop the best treatment in the context of the patient’s genetic vulnerabilities.

At the same time, our successful completion of the first combined lung-liver transplant in North Texas – an extremely rare and challenging procedure – is yet another example of UT Southwestern clinicians using innovative techniques to provide the most advanced care for patients with complex medical problems.

Since optimal medical care is increasingly a team effort, we were very pleased that the nursing program of UT Southwestern University Hospitals achieved Magnet status in July 2016, a designation that is recognized as the gold standard of nursing excellence.

To carry on UT Southwestern’s history of excellence in science and medicine, UT Southwestern faculty are dedicated to providing medical, graduate, and allied health profession students with the best education possible to fulfill their career goals and to prepare them to become leading scientists and clinical practitioners.

At the same time, we are expanding the Medical Center’s reach through new clinical programs and facility enhancements. This year we will see completion of the Radiation Oncology Building adjacent to the BioCenter on East Campus, and work is well underway on the education and clinical building that will be the first phase of the master plan for West Campus. We will also be opening an ambulatory care facility at the UT Southwestern Monty and Tex Moncrief Medical Center at Fort Worth.

To position UT Southwestern for success in the changing landscape of health care delivery and to provide the citizens of North Texas with expanded, comprehensive access to quality health care, we have created Southwestern Health Resources, a clinically integrated network involving UT Southwestern and Texas Health Resources that began operations in April 2016. The network leverages the strengths of UT Southwestern and Texas Health Resources, encompassing 31 hospitals, 300 clinics, and more than 2,600 physicians across a 16-county area.

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At UT Southwestern, Accelerating the Future of Medicine is an aspiration that reflects our commitment to excellence and innovation in education, research, and patient care – now and into the future. On behalf of the entire campus community, I thank you for your generous support and continued commitment to UT Southwestern’s mission and goals.

Sincerely,

Daniel K. Podolsky, M.D.
President, UT Southwestern Medical Center
Brain disease affects some 50 million people in the U.S., causing a ripple effect of devastation beyond the patient. UT Southwestern, home to premier scientists and physicians in the neurosciences, is taking on the enormous challenge of finding better treatments, cures, and preventions for all types of neurological disorders through the Peter O’Donnell Jr. Brain Institute. Through gene editing, biomarker analysis, and other advanced scientific techniques, the goal is to connect research to better care.
Brain disease in its various forms – whether traumatic, degenerative, psychiatric, or developmental – is estimated to affect some 50 million people in the U.S. On its current trajectory, the impact of brain disorders will only grow, causing a devastating social burden to patients and their families and a staggering economic burden that is approaching $1 trillion to our society.

With some of the best scientists and specialists in the nation, UT Southwestern's Peter O'Donnell Jr. Brain Institute is poised to make lifesaving medical and scientific advances to help those affected by brain disorders. Through research, UT Southwestern scientists are making fundamental neuroscience discoveries, and at the same time pioneering clinicians are translating research advances to patient care.

The O'Donnell Brain Institute's primary goal is to improve, extend, and save the lives of people affected by brain disorders and injuries. To accomplish this, researchers are seeking a basic understanding of how the nervous system functions in behavior and cognition, pursuing advances in brain imaging technology, and studying new therapies for treatment of neurological and brain diseases. By leveraging clinical expertise across multiple specialties, UT Southwestern aims to provide the nation's best and most comprehensive acute and restorative medical care.

Much is still unknown about how the brain works, with its vast complex of interconnected circuits encompassing 86 billion neurons. A comprehensive model of the human brain in health and disease remains incomplete, demonstrating the compelling need for research such as that done by faculty associated with the O'Donnell Brain Institute. Despite progress in some areas, a lack of cures for Alzheimer's, Parkinson's, Lou Gehrig's, and other neurological diseases drives scientists to focus on the challenging potential for making lifesaving discoveries.

What we do know is that the brain continually creates new connections and relies on the ability to network those connections to think and plan, to create new thoughts and retrieve old memories, and to heal from injuries.

"With so much still unknown about how the brain heals or becomes susceptible to injury and disease, the potential for lifesaving breakthroughs is significant. Our goal at the O'Donnell Brain Institute is to accelerate medical discoveries to improve the lives of everyone affected by brain diseases," 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.

Fueled by the generosity of Edith and Peter O'Donnell Jr., a growing number of philanthropic partners, and state and federal support, these advances will benefit for generations to come patients who are facing diseases or disorders including Alzheimer's disease, autism, brain tumors, epilepsy, muscular dystrophy, Parkinson's disease, depression, mental illness, headache and migraine pain, sleep disorders, spinal cord injury, stroke, and traumatic brain injury.

The O'Donnell Brain Institute, established in 2015 with a $36 million gift from the O'Donnell Foundation, is working to galvanize efforts of clinicians and scientists across specialties that include brain injury and repair, psychiatric disorders, neurology, neuroradiology, neurosurgery, biochemistry, bioinformatics, molecular genetics, and physical medicine and rehabilitation.

Some of the most exciting, breakthrough work is focused on understanding why certain brain regions are vulnerable to neurodegenerative diseases such as Alzheimer's and Parkinson's. Research in the Center for Alzheimer's and Neurodegenerative Diseases, led by founding...
In brain science, areas ripe for breakthroughs include neuromodulation, neurodegenerative therapies and neuroprotection, neuroimaging, neuroscience research, and regenerative medicine, according to Dr. Christopher Madden.

Director Dr. Marc Diamond, seeks to discover why tau proteins form certain shapes in the brain, contributing to these diseases. “We now know that completely different problems in the brain are caused by the way this protein self-assembles into different shapes,” said Dr. Diamond, who holds the Distinguished Chair in Basic Brain Injury and Repair and is also Professor of Neurology and Neurotherapeutics, and of Neuroscience.

Scientists in the Center have developed 18 different tau aggregates, or “strains,” that have predictable types of pathology. It is hoped that identifying aggregates specific to diseases in blood or spinal fluid might lead to the early detection of diseases before symptoms appear. In turn, this early warning could lead to potential preventive therapies. In addition, Dr. Diamond is co-inventor of the first anti-tau antibody therapy for dementia, which currently has advanced to human trials.

Other areas of high potential for scientific and medical breakthroughs at UT Southwestern involve neuromodulation, neurodegenerative therapies and neuroprotection, neuroimaging, neuroscience research, and regenerative medicine involving gene editing, said Dr. Christopher Madden, Associate Vice President and Clinical Director of the O’Donnell Brain Institute.

Neuromodulation therapies such as deep-brain stimulation, for example, are being used at UT Southwestern to treat patients with Parkinson’s disease, epilepsy, pain, and depression. These therapies show promise for targeted recovery in traumatic brain injury, stroke, and other neurodegenerative diseases.

“The brain is a vast complex of interconnected circuits where our intellect, memories, identities, and the seat of consciousness reside,” said Dr. Madden, who is also Professor of Neurological Surgery. “We must better understand the underlying pathophysiology of these diseases in order to develop appropriate courses of therapy, medications, and, eventually, cures.”

He believes that advances will be built upon the scientific rigor, interdisciplinary collaboration, and open innovation that have been the hallmarks of UT Southwestern’s culture and campus.

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Using novel gene-editing techniques, researchers in UT Southwestern’s Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center aim to one day find a cure for a devastating muscle disease that weakens the muscles and often leads to premature death.

The Center studies Duchenne muscular dystrophy, an inherited form of muscular dystrophy that is characterized by progressive muscle degeneration. It usually presents itself in boys ages 3 to 5 and often leads to death by the early 30s. The disorder is caused by a mutation in the gene dystrophin, or DMD, which creates the protein dystrophin that helps keep muscle cells intact.

Gene editing, a revolutionary, game-changing technology in biomedical research, enables researchers to edit parts of the genome by deleting or changing parts of the DNA sequence. A particular gene-editing technology called CRISPR/Cas9 developed in 2012 allows precision modification of the genome and has been explored as a potential means to correct disease-causing mutations.

In late 2015, the National Institutes of Health awarded UT Southwestern a $7.8 million grant to establish the Wellstone Center, one of six nationally. Wellstone Centers of Excellence work to translate scientific findings and technological developments into novel treatments for muscular dystrophy, and to promote basic, translational, and clinical research.

Dr. Eric Olson, Chairman of Molecular Biology and Director of the Hamon Center for Regenerative Science and Medicine, co-directs the Wellstone Center with Dr. Pradeep Mammen, Associate Professor of Internal Medicine and Medical Director of UT Southwestern’s Neuromuscular Cardio-myopathy Clinic.

“The NIH’s investment in the Wellstone Center team significantly enhances the speed with which this potentially life-changing approach can be translated into clinical application,” 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.

Wellstone Center researchers are currently working on two main projects: One seeks to correct muscular dystrophy in a mouse model of Duchenne muscular dystrophy using a gene-editing technique called Myoediting; the other project will use blood cells from Duchenne muscular dystrophy patients to create stem cells, called induced pluripotent stem cells (iPSCs), which can be used for Myoediting to delete the DMD mutation in the patient’s cells. The goal is to eventually take potential therapies developed from this gene-editing technique to human clinical trials.

“Our challenge is to translate this basic science discovery into an effective clinical therapy to improve the lives of patients with Duchenne muscular dystrophy,” Dr. Mammen said.

Foundational to this research, Dr. Olson’s team in 2014 used CRISPR/Cas9 gene-editing technology to correct the DMD mutation in the germ line of mdx mice, a mouse model of Duchenne muscular dystrophy, to prevent muscular dystrophy. Since germ line editing is not feasible in humans, approaches to deliver CRISPR/Cas9 components into mdx mice were explored. In 2016, the Olson team reported in Science that gene-editing components could be effectively delivered to the muscles of mice using a virus. This type of postnatal gene editing restored dystrophin expression to the muscle and heart and enhanced skeletal muscle function. This method provides an approach to correct mutations responsible for Duchenne muscular dystrophy and other disorders resulting from a single gene modification after birth.
Using a new gene-editing technique, a team of scientists at UT Southwestern Medical Center stopped progression of Duchenne muscular dystrophy (DMD) in young mice.

If efficiently and safely scaled up in DMD patients, this technique could lead to one of the first successful genome editing-based treatments for this fatal, muscle-wasting disease.

This work represented the first major finding of the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center at UT Southwestern, which was established in 2015 with $7.8 million in funding from the National Institutes of Health.

“UT Southwestern is the perfect environment for the Wellstone Center. We can merge cutting-edge science with clinical application,” said Dr. Olson, who holds the Robert A. Welch Distinguished Chair in Science, the Pogue Distinguished Chair in Research on Cardiac Birth Defects, and the Robert A. Welch Distinguished Chair in Science.

In 2014, Dr. Olson’s team first used this technique – called CRISPR/Cas9-mediated genome editing – to correct the mutation in the germ line of mice and prevent muscular dystrophy. This paved the way for novel genome editing-based therapeutics in DMD.

It also raised several challenges for clinical applications of gene editing. Since germ line editing is not feasible in humans, strategies would need to be developed to deliver gene-editing components to postnatal tissues.

To test the therapeutic potential of CRISPR/Cas9-mediated genome editing in vivo, researchers delivered gene-editing components to the mice via adeno-associated virus 9 (AAV9). DMD mice treated with this technique produced dystrophin protein and progressively showed improved structure and function of skeletal muscles and the heart.

The gene-editing approach permanently corrected the DMD mutation that causes the disease in young mice.

“Because it eliminates the cause of the disease, this gene-editing technique is different from other therapeutic approaches,” said Dr. Eric Olson, Chairman of Molecular Biology, Co-Director of the Wellstone Center, and Director of the Hamon Center for Regenerative Science and Medicine. In addition, Dr. Olson holds the Annie and Willie Nelson Professorship in Stem Cell Research, the Pogue Distinguished Chair in Research on cardiomyopathy.

