

2013 ANNUAL REVIEW

# SOUTHWESTERN

## MEDICINE

THE MAGAZINE OF UT SOUTHWESTERN MEDICAL CENTER

Where Innovation and Compassion  
Come Together



# SOUTHWESTERN MEDICINE

VOLUME 23 / NUMBER 1 / FEBRUARY 2014

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A generation ago, research from UT Southwestern physician-scientists had a transformative effect on the treatment of cholesterol. History may be about to repeat itself.



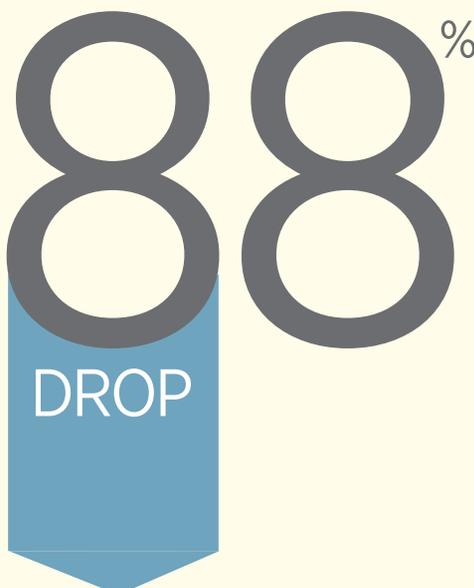
By Deborah Wormser

In 2006, UT Southwestern Medical Center geneticists Dr. Helen Hobbs and Dr. Jonathan Cohen reported on an African-American mother and aerobics instructor from North Texas who had two rare genetic mutations that resulted in strikingly low blood levels of artery-clogging LDL cholesterol.

Writing in *The American Journal of Human Genetics*, the geneticists noted that the woman – the first person ever identified with two cholesterol-lowering mutations in the *PCSK9* (proprotein convertase subtilisin-like kexin type 9) gene – appeared healthy. Exhaustive medical testing in the Hobbs-Cohen lab in the Eugene McDermott Center for Human Growth and Development had turned up no ill effects from living almost entirely without LDL cholesterol since birth.

Their report is widely credited with providing the scientific basis for today's race among pharmaceutical companies to develop what may become the next blockbuster class of cholesterol-lowering drugs: *PCSK9* inhibitors.

That same year, using data from the large federal Atherosclerosis Risk in Communities Study, the two UT Southwestern researchers published more striking findings. They reported in *The New England Journal of Medicine* that having just one cholesterol-lowering *PCSK9* mutation – rather than two – still reduced the long-term risk of cardiovascular disease by a jaw-dropping 88 percent in African-Americans in the study who had the mutation, despite high levels of other heart disease risk factors.



Meanwhile, their colleague Dr. Jay Horton, now Chief of the Division of Digestive and Liver Diseases, worked on mouse models to characterize how the protein created by the *PCSK9* gene functioned in the LDL-cholesterol pathway.

The findings of the three UT Southwestern faculty members could have a transformative effect on the treatment of cholesterol, much like the work of two of their renowned UTSW colleagues from a generation ago.

Their work was made possible by a very special study and a unique university culture that many would describe as different by design.

Dr. Hobbs directs the Dallas Heart Study (DHS), the first large epidemiological study ever done in North Texas. She also directs the McDermott Center, which is the University's Center for Human Genetics.

The initial round of the heart study, DHS-1 (2000-2002), and the follow-up study, DHS-2 (2007), led to the *PCSK9* discoveries, as well as several advances in other genetic/metabolic conditions such as non-alcoholic fatty liver disease, a burgeoning public health problem exacerbated by the obesity epidemic. With new funding, Dr. Hobbs and colleagues hope to bring the interdisciplinary team of investigators together again soon for DHS-3.

### Some like it hot

The media have focused on the speed at which the *PCSK9* saga moved from scientific discovery to drug development; indeed, Phase III trials were under way within seven years of the 2006 report. From that perspective, the R&D has rocketed along, becoming perhaps a case study in translational medicine.

The *PCSK9* story, in fact, began more than three decades ago when Dr. Hobbs, a Boston native, arrived to complete her residency at Parkland Memorial Hospital during the record-setting North Texas heat wave of 1980. "It was 114 degrees. Terrible," laughed the gregarious physician-scientist.

The heat didn't faze her. She always thrived on hard work under challenging conditions. Plus, she'd been on a trajectory to clinical medicine from her undergraduate days at Stanford University through medical school at Case Western Reserve University and an internship at Columbia-Presbyterian Medical Center.



Dr. Donald Seldin with then-Chief Resident Dr. Helen Hobbs, circa 1982.

She stood out from the start and was a natural for Chief Resident, recalled Dr. Donald Seldin, legendary former Chair of Internal Medicine and the man whom Dr. Hobbs credits with changing the course of her life.

“She exploded into the house staff at Parkland Hospital,” Dr. Seldin said. “In a short time, her unique qualities became apparent: a deep interest in patient illnesses, approached with both humane sympathy and a broad command of the deranged physiology that underlies disease processes. Her enthusiasm for clinical medicine, especially as its roots are unraveled by medical science, elevated the spirit of the house staff so that routine clinical issues became exciting clinical adventures.”

Dr. Seldin suggested that Dr. Hobbs try research in what he considered the very best lab at UT Southwestern: the one run jointly in molecular genetics by Dr. Joseph L. Goldstein and Dr. Michael S. Brown, who were doing some important research on cholesterol. She joined their lab in 1983.

Dr. Seldin remembers Dr. Hobbs’ performance in the Brown-Goldstein lab as a triumph. She remembers it differently.

“I wasn’t a natural in the lab,” she said. “It was very hard for me to acclimate to the pace of science. I was used to medicine where things moved very quickly, and it took me a while to take delight in the slower pace of science.” It was, she recalled, a tough and rigorous but supportive environment.

Dr. David Russell, then an Assistant Professor of Molecular Genetics and now Vice Provost and Dean of Basic Research, offered a hand. “He really helped me by teaching me how to design experiments and how to work with DNA,” she said.

Dr. Hobbs was still a postdoctoral student when her mentors were awarded the 1985 Nobel Prize in Physiology or Medicine for their landmark research identifying the LDL receptor system and showing how genetic defects in the LDL receptor could produce cholesterol levels high enough to lead to atherosclerosis and heart attacks in childhood.

Their research is credited with paving the way for development of the statin class of cholesterol-lowering drugs that came on the market more than 25 years ago and remain among the top-selling pharmaceuticals in the world. If *PCSK9* inhibitors become a therapy for patients unable to tolerate or reach cholesterol goals on statins alone – the niche for which they are targeted – it would be a case of lightning striking twice for UT Southwestern research.

Dr. Hobbs’ experience straddling clinical science and medical research had changed her. After living in both worlds, she understood that complex diseases like heart disease and metabolic disorders were going to have myriad genetic underpinnings, and she realized that the details mattered, she said.



Dr. Hobbs, Dr. Cohen

### A dynamic duo

In August 1989, Dr. Cohen arrived in Texas after earning a Ph.D. at the University of Cape Town, South Africa, to begin his postdoctoral research in metabolism at the Center for Human Nutrition under its Director, Dr. Scott Grundy, renowned for his work on dietary fats and cholesterol metabolism.

In contrast to Dr. Hobbs' warm enthusiasm, Dr. Cohen is cool and calculating in the most quantitative way. His most emotional response, still expressed in completely scientific terms, came when asked to describe his first impression of Dr. Hobbs.

"She just radiated energy," he said.

Had Dr. Grundy been a less generous mentor, or had the UT Southwestern culture been less open, the Hobbs-Cohen partnership might never have begun.

Dr. Cohen was halfway through his postdoctoral research in metabolism when he realized that he needed to learn genetics. He went to talk to his mentor, expecting perhaps to be allowed to spend a brief time in another laboratory learning techniques from other postdocs.

Instead of merely supporting the idea, Dr. Grundy was all in. He went to Dr. Hobbs, then an Assistant Professor of Internal Medicine and of Molecular Genetics as well as Chief of the Division of Medical Genetics at the medical school, and suggested she take over Dr. Cohen's training.

"Dr. Grundy's generosity toward me was very unusual. I have never heard of anything like it," Dr. Cohen said. As a Fellow in the Center for Human Nutrition, Dr. Cohen was considered one of the Center's most promising postdoctoral researchers.

Dr. Hobbs said yes, Dr. Cohen became her postdoc, and the two published a paper together in 1992. Following his postdoctoral training, Dr. Cohen joined the UTSW faculty in internal medicine, continuing his ongoing association as an investigator in the Center for Human Nutrition, an affiliation now entering its 25th year. He and Dr. Hobbs wouldn't work together again until 1999; by that time, they were both tenured faculty members.

## ‘Best possible study’

During the 1990s, Dr. Hobbs’ research took her into physiology and cell biology and then back into genetics, followed by more work on LDL metabolism. Her lab identified two genetically recessive forms of severe high cholesterol. Dr. Cohen, meanwhile, researched genetic determinants of cholesterol levels.

One day, Dr. R. Sanders “Sandy” Williams, then head of cardiology and now President of the Gladstone Institutes in San Francisco, told Dr. Hobbs about a call for applications from the Donald W. Reynolds Foundation in Las Vegas. The foundation was offering a 10-year, \$60 million grant to create one center in the country for cardiovascular disease research extending from genetics to the population, and he wanted her involved.

“I wasn’t very enthusiastic about it,” Dr. Hobbs said. “I’d just found these genes, and I was really excited about developing animal models and studying the mechanism to see why these genetic mutations caused severe hypercholesterolemia and severe coronary disease.”

In addition, there were factors that made the grant a long shot: There wasn’t a single population-based study in Dallas, and the University’s epidemiological footprint was small. But UT Southwestern had everything else required. Most importantly, it had internationally known researchers in genetics, cholesterol, cardiovascular disease, and metabolism, as well as a stellar reputation for collaborating across disciplines.

Dr. Hobbs and Dr. Ron Victor, now Director of the Cedars-Sinai Center for Hypertension in Los Angeles, became co-Principal Investigators of what would become the DHS. Dr. Hobbs and Dr. Cohen created and wrote the genetics section of the grant proposal, the first time they’d worked closely together since his post-doc days. Eventually, some 50 UT Southwestern researchers would be involved in some aspect of the massive study that Dr. Hobbs now directs.