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Approximately 20 clinicians and scientists from multiple disciplines at UT Southwestern are currently affiliated with the Wellstone Center, with plans to expand faculty participation. UT Southwestern’s clinical and research efforts in muscular dystrophy fall under the umbrella of the Peter O’Donnell Jr. Brain Institute.

Funding for the Wellstone Center totals $7.8 million over five years from the National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute, both institutions of the National Institutes of Health.

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UTSW-led Study Identifies Brain-based Biomarkers in Psychosis

In a groundbreaking study led by UT Southwestern Medical Center, a comprehensive set of empirical brain-based biomarkers has been established to aid in diagnosis and treatment of psychosis.

This study is among research taking place at UT Southwestern’s Peter O’Donnell Jr. Brain Institute, a comprehensive initiative dedicated to better understanding the basic molecular workings of the brain and applying these discoveries to the prevention and treatment of brain diseases and injuries.

Identification and study of biomarkers – measurable substances such as levels of a specific protein in the blood whose presence is indicative of a disease, infection, or environmental exposure – is a growing field of research that often can help diagnose, predict risk of, or even assist in developing targeted, more effective therapies for various conditions. Statistical modeling of clinical and biomarker data sets can facilitate redefinition and reconceptualization of complex human diseases.

In this case, the gold standard for diagnosis of psychosis to date has been clinical observation, classifying patients into schizophrenia, schizoaffective, and bipolar disorders. But in this study, the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) identified three neurobiologically distinct biotypes that do not always match up with the conventional clinical diagnosis.

An estimated 19 million Americans, or 6 percent of the U.S. population, experience schizophrenia, schizoaffective, or bipolar disorders.

“Building diagnoses based on biology, not just phenomenology, makes it possible for the biological bases of these brain disorders to stand out as molecular targets for disease definition and novel treatments,” said Dr. Carol Tamminga, Chair of Psychiatry at UT Southwestern, who leads the consortium.

The B-SNIP consortium, which includes researchers from five other institutions, published its findings in late 2015 in the American Journal of Psychiatry.

“In the end, we found the term ‘psychosis’ might actually describe a number of unique psychiatric disorders, just as the term ‘congestive heart failure’ might describe a range of cardiac, renal, and pulmonary disorders, each having distinctive mechanisms and treated with specific remedies,” said Dr. Elena Ivleva, Assistant Professor of Psychiatry and the study co-leader at UT Southwestern.

Considerable evidence has shown that a symptom-based diagnosis of psychotic illness incompletely captures biologically meaningful differentiations, often resulting in less-than-satisfactory treatments.

In the study, participants submitted to various cognitive, eye-tracking movement, and electroencephalography (EEG) tests as well as several modalities of magnetic resonance imaging (MRI). The group included individuals diagnosed with psychosis, their first-degree relatives, and a control group of participants. Analysis of the results of the biomarker battery in 1,872 of those tested demonstrated three distinct clusters, or biotypes, of psychoses. Participants were considered equally ill with psychosis, regardless of biotype, and each group’s phenomenology overlapped, Dr. Tamminga added.

“What’s puzzling and fascinating at the same time is that all three biologically driven Psychosis Types Identified by Brain-based Biomarkers

BIOTYPE 1
- Most-impaired group
- Most brain tissue damage of three biotypes
- Poor cognition and eye-tracking capabilities
- More likely to have schizophrenia (59 percent)
- Tendency toward severe psychotic symptoms

BIOTYPE 2
- Cognitive impairment and poor eye-tracking
- High brain wave response as measured by EEG
- Often rated as overstimulated, hyperactive, or hypersensitive
- Observable gray matter loss, but less than in Biotype 1
- Worse scores on mood scales, such as depression and mania

BIOTYPE 3
- Least-impaired biotype
- Near-normal evaluations of cognition, EEG function, and brain structure
- Symptoms of moderate severity
- More likely to have bipolar disorder (60 percent)

In the end, we found the term ‘psychosis’ might actually describe a number of unique psychiatric disorders, just as the term ‘congestive heart failure’ might describe a range of cardiac, renal, and pulmonary disorders, each having distinctive mechanisms and treated with specific remedies,” said Dr. Carol Tamminga, Chair of Psychiatry at UT Southwestern, who leads the consortium. “Building diagnoses based on biology, not just phenomenology, makes it possible for the biological bases of these brain disorders to stand out as molecular targets for disease definition and novel treatments.”

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Depression has been associated with both insomnia – lack of sleep – and hypersomnia – excessive sleepiness. Researchers in UT Southwestern’s Center for Depression Research and Clinical Care have identified two biological markers for hypersomnia. Exercise decreased the levels of the two biomarkers, resulting in a reduction in excessive sleepiness, the researchers found. "Hypersomnia, as well as insomnia, has been linked in the development, treatment, and recurrence of depression. Sleep disturbances are also some of the most persistent symptoms in depression. Identifying these biomarkers, combined with new understanding of the important role of exercise in improving several aspects of depression including cognition, self-efficacy, energy, and motivation, together with reducing hypersomnia, has major implication for the treatment of depression," said Dr. Madhukar Trivedi, Director of the Center, Chief of the Mood Disorders Division of Psychiatry, and holder of the Betty Jo Hay Distinguished Chair in Mental Health, and the Julie K. Hersh Chair for Depression Research and Clinical Care.

The biomarkers were identified based on blood samples from participants in the Treatment with Exercise Augmentation for Depression (TREAD) study, which examined the effects of exercise on depression. Four biomarkers were examined – brain-derived neurotrophic factor (BDNF), tumor necrosis factor alpha (TNF-α), IL-1β, and IL-6. Levels of these biomarkers were measured from blood samples collected before and after the 12-week exercise intervention.

Reductions in two biomarkers, BDNF and IL-1β, were found related to reductions in hypersomnia. Interestingly, these biomarkers were unique to hypersomnia and were not associated with changes in insomnia. Researchers did find that people with lower baseline levels of IL-1β had greater improvement in insomnia.

The findings, reported in Translational Psychiatry in late 2015, suggest distinct mechanisms are involved in insomnia versus hypersomnia, and that further research will be needed to identify the appropriate treatments to match these sleep-disturbance biomarkers.

A UT Southwestern study found three distinct brain-based biomarkers of psychosis.

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New Biomarkers Show Exercise Helps Reduce Daytime Sleep Disorder

Dr. Madhukar Trivedi (right) confers with one of the patients who took part in a recent study that identified biomarkers for hypersomnia, a condition associated with excessive daytime sleepiness.

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From research using nanoparticles and advanced cryo-electron microscopy to historic clinical achievements such as the first lung-liver transplant in North Texas, UT Southwestern continues to pursue and achieve breakthrough scientific discoveries and deliver revolutionary, lifesaving patient care.
The three advanced instruments and the building to house them received funding from an anonymous donor, UT Southwestern, the Cancer Prevention and Research Institute of Texas (CPRIT), the UT System’s Science and Technology Acquisition and Retention program, and the Howard Hughes Medical Institute (HHMI). Because minute temperature changes and sound vibrations from talking can disrupt the highly sensitive instruments, the microscopes are operated remotely and kept in a special climate- and humidity-controlled, vibration-protected building.

“This facility marks a milestone in the evolution of our structural biology research efforts at UT Southwestern. We are grateful to our supporters whose visionary generosity has helped us create this exceptional facility aimed at making fundamental basic discoveries that can be foundational for advances in medicine,” said Dr. Daniel K. Podolsky, President of UT Southwestern, who holds the Cryo-electron Microscope Center Zooms in on Life at Atomic Scale

In May, UT Southwestern Medical Center opened a new $17 million cryo-electron microscope (cryo-EM) facility housing a unique collection of instruments that researchers can use to view 3-D images of objects as tiny as an atom all the way up to intact cells.

“We are the only institution in the world with this configuration of instruments,” said Dr. Sandra Schmid, Chair of the Department of Cell Biology and holder of the Cecil H. Green Distinguished Chair in Cellular and Molecular Biology. “It establishes UT Southwestern as one of the world’s top facilities for cryo-EM structural biology.”

The facility’s three cutting-edge instruments – a Titan Krios, a Talos Arctica, and a Scios DualBeam for thin-slice cryo-electron tomography – provide the technologies to help accelerate UT Southwestern’s biomedical investigations on everything from cancer biology to drug discovery and run 24 hours a day, seven days a week. The instruments represent a significant advancement in the scientific field known as structural biology, and for work at UT Southwestern. By studying 3-D structures at atomic resolution, scientists can uncover new clues about the molecular machinery of cells and how molecules involved in diseases might be targeted with drugs.

These instruments analyze specimens that have been rapidly frozen to prevent the formation of damaging ice crystals. The specimens are then viewed in special holders under conditions that keep them at cryogenic temperatures (minus 321 degrees Fahrenheit).

How the Instruments Work

- The Scios DualBeam is a molecular sandblaster that precisely carves very thin slices of cells that can be transferred to and imaged in three dimensions on the Titan Krios.
- A robotic arm inside the Titan Krios transfers frozen samples from their storage containers into the microscope for viewing while maintaining a vacuum and cryogenic temperatures. The microscope, which is about 12½ feet tall and weighs 2 tons, can hold and precisely move 12 samples in an automated manner so that thousands of images can be recorded, processed via computers, and interpreted to generate 3-D images for study.
- The Talos Arctica is a fully automated but less powerful instrument that enables researchers to screen for optimal conditions before moving on to the Titan Krios.
- This imaging is facilitated by new high-tech cameras capable of directly recording electrons, unlike conventional cameras that must first convert the electrons’ energy to light, losing sensitivity in the process.

Team members in the cryo-electron microscope facility view 3-D images of objects obtained from the high-powered Titan Krios microscope (background).
The new facility is a joint effort of the Departments of Cell Biology and Biophysics. Dr. Schmid, Dr. Michael Rosen, Chair of Biophysics and an HHMI Investigator at UT Southwestern; and Dr. Daniela Nicastro, Associate Professor of Cell Biology and Biophysics and a CPRIT Scholar, spent four years planning and building the facility, which is a shared resource across the academic medical center. Scientists can schedule time on the microscopes and even view their images from remote locations via computer, enabling international collaborations.

"In addition to the unique configuration, we are using these instruments collaboratively to further research campuswide – from basic research to answer fundamental scientific questions to translational investigations in which those answers may result in potential treatments for human disease," said Dr. Rosen, who has additional appointments in Biochemistry and in the Cecil H. and Ida Green Comprehensive Center for Molecular, Computational, and Systems Biology, and who holds the Mar Nell and F. Andrew Bell Distinguished Chair in Biochemistry.

With funding from a CPRIT grant, Dr. Nicastro is studying mistakes in DNA repair that are thought to drive the development of cancer. "Before you can understand how a process goes wrong, you have to understand how it works," she explained. "And seeing is believing!"

Cryo-EM and EM tomography allow biological specimens to be viewed in a more lifelike state and environment than X-ray crystallography, the longtime gold standard of structural biology that requires assembling molecules into crystals. Many of biology's most intriguing molecules have proved notoriously resistant to crystallization, Dr. Schmid explained. Cryo-EM tomography is a more powerful cellular imaging technique to view and study how proteins interact, work, and are spatially arranged within cells – a technology that enhances our understanding of fundamental processes underlying cellular functions integral to the health of all living things.