“This was typical Helen,” Dr. Cohen remembers. “When we set out to do this, she asked: ‘What is the best possible study we could do, assuming there were no logistical or financial limitations? What would be the ideal study?’”

Her expansive perspective and his rational outlook proved the perfect balance: They challenged each other to visualize the ideal approach and to imagine all the rate-limiting aspects and the challenges they posed. Together, they brainstormed a new approach.

For genetic studies, the biggest limitation was a focus on genes to the detriment of phenotypes, the physical traits caused by the genes. They decided the ideal study would place equal emphasis on phenotypes and on genotypes.

“We knew that genomics was coming, that we were going to be able to sequence everybody’s genome. But what was going to be rate limiting was being able to have a well-characterized population at our fingertips to be able to test our hypotheses. That’s what the Dallas Heart Study did,” Dr. Hobbs said.

The underlying assumption of the DHS was that successfully identifying new risk factors for cardiovascular disease would require the availability of an exquisitely characterized (phenotyped), multiethnic population in proximity to UT Southwestern. That’s where the precision of Dr. Hobbs’ medical training kicked in.

“What is typical of large epidemiological studies is to focus on numbers, large numbers, to the detriment of getting really careful, precise phenotypes (traits),” Dr. Hobbs said. “We wanted everything that we did to be state-of-the-art in terms of any kind of measurement we did.”

In addition, they decided to oversample African-Americans, a group traditionally under-represented in medical research. Ultimately, the Dallas Heart Study enrolled nearly 6,000 people, more than half of them African-American.

## Fertile ground

UT Southwestern got the Reynolds grant in 1999. Within a year, Dr. Victor left the University and Dr. Hobbs became sole administrator and Principal Investigator for the study. She was selected as an Investigator in the prestigious Howard Hughes Medical Institute in 2002.

The Dallas Heart Study would prove to be fertile ground for the exploration of the *PCSK9* gene.

While Dr. Hobbs and Dr. Cohen, now running a joint laboratory, and their colleagues in UT Southwestern's Donald W. Reynolds Cardiovascular Clinical Research Center continued to enroll North Texans in the DHS, Dr. Horton was using mice to probe the role of *PCSK9* in cholesterol metabolism.

Microarrays were in the early days of development, and Dr. Horton's laboratory was using them in transgenic and knockout mice developed in the Brown-Goldstein lab during Dr. Horton's postdoc days. His lab was looking for new genes that appeared intimately involved in cholesterol metabolism. Again, UT Southwestern's culture of generosity made a difference. The Brown-Goldstein lab never asked for the return of its mice, even when their potential significance became apparent, said Dr. Horton, Professor of Internal Medicine and Molecular Genetics.

"An important breakthrough came in 2003 when a group of French researchers identified the gene that encodes the *PCSK9* protein, showing that an apparent gain-of-function mutation in this gene was associated with a rare form of high cholesterol that accelerated heart disease development in people," Dr. Horton said, adding that the French team did not know how the protein functioned.

Dr. Horton went back to his mice, finding that *PCSK9* protein seemed to be affecting the function of LDL receptors, which are primarily in the liver. "When we studied transgenic knockout mice that made a lot of this protein, we found that the LDL receptors disappeared from the mouse livers and blood cholesterol levels went extremely high," Dr. Horton said.

Meanwhile, the Dallas Heart Study provided a way to test a hypothesis in humans: If a gain-of-function mutation made LDL cholesterol levels soar, a loss-of-function mutation should make them fall. In general, loss-of-function mutations are more common than the other sort, the researchers explained.

The search was on, and the UT Southwestern geneticists knew just where to look. Drs. Hobbs and Cohen pored over the DHS data.

Looking at DHS participants with LDL cholesterol levels at the lowest end of the range, they found two different mutations in the *PCSK9* gene that result in loss of function (no *PCSK9* protein being produced). One of every 50 African-Americans in the study had one of these mutations, resulting in lower plasma levels of LDL cholesterol.

The researchers then collected blood from the families of those individuals. They identified one DHS participant with a *PCSK9* mutation who was married to a man who also had one. The researchers got permission to test the couple's children, finding one daughter (the aerobics instructor) who had inherited two mutations, one from each parent.

"The importance of the human studies in the Dallas Heart Study was that they provided immediate translation of the mouse findings to humans," Dr. Horton said. "Without the genetics and without the Dallas Heart Study, it would have taken years to get to that point because obviously mice are not men."

## Basic science to human biology

While worldwide attention centers on the incredible speed from discovery to drug development, the focus at UT Southwestern remains on the carefully constructed experimental structure and the equal amount of care that has gone into creating an environment where scientists feel comfortable crossing disciplines and sharing research, mice, and even, occasionally, postdocs.

"I think there is a collaborative culture here that doesn't exist in many institutions. And I think that's probably the result of Drs. Brown and Goldstein, because they've proved that you can have a lifelong collaboration, share in the research, and share in the rewards," said Dr. Horton, who attends the weekly Brown-Goldstein lab meetings whenever possible.

Dr. Horton's lab made some other significant findings credited with speeding drug development, including the discovery that PCSK9 circulates and functions in the blood and that the loss-of-function mutation leads to ultrafast clearing of LDL from the blood.

Injectable monoclonal antibodies are now under investigation. Phase II drug trials showed substantial drops in plasma LDL cholesterol levels when the drugs were injected every few weeks – from levels substantially over 100 down to 50 or lower. So far, there are no reports of an oral PCSK9 inhibitor.

"The Dallas Heart Study has been an enormous resource for multiple investigators at UT Southwestern, in both basic science and in epidemiology," Dr. Horton said. "Having that resource has the potential to significantly speed our basic discoveries and, more importantly, it has provided a direct link between basic science and human biology. We hope it will lead to better prevention of cardiovascular disease."

And, quite possibly, to the next big thing in cholesterol-lowering therapy.



Dr. Jay Horton

*Since 1991, Drs. Brown and Goldstein have served on the board of Regeneron Pharmaceuticals Inc., one of the many companies working to develop PCSK9 inhibitors. Dr. Hobbs serves on the board of Pfizer Inc., another company testing the antibodies. Other companies involved in PCSK9 inhibitor development include Amgen and Sanofi.*

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

**Dr. Cohen** holds the C. Vincent Prothro Distinguished Chair in Human Nutrition Research.

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

**Dr. Grundy** holds the Distinguished Chair in Human Nutrition.

**Dr. Hobbs** 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. Horton** holds the Dr. Robert C. and Veronica Atkins Chair in Obesity & Diabetes Research.

**Dr. Russell** holds the Eugene McDermott Distinguished Chair in Molecular Genetics.

**Dr. Seldin** holds the William Buchanan Chair in Internal Medicine.

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\*Artistic rendering - does not depict actual lab standards and safety precautions used at UT Southwestern.

# Two Degrees Of Separation

*For more than three decades, the Medical Scientist Training Program at UT Southwestern has been attracting outstanding students and producing impressive results. **By Alex Lyda & Patrick Wascovich***



*Dr. Andrew Zinn,  
1988 MSTP graduate*

Each year, across the nation, a few hundred medical school students are pursuing not one, but two degrees simultaneously – one that teaches them how to care for patients and a second that is focused on research.

Having health care team members with the capacity to address, decipher, and combine the language and application of patient-centered medical care with that of laboratory-based science is proving invaluable. At UT Southwestern Medical Center, the dual-degree Medical Scientist Training Program (MSTP) is focused on graduating physician-scientists with the advanced knowledge and clinical skills to blend basic science and medicine.

Trained as M.D.s to diagnose and treat patients, while also educated as Ph.D.s in laboratory processes, physician-scientists are able to break down human health challenges into their biologic pathologies and translate their findings to patient care. The explosion of knowledge in the biomedical sciences has created challenges to those who work to understand the cellular and molecular basis of disease and to apply that knowledge in a practical way to benefit patients directly.

About a dozen UT Southwestern faculty members – including Dr. Andrew Zinn, recently named the eighth Dean of the UT Southwestern Graduate School of Biomedical Sciences – are themselves graduates of the Medical Center's MSTP. In addition to his new appointment, Dr. Zinn, a 1988 graduate, continues to lead the MSTP as well. In all, there are approximately 150 faculty who hold combined M.D./Ph.D.

degrees among UT Southwestern's roster of more than 2,700 full- and part-time faculty members.

"M.D./Ph.D. students receive rigorous clinical and research training in an integrated fashion," said Dr. Zinn, who also is a Professor of Internal Medicine in the Eugene McDermott Center for Human Growth and Development. "In the past, many physician-scientists gained exposure to research during medical school and went on to conduct additional research during their fellowship years. Some of our most successful faculty members, such as Nobel Laureates Drs. Michael Brown and Joseph Goldstein, pursued this path. There is less time for research, however, in today's undergraduate and postgraduate medical curricula. It is telling that Dr. Brown himself champions M.D./Ph.D. training, as demonstrated by his long-standing tenure as program director/co-director."

Dr. Brown, who shared the 1985 Nobel Prize in Physiology or Medicine with Dr. Goldstein for their discovery of the basic mechanism of cholesterol metabolism, said, "At many academic medical institutions, the separation between basic scientists and physicians is growing astronomically. That's why I spend so much time with the MSTP. We train a single person in both roles. Our hope is that those people can go out and do both things. I believe in our M.D./Ph.D. program. The time you can spend doing both science and medicine, it's Nirvana as far as I'm concerned."

The MSTP at UT Southwestern began 35 years ago and is one of fewer than 50 M.D./Ph.D. programs across the country funded by the National Institutes of Health to train new generations of physician-scientists. The UT Southwestern program has produced more than 210 alumni who are now engaged in research and clinical care at academic medical centers across the country.

Almost 60 alumni have remained in Texas. Others are now at Harvard University/Brigham and Women's Hospital; Vanderbilt University Medical Center; Johns Hopkins University School of Medicine; Columbia University; University of California, San Francisco School of Medicine; Yale School of Medicine; Stanford University; Washington University in St. Louis; and Memorial Sloan-Kettering Cancer Center, among others. In the commercial marketplace, UT Southwestern MSTP graduates have held positions with companies that include Bristol-Myers Squibb, Merck Research Laboratories, Amgen, Johnson & Johnson affiliate Centocor Research and Development (now Janssen Biotech), and Arena Pharmaceuticals.



*"I believe in our M.D./Ph.D. program. The time you can spend doing both science and medicine, it's Nirvana as far as I'm concerned."*

*- Dr. Michael Brown*

Dr. Dianna McGookey Milewicz, a charter member of the MSTP at UT Southwestern, now leads the M.D./Ph.D. program at UT Health Science Center at Houston, where she is a Doris Duke Distinguished Clinical Scientist and holds the President George Bush Chair in Cardiovascular Medicine.

"UT Southwestern provided excellent clinical and research training that served as the foundation for my entire career," Dr. Milewicz said. "The individuals who trained me – Dr. Jean Wilson [Professor Emeritus of Internal Medicine], Dr. Richard Anderson [former Chair of Cell Biology], Drs. Brown and Goldstein, Dr. Jim Willerson [former Director of Cardiology

and former President of the UT Health Science Center at Houston] – supported me throughout my career, and I will always be grateful for this support.

"I learned to think like a scientist when addressing clinical problems," she added. "I also learned that studying rare genetic syndromes can provide insight into the molecular pathology of more common diseases, which is why I have focused my career on the molecular pathology of relatively rare genetically triggered vascular diseases."

### A distinctive program

At UT Southwestern, approximately 10 MSTP participants are selected each year from among many highly qualified applicants. Interested undergraduate students from among the country's most prestigious universities compete for the coveted slots.

After completion of training, they are accepted into some of the most sought-after residencies in the country. The nine 2013 MSTP graduates, for example, are now in clinical residencies at academic medical centers that include UT Southwestern, The Children's Hospital of Philadelphia, Vanderbilt University Medical Center, Northwestern University Feinberg School of Medicine, and Barnes-Jewish Hospital, affiliated with Washington University in St. Louis.

"Our program is distinctive because it provides participants with top-notch clinical training and with mentoring by world-class scientists in a highly collaborative, nurturing environment," Dr. Zinn said. "I cannot think of another M.D./Ph.D. program whose co-director is a Nobel Laureate."

The UT Southwestern program typically consists of two years of medical school; a minimum of three years of graduate study and dissertation research, leading to the Ph.D. degree in a biomedical science; and then clinical studies and rotations for the final two years of medical school, leading to the M.D. degree.

When first immersed in the two years of preclinical medical school instruction, UT Southwestern medical students are taught by a faculty that includes no fewer than 18 members of the Institute of Medicine, a highly prestigious elected group that advises the federal government on crucial issues involving medical care, research, and education.

When UT Southwestern's MSTP participants move into their various biomedical investigative disciplines, their years of graduate study, dissertation research, and completion are guided by



*“Whatever you do, you have to make sure you love doing it and are happy that it consumes your waking hours. It’s the only way I’ve been able to get everything done.”*

*- Gaurab Chakrabarti, MSTP student*

a cadre of mentors few institutions can match. Some of the Medical Center’s most noted faculty members regularly participate in the program – Nobel Laureates Drs. Brown, Goldstein, Alfred Gilman, and Bruce Beutler (who alone have mentored nearly two dozen MSTP students), and National Academy of Sciences members such as Drs. Eric Olson, Beth Levine, Melanie Cobb, David Mangelsdorf, Steven McKnight, Helen Hobbs, and David Russell.

And the 26 current post-Ph.D. trainees now completing their final two years of medical school are integrating science and medicine in the patient rooms of UT Southwestern University Hospitals & Clinics, Parkland Memorial Hospital, and Children’s Medical Center Dallas.

### ‘Delayed gratification’

For most MSTP students, the rigorous program typically takes about eight years to complete. Those selected receive a stipend and tuition allowance.

Going from medical school, where every detail is scheduled, to graduate school – where students must determine what classes they will take, what research investigations to pursue, even when they are willing to be done for the day – is a challenge. Staying the course of this extended and demanding dual-degree program requires sacrifice and perseverance, Dr. Zinn said.

“It also involves delayed gratification,” he added. “Students will be in their 30s by the time it’s all done.

“But I have never regretted pursuing it. I loved medical school, I loved graduate school, and I loved my residency, my postdoctoral work, being on the faculty, and everything else that went along with it.”

In the years since 1978, when the MSTP program began at UT Southwestern, the Medical School has conferred about 7,000 degrees, and the UT Southwestern Graduate School of Biomedical Sciences has about 2,700 alumni; of this cumulative total of 9,700 degrees, 2.2 percent were awarded to physician-scientists who completed the requirements of the M.D./Ph.D. program.

Identifying good MSTP candidates is one of the great challenges of the selection process, according to Dr. Russell, UT Southwestern’s Vice Provost and Dean of Basic Research and a long-time faculty member who has been associated with the MSTP since the 1980s.

High scores on the Medical College Admission Test and exceptional undergraduate grade-point averages aside, Dr. Russell said he looks for passion and a well-rounded disposition when interviewing MSTP candidates.

“We want our students not only to be passionate about learning good clinical practices and working on hospital ward teams, but also to have a detailed knowledge of disease processes,” said Dr. Russell, who also is a Professor of Molecular Genetics. “The latter might be gained from studying a fruit fly, but ultimately this knowledge must be applicable to our own species. If someone is overly rigid or lacks strong interpersonal skills, he or she will struggle in the creative world of the physician-scientist.”

## Taking flight

Initially under the direction of Dr. Wilson, the demanding M.D./Ph.D. program, like all UT Southwestern degree programs, has always been based solely on merit. NIH funding began in 1982, but UT Southwestern's MSTP took flight in 1988, when Dallas businessman and philanthropist Ross Perot provided \$20 million over a decade for a variety of initiatives, chief among them the combined degree program.

"The value of upgrading the MSTP [was] incalculable," Dr. Errol C. Friedberg, Professor Emeritus of Pathology, wrote in his 2007 history of the Medical Center, *From Rags to Riches*. "Mr. Perot's contribution enabled UT Southwestern to mount the single largest program in the country."

Mr. Perot's support allowed UT Southwestern to grow the program fourfold. The Perot family and its foundation later extended their support as part of a \$50 million commitment to UT Southwestern's *Innovations in Medicine* campaign.

The results are telling. The UT Southwestern program awarded its first degrees in 1984; from 1986 to 1989, just six students completed the M.D./Ph.D. program. Between 1991 and 1995, however, UT Southwestern awarded 16 students the prestigious combination, and over the next five years, another 44 students earned combined M.D./Ph.D. degrees. Since 2001, the MSTP program has graduated, on average, 10 students annually.

"The program is a long-term investment in the future," Dr. Zinn said. "It requires a lot of sacrifice, but it can be such a rewarding profession."

"Stipend support during M.D./Ph.D. training relieves future physician-scientists of the burden of taking on debt to finance their protracted training, which can cripple their research career aspirations."

## Becoming a physician-scientist

MSTP students must not only be dedicated and willing to work hard, but to manage the dual degree program successfully, they also must be very effective at time management.

Current MSTP student Gaurab Chakrabarti understands what it takes.

Mr. Chakrabarti navigates his day by one clear, overriding compass: time. The time needed to complete a task, to wait for a molecular reaction to occur, to provide insight to an inquisitive visitor.

Darting in and out of the laboratory of Dr. David Boothman, Professor of Pharmacology and Radiation Oncology in the Eugene McDermott Center for Human Growth and Development, this past summer, Mr. Chakrabarti took a 45-minute break between experiments to discuss his journey thus far. The interview was marked precisely by a digital stopwatch on the empty table where he sat.

Mr. Chakrabarti, a 25-year-old Sugar Land native, entered his fourth year of the program at the start of the academic year in September.

"Whatever you do, you have to make sure you love doing it and are happy that it consumes your waking hours. It's the only way I've been able to get everything done," Mr. Chakrabarti said.

The MSTP program, he said, represents "unsiloed" opportunity and the freedom to pursue complex questions in medicine while learning the fundamentals of science and clinical care that undergird the field.

"Whether it's a dataset or preparing a meal, I am constantly giving myself deadlines," Mr. Chakrabarti said. "I have a pretty good track record with myself. While the deadlines may seem semi-artificial, they are effective."

## Pursuing parallel passions

Dr. Christine Kim Garcia understands well the demands on an MSTP student's time; in the 1990s, she was a UT Southwestern MSTP student herself, on her way to fulfilling a dream.

Early on, she knew exactly what she wanted to do with her life.

"I told my first-grade teacher I was going to be a physician," she said.

By the time she graduated from Texas A&M University with a bachelor's degree in chemistry, her career course was set. The MSTP at UT Southwestern would allow her to pursue her dual passions: medicine and research, two disciplines that can seem worlds apart.

"You're using different parts of your brain," Dr. Garcia said. "With research, you have to really enjoy detective work and discovery. You have to be OK with not knowing all the answers. But when you work in a lab, you feel like you are at the forefront of medicine – you're making breakthroughs."

She also found that switching from the camaraderie of the medical school classroom to the solitude of a laboratory was a challenging transition. Today, Dr. Garcia, Associate Professor of Internal Medicine in the Eugene McDermott Center for Human Growth and Development



at UT Southwestern, is grateful for the unique opportunity to blend her passions into an immensely satisfying career.

Dr. Garcia, a faculty member since 2005, did doctoral work with Drs. Brown and Goldstein. After completing medical school and her internal medicine residency at UT Southwestern, she finished postdoctoral fellowships in pulmonary disease and critical care medicine, and then in molecular genetics under Dr. Hobbs.

Dr. Garcia now focuses on defining the genetic determinants of adult-onset pulmonary disease, the third-leading cause of death in the U.S. Investigations by Dr. Garcia and her UT Southwestern colleagues have been published in top journals, such as *Science* and the *Proceedings of the National Academy of Sciences*.

Other MSTP graduates on the faculty also are melding medicine and science while forging their careers.

Dr. Deepak Nijhawan, Assistant Professor of Internal Medicine and Biochemistry, has launched a research program in the Department of Biochemistry that uses chemistry to identify new targets for lung cancer treatment – research that reflects his reason for pursuing the combined-degree program.