Cryo-electron Microscopy

- The technology involves imaging specimens at cryogenic temperatures by electron microscopy.
- Benefits over X-ray crystallography include the ability to quickly create high-resolution models of molecules sometimes resistant to other approaches.
- The first reported use of this technology (published in 1975) related to the structure of bacteriorhodopsin.
- A key advance in the field in the 1980s and 1990s involved the use of liquid ethane to flash-freeze proteins in solution and hold them still.
- By 2012, electron microscopes evolved that could capture images of a molecule at dozens of frames per second.

The Mechanics of Cryo-EM

An electron beam is fired at a frozen protein solution. The transmitted electrons pass through electromagnetic lenses to create a magnified image on a detector, from which the structure of the protein can be worked out.

Standing more than 12 feet tall, the mammoth Titan Krios generates cryo-electron microscope images that can be used to reconstruct 3-D molecules with atomic resolution. To achieve this precision, the extraordinarily sensitive microscope is housed in a special vibration-isolated and climate-controlled area and is operated remotely from a computer control room via robotic controls for 24/7 high-throughput data collection.

The first reported use of this technology (published in 1975) related to the structure of bacteriorhodopsin. A key advance in the field in the 1980s and 1990s involved the use of liquid ethane to flash-freeze proteins in solution and hold them still.

By 2012, electron microscopes evolved that could capture images of a molecule at dozens of frames per second.
“For the first time, we have image data of these processes at a resolution that allows us to computationally model, for example, the signaling patterns that may confer drug resistance in cancer cells,” explained Dr. Danuser, whose Department was formed in 2015 with an extraordinary $25 million gift from Dallas entrepreneur and philanthropist Lyda Hill. Bioinformatics provides tools for analyzing extremely large sets of research data to address scientific and clinical challenges.

The 3-D imaging approach, detailed in *Developmental Cell*, enables researchers to study cells in controlled microenvironments at a level of detail that should accelerate the pace of discovery in many fields of biology, Dr. Danuser explained.

“It’s a two-photon, light-sheet microscope that allows 3-D time-lapse imaging of cells deep within physiologically realistic microenvironments,” said Dr. Reto Fiolka, Assistant Professor of Cell Biology at UT Southwestern and a corresponding author of the study, which was supported by grants from the Cancer Prevention and Research Institute of Texas (CPRIT) and the National Institutes of Health.

Using the new microscope and software, the researchers created 3-D images of the detailed shapes that skin and lung cancer cells develop as they move through tissue. They also created images and movies of the dynamic activation of a key signaling molecule (PI3-kinase) that is involved in many cellular processes.
Using Nanoparticles to Deliver Tumor-suppressing Therapy

UT Southwestern Medical Center chemists have successfully used synthetic nanoparticles to deliver tumor-suppressing therapies to diseased livers with cancer, an important hurdle scientists have been struggling to conquer.

Late-stage liver cancer is a major challenge for therapeutic intervention. Drugs that show promise in healthy, functioning livers can cause devastating toxicity in cirrhotic livers with cancer, the researchers explained.

UT Southwestern scientists crafted synthetic “dendrimer” nanoparticles that are able to provide the tumor-suppressing effect without further damaging the liver or neighboring tissue. The use of microscopic nanoparticles – which has surged since approval of the first nano-drug in 1995 – is an area of intense interest in drug development because of this exact ability to reduce toxic side effects of drugs.

“We have synthesized highly effective dendrimer carriers that can deliver drugs to tumor cells without adverse side effects, even when the cancerous liver is consumed by the disease,” said Dr. Daniel Siegwart, Assistant Professor of Biochemistry and with the Harold C. Simmons Comprehensive Cancer Center. “We found that efficacy required a combination of a small RNA drug that can suppress cancer growth and the nontoxic carrier, thereby solving a critical issue in treating aggressive liver cancer and providing a guide for future drug development.”

Primary liver cancer, a chronic consequence of liver disease, is a leading cause of cancer death and a major global health problem. Each year in the United States, about 20,000 men and 8,000 women get liver cancer, and the 5-year survival rate is only 17 percent, according to the Centers for Disease Control and Prevention. The percentage of Americans who get liver cancer has been rising slowly for several decades, with higher rates in Asians and in Hispanic and African-American men.
An experimental nanoparticle therapy that combines low-density lipoproteins (LDL) and fish oil preferentially kills primary liver cancer cells without harming healthy cells, UT Southwestern Medical Center researchers have found.

"This approach offers a potentially new and safe way of treating liver cancer, and possibly other cancers," said Dr. Ian Corbin, Assistant Professor in the Advanced Imaging Research Center and of Internal Medicine at UT Southwestern. “The method utilizes the cholesterol carrier LDL combined with fish oil to produce a unique nanoparticle that is selectively toxic to cancer cells."

Primary liver cancer, or hepatocellular carcinoma, is the sixth most prevalent type of cancer and the third-leading cause of cancer-related deaths worldwide, according to the National Cancer Institute.

Fish oils are particularly rich in omega-3 fatty acids such as docosahexaenoic acid, also known as DHA. Although several studies have reported an association between cancer prevention and omega-3 fatty acids, the link is not fully understood. The study, conducted in genetic mouse models with a highly aggressive form of liver cancer, demonstrated that the miRNA nanoparticles inhibited tumor growth and dramatically extended survival. The results were published in the journal Proceedings of the National Academy of Sciences.

To further this research, the Siegwart lab team is working to develop an array of siRNA-, miRNA-, mRNA-, and CRISPR-based strategies to manipulate gene expression in tumors and develop the next generation of cancer therapies. In collaboration with Dr. Zhu; Dr. Adam Yopp, Assistant Professor of Surgery; and Dr. Amit Singal, Associate Professor of Internal Medicine and Clinical Sciences and a Dedman Family Scholar in Clinical Care, the Siegwart lab is using RNA-loaded dendrimer nanoparticles to treat mice harboring human patient-derived xenograft (PDX) tumors, with the ultimate goal to provide patient-centered treatment guidance. This dendrimer technology has generated commercial interest and is currently in preclinical development for treatment of lung and liver cancer.

Critical to understanding this problem and developing the new therapy was a close collaboration between Dr. Siegwart and Dr. Hao Zhu, Assistant Professor at the Children's Medical Center Research Institute at UT Southwestern and a practicing oncologist.

"Early-stage disease can be cured with surgery, but there are few options for cirrhotic patients with advanced liver cancers," said Dr. Zhu, also Assistant Professor of Internal Medicine and Pediatrics at UT Southwestern.

The failure of five phase III human clinical trials of small-molecule drugs to treat hepatocellular carcinoma – the most common form of liver cancer – prompted the researchers to develop nontoxic carriers and explore "miRNA" therapies as a promising alternative. MicroRNAs (miRNAs) are short nucleic acids that can function as natural tumor suppressors, but they require delivery strategies to transport these large, anionic drugs into cells. Previously, no existing carrier had been able to provide effective delivery to late-stage liver cancer without amplified toxicity, which negates the desired effect.

To address this problem, UTSW scientists chemically synthesized more than 1,500 different types of nanoparticles, which allowed discovery of lead compounds that could function in the heavily compromised cancerous liver. Synthetic, man-made nanoscale compounds called dendrimers provided an opportunity to screen different combinations of chemical groups, physical properties, and molecular size, Dr. Siegwart said. This approach led to the identification of dendrimers to deliver miRNA to late-stage liver tumors with low liver toxicity.

The study, conducted in genetic mouse models with a highly aggressive form of liver cancer, demonstrated that the miRNA nanoparticles inhibited tumor growth and dramatically extended survival. The results were published in the journal Proceedings of the National Academy of Sciences.

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Researchers synthesized a microRNA nanoparticle that successfully penetrated late-stage liver tumors to deliver drug therapy without toxic side effects.

UTSW scientists chemically synthesized more than 1,500 different types of nanoparticles, which allowed discovery of lead compounds that could function in the heavily compromised cancerous liver.

The illustration below depicts the molecular structure of the LDL-DHA nanoparticle used by UTSW researchers that effectively killed primary liver cancer cells. A key ingredient of the experimental therapy is fish oil.
is not as clear-cut in relation to established
tumors, Dr. Corbin said.

In this study, conducted in rats, the
newly formulated LDL-DHA nanoparticles
were injected into the artery leading to the
liver, the site of the cancer, he said.

“This research study clearly demonstrates
the anticancer potential of omega-3 fatty
acids,” he said, adding that while the study
showed significant cancer cell toxicity, it is
too soon to tell whether the approach is able
to kill every cancer cell. Future experiments
will examine that question, as well as whether
the LDL-DHA strategy improves long-term
cancer survival, he added.

Dr. Corbin, a member of the Harold C.
Simmons Comprehensive Cancer Center, led
a multidisciplinary team spanning the fields
of lipid biochemistry, cancer biology, nutri-
tional science, biotechnology, and advanced
imaging to create and characterize the novel
nanoparticle formulation.

Nanoparticles: A New Frontier in Medicine

Devices ranging in size from 1 to 100 nanome-
ters – smaller than a human cell – hold the
promise of one day traveling through
the bloodstream to attack cancer cells
at their very start.

In 1981, the scanning
tunneling microscope
was invented at IBM’s
tab in Zurich, Switzer-
land, allowing scientists to create spatial images of individual atoms for
the first time.

In 1985, researchers in
Texas discovered the
Buckminsterfullerene,
or buckyball, a carbon
molecule that looks like a microscopic
soccer ball with a latticed exterior.
These and similar molecules are now
being looked at as tiny containers to
carry cancer-killing drugs.

In 1995, Doxil (doxorubicin
hydrochloride liposome injection)
became the first
FDA-approved nanodrug, designed to
treat AIDS-related Kaposi sarcoma.

In 2004, the National
Cancer Institute
established the
Alliance for Nanotech-
ology in Cancer program to develop nanotechnology for the diagnosis,
treatment, and prevention of cancer.

In 2012, initial results
were announced from
the first clinical trial to
test a nanoparticle
capable of delivering a drug directly to
a tumor. Preliminary phase 2 results
were presented in 2014.

Approximately 30 to
40 clinical trials are
now underway using
nanotechnology to

treat cancer. They include everything
from a nanoscale liposome designed to
carry a precise drug mixture to
acute myeloid leukemia tumors to
an antibody that targets and delivers
chemotherapy to HER2-positive
metastatic breast cancers.

Sources: The National Cancer Institute’s Alliance for Nanotechnology, PubMed, the Department of Energy, and Drugs.com.

Patients Take Flight
to Further Science on
Zero-gravity Effects

Four cancer patients experienced a thrilling ride of a lifetime last year – a ride with a purpose
to further research into how zero-gravity
conditions in space affect the health of astronauts.

UT Southwestern Medical Center
researchers, in conjunction with NASA,
took the patients on a zero-gravity ride into
the upper atmosphere to study why similar
conditions on the International Space Station
sometimes affect the vision of astronauts
staying there for extended periods.

The research was led by Dr. Benjamin
Levine, Director of the Institute for
Exercise and Environmental Medicine (IEEM)
at Texas Health Presbyterian Hospital Dallas,
a partnership between UT Southwestern and
Texas Health Resources. The Institute studies
human physiology in health and disease,
especially physiology under extreme conditions.

Dr. Levine is known internationally for his
research on how unusual conditions such as
space, high altitudes, and intense exercise
affect the health of astronauts, Olympic ath-
letes, long-distance swimmers, and others.

Dr. Levine set out to test NASA’s hypotho-
thesis that long-term increased pressure in the
brain caused by the zero-gravity environment
leads to the vision deterioration experienced
by astronauts. Earlier results from 2015 in
four men showed that while intracranial pressure
rose during the periods of zero gravity, it
did not rise as much as it did when the
four participants were placed in a flat,
sleeping position.

“It cannot be that this eye problem is
due to a pathologically elevated pressure
in the brain because it’s not higher than it
is when you are lying down sleeping every
night,” said Dr. Levine, also a Professor of
Internal Medicine at UT Southwestern and
holder of the Distinguished Professorship in
Exercise Sciences. “On Earth, we are upright
for most of the day. In space, you can’t ‘stand
up’ in zero gravity. And so, it may be that

(Top) “If we can gain some insight into why the astronauts’ eyesight is affected,
let’s do this.” – research participant Trent Barton
(Bottom) “Your stomach doesn’t really know what it’s doing or where it’s going.”
– research participant Wendy Schnaars
even a mildly elevated intracranial pressure, without the daily lowering of the pressure by being upright, is what’s causing that adaptive change in the back of the eye.”

The study enlisted the help of volunteer cancer patients who had permanent ports for delivery of chemotherapy, which provided a unique opportunity for researchers to take readings on pressure changes within the brain.

"I harkened back to my residency days working with leukemia patients and remembered that some patients have these ports – they’re called Ommaya reservoirs – placed to deliver chemotherapy to cancer microcells in the brain,” Dr. Levine said. “I scoured the country to find these patients.”

Dr. Benjamin Levine is internationally known for his research on how unusual conditions such as space, high altitudes, and intense exercise affect the health of astronauts, Olympic athletes, long-distance swimmers, and others.

For the study, three women and one man experienced the thrill of weightlessness as a NASA C-9 plane climbed to 34,000 feet, then swooped down to 26,000 feet above the Gulf of Mexico. Forty times the plane climbed and then dropped, creating 40 intervals of weightlessness and recordings to match. Volunteers underwent pretesting to ensure the flight would be safe for their vision and would not negatively affect their health.

Dr. Louis “Tony” Whitworth, Professor of Neurological Surgery and Radiation Oncology at UT Southwestern, was the neurosurgeon in charge of accessing the patients’ ports.

“All of the participants did just fine. We had no problems, so I got to enjoy the weightlessness. I’m a bit of an adrenalin junkie, so it was pure fun,” said Dr. Whitworth, who accompanied the patients on their flights.

Growing up in Orlando, Fla., Trent Barton, one of the study participants, witnessed space shuttle launches at nearby Cape Canaveral. “I saw every last one. Many times we watched them live at the space center. Other times we could walk out the back door and watch. You just had to know which direction to look.”

Although watching so many space shuttle launches piqued Mr. Barton’s interest in spaceflight, it was his experience as a cancer patient that caused him to volunteer to participate in the research. “When I had cancer, so many people donated to me and my family. That was the hand of God giving to us,” said Mr. Barton, who now lives in Dallas. “This is my opportunity to give back.”

The National Space Biomedical Research Institute (NSBRI) funded the research. NSBRI leads a national program to mitigate the health risks related to human spaceflight and applies associated discoveries to improve life on Earth.

As an outgrowth of this work, researchers are now studying how to apply this knowledge to patients with traumatic brain injury in the ICU. A research team that includes Drs. Levine and Whitworth; Dr. Bert Vargas, Associate Professor of Neurology and Neurotherapeutics; and Dr. Justin Lawley, Instructor in Internal Medicine, received a grant from UTSW’s Texas Institute for Brain Injury and Repair to pursue this research.

"UT Southwestern wants to be – and continues to be – at the forefront of complicated surgeries such as this,” said Dr. Fernando Torres, Professor of Internal Medicine and Medical Director of Lung Transplantation at UT Southwestern. "Given our expertise in transplantation, we are able to help patients with difficult situations like this that other centers might not accept.”

The first dual lung and liver transplant was performed in 1994, and until this surgery, only 74 combined lung and liver transplants had been completed in the U.S., based on the latest available data from United Network for Organ Sharing (UNOS), the nonprofit organization that manages the nation’s transplants. UT Southwestern, one of the leading medical centers in the country in...
liver transplant, has performed more than 60 lung transplants each year for the last four years, and more than 500 lung transplants overall, ranking the Medical Center in the top 10 among all the centers in the country that are currently performing lung transplants, according to UNOS.

Orchestration of the 12-hour, dual-team surgery on Jan. 13, 2016, involved more than a dozen physicians and other team members – one team to remove and replace the lungs, and a second to remove and replace the liver.

Time also was a critical factor – as it is for all transplants – because there’s a need to minimize the amount of time between organ removal and organ transplant, and minimize the amount of time the new organs are outside the body. For that reason, the team of experts decided to remove one lung and complete that transplant operation before removing the second lung. That way, the team would avoid having to put Mr. Ferrell on a heart-lung bypass machine.

“The lungs were implanted without much of the difficulty we had anticipated and planned for, and the transition from lung to liver transplant was seamless,” said Dr. Michael Wait, Professor of Cardiovascular and Thoracic Surgery at UT Southwestern, who performed the lung transplant.

Dr. Wait is also Chief of the Cardiovascular and Thoracic Surgery Service at Clements University Hospital.

Fellow transplant surgeon Dr. Malcolm MacConmara, Assistant Professor of Surgery, who performed the liver transplant, was equally pleased by the success of the liver teams.

“The surgery had to be carefully planned and coordinated. You have two different surgical teams – the thoracic team putting in the lungs and the abdominal team putting in the liver – and it all has to be carefully thought out in advance,” said Dr. MacConmara, who is dually trained in transplant surgery and immunology.

While lung disease is present in more than 95 percent of patients with cystic fibrosis, liver disease affects only about 25 percent of CF patients, and liver cirrhosis occurs in only about 8 percent, according to Dr. Raksha Jain, Assistant Professor of Internal Medicine and Medical Director of the Adult Cystic Fibrosis Program at UT Southwestern.

Dr. Jain, a Dedman Family Scholar in Clinical Care, has been part of Mr. Ferrell’s care team since he first came to UT Southwestern in 2013.

Despite doing everything his UT Southwestern physicians asked of him, Mr. Ferrell’s lungs and liver were failing and needed to be replaced. On the evening of Jan. 12, 2016, Mr. Ferrell got a call that a donor for both organs had been found.

The surgery began at 7:51 a.m. the next day at Clements University Hospital. The first team successfully removed one lung, replaced it, took out the second lung, and replaced it. Then the liver transplant surgery team stepped up, using a piggyback technique that leaves in place an important vein that returns blood from the abdominal organs to the heart, which helped keep Mr. Ferrell stable. The liver team completed its transplant at 6:35 p.m. and the thoracic team closed his chest at 7:55 p.m. Mr. Ferrell was discharged from the hospital on Feb. 5, stayed in the Dallas area for close monitoring over the next two months, then returned home in April 2016.

For the first time in two years, Mr. Ferrell is now able to walk outside without use of an oxygen tank and to breathe in fresh outdoor air.

“I feel pretty good now. I have more energy,” Mr. Ferrell said. “I’m interested in studying computer programming or engineering, and I’d like to visit Japan someday. I’d like to see the cherry blossoms. The cherry trees bloom for one week.”
In early 2016, UT Southwestern Medical Center surgeons performed the first lung transplant in Texas using donated lungs treated with a technology known as ex-vivo lung perfusion (EVLP).

EVLP allows physicians to evaluate and recondition lungs, making lungs that would have been unsuitable for transplantation potentially viable. UT Southwestern is one of 16 medical centers across the country – and the only one in Texas – participating in a national clinical trial of the technology.

“Currently, more than 70 percent of potential donor lungs are deemed unusable,” said Dr. Fernando Torres, Professor of Internal Medicine and Medical Director of Lung Transplantation at UT Southwestern. “EVLP technology is an assessment tool that allows us to evaluate organs that are marginal over an extended period of time.”

In 2015, 2,057 lung transplants were performed in the U.S., but more than 200 people died while awaiting a lung transplant, including 22 Texans, according to data from the United Network for Organ Sharing (UNOS), the nonprofit organization that manages the nation’s organ transplant system. EVLP is expected to increase the number of lungs available for transplant by 10 to 15 percent.

“Some of the lungs we see are clearly not usable because of infections, bad contusions, and so on, but with others, it’s simply not clear,” said Dr. Pietro Bajona, Assistant Professor of Cardiovascular and Thoracic Surgery and Director of the EVLP Program. “We can put the questionable lungs in the machine, ventilate them, perfuse them with a special solution, and then after a few hours test them.”

In April 2016, marking a historic milestone in UT Southwestern’s lung transplant program, former Oklahoma school superintendent John Herzig became the first patient in Texas to be transplanted with lungs that were evaluated with EVLP technology. His health had been deteriorating due to pulmonary fibrosis, a scarring of the lungs that leads to severe breathing problems.

Following the donation of a potentially viable set of lungs, Dr. Bajona tested the lungs in an ex-vivo device. After about three hours, the team of physicians determined the lungs were usable, and Dr. Matthias Peltz, Surgical Director of Cardiac Transplantation and Mechanical Circulatory Support and Associate Professor of Cardiovascular and Thoracic Surgery, led the surgical team that performed the transplant.

“I’m so grateful to the family who agreed to donate these lungs,” Mr. Herzig said, “and thankful for the new technology that helped make them available, so now I’ll have that opportunity to play with my grandson and watch him grow.”
preparing for the next generation of medicine and science

So much has changed since UT Southwestern opened more than 70 years ago as a small medical college. Today, it is a vibrant, expansive campus laser-focused on medical care, research, and education. That evolution continues, including growth through innovative alliances, program and facility enhancements, and educational curriculum improvements—all aimed at meeting health care needs of the future.
Southwestern Health Resources Unfolds, Expanding UTSW’s Reach and Capabilities

Southwestern Health Resources – the clinically integrated health care network formed by UT Southwestern and Texas Health Resources in December 2015 – continued to develop and grow in 2016 with the announcement of its executive leadership and expansion of its affiliated physicians network.

The network was created to broaden and simplify North Texans’ access to leading medical care by blending the strengths of two of the state’s largest health care providers. The breadth of Southwestern Health includes 31 hospitals and 300 clinics throughout North Texas, as well as an expansive network of over 2,000 physicians who can offer the full range of expertise in primary and specialty care across a 16-county area with more than 6 million residents. The scale of the network creates opportunities for patients to receive care that is both cost-effective and of the highest quality.

With a broader scope of clinical and research facilities, the network also is providing new educational opportunities for students and residents, as well as important opportunities to expand clinical research efforts.

Dr. Daniel K. Podolsky, President of UT Southwestern, and Barclay Berdan, Chief Executive Officer of Texas Health, co-chair the network’s Board of Directors. In 2016, five senior executives were appointed to oversee Southwestern Health’s joint clinical operations, joint physician network, population health services company, and market relations.

“[T]hese five executives bring dynamic leadership to address the needs of patients and support the efforts of physicians and other caregivers throughout the network. They also possess the essential expertise to effectively manage large hospitals, physician groups, and clinical programs needed to successfully achieve the clinical, research, and educational as well as financial goals of this collaboration,” said Dr. Podolsky, 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.

Dr. John Warner
Dr. Warner, Vice President and CEO of University Hospitals, and Professor of Internal Medicine, is Senior Executive Officer of the joint operating company that oversees the network’s three major hospitals: UT Southwestern’s William P. Clements Jr. University Hospital and Zale Lipshy University Hospital, and Texas Health Resources’ Texas Health Presbyterian Hospital of Dallas. Dr. Warner holds the Jim and Norma Smith Distinguished Chair for Interventional Cardiology, and the Audre and Bernard Rapoport Chair in Cardiovascular Research.