“I always wanted to work on solving scientific problems with immediate relevance to human disease, and the MSTP provided the ideal educational experience to achieve that goal,” he said. “In the medical portion of the training, we

*“With research, you have to really enjoy detective work and discovery. You have to be OK with not knowing all the answers. But when you work in a lab, you feel like you are at the forefront of medicine – you’re making breakthroughs.”*

*- Dr. Christine Kim Garcia,  
1996 MSTP graduate*

learned the science of human disease and the best available treatments, whereas in the Ph.D. training, we learned how to answer questions that advanced the science of human disease in order to improve treatments.”

Dr. Rhea Sumpter Jr., Instructor of Internal Medicine, was attracted to the program for many of the same reasons. He said his clinical training helped him identify research questions that would affect his understanding of human disease. The program also allowed him to fast-track his residency and get back to the lab quickly.

"I count several former MSTP students among my closest friends, and I also established strong mentor relationships with several faculty members, relationships that have been invaluable assets at key points in my career," he said.

### A future of opportunity

Dr. Zinn's own career was shaped by his ability to bridge medicine and science. "I could not have had the career I have without M.D./Ph.D. training," he said. "My research involves understanding the molecular basis of human genetic diseases. Without clinical training, I could not have identified the research opportunities afforded by unique patients with rare genetic disorders. Without research training, I could not have capitalized on these opportunities."

In his current faculty and administrative roles, Dr. Zinn continues to guide and mentor those wanting to connect medicine and science.

"Being an M.D./Ph.D. has enabled me to foster connections between basic and clinical/translational science, epitomized by our recent Clinical and Translational Science Award and our new William P. Clements Jr. University Hospital," he said.

There's a bright future, he added, for academic, clinical, and research institutions that appreciate and respond to the advantages combined-degree team members bring.

"M.D./Ph.D.s are assuming leadership roles in biomedical science," Dr. Zinn said. "For example, the current director of the NIH, Francis Collins, is an M.D./Ph.D."

"M.D./Ph.D.s also are playing an increasing role in the biotechnology and pharmaceutical industries. A growing proportion of physician research will be done by physician-scientists, who already hold 40 percent of all NIH grants awarded to M.D.s, despite being just 3 percent of medical school graduates."

*Lin Lofley and Jan Jarvis contributed to this story.*

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*Dr. Beutler is Director of the Center for the Genetics of Host Defense and a Regental Professor. He holds the Raymond and Ellen Willie Distinguished Chair in Cancer Research, in Honor of Laverne and Raymond Willie, Sr.*

*Dr. Boothman, Professor of Pharmacology and Radiation Oncology in the Harold C. Simmons Comprehensive Cancer Center, holds the Robert B. and Virginia Payne Professorship in Oncology.*

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

*Dr. Cobb, Professor of Pharmacology, holds the Jane and Bill Browning Jr. Chair in Medical Science.*

*Dr. Garcia holds the Kern and Marnie Wildenthal President's Research Council Professorship in Medical Science.*

*Dr. Gilman is a Regental Professor Emeritus.*

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

*Dr. Hobbs, Director of the Eugene McDermott Center for Human Growth and Development, 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, and is a Howard Hughes Medical Institute Investigator.*

*Dr. Levine, Professor of Internal Medicine and Microbiology, holds the Charles Cameron Sprague Distinguished Chair in Biomedical Science and is an HHMI Investigator.*

*Dr. Mangelsdorf, Chairman of Pharmacology, holds the Raymond and Ellen Willie Distinguished Chair in Molecular Neuropharmacology in Honor of Harold B. Crasilneck, Ph.D., and the Distinguished Chair in Pharmacology, and is an HHMI Investigator.*

*Dr. McKnight, Chairman of Biochemistry, holds the Sam G. Winstead and F. Andrew Bell Distinguished Chair in Biochemistry, and the Distinguished Chair in Basic Biomedical Research.*

*Dr. Olson, Director of the Nancy B. and Jake L. Hamon Center for Basic Research in Cancer, holds the Pogue Distinguished Chair in Research on Cardiac Birth Defects, the Robert A. Welch Distinguished Chair in Science, and the Annie and Willie Nelson Professorship in Stem Cell Research.*

*Dr. Russell holds the Eugene McDermott Distinguished Chair in Molecular Genetics.*

*Dr. Zinn holds the Rolf Haberecht and Ute Schwarz Haberecht Deanship of the UT Southwestern Graduate School of Biomedical Sciences.*

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By Debbie Bolles

# Taking Aim at Alzheimer's

*The odds of getting Alzheimer's disease increase significantly as a person ages.*

*Researchers and physicians at UT Southwestern are working tirelessly to find better treatments – and hopefully a cure – for this devastating disease.*

Lonna Atkins knew the odds were stacked against her. Eight of her 11 siblings had developed Alzheimer's disease, so the 73-year-old Dallas grandmother assumed that one day she would be next.

"She was prepared to have Alzheimer's disease," said Jim Atkins, 73, her husband of 53 years and now her primary caregiver. "She always thought she would have it. But even when the day came, I was devastated."

The signs initially weren't obvious. But Mrs. Atkins, so attuned to the symptoms of Alzheimer's because of how it had ravaged her family, one day realized that her memory wasn't what it used to be. In 2004, she sought testing at UT Southwestern Medical Center's Alzheimer's Disease Center (ADC), and the results confirmed her suspicions.



Jim and Lonna Atkins

*“There is something that is permissive about aging that allows the pathology of the genes that cause Alzheimer’s disease to take hold. That is the main risk factor – aging.”*

– Roger Rosenberg, M.D.

The disease progressed slowly, so the Atkinses used the time to prepare themselves by accessing the support groups and training classes made available through the ADC and the Alzheimer's Association.

"Alzheimer's is a horrible disease to have, but we have gotten such great support and care from UT Southwestern," Mr. Atkins said. "I think if you are going to have it, it is good to know UT Southwestern has the resources to help. Going to the Alzheimer's Disease Center is like visiting with friends who know a tremendous amount about what you are going through."

As the Atkinses deal with this neurodegenerative disease that slowly robs the patient of skills to function independently, life goes on. The couple recently moved to a retirement center equipped to provide extra assistance. Mrs. Atkins remains under the care of Dr. Mary Quiceno, Assistant Professor of Neurology and Neurotherapeutics.

Mrs. Atkins and her husband, both active participants in several research programs at the ADC, hope the groundbreaking work taking place at UT Southwestern on causes and potential cures of this debilitating disease may one day help others avoid the journey they are now on.

## A rising tide

Alzheimer's disease is an incurable and progressive type of dementia that deprives an estimated 5.2 million Americans of their memory and thinking. The disease can affect people as young as age 40, although the typical patient notices symptoms at age 65 or older. Without a cure, the number of cases is predicted to rise to 12 million by 2030. Symptoms usually develop slowly and worsen over time.

Established in 1988, the Alzheimer's Disease Center at UT Southwestern is dedicated to finding ways to treat and prevent the illness and is one of 29 such specialty centers in the country funded by the National Institute on Aging (NIA), a branch of the National Institutes of Health. Clinicians and researchers at UT Southwestern's center evaluate patients and conduct scientific research into the causes of Alzheimer's. The team is divided into five core groups that: 1) conduct clinical research; 2) study the neuropathology of Alzheimer's;

3) provide education and outreach to the community; 4) support data management; and 5) provide administrative functions.

"We are making major progress in understanding the basic biology of Alzheimer's disease and testing new therapies to prevent and slow the symptoms of memory and cognitive loss," said Dr. Roger Rosenberg, Director of the ADC and Professor of Neurology and Neurotherapeutics and Physiology. "Our goal is to provide information about Alzheimer's research, offer support for people living with the disease, and inform the community of our research efforts."

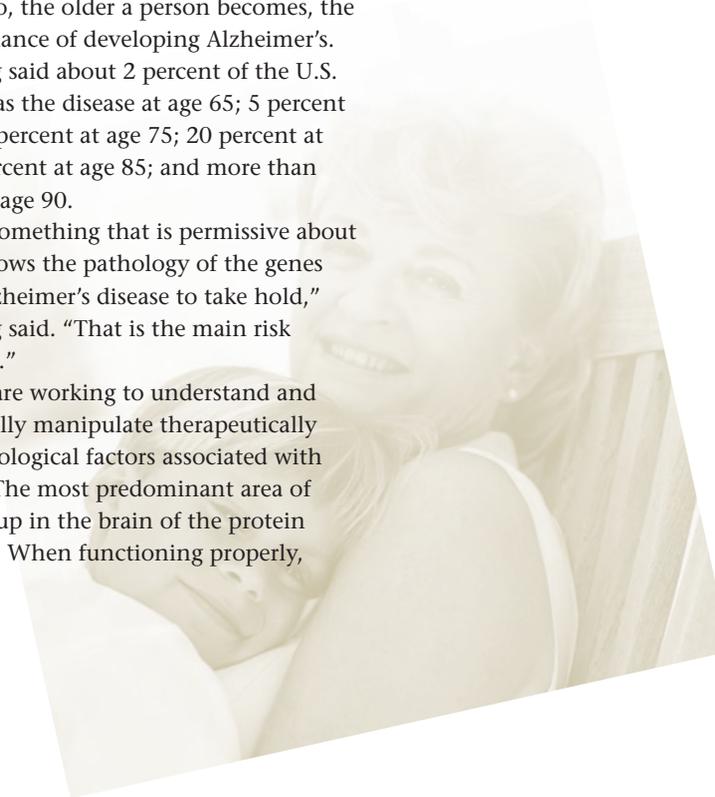
## Understanding the disease

In 1901, German physician Dr. Alois Alzheimer examined patient Auguste Deter for severe memory loss. Mrs. Deter's answers to questions were uncertain or nonsensical, and she also had profound mood swings and delusions. Eventually, she became demented and died in 1906. Upon examining her brain, Dr. Alzheimer discovered a massive loss of neurons and the presence of amyloid plaques and neurofibrillary tangles, hallmarks of the disease now named after him.