Dr. Bruce Meyer
Dr. Meyer, Executive Vice President for Health System Affairs and Professor of Obstetrics and Gynecology, is the Senior Executive Officer of Southwestern Health’s Population Health Services Company, which will provide data about outcomes and costs of care, as well as coordination and transitions of care, while ensuring the Southwestern Health physician and hospital networks have the tools needed to achieve clinical integration and manage network performance. Dr. Meyer holds the T.C. Lupton Family Professorship in Patient Care, in Honor of Dr. John Dowling McConnell and Dr. David Andrew Pistenmaa.

Dr. Mack Mitchell
Dr. Mitchell, Vice President for Medical Affairs and Professor of Internal Medicine, is the Chief Medical Officer of the physician network, working alongside Dr. Varga.

Marinan R. Williams
Ms. Williams, Senior Executive Officer, Market Relations, is responsible for developing strategic relationships with employers, employee benefits consultants, and government agencies, and for managing contractual relationships with payers and purchasers of health care contracts. She previously worked as Chief Operating Officer for Scott & White Health Plan.
Officially launched in April 2016, the integrated network benefits both consumers and caregivers without changing the relationships patients have with their physicians. With the combined resources of the network, patients experience better coordinated care and increased access to specialty services and clinical trials. Patients, physicians, employers, and insurers benefit from the network’s efficiencies and quality initiatives, and from the resulting improved outcomes and reduced redundancies.

“The network will foster expanded collaboration between physicians and care teams across the entire region, bolstered by the critical infrastructure needed to share best practices and cutting-edge innovation,” Dr. Podolsky said.

Formation of the network does not alter UT Southwestern’s or Texas Health’s existing relationships, including UT Southwestern’s relationships with Parkland Memorial Hospital, Children’s Medical Center Dallas, and Dallas Veterans Affairs Medical Center. But the network does enable the two organizations to thrive in the changing landscape of health care delivery, to adapt more readily, and to respond appropriately to patients’ needs and expectations.

Recruitment of physicians into the network – the backbone of the collaboration – has been significant and includes UT Southwestern faculty, community-based physicians in the UT Southwestern Clinically Affiliated Physicians (UTSCAP) program, primary care physicians throughout North Texas, and physicians employed by Texas Health.

“Patients will benefit from access to care from a comprehensive and coordinated network of physicians encompassing all specialties and other caregivers, all working together to improve outcomes and manage costs more effectively,” Dr. Podolsky said.

UTSW Elevates Nursing Program and University Hospitals With Magnet Achievement

The hundreds of nurses who support UT Southwestern’s hospitals and clinics as front-line providers and stewards of exceptional patient care celebrated a significant milestone last year with the Medical Center’s achievement of Magnet designation, recognized as the gold standard of nursing excellence.

Only 7 percent of hospitals nationally receive this designation, the highest honor awarded by the American Nurses Credentialing Center (ANCC).

Magnet designation signifies that an organization’s nurses provide excellent, evidence-based patient care, advance their practice through research and professional development, and are recognized and respected by their colleagues for the important role they play on the patient care team. The achievement advances UT Southwestern’s commitment to providing outstanding patient care, and to arming nurses with the best tools, research, and educational opportunities to serve patients now and in the future.

By coming to a Magnet hospital, patients can expect to receive a higher level of nursing care and to experience shorter lengths of stay, increased satisfaction, and reduced risk of falls, medication errors, and post-procedure complications.

“Magnet status assures patients that they are choosing an institution that provides exceptional nursing care – it reflects the extraordinary dedication and professionalism of our nursing colleagues to the care of our patients,” 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 B. and Bryan Wildenthal Distinguished Chair in Medical Science.

The Magnet designation strengthens UT Southwestern’s ability to attract and retain the most talented nurses to care for patients. One aspect of the achievement entails having nurses incorporate research and evidence-based care into their practice, which leads to patients receiving the most up-to-date care and furthers the Medical Center’s research mission. For example, one research project on post-chemotherapy patients by Linda Chan, BSN, RN, OCN, examined the effects of extended home care precaution.

UTSouthwestern's nursing program achieved Magnet designation in July, considered the gold standard of nursing excellence.
Nurses gathered at William P. Clements Jr. University Hospital on July 20, 2016, for a "special announcement" – a prearranged call notifying UT Southwestern whether it would receive Magnet designation.

Education. The study’s outcomes have been modeled nationally as a best practice.

"This organization has worked so hard to get to this point," said Victoria England, Director of Nursing Excellence/Magnet at UT Southwestern. "We literally went from zero nurse-led research projects to 43 in less than five years."

UT Southwestern is already thinking of the future, having made a commitment to helping nurses achieve advanced degrees. By 2020, the goal is for 80 percent of UTSW’s bedside nurses to have a Bachelor of Science in Nursing (BSN) degree or higher. Today, 70 percent of UT Southwestern nurses have a BSN and 234 nurses have advanced practice certifications or degrees.

News of the Magnet designation came on July 20, 2016, when UT Southwestern nurses gathered at William P. Clements Jr. University Hospital for a "special announcement" – a prearranged call notifying UT Southwestern whether it would receive Magnet designation.

Executives in attendance included Vice President and CEO of University Hospitals Dr. John Warner, Chief Nurse Executive Susan Hernandez, and Ms. England.

During the call, Dr. Donna Havens, Chair of the Commission on Magnet Recognition, noted that UT Southwestern had achieved an impressive five "Exemplars" of processes worthy of being emulated by others on the journey to excellence.

Afterward, Ms. Hernandez addressed the crowd. "Thank you to everybody we have worked with on this journey," she said. "This is you. This is your work. We did it together as a team. And what it shows is this journey is not about an individual. Because if it were, we couldn’t have pulled it off. Think back to everything you’ve done, and don’t let it stop. Keep going, and celebrate your work."

Ms. Hernandez then called on Dr. Warner, who holds the Jim and Norma Smith Distinguished Chair for Interventional Cardiology, and the Audre and Bernard Rapoport Chair in Cardiovascular Research.

"I am proud of our nursing colleagues who led this effort, and of the thousands of others across our organization – doctors and staff at every level and in every discipline – whose teamwork and commitment resulted in our earning Magnet designation," Dr. Warner said. "This is an exciting achievement for UT Southwestern University Hospitals, and is especially meaningful for our patients. The enriched nursing practice environment of Magnet organizations has been shown to drive the delivery of high-quality care, and our new Magnet status underscores our own commitment to providing our patients and their families with truly exceptional care."

The announcement led to celebrations across campus – at Clements University Hospital, Zale Lipshy University Hospital, the Harold C. Simmons Comprehensive Cancer Center, Professional Office Building 2, and elsewhere. Members of patient care teams and administrators at Clements University Hospital cheered, blew noisemakers, and bounced beach balls in jubilation.

"This is an exciting achievement for UT Southwestern University Hospitals. … Our new Magnet status underscores our own commitment to providing our patients and their families with truly exceptional care." – Dr. John Warner

After the event, Ms. Hernandez said, "Receiving the Magnet designation is a tremendous honor, but our journey doesn’t end today. It continues every day, as we strive to keep raising the bar for a higher standard of excellence in patient care."

Nurses joined in celebrations across campus when official word came that Magnet status had been awarded.
For the pioneering UT Southwestern Medical School Class of 2019, exposure to the real world of medicine has begun. With the first phase of the new integrated curriculum completed, many students are starting their clerkship periods now – six months earlier than any preceding class.

The earlier clerkship period that began in January enables second-year students to explore more clinical fields to assist in selecting their specialties. Meanwhile, a new group of first-year students is now heavily immersed in studies under the revised curriculum, which is currently in its second year.

Katherine Pouns and Reed Macy, co-Presidents of the Class of 2019, said they were looking forward to their clerkships and recognized their important roles as members of the curriculum’s first test class of 239 students. They reflected on their experience with the shortened preclerkship period and the integrated classes.

The first semester – heavy on core science classes (Basic Science Foundation) as well as labs – included biochemistry, anatomy, and histology. Bookwork and labs soon gave way to systemic instruction.

“The second semester marked the beginning of our Integrated Medicine curriculum,” Ms. Pouns said. “Instead of having a separate first-year physiology block and pathology organ blocks in the second year, we began the system/organ blocks the second semester of year one.”

Each Integrated Medicine block, Ms. Pouns said, incorporated quizzes, team-based learning (TBL) instruction, simulation sessions, and gross pathology sessions that provided different ways to learn the material.

TBL instruction is a structured form of small-group learning that emphasizes student preparation outside of class and application of knowledge in class. Students are organized into diverse teams of six students who work together throughout the course.

In 2013, Dr. J. Gregory Fitz, Executive Vice President for Academic Affairs and Provost, Dean of the Medical School, and holder of the Nadine and Tom Craddick Distinguished Chair in Medical Science and the Atticus James Gill, M.D. Chair in Medical Science, formed a committee of five academic leaders to develop a comprehensive change to the curriculum. Since the school opened in 1943, the curriculum has evolved with the changing landscape of medicine, but it had not implemented a complete overhaul until 2015.
The first semester was rigorous, and I learned a lot in the classes. I’m still digesting it, still figuring things out. This new curriculum is fast-paced, and our peers are really sharp.

Reed Macy, Class of 2019 co-President

I like the team-based learning exercises. You get to be very interactive. I can see how a good TBL exercise helps to develop doctors who are critical thinkers, team workers, and problem-solvers.

Katherine Pouns, Class of 2019 co-President

The new curriculum is one of the many reasons I came to UT Southwestern. The improvements derived from the contributions of this class will benefit future generations of students, and the faculty has been open and helpful in listening to us and making adjustments, both retroactively and proactively, to make this transition in curriculum as smooth as possible.

Gene Hu, Class of 2019 curriculum representative

Much of our outstanding curriculum has been taught before but has now been rearranged for integration and efficiency,” said Dr. Burns, who holds the Jane B. and Edwin P. Jenevein, M.D. Chair in Pathology.

Systemic instruction, for instance, results in many more faculty members presenting to the students.

“We’ve had M.D.s as well as Ph.D.s teaching us,” Mr. Macy said. “In the first year we’ve had more than 100 professors present. That’s the great thing about UT Southwestern – there’s an ocean of resources to draw from.”

Dr. Stull said integration of classes eliminated some redundancies. A highlight of the new curriculum is the inclusion of a TBL environment, he added. In 2015, UT Southwestern renovated the second floor of the South Campus Library into the largest team-based learning center of its kind in the U.S.

In 2015, UT Southwestern renovated the second floor of the South Campus Library into the largest team-based learning center of its kind in the U.S.

In developing and implementing the new curriculum, the faculty has really stepped up to the challenge and has been remarkable,” Dr. Stull said. “We’re improving the experience and education for our students, which we hope in turn will make them better doctors.”

Those efforts to improve the educational experience continue. In the planning stages is a state-of-the-art Simulation Center that will be built on West Campus featuring high-fidelity simulators of patients. The mannequins will be used to teach responses to life-threatening medical problems such as cardiac arrest and shock before students encounter those emergencies in real life.

The challenge to stay current in medical education is daunting, given that some experts say medical knowledge doubles every four to five years. On the flip side, some medical information published is based on early-stage research that is quickly outdated by newer findings.

Changes in health care delivery are also transforming our approach to medical education. In addition to scientific knowledge and clinical skills, for our students to be effective and successful physicians in providing optimal patient care, they must also develop capabilities in areas such as quality improvement, cost effectiveness, collaboration, and teamwork,” 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.
UT Southwestern’s three degree-granting schools aim to prepare students for exemplary medical, health care, or research careers. Ever-changing advances in medicine, science, and technology mean schools must adjust as well to equip students with the latest tools and knowledge to do their jobs. Below are some highlights of recent changes, or proposed adjustments, to UT Southwestern educational programs.