Although there is no cure for Alzheimer's, scientists today know significantly more about disease risk factors and causes. Some risk factors are genetic – related to family history and ethnicity. Also, the older a person becomes, the greater the chance of developing Alzheimer's. Dr. Rosenberg said about 2 percent of the U.S. population has the disease at age 65; 5 percent at age 70; 10 percent at age 75; 20 percent at age 80; 40 percent at age 85; and more than 50 percent at age 90.

"There is something that is permissive about aging that allows the pathology of the genes that cause Alzheimer's disease to take hold," Dr. Rosenberg said. "That is the main risk factor – aging."

Scientists are working to understand and then potentially manipulate therapeutically the known biological factors associated with Alzheimer's. The most predominant area of focus is buildup in the brain of the protein beta-amyloid. When functioning properly,





this protein suppresses nerve activity involved with memory and learning. Its normal function can be likened to a traffic light, restraining nerve cells from getting overly excited when they receive stimulating signals from neighboring cells. People with Alzheimer's, however, accumulate too much beta-amyloid, causing the traffic light to get stuck on "red" and nerve cells to become less responsive.

Another protein that plays a role is tau, which, like beta-amyloid, also can malfunction and accumulate in the brains of Alzheimer's patients, forming neurofibrillary tangles, or clumps, inside neurons.

Research to understand these malfunctioning proteins continues, including studies related to the possible influence of calcium signaling on beta-amyloid. Dr. Ilya Bezprozvanny, Professor of Physiology, has found that calcium signaling is abnormal in mouse models of aging neurons.

*“We must get better at identifying the disease early and stopping it in its tracks. Fortunately, we now recognize at a stage earlier than ever those patients who are at risk.”*

“We documented a significant increase in calcium levels stored in an intracellular signaling compartment called the endoplasmic reticulum,” Dr. Bezprozvanny said. “The resulting compensatory responses in neurons cause abnormal neuronal activity and loss of synapses. Thus, for many patients, a malfunction in calcium signaling that causes a buildup of calcium levels is a primary cause of memory loss in aging and Alzheimer's.”

Calcium-blocker drugs might counteract this malfunction, halting the buildup of beta-amyloid in the brain and Alzheimer's development, Dr. Bezprozvanny said. One such drug, memantine, is already approved for Alzheimer's treatment, but Dr. Bezprozvanny said more effective calcium blockers are needed, and his laboratory is working toward that goal.

## Searching for a cure

For the past decade, Dr. Rosenberg has been working on a vaccine that he hopes will prevent Alzheimer's or at least slow its progression. He has even received a patent for a vaccine that uses DNA to create antibodies against beta-amyloid. In mouse models, the vaccine reduced beta-amyloid in the brain by 50 percent.

“If you could do the same in patients, then onset of the disease would be delayed by roughly five years. In a large population, that would reduce the prevalence of the disease by half,” Dr. Rosenberg said. “Those are impressive numbers.”

According to Dr. Rosenberg, an optimistic time frame for finishing up preclinical work on the vaccine is approximately two years and then, if all goes well, about five more years to complete a clinical trial. Three other groups outside of UT Southwestern are working on similar vaccines, but, so far, none has been approved.

At the same time, research suggests people can take certain steps that may prevent or delay Alzheimer's. Those preventive measures include exercising regularly and making certain dietary changes.

“We're seeing evidence that people who are the most physically active, even later in life, show less brain shrinkage and other signs associated with dementia,” said Dr. Quiceno, who leads the ADC's education core and provides nutritional and dietary advice to patients in her clinic.

One study under way at UT Southwestern is designed to determine whether individuals with mild cognitive impairment – often considered a precursor to Alzheimer's – can benefit from a regular fitness program. The study participants, who do not exercise regularly, are placed either in a supervised, individually tailored aerobic exercise program or in one that focuses on flexibility and strength training. Over a year, researchers will track the effects of exercise on both cognitive and cardiovascular health, as well as changes in proteins that damage or protect brain cells.

Another prevention-targeted trial at UT Southwestern will test an anti-amyloid antibody drug on adults not suspected of having Alzheimer's. The multicenter Anti-Amyloid

Treatment of Asymptomatic Alzheimer's Disease (A4) trial, set to launch in 2014, will treat about 6,000 participants age 65 or older with either an anti-amyloid drug or a placebo over a three-year period. The trial will test the hypothesis that decreasing the amyloid burden in the brain during preclinical stages of the disease impacts downstream neurodegeneration and delays cognitive decline.

As for nutrition, several studies suggest beneficial anti-Alzheimer's effects obtained from certain foods and supplements, said Dr. Quiceno. These include resveratrol, a substance found in red grapes, red wine, and dark chocolate; Mediterranean diet foods such as fish, nuts, and oils; algal DHA, a type of omega-3 fatty acid; and turmeric, a supplement or spice common in Indian food.

## Early diagnosis is key

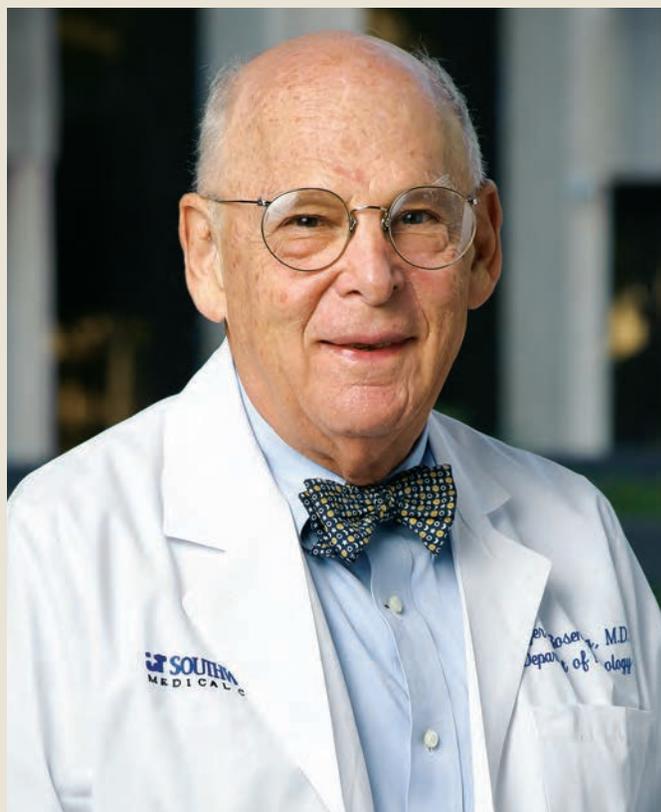
One of the challenges of Alzheimer's is that most patients don't seek help until they develop symptoms, by which time too much damage to the brain has already occurred for treatment to be effective.

"We must get better at identifying the disease early and stopping it in its tracks," said Dr. Rosenberg. "Fortunately, we now recognize at a stage earlier than ever those patients who are at risk."

Through advanced brain imaging and biochemical studies of cerebrospinal fluid, which surrounds the brain, physicians can identify those most at risk before they show any symptoms. With such tests, plus an examination of the patient and a detailed medical history, a diagnosis of Alzheimer's can be made with about 90 percent accuracy, according to Dr. Rosenberg.

A major advance came in 2012 with Food and Drug Administration (FDA) approval of the first amyloid imaging agent, called Amyvid, for use in positron emission tomography (PET) brain scans. Amyvid is a radiopharmaceutical that binds to amyloid plaque in the brain and "lights up" on a PET scan, allowing radiologists to identify the presence of this harmful protein. It's being used both clinically and in research projects.

PET scans for suspected Alzheimer's are often expensive or invasive, however, and not every patient is able or willing to undergo them. Because of that, UT Southwestern researchers, including Dr. Dwight German, Professor of Psychiatry, continue to develop other diagnostic tools.



Dr. Roger Rosenberg

A diagnostic blood test developed in Dr. German's laboratory uses synthetic molecules that function as immune-system readers to seek out and identify disease-specific antibodies. Research continues to pinpoint antibodies that will be useful as blood biomarkers to identify those found in early-stage Alzheimer's. Meanwhile, Dr. German is collaborating with other research centers to refine a separate blood test that calculates risk for Alzheimer's through mathematical analysis of blood proteins.

## Advancing treatment

Despite the ability to diagnose Alzheimer's earlier than ever, for those already suffering symptoms, treatment options are limited. Researchers are continuing to test new drugs and other therapeutic interventions that appear promising.

"Right now, there is no therapy for Alzheimer's directed at the biology of the disease that can reverse it. There are only three therapies approved by the FDA that offer symptomatic relief," Dr. Rosenberg said.

UT Southwestern participates in numerous clinical trials aimed at finding better treatments. One that could potentially be game-changing will test use of intranasal insulin in Alzheimer's patients. This 30-center national trial, set to launch in 2014, will measure improvements in cognition over a year's period in participants given either insulin or a placebo. Leading the UT Southwestern arm of the trial is Dr. Kyle Womack, Assistant Professor of Neurology and Neurotherapeutics and Psychiatry.

"Patients with Alzheimer's have reduced levels of insulin and insulin resistance within the brain. This produces damage to the synapses where neurons communicate," Dr. Womack said. "By giving insulin intranasally, it can be delivered directly to the brain without affecting blood levels of insulin or glucose. A pilot trial of this approach had promising results."

UT Southwestern offers patients all the current treatments for Alzheimer's, plus access to new clinical trials such as these and others. Dr. Quiceno cautions, however, that "before treatments can even be considered, a precise diagnosis is critical. UT Southwestern is able to provide this through our experienced clinicians and availability of neuropsychological experts and biomarker tests. Continued support and collaboration with community-based partners, as well as ongoing care and education provided by our physicians, our nurse practitioners, and research personnel, are all part of the treatment plan."

## Supporting the cause

A 2013 study sponsored by the NIA estimates the cost of Alzheimer's disease treatment in the U.S. at \$157 billion to \$215 billion annually. That's more than the cost of treating cancer or cardiovascular disease because Alzheimer's

patients live longer than cancer patients or heart attack victims – an average of eight years after diagnosis.

"Yet, federal support for Alzheimer's research remains about one-tenth of what is spent for cardiovascular disease and cancer – roughly \$500 million annually – compared to \$4 billion to \$6 billion, respectively, for those two diseases," Dr. Rosenberg said.

In 2011, the ADC received a five-year, \$9 million federal grant to support its Alzheimer's research, representing 28 years of continuous NIH funding. Other support comes from the state-funded Texas Alzheimer's Research and Care Consortium (TARCC), in which UT Southwestern and five other member institutions collaborate on Alzheimer's research, including the collection of genetic and blood biomarker data for the Texas Alzheimer's DataBank. UT Southwestern receives about \$750,000 annually for Alzheimer's research from TARCC.

Friends of the Alzheimer's Disease Center, a group that has contributed more than \$1 million since 1996 toward research efforts into neurodegenerative diseases, also helps further UT Southwestern's work on Alzheimer's. Seed money from the Friends helps junior researchers embark on important investigations into Alzheimer's and other neurodegenerative diseases and attracts additional funding from governmental agencies, advocacy organizations, and other supporters.

Last year, the Friends awarded four \$65,000 grants to UT Southwestern faculty members Dr. Kevin King, Assistant Professor of Radiology; Dr. Yun Liu, Instructor of Neuroscience; Dr. Steven Patrie, Assistant Professor of Pathology; and Dr. Fu Lye "Martin" Woon, Assistant Professor of Psychiatry. Their diverse research projects, respectively, involve studying the effect of aortic stiffness on brain damage and cognitive decline; investigating how two proteins affect the formation and degeneration of synapses; searching for warning signs of Alzheimer's by characterizing signs of inflammation; and using ADC data to develop a model to help clinicians determine whether a patient with mild cognitive impairment will improve.

Two specialized research centers at UT Southwestern also have been funded through generous donations – the Winspear Family Special Center for Research on the Neuropathology of Alzheimer's Disease, directed by Dr. Charles White, Professor of Pathology; and the Center for Alzheimer's and Neurodegenerative Diseases, directed by Dr. Joachim Herz,

Professor of Molecular Genetics, Neuroscience, and Neurology and Neurotherapeutics. The Winspear Center was established in 2002 by a gift from the William and Margot Winspear family, while a \$2 million challenge grant set up the Center for Alzheimer's and Neurodegenerative Diseases in 2010.

## Help in a time of need

Joanne Bara knows too well the indignities and indiscriminate nature of Alzheimer's disease. It deprived her of both parents, first taking her mom and then her dad.

Ms. Bara and her late parents, Donald and Myra Quig, have a connection with the ADC dating back more than a dozen years. Before Mrs. Quig died in 2006, her husband and daughter took advantage of the Center's support resources, including a caregiver support group that meets monthly. Mr. Quig, also diagnosed with Alzheimer's, succumbed to the disease in 2010.

"The physicians and employees at UT Southwestern were a tremendous support during my parents' journey through the disease. We were part of the 'family' and treated as such," said Ms. Bara.

As Ms. Bara approaches the age at which her mother was diagnosed, she said she gets a bit more nervous about appointments as a "normal control subject" in studies at the ADC.

"At the same time," she added, "I feel comfort knowing that if by chance I am diagnosed, I will have access to new and innovative treatment options and know that my children will have unparalleled support to cope with the challenges that may lie ahead."



Joanne Bara

*Jeff Carlton contributed to this story.*

*Dr. Bezprozvanny holds the Carl J. and Hortense M. Thomsen Chair in Alzheimer's Disease Research.*

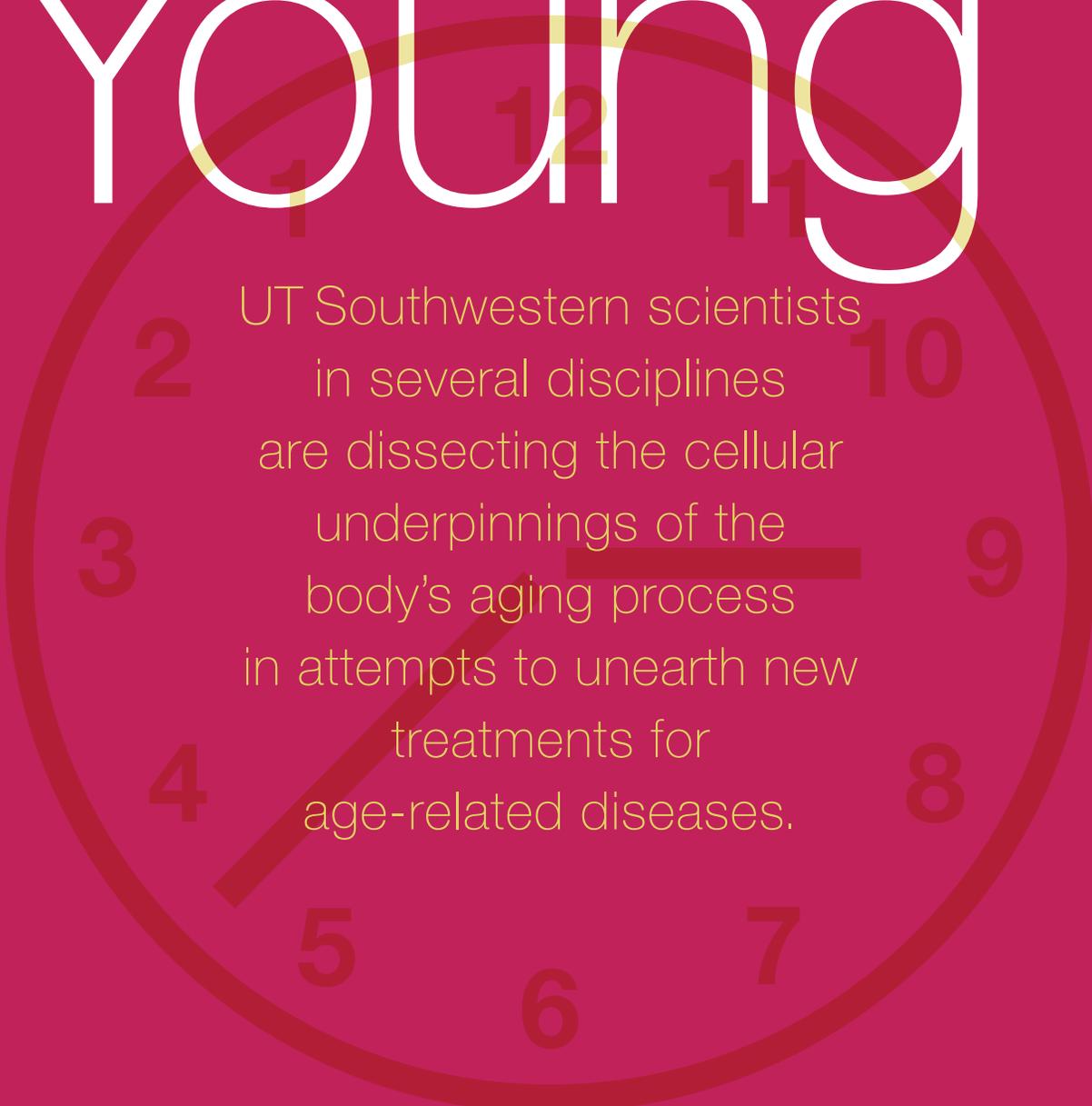
*Dr. Herz holds the Thomas O. and Cinda Hicks Family Distinguished Chair in Alzheimer's Disease Research.*