UT Southwestern Medical School

- The reformed curriculum, implemented in 2015 for new students, moved smoothly into its second year, with an emphasis on active learning in a new state-of-the-art Team-Based Learning Center, small-group simulations with high-fidelity mannequins, and online instructional material with electronic testing.
- The preclerkship period incorporates a cohesive, multidisciplinary approach for foundational material and integrated medicine based on organ systems.
- The clerkship period introduces care clerkships six months sooner for clinical training with patients in hospitals and outpatient clinics.
- All medical students now take a Scholarly Activity course for an individual research project, with opportunities in clinical and translational research, medical education, global health, biomedical research, community health, and biomedical innovations.
- During the clerkship period, novel electives in the Growth and Exploration curriculum—such as Exploration of Psychiatry Addiction Medicine—provide students a way to explore a variety of career opportunities.

UT Southwestern Graduate School of Biomedical Sciences

- An innovative “umbrella” curriculum has been added with nine Ph.D. programs that emphasize learning in the laboratory by completing required didactic coursework in one year.
- An Organic Chemistry Ph.D. Program and a Medical Physics Track in the Biomedical Engineering Ph.D. Program were added.
- A collaborative Biostatistics Ph.D. Program with Southern Methodist University launched in mid-2015. Students take classes at SMU their first year before conducting research at UTSAW.
- A new Matlab Boot Camp gives students a foundation for advancing research projects with tailored computational data analysis solutions.
- A revised Master of Science in clinical science curriculum provides junior faculty with the tools to conduct clinical research that results in publications and funded grants.

UT Southwestern School of Health Professions

- The Radiation Therapy Program is preparing to enhance curricular content and transition from a post-baccalaureate certificate to a master’s degree program.
- Preliminary authority has been granted for the development of a doctoral program in applied clinical research to foster both patient-oriented and translational research.
- The interprofessional course offered through the Department of Health Care Sciences has been expanded to include TeamSTEPPS (Team Strategies and Tools to Enhance Performance and Patient Safety) training and more patient interaction with student health care teams.

Growing to Meet Future Needs

Since its formation in 1943 as a small wartime medical college, UT Southwestern Medical Center has grown exponentially to become one of the nation’s top academic medical centers. Today, it is a sprawling campus, encompassing multiple buildings in the Southwestern Medical District, plus satellite clinics in Park Cities, Richardson/Plano, and Las Colinas, and an expanding presence in Fort Worth. To keep pace with the growth of medical, research, and educational efforts, plans for the next transformative stages of UTSAW’s ongoing evolution are in the works. At right are some highlights of current building projects.

Radiation Oncology Center

- The $66 million facility is targeted to open in spring 2017.
- Relocating services from other campus sites, the new three-story center will consolidate radiation oncology patient care into a single, 63,000-square-foot building.
- Features include seven treatment vaults and a dedicated area for each major disease site—such as brain, breast, or gastrointestinal cancer.
- The center will be the largest individual facility for radiation treatment in North Texas, and it will be home to some of the world’s leading therapeutic technology, enhancing disease-site specialization for cancer patients.

UT Southwestern Monty and Tex Moncrief Medical Center at Fort Worth

- The new 6.3-acre campus in Fort Worth’s medical district—UT Southwestern’s first named campus outside of Dallas—will build on recent UTSAW expansions at the nearby Moncrief Cancer Institute.
- The first building at the site, located at the intersection of Pennsylvania Avenue and Main Street, will be a multidisciplinary outpatient facility.
- The Center, expected to be completed and ready for occupancy in mid-2017, will be an exemplary health care facility serving our community in the south Fort Worth area.

West Campus Improvement

- The former site of St. Paul University Hospital is now known as UT Southwestern’s West Campus, and the $875 million West Campus Facilities Replacement Plan will unfold in five phases over 20 years.
- Ultimately, the plan will add 1.1 million square feet of facility space.
- The first phase involves construction of a nine-story, 305,000-square-foot academic and clinical building (above) that will house faculty offices, outpatient clinics, and a state-of-the-art simulation center, all estimated to be completed in early 2018.
- The high-tech simulation center in the nine-story building 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 nine-story building will include 220 exam rooms and procedure rooms for multiple specialties.
- An 805-space parking garage also will be added as part of phase 1.
Each person’s DNA is unique, providing clues about his or her health waiting to be unlocked. Using this information, researchers at UT Southwestern are identifying more effective, individualized disease treatments and pinpointing biomarkers that can aid in diagnosis or prevention. Biomarkers can also predict response to immunotherapy, a type of treatment in which the immune system is supercharged to fight off disease.
Demonstrating the potential of precision medicine, an international study based at UT Southwestern Medical Center used next-generation DNA sequencing technology to identify more than 1,000 gene variants that affect susceptibility to systemic lupus erythematosus (SLE).

“SLE starts when the immune system attacks multiple organ systems in the body, which can result in a complex array of symptoms that are difficult to manage clinically and can lead to organ damage,” said Dr. Edward Wakeland, Professor of Immunology at UT Southwestern and co-senior author of the study published last year in *eLife*. “Our findings support the potential of precision medicine to provide clinically relevant information about genetic susceptibility that may ultimately improve diagnosis and treatment.”

Dr. Wakeland, an expert in next-generation sequencing applications, leads a new DNA-sequencing initiative to take this technology to the next level to advance patient treatment in areas such as cancer and autoimmune disease. (See related story on page 56.) For years, Dr. Wakeland’s laboratory has served as the Medical Center’s Genomics and Microarray Core Facility.

In addition, the two-year study identified many of the specific regulatory variations that were changed in SLE patients and demonstrated that accurately identifying such so-called causal variants increased the accuracy of the genetic association of individual SLE risk genes with susceptibility to SLE.

“Prior to our study, such a comprehensive sequence analysis had not been done and little was known about the exact genetic variations that modify the functions of the genes that cause SLE,” added Dr. Wakeland, who holds the Edwin L. Cox Distinguished Chair in Immunology and Genetics.

The scientists began their comprehensive sequence analysis using the DNA samples of 1,349 American Europeans (773 with SLE disease and 576 without) from sample collections at UT Southwestern, the University of Southern California, UCLA, Oklahoma Medical Research Foundation, and the Université Catholique de Louvain in Belgium.

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The DNA sequencing study pinpointed more than 1,000 genetic mutations associated with lupus.
scattered throughout the genome. They found that SLE risk is associated with specific clusters of DNA variations, commonly called haplotypes, and that some haplotypes increased the risk for SLE while others provided protection from SLE.

After identifying the sets of DNA variants that increased SLE susceptibility in Caucasians, they used multiple public databases, including the international 1000 Genomes Project (2,504 genomic samples from the global human population) to determine whether these haplotypes also were found in South American, South Asian, African, and East Asian populations.

They discovered that the variants and haplotypes were distributed across sub-populations worldwide. Their findings indicate that many common haplotypes in the immune system are shared at different frequencies throughout the global population, suggesting that these variations in the immune system have ancient origins and persist in populations for long periods, Dr. Wakeland said.

Dr. Wakeland and colleagues plan to continue the research by obtaining more DNA samples and expanding their analysis to additional SLE risk genes with the goal of obtaining a data set that can be used to predict an individual's unique risk of SLE, as well as the likelihood of benefiting from specific treatments.

“It is feasible that this same type of genetic analysis will allow the clustering of SLE patients into specific groups, based on their genetic predispositions, which would improve clinical management and potentially allow the development of more targeted therapies,” Dr. Wakeland said.

Researchers Uncover Mutation that Causes Rare Disease

UT Southwestern Medical Center researchers have discovered a mutation that causes a rare systemic disorder known as X-linked reticulate pigmentary disorder (XLPDR) and, significantly, the unexpected cellular mechanism by which the mutation causes the disease.

For Tom Vansyckle, it was an emotional moment when Dr. Andrew Zinn, Dean of the UT Southwestern Graduate School of Biomedical Sciences, told him that the genetic mutation linked to his two sons’ disorder had been found. The research was published in mid-2016 in *Nature Immunology*.

“It felt like a dream,” Mr. Vansyckle said. “I called Dr. Zinn the next morning and asked him, ‘Is this really real or did I dream that this happened?’ ”

Symptoms of XLPDR, a hereditary X chromosome-linked disease, include blotchy skin pigmentation, unusual facial features, inability to sweat, and recurrent bacterial lung infections. The condition also causes cornea scarring, leading to blindness in many patients. Worldwide, only 14 families are known to have XLPDR.

Although the study’s findings do not translate into an immediate cure for brothers Spencer and Tyler Vansyckle of Waco, Texas, they hold promise for development of therapies targeted at the now-known mutation that causes XLPDR: the *POLA1* gene, a core enzyme involved in DNA replication.

Dr. Zinn, also a Professor of Internal Medicine and in the Eugene McDermott Center for Human Growth and Development who holds the Rolf Haberecht and Ute Schwarz Haberecht Deanship of the UT Southwestern Graduate School of Biomedical Sciences, began working to identify the genetic mutation that causes this disease after he met the Vansyckle family. Whole-genome sequencing led to the answer. The mutation, as it turned out, was not in an exon – a part of a gene that codes for proteins – but rather in a non-coding intron section of DNA.

Brothers Spencer (left) and Tyler Vansyckle have the rare genetic disease X-linked reticulate pigmentary disorder, which makes their eyes especially sensitive to sunlight.
Researchers next attempted to understand how the genetic mutation led to the phenotype of this disease. Dr. Ezra Burstein, Associate Professor of Internal Medicine and Molecular Biology and a UTSW Disease-Oriented Clinical Scholar, and Dr. Petro Starokadomskyy, research scientist, made a connection between POLA1 deficiency and an immune reaction in the cytoplasm, or fluid portion, of cells. The researchers pinpointed the cause of this unusual state as constant activation of the interferon pathway – the body’s principal cellular system for fighting viral infections.

Beyond finally revealing a disease cause, UT Southwestern’s research suggests a possible treatment route. “Finding a way to block or slow the interferon pathway could someday help these patients,” Dr. Burstein said.

At a Glance: XLPDR

- An extremely rare disease, it is estimated to affect only 20 people worldwide.
- The gene that causes the disease is on the X-chromosome, so it seriously affects only boys, although girls can be carriers who pass the condition on to male children.
- Characteristics include unusual skin markings and hair that looks slicked back.
- Because recurring lung infections are common, patients are often misdiagnosed as having cystic fibrosis.
- Many with XLPDR produce little or no sweat, have painful sensitivity to light, and eventually lose their eyesight.
- The XLPDR mutation affects the immune system, causing patients’ bodies to react as if they are under constant viral attack. Ironically, this makes them especially vulnerable to bacterial and fungal diseases.

Trial Advances Game-changing Immunotherapy for Lung Cancer

The success of an international clinical trial that UT Southwestern Medical Center took part in paved the way for approval of an immunotherapy drug to treat advanced-stage lung cancer – signifying a major advancement in immune system-boosting alternatives to chemotherapy.

In late 2015, an international team of cancer researchers compared the immunotherapy drug nivolumab and the chemotherapy drug docetaxel in patients with nonsquamous non-small cell lung cancer (NSCLC) whose disease had progressed after finishing first-line chemotherapy. The results, reported that year in the New England Journal of Medicine, were significant because options for these patients are generally limited.

“This clinical trial showed that people with lung cancer not only lived longer when treated with the immunotherapy drug nivolumab, but their quality of life was better and toxicities were fewer and less severe,” said Dr. David Gerber, Associate Professor of Internal Medicine at UT Southwestern.