*Dr. Patrie is a John L. Roach Scholar in Biomedical Research.*

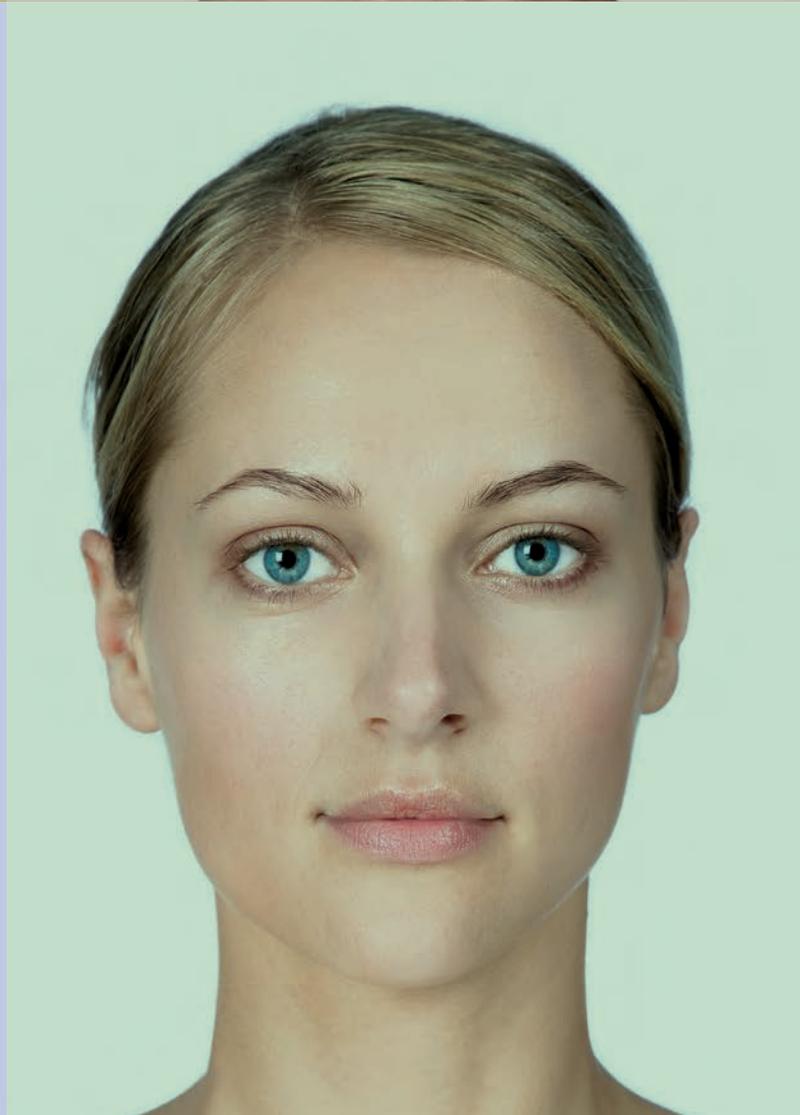
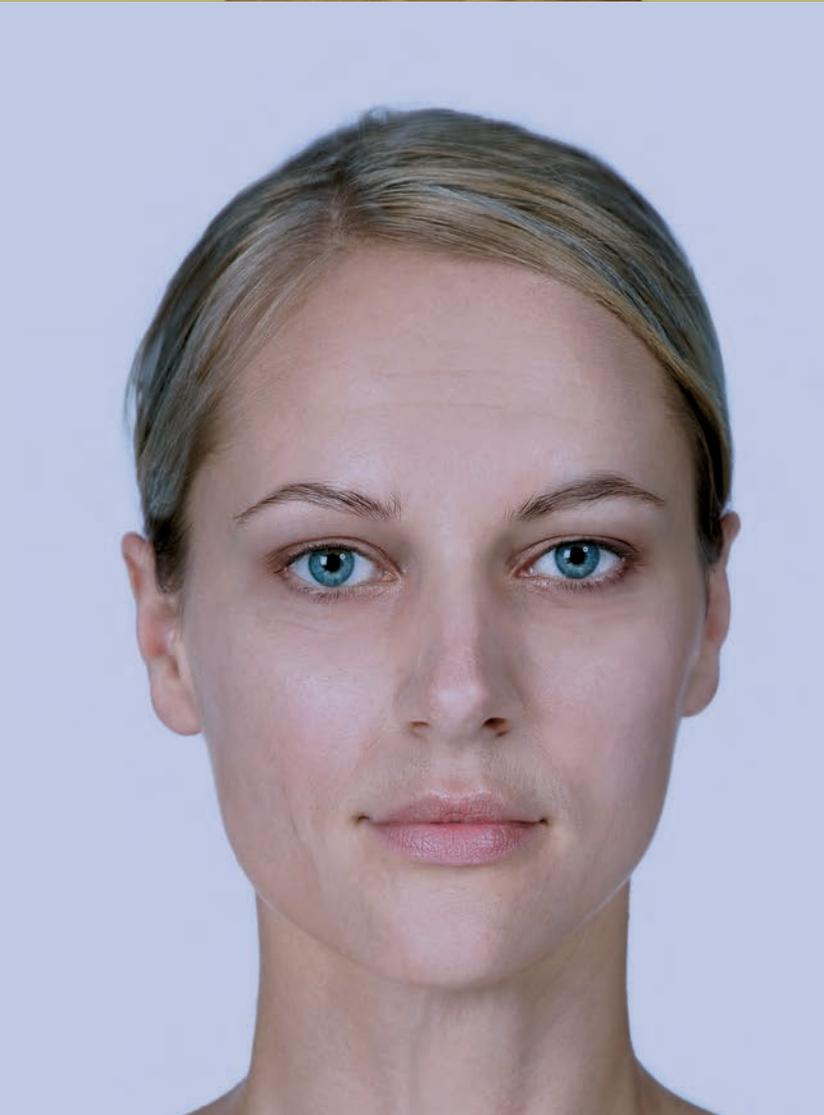
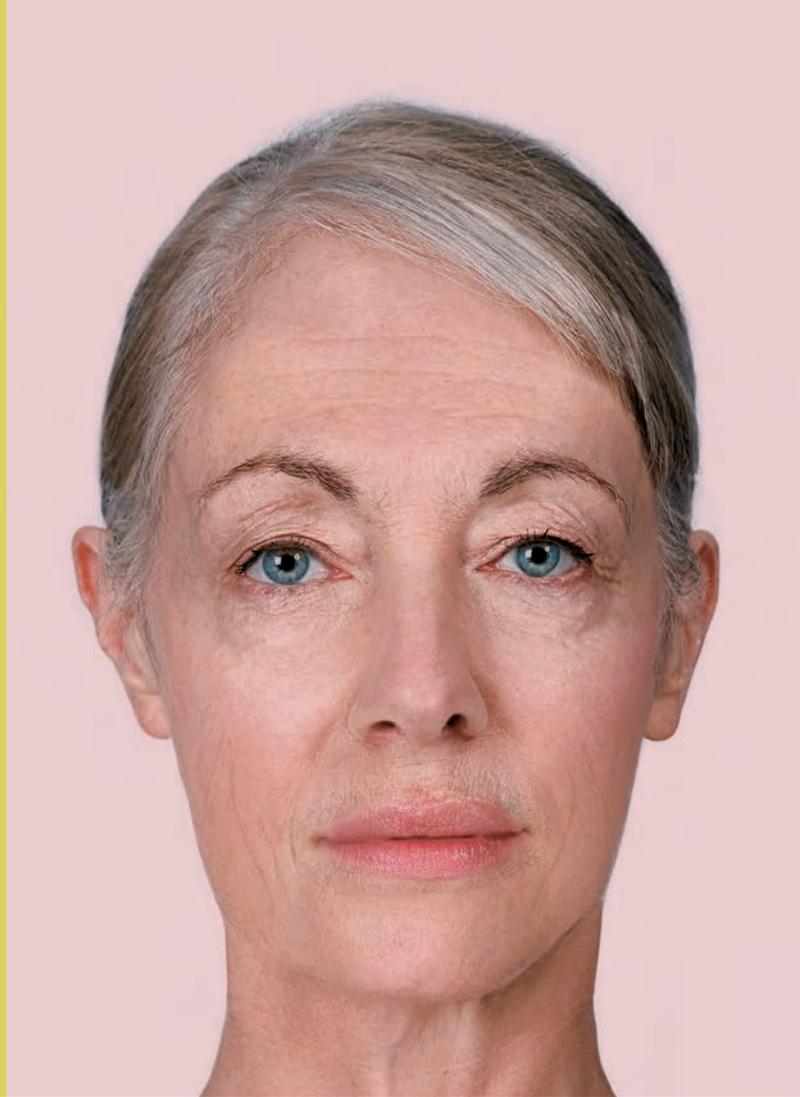
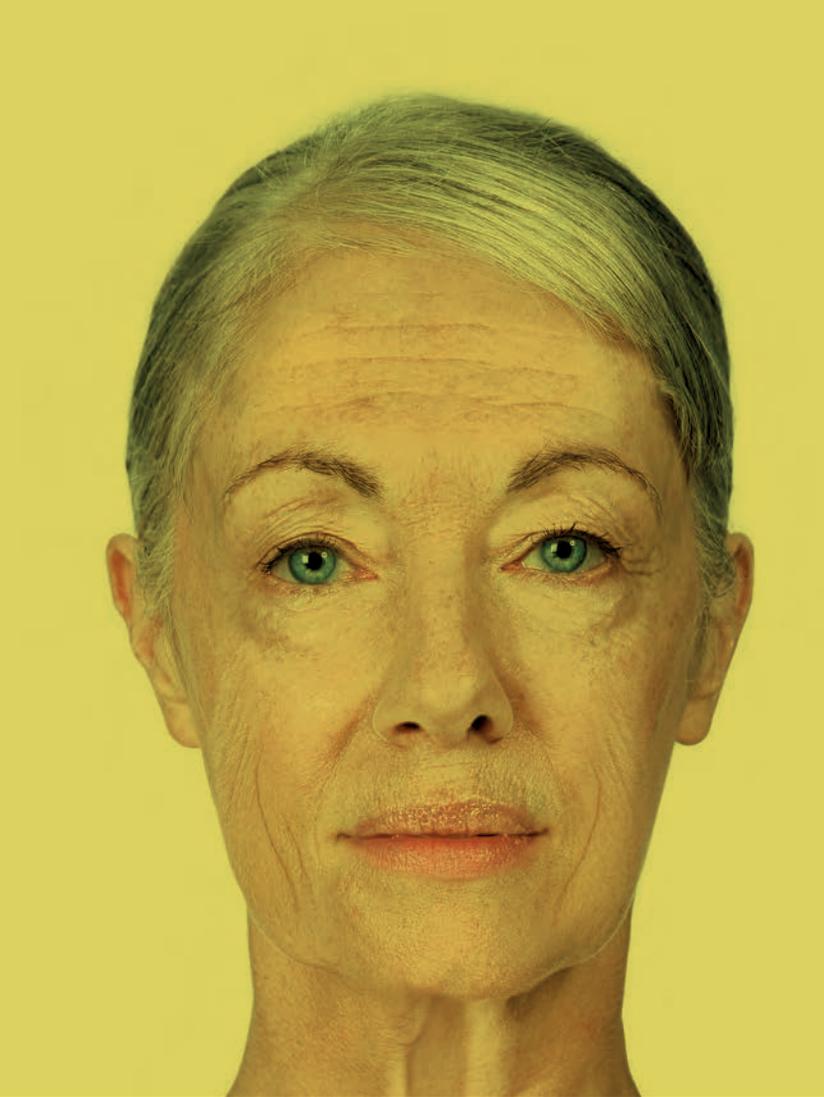
*Dr. Rosenberg holds the Abe (Brunky), Morris and William Zale Distinguished Chair in Neurology.*

*Dr. White holds the Nancy R. McCune Distinguished Chair in Alzheimer's Disease Research.*

# Forever Young



UT Southwestern scientists in several disciplines are dissecting the cellular underpinnings of the body's aging process in attempts to unearth new treatments for age-related diseases.





was hard at the dawn of the 20th century. As the Industrial Revolution was coming to a close, the typical American born in the early 1900s could expect to live only until age 49, on average. More than a century later, the average American's life expectancy extends to 78 years, due in large part to the discovery of antibiotics and other miracles of modern medicine.

Today, heart disease, diabetes, cancer, and other ailments that often go hand in hand with aging are the killers of most Americans. So what if it were possible to reduce some of the natural declines that occur as the body ages?

Over the past 20 years, UT Southwestern Medical Center researchers have been at the forefront in prolonging life expectancy. By manipulating the molecular processes at work in the human body, they hope to slow or even halt the aging process. As lofty as that goal seems, they are nonetheless applying their discoveries to new ways of fighting diseases often tied to aging, such as cancer, Alzheimer's disease, and chronic kidney disease.

### The immortal cell

Telomeres, the lengths of DNA bits found at the ends of chromosomes, get shorter as a person ages. This genetic evolution fascinates Drs. Jerry Shay and Woodring Wright, who have spent their careers trying to understand how and why dwindling telomeres expedite the aging process.