Based on the success of the trial, the Food and Drug Administration approved nivolumab to treat advanced lung cancer. Previously, it had been approved for squamous non-small cell lung cancer and certain types of melanoma. Nivolumab works by inhibiting the function of the PD-1 protein, which blocks the body’s immune system from attacking cancerous cells. Nivolumab treatment is promising because the drug is effective, often well-tolerated, and appears to be beneficial in several types of cancer.

Nivolumab is but one drug in the rising category of immunotherapeutics, and the potential for new, lifesaving therapies to treat a broad range of cancer types is significant.

Dr. Ezra Burstein, Dr. Andrew Zinn, and Dr. Petro Starokadomskyy (left to right) led a study that identified the mutation that causes XLPDR, which worldwide only 14 families are known to have.

Donna Fernandez participated in an international clinical trial led by Dr. David Gerber that evaluated an immunotherapy drug for lung cancer treatment.
At a Glance: Cancer Immunotherapy Trial

- Compared immunotherapy drug nivolumab vs. the chemotherapy drug docetaxel in patients with nonsquamous non-small cell lung cancer who had failed to respond to first-line therapies.
- Phase 3 clinical trial followed more than 500 patients for at least a year.

Survival rates at one year: 31 percent for nivolumab and 39 percent for docetaxel.
- Confirmed objective response rate: 19 percent for nivolumab and 12 percent for docetaxel.
- 79 percent of participants were current or former smokers.
- Trial's success led to approval of nivolumab in late 2015 for treatment of advanced lung cancer.

"The idea behind immunotherapy is to kick-start the body's natural immune response to a cancer. Cancer develops and grows in part because it has put the brakes on the immune response. These drugs take the foot off the brake, allowing the immune system to accelerate and attack the cancer," he explained.

The Simmons Cancer Center is the only National Cancer Institute (NCI)-designated comprehensive cancer center in North Texas and one of just 47 NCI-designated comprehensive cancer centers in the nation. In addition, the Simmons Cancer Center is among only 30 U.S. cancer research centers to be named a National Clinical Trials Network Lead Academic Participating Site, a prestigious designation by the NCI.

Donna Fernandez of Rockwall, Texas, said nivolumab has improved her quality of life. A smoker for 40 years, Mrs. Fernandez was diagnosed with NSCLC several years after quitting smoking in 2007. She'd been fighting stage 4 lung cancer for the past four years and needed another option after her initial round of chemotherapy wasn't successful. She decided to join the trial at UT Southwestern.

The one-year survival rate was 51 percent in the nivolumab group versus 39 percent in the docetaxel group.

In addition to studying safety and efficacy, the trial examined the protein biomarker PD-L1, which is believed to play a role in suppressing the immune system. The study results suggested that patients with a higher level of PD-L1 in their cancers may experience the greatest benefit from nivolumab, which targets the related molecule PD-1. Using a biomarker helps oncologists predict which patients will do best on which treatment and plan their treatment accordingly. Other promising predictive biomarkers for cancer immunotherapies include the degree of immune cell infiltration within a tumor and the number of mutations a tumor has.

"The more mutations a cancer has, the more foreign it appears to the body, thus marking it for immune attack," Dr. Gerber explained. "With lung cancer, we see the greatest number of tumor mutations – and the greatest benefit from immunotherapy – among individuals with the heaviest smoking history."

UT Southwestern has taken part in a number of other nivolumab trials, including a phase 1 study examining nivolumab combinations with chemotherapy, targeted therapies, and other immunotherapies. Other types of cancer have also shown benefit from nivolumab and other immunotherapies.

To further this research, one of Dr. Gerber’s studies will examine whether survival rates improve in patients with locally advanced lung cancer who are given immunotherapy after standard chemotherapy and radiation treatments.

"The new immunotherapy treatments convey the risk of unpredictable, possibly severe, and potentially irreversible autoimmune toxicities affecting a variety of organs. With combination immunotherapy regimens, rates of these adverse events may exceed 50 percent," he said. "The new immunotherapy treatments convey the risk of unpredictable, possibly severe, and potentially irreversible autoimmune toxicities affecting a variety of organs. With combination immunotherapy regimens, rates of these adverse events may exceed 50 percent," said Dr. Saad Khan, Assistant Professor of Internal Medicine and a member of the Simmons Cancer Center.

The researchers studied 210,509 lung cancer patients over age 65 and applied two different algorithms to measure the presence of an autoimmune disease.

"Since the use of cancer immunotherapy is growing, examining the effectiveness and toxicity of these promising treatments among patients with autoimmune diseases will be critical," said Dr. David Gerber, Associate Professor of Internal Medicine, Co-Director of the Lung Cancer Disease-Oriented Team, and Co-Leader of UT Southwestern’s Experimental Therapeutics Program.

"No one thought I’d still be alive. I’m not just alive – I’m living life to the fullest," said Mrs. Fernandez, who receives treatment every two weeks. Except for a little fatigue the day after treatment, she said she is able to continue with her normal activities, including agility training with her dogs.

The phase 3 clinical trial followed more than 500 patients such as Mrs. Fernandez who had NSCLC: 287 received nivolumab and 268 received docetaxel chemotherapy.

The results, reported last year in JAMA Oncology, are significant because the use of immunotherapy for cancer treatment is expanding, and clinical trials of immunotherapy have routinely excluded patients with autoimmune disease. An autoimmune disorder occurs when the immune system attacks healthy body tissue by mistake.

The UT Southwestern cancer researchers calculated that between 14 and 25 percent of lung cancer patients reviewed also had autoimmune disease, and these individuals were more likely to be female and older.

Dr. Saad Khan, Dr. Sandi Pruitt, Dr. David Gerber, and Dr. Lei Xuan found that a significant percentage of lung cancer patients also have autoimmune disease.

**Immunotherapy: The Autoimmune Disease Downside**

A significant proportion of lung cancer patients also have autoimmune disease, which may make them unsuitable for increasingly popular immunotherapy treatments, a team of researchers at UT Southwestern Medical Center’s Harold C. Simmons Comprehensive Cancer Center has found.

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Brilliant ideas and hard work lead to discovery, just as breakthroughs inspire continued advancement. The exceptional, groundbreaking research of UT Southwestern scientists led to prestigious honors last year, including the Passano Award for important discoveries in cholesterol research and an extraordinary, rare national grant to pursue more effective kidney cancer treatments.
Hobbs, Cohen Recognized for Groundbreaking Cholesterol Research

UT Southwestern geneticists Dr. Jonathan Cohen and Dr. Helen Hobbs received one of the nation’s highest honors in biomedical science last year – the 2016 Passano Award – for developing and applying transformative genetics techniques to the understanding of lipid metabolism related to heart disease.

The award from the Passano Foundation recognizes exemplary U.S.-based research that leads to real-world applications in clinical medicine. The research of Dr. Cohen and Dr. Hobbs, a Howard Hughes Medical Institute Investigator and Director of the Eugene McDermott Center for Human Growth and Development, laid the foundation for development of a new class of drugs to treat high cholesterol, including two drugs approved in 2016 by the Food and Drug Administration.

The honor highlights UT Southwestern’s commitment to transformational medical and scientific research by its esteemed faculty, which currently includes five Nobel Prize winners, 18 members of the National Academy of Medicine, 22 members of the National Academy of Sciences, 16 members of the American Academy of Arts and Sciences, and 13 Howard Hughes Medical Institute Investigators.

“The pioneering research of Dr. Cohen and Dr. Hobbs has provided important novel insights into the genetic basis of cholesterol metabolism. These insights have made possible the development of categorically new therapeutic agents that can benefit vast numbers of people facing cardiovascular disease,” 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.

Dr. Hobbs, Chief of Clinical Genetics and Professor of Internal Medicine and Molecular Genetics, and Dr. Cohen, Professor of Internal Medicine and with the McDermott Center, have worked together for nearly two decades and co-direct the Hobbs-Cohen Lab in the McDermott Center.

“It is an honor for my colleague, Dr. Cohen, and me to receive this prize in recognition of work carried out in conjunction with the many terrific students and fellows in our lab,” said Dr. Hobbs, who holds the Eugene McDermott Distinguished Chair for the Study of Human Growth and Development, the Philip O’Bryan Montgomery, Jr., M.D. Distinguished Chair in Developmental Biology, and the 1995 Dallas Heart Ball Chair in Cardiology Research. Dr. Cohen holds the C. Vincent Prothro Distinguished Chair in Human Nutrition Research.

Research by Dr. Hobbs and Dr. Cohen focuses on identifying genetic factors that contribute to variations in the levels of cholesterol in the blood, especially LDL cholesterol, often referred to as “bad cholesterol.” High levels of LDL cholesterol in the blood increase the risk of a heart attack. The Hobbs-Cohen team discovered how certain genes predispose people to heart attacks and others protect – discoveries that pointed to new targets for drug development. By studying individuals with unusually high or unusually low serum lipid levels, the Hobbs-Cohen team revealed the central role of PCSK9, a protein that degrades receptors for LDL, leading to the development of drugs that inactivate PCSK9, resulting in lowered LDL.

In addition, the Hobbs-Cohen laboratory identified the first genetic cause of non-alcoholic fatty liver disease, an increasingly common disorder that is associated with cirrhosis and liver cancer. Their discoveries grew out of the Dallas Heart Study, which provided a large database of individuals for whom researchers had both genetic information and information on physical traits to study. Co-founded by Dr. Hobbs, the Dallas Heart Study involves more than 6,000 ethnically diverse participants and receives funding from the Donald W. Reynolds Foundation. Now underway for more than 16 years, it has led to more than 200 published papers. Phase 3 of the study is now in the works, and will have a general scientific focus on healthy aging.

The connection between genetics and atherosclerosis – a clogging of the arteries that is a leading cause of heart attacks and stroke – was highlighted more than 30 years ago in the work by Nobel Laureates Dr. Michael Brown and Dr. Joseph Goldstein at UT Southwestern. Dr. Brown is Director of the Erik Jonsson Center for Research in Molecular Genetics and Human Disease, and Dr. Goldstein is Chairman of the Department of Molecular Genetics. Their research led to the development of statins, one of the most widely prescribed medicines in the world. Dr. Brown holds The W. A. (Monty) Moncrief Distinguished Chair in Cholesterol and Atherosclerosis Research, and the Paul J. Thomas Chair in Medicine. Dr. Goldstein holds the Julie and Louis A. Beecherl, Jr. Distinguished Chair in Biomedical Research, and the Paul J. Thomas Chair in Medicine.
These funds will support a variety of new and ongoing activities, including the development of a new drug therapy now in clinical trials.

The UT Southwestern SPORE program involves four innovative disease and clinical research teams targeting adult and pediatric kidney cancer, as well as a patient advocate group, developmental research program, career enhancement program, and core facilities to support these efforts through data analysis, imaging technology, and a tissue repository.

The four research teams will:

- Search for biomarkers to identify kidney cancer tumors most likely to respond to a HIF-2α inhibitor, as well as to anticipate ways in which these tumors may evade the drug's impact.
- Investigate the function of a gene that identifies a cluster of particularly aggressive tumors associated with clear-cell renal cell carcinoma, in hopes of identifying vulnerabilities that can be targeted with drugs.
- Examine kidney cancer metabolism to distinguish aggressive from less-active tumors, potentially yielding a tailored treatment approach.
- Test novel treatments for childhood kidney cancer by researching the implications of a Wilms tumor subtype.

In a series of landmark findings over the past 20 years, UT Southwestern researchers have identified and characterized a key protein called HIF-2α involved in kidney cancer. These findings led to development of a drug therapy now in clinical trials.

Thirteen distinguished research leaders – all nationally recognized in their field of expertise – will lead the team of more than 40 scientists that will focus on developing new approaches toward this disease, which is particularly deadly,” Dr. Cobb said.

This award marks the second SPORE grant for UT Southwestern, which for 20 years has led a multi-institutional SPORE program in lung cancer that is the largest thoracic oncology effort in the U.S.

Nearly 400,000 Americans are currently living with kidney cancer, which is the fourth most commonly treated cancer at UT Southwestern. It is usually found indirectly, through a scan performed for a different reason, for example. More than 60,000 people are expected to be diagnosed with kidney cancer this year.
UT Southwestern’s three degree-granting institutions train about 3,600 medical, graduate and postdoctoral fellows each year.

Dr. Carlos Girud, to Associate Vice President for Clinical System Affairs.
Dr. Juan Guerra Jr., to Vice President for Facilities Management.
Dr. Lora Hooper, to Chair of Immunology.
Dr. Chua-Long Huang, to the Ruth W. and Milton P. Levy Sr. Chair in Molecular Neurology.
Dr. Kimberly Huber, to Chair of the Neuroscience Graduate Program.
Dr. Heidi Jacobo, to the James N. Gilliam, M.D. Chair in Dermatology.
Dr. Celia Jenkins, to the McKennie Foundation Chair in Psychiatry I.
Dr. Alex Kane, to the Crystal Charity Ball Distinguished Chair in Plastic Surgery.
Kenneth Kellogg Jr., to Assistant Vice President of Budget and Resource Planning.
Kim Hoggatt Krumwiede, to Associate Dean for Academic Affairs.
Xi Lai, to Assistant Vice President, Enterprise Data Services.
Mark Lane, to Assistant Vice President for Communications.
Dr. Lu Li, to the Thomas L. Shields, M.D. Professorship in Dermatology.
Jodi Levy, to Assistant Vice President, Business Administrative Systems.
Dr. Christopher Madden, to Associate Vice President and Clinical Director, Peter O’Donnell Jr. Brain Institute.
Dr. Jorge Marrero, to Associate Vice President and Clinical Transformation Officer.
Donald McLaughlin, to Assistant Vice President, Support Services for the Affairs - Medical Risk Management.
Dr. Rebecca Minter, to the Alvin Baldwin, Jr. Chair in Surgery.
Dr. Mack Mitchell, to Vice President for Medical Affairs for the Medical Service, Research, and Development Plan (MSRDP) and Chief Medical Officer of the Southwestern Health Resources Physician Network.
Dr. Orson Moe, to Chief of the Division of Nephrology.
Dr. Venkatwara Mootha, to the Paul T. Stoffel/Centex Professorship in Clinical Care.
Dr. Allen Morey, to the Distinguished Chair in Urology for Urologic Reconstruction in honor of Allen F. Morey, M.D.
Dr. Sean Morrison, to the Kathryne and Gene Buhrop Distinguished Chair in Pediatric Research at Children’s Research Institute at UT Southwestern.
Darren Nelson, to Assistant Vice President, Human Resources Administration.
Dr. Marc Nivet, to Executive Vice President for Institutional Advancement.
Dr. Dooja Pan, to Chair of Physiology, and to the Focused A. and Val Imn Bashour Distinguished Chair in Physiology.
Dr. Chandrasekhar Pasare, to the J. Wayne Streilein, M.D. Professorship in Immunology.
Dr. Trish Perl, to Chief of Infectious Diseases, and to the Jay P. Sanford Professorship in Infectious Diseases.
Dr. Margaret Phillips, to Chair of Biochemistry, and to The Sam G. Winstead and Andrew Bell Distinguished Chair in Biochemistry.
Joan Porter, to Associate Vice President for Legal Affairs - Medical Risk Management.
Dr. Marilyn Punnaro, to the Nadine and Tom Craddock Professorship in Medical Education.
Dipti Ranganathan, to Associate Vice President, Academic and Administrative Information Systems.
Mark Rauschuber, to Associate Vice President and Chief Information Officer, UT Southwestern Information System.
Dr. Robert Rege, to Associate Dean for Undergraduate Medical Education.
Dr. Elliott Ross, to Associate Dean of Scientific Integrity.
A. Chris Rubio, to Associate Vice President for Neuroscience Services.
Dr. Hesham Sadek, to the J. Fred Schollkopf, Jr. Chair in Cardiology.
Dr. Arthur Sagalowsky, to the Cayce and W. Plack Carr, Jr. Professorship in Medical Education.
Dr. Debrah Scharp, to the Dr. Charles F. Gregory Distinguished Chair in Orthopaedic Surgery.
Dr. Hongtao Yu, to The Kent and Jodi Foster Foundation to support the office of the Medical Director for the Department of Surgery.
Dr. Larry Thornton, to the McKenzie Foundation Chair in Psychiatry II.
Dr. Paul Tiwana, to the Dr. Douglas and Diane Sinn Chair in Oral and Maxillofacial Surgery.
Dr. Seth Toomay, to Interim Chief Medical Officer for Ambulatory Care.
Dr. Madhukar Trivedi, to the Julie K. Hersh Chair for Depression Research and Clinical Care.
Dr. Lornisa Velasquez-Daoubon, to the Michael P. Waincott, M.D. Professorship in Emergency Medicine.
Dr. Babu Welch, to the Duke Samson Chair of Neurological Surgery.
Dr. Narmin R. Williams, to Senior Executive Officer, Market Relations, Southwestern Health Resources.
Dr. Dane Wuckich, to Chair of Orthopaedic Surgery, and to the Dr. Charles F. Gregory Distinguished Chair in Orthopaedic Surgery.
Dr. Marilynn Punaro, to Chair in Infectious Diseases.
Dr. Chou-Long Huang, to the Alvin Baldwin, Jr. Chair in Surgery.
Dr. Paul T. Stoffel/Centex Professorship in Oncology.
Dr. Venkateswara Mootha, to the Paul T. Stoffel/Centex Professorship in Clinical Care.
Dr. Tedd M. Shank, to Associate Dean for Undergraduate Medical Education.
Dr. Mack Mitchell, to Vice President for Medical Affairs for the Medical Service, Research, and Development Plan (MSRDP) and Chief Medical Officer of the Southwestern Health Resources Physician Network.
Dr. Orson Moe, to Chief of the Division of Nephrology.
Dr. Robert Rege, to Associate Dean for Undergraduate Medical Education.
Dr. Elliott Ross, to Associate Dean of Scientific Integrity.
A. Chris Rubio, to Associate Vice President for Neuroscience Services.
Dr. Hesham Sadek, to the J. Fred Schollkopf, Jr. Chair in Cardiology.
Dr. Arthur Sagalowsky, to the Cayce and W. Plack Carr, Jr. Professorship in Medical Education.
Dr. Debrah Scharp, to the Dr. Charles F. Gregory Distinguished Chair in Orthopaedic Surgery.
Dr. Hongtao Yu, to The Kent and Jodi Foster Foundation to support the office of the Medical Director for the Department of Surgery.
Dr. Larry Thornton, to the McKenzie Foundation Chair in Psychiatry II.
Dr. Paul Tiwana, to the Dr. Douglas and Diane Sinn Chair in Oral and Maxillofacial Surgery.
Dr. Seth Toomay, to Interim Chief Medical Officer for Ambulatory Care.
Dr. Madhukar Trivedi, to the Julie K. Hersh Chair for Depression Research and Clinical Care.
Dr. Lornisa Velasquez-Daoubon, to the Michael P. Waincott, M.D. Professorship in Emergency Medicine.
Dr. Babu Welch, to the Duke Samson Chair of Neurological Surgery.
Generous contributions and pledges of $100,000 to $299,999 were received from a number of additional donors, including the following new commitments from:

- Alex's Lemonade Stand Foundation to support childhood cancer research.
- Rita Allen Foundation to support research.
- ASN Foundation for Kidney Research to support kidney research.
- Cancer Research Institute to support cancer research.
- Chicago Community Trust to support research.
- Mr. and Mrs. John A. Cole to support prostate cancer research.
- Mr. and Mrs. Harlan R. Crow to support education, research, and clinical care.
- Gary Cunningham, M.D., to Southwestern Medical Foundation to establish an endowment to support the Department of Obstetrics and Gynecology.
- Care Alzheimer’s Fund to support Alzheimer’s disease research.
- Curing Kids Cancer Inc. to support Ewing’s sarcoma research.
- Food Allergy Research & Education to support the FARE Clinical Network.
- Foundation for Prader-Willi Research to support research into Prader-Willi syndrome.
- Friedreich’s Ataxia Research Alliance to support ataxia research.
- Mr. and Mrs. Mark D. Gibson, through The Melchizedek Fund of Communities Foundation of Texas, to Southwestern Medical Foundation to support education, research, and clinical care.
- Mr. and Mrs. Irwin J. Grossman to Southwestern Medical Foundation to support diabetes research.
- Mr. and Mrs. David C. Haley to Southwestern Medical Foundation to support research.
- Ms. Linda W. Hart and Mr. M. Atkins, M.D., Professorship in Palliative Care, in Honor of Steven Leach, M.D.
- International Human Frontier Science Program Organization to support research.
- Robert Wood Johnson Foundation to support research.
- The estate of Jeannette Josephy to support programs in medical research, and clinical care.
- Sidney Kimmel Foundation for Cancer Research to support cancer research.
- Mr. and Mrs. Donald P. Krovowitz and the Stacey and Donald Krovowitz Charitable Foundation to support urological diseases research.
- The Esther A. and Joseph Klingenstein Fund Inc. to support research.
- Susan G. Komen for the Cure to support mammography outreach and cancer research.
- Lymphatic Malformation Institute to support research.
- Willis C. Middrey, M.D., to support endowments in liver disease research.
- Nancy W. Marcus to Southwestern Medical Foundation to support pancreatic cancer research.
- Maureen A. Murry, M.D., and Albert Compton Broders III, M.D., to support the Shaun Oxford, M.D., Endowed Scholarship Fund, the James M. Atkins, M.D., Professorship in Emergency Medical Services, and the Carolyn and Erwin R. Thal, M.D., Chair in Trauma Surgery.
- Cozen O’Connor to support lung cancer research.
- Pew Charitable Trusts to support research.
- Radiation Oncology Institute to support research.
- Research to Prevent Blindness Inc. to support ophthalmologic research.
- Rett Syndrome Research Trust Inc. to support research.
- Darrell K Royal Research Foundation to prevent lymphoma.

St. Paul Medical Foundation to support programs in research and patient care.
- Mary R. Saner Charitable Trust to support patient care.
- The estate of Ellen van Raalte Karelson Solender to Southwestern Medical Foundation to support cancer research.
- Sons of the Flag to support a fellowship in burn care.
- Mr. and Mrs. Gerald H. Stool to Southwestern Medical Foundation to support programs in medical education, research, and clinical care.

$817,986 from the estate of Lydia Bryant; $791,730 from the Burroughs Welcome Fund to support research; $646,328 from Juvenile Diabetes Research Foundation International to support diabetes research; $604,025 from the American Diabetes Association Research Foundation Inc. to support diabetes research; $600,000 from David M. Crowley Foundation to support research in the areas of cancer, neurologic surgery, memory loss, and neuromodulation, as well as to support the Facial and Reanimation Program and the David M. Crowley Research and Rehabilitation Laboratory; $550,000 from the Communities Foundation of Texas to support the Jeannet Shelby Pancreatic Cancer Research Grants Program and the Sharon Shelby High-Risk Pancreas Screening Clinic; $535,000 from the Welch Foundation to support research; $519,354 from the Alliance for Lupus Research to support research; $500,000 from Paula M. Modo to Southwestern Medical Foundation to support education, research, and clinical care.