"Every time cells divide, telomeres get a little bit shorter. Over a lifetime, they go from 15,000 to 20,000 units down to maybe 5,000 or less, so you lose about three-quarters of your telomeres," said Dr. Shay, Vice Chair of Cell Biology and an internationally recognized expert on how these chromosomal elements act as an aging biomarker.

A person with plentiful, long telomeres tends to be younger and healthier, while a person with dwindling and short telomeres is typically older and more susceptible to age-related diseases. Rejuvenating and lengthening telomeres would seem to be the obvious answer to extending life, yet it's not that simple.

Researchers working in the laboratory of Dr. Shay and Dr. Wright, Professor of Cell Biology and Internal Medicine, found that the enzyme telomerase can cause telomeres to grow again and potentially extend life, but there is a deadly tradeoff: Telomerase also has been linked to cancer, which by its simplest definition is abnormal cells growing out of control.

"In 1994 we showed that telomerase was turned on in almost all cancers. We looked at hundreds of cancer cell lines and showed that telomerase keeps cells immortal," Dr. Shay said. "We also showed that experimentally inserting the telomerase gene in normal cells without telomerase did not cause them to become cancerous, but did permit them to divide indefinitely. Importantly, telomerase is not only expressed in cancer cells, but also in certain dividing stem cells that regenerate tissues when damaged."

While work is under way to get around the enzyme's cancer-inducing effect, researchers are learning more about how telomerase functions in relation to aging, telomere shortening, and disease development. In some diseases, such as idiopathic pulmonary fibrosis, dyskeratosis congenita, and a subset of bone marrow failure syndromes, mutations often can be found in the two genes that encode telomerase. As a result, people suffering from these diseases frequently have extremely short telomeres and signs of premature aging.

"Telomere shortening can lead to cell cycle arrest, so you run out of stem cells. In combination with other alterations, this can lead to genomic instability and cancer," Dr. Shay said. "If you don't have enough telomeres, you wind up getting diseases earlier in life."

Outside of activating telomerase, investigators have yet to pinpoint other means of keeping telomeres in good health. Meanwhile, a test that measures a person's telomeres relative to those of others in the same age group could soon become a standard aging biomarker test, similar to cholesterol measurement. Currently, telomere tests are offered by only a handful of private companies because the science is so new.

"If your telomeres indicate you're biologically younger than you are, then you're in good shape; just keep doing what you've been doing. However, if your telomere test indicates

you are biologically older than your chronological age, that's when I say it's like a tap on the shoulder. It doesn't mean you're going to die tomorrow. It just indicates something's wrong," Dr. Shay said.

Lifestyle changes such as stress reduction, weight loss, and exercise have been shown to slow the extent of telomere shortening, he added, indicating that healthy habits can ward off a variety of health problems such as heart disease, diabetes, and cancer, in the end extending a person's life expectancy.

### Transplants of the future

Another focus of the Shay and Wright lab is tissue regeneration.

Now that the pair has discovered how to create immortal cell lines that continue to divide and grow without becoming cancerous by using telomerase to manipulate stem cells, they have turned their attention to making cells that are accepted by the immune system, even if there isn't a tissue match. In mouse models, researchers are attempting to re-create full organs

such as lungs from a base cellular matrix. The hope is that new organs can be created and used for anyone in need of a transplant.

Even though that level of breakthrough is years away, the hope is "to create whole organs as universal donors for transplantation so that you don't have to wait for a tissue match," Dr. Wright said. "This could be done on a mass scale and make the problem of limited organs for transplantation a thing of the past. The implications of this are mind-boggling."

Similar research also is taking place in bone marrow transplantation. Once scientists learn how to grow bone marrow stem cells outside the body, these cells then could be manipulated with telomerase to elongate telomeres and potentially be transplanted back into the patient as young, healthy stem cells. Exposing only bone marrow stem cells to telomerase may negate cancer-inducing effects, Dr. Wright explained.

**Lifestyle changes such as stress reduction, weight loss, and exercise have been shown to slow the extent of telomere shortening, indicating that healthy habits can ward off a variety of health problems such as heart disease, diabetes, and cancer.**

Dr. Woodring Wright (left) and Dr. Jerry Shay have spent their careers trying to understand how and why dwindling telomeres (lengths of DNA bits, magnified behind them) expedite the aging process.



## The anti-aging hormone

Twenty years ago, Dr. Makoto Kuro-O was working as a cardiologist in Japan, researching the molecular basis of hypertension. During his investigation, Dr. Kuro-O accidentally disrupted an unknown mouse gene, ending up with a batch of transgenic rodents that aged 12 times faster than average mice.

“Normal mice live about 2.5 years, but this particular strain lived only 2.5 months. They’d grow a little bit but then quickly deteriorate and die,” said Dr. Kuro-O, Adjunct Professor

of Pathology, now at Jichi Medical University in Tochigi, Japan.

It took four years for Dr. Kuro-O to pinpoint which of about 20,000 mouse genes he had manipulated, then another eight years to discover exactly how this gene, which he named

**While scientists aren’t quite ready to recommend *Klotho* supplements to healthy adults to prolong life, these findings could aid in developing better treatments for those with chronic kidney disease.**

*Klotho*, worked. Dr. Kuro-O’s research focused exclusively on *Klotho* once he joined the UT Southwestern faculty in 1998, one year after his breakthrough discovery of *Klotho* was reported in *Nature*.

“When we made transgenic mice that overexpressed *Klotho*, they lived about six months longer than normal mice. That’s why we thought it might be a gene that suppressed aging,” Dr. Kuro-O said.

He discovered that, as with many biological processes, the relationship between *Klotho* and aging wasn’t a straightforward cause and effect. In 2004 a Japanese research group that manipulated the hormone fibroblast growth factor 23 (FGF23) reported nearly identical premature aging in mice, leading Dr. Kuro-O to suspect a connection. Further experiments at UT Southwestern confirmed it.

“FGF23 is a hormone that stimulates phosphate excretion into urine, and *Klotho* is its receptor,” Dr. Kuro-O said. “If this endocrine system is not functioning well, then phosphate retention may occur, and that will accelerate aging.”

While scientists aren’t quite ready to recommend *Klotho* supplements to healthy adults to prolong life, these findings could aid in developing better treatments for those with chronic kidney disease, an ailment related to malfunction of the FGF23-*Klotho* endocrine system and phosphate retention.



“Chronic kidney disease can be viewed as premature aging. When it progresses, *Klotho* expression goes down progressively, so there is a correlation,” Dr. Kuro-O said. “By at least maintaining the *Klotho* expression level in the kidneys, we may slow down the deterioration or decline of renal function.”

Drugs already are available that activate *Klotho*, such as troglitazone, which is used to treat type 2 diabetes. Until recently, however, nobody knew that such drugs also could be helpful in treating kidney disease.

“Troglitazone increases insulin production, so that’s why it’s used to treat diabetes. People did not realize it can also increase *Klotho* expression. So this drug actually may be good not only for diabetes but also for its complication, kidney disease,” Dr. Kuro-O explained.



Dr. John Abrams aims to determine how the regulatory network of *p53* – the most commonly mutated gene in cancer – may be involved in extending life span.

### Another cancer connection

The Catch-22 situation of telomerase promoting cancer while also rejuvenating telomeres to extend life bears a remarkable similarity to the suspected molecular action of the tumor-suppressor gene *p53*.

*p53*, the most commonly mutated gene in cancer, works by regulating the expression of so-called target genes, similar to an integration device that responds to stimuli by operating switches that turn sets of genes on and off. Dr. John Abrams, Professor of Cell Biology, aims to determine how *p53*'s regulatory network may be involved in extending life span.

"There is some evidence to suggest that if we were able to eliminate the cancer problem when you knock out *p53*, animals might live longer," Dr. Abrams said. How *p53* controls longevity is the question he hopes to answer.

Investigation in the Abrams lab led to the finding that *p53* binds to specific regulatory places on chromosomes called enhancers. Using cells from flies, mice, and humans, researchers now are studying whether aging

affects *p53*-influenced chromosomal organization, called chromatin conformation assembly, or vice versa.

"We are currently testing whether alteration of chromatin conformation is a biomarker of aging," Dr. Abrams said. "If this idea turns out to be a validated hypothesis, then we could in principle identify ways to potentially reset the clock on those changes in chromatin conformation."

Such genetic manipulation could lead to new interventions for some age-associated pathologies, Dr. Abrams said, by putting the brakes on excessive cell death, or apoptosis.

### Recycling and renewal

Another factor influencing the speed of aging is autophagy, the body's natural cellular recycling process, in which cells devour their own damaged or unneeded parts.



Dr. Beth Levine

“Autophagy is the major mechanism for removing organelles and preventing the process that leads to aging,” said Dr. Beth Levine, Director of the Center for Autophagy Research and an Investigator in the Howard Hughes Medical Institute at UT Southwestern. “We are working on developing autophagy-inducing agents.”

Two genes that turn on the autophagy process, *beclin 1* and *beclin 2*, have been

identified through work in Dr. Levine’s lab. Evidence indicates that defects in expression or function of the *beclin 1* gene in particular may contribute to aging, cancer, neurodegenerative diseases, and infectious diseases.

In early 2013, scientists in Dr. Levine’s lab synthesized an autophagy-inducing peptide that could potentially be developed into a new drug to treat infections and neurodegenerative disorders. Mice treated with the peptide, called

Tat-beclin 1, were resistant to several infectious diseases, including West Nile virus. Human cells treated with the peptide were resistant to HIV infection.

“Activation of autophagy has potential application in a

broad range of diseases,” Dr. Levine said. “Neurodegenerative diseases would be the area of most pharmaceutical interest because clinical trials could be designed more easily to evaluate drug efficacy.”

Dr. Levine and her colleagues were also the first to find that the autophagy pathway was necessary for extended life span, which occurs when there are mutations in the body’s insulin-signaling pathway or when caloric intake is restricted. In fact, in these settings the average life span of worms is doubled – but only if the worms can activate autophagy. Recently, researchers in the lab also found that exercise – which is associated with longevity in humans

– is a strong activator of autophagy. Whether increased autophagy in humans can improve longevity remains unknown, but all research to date suggests this is likely.

### Preventing cell death

Just as the quantity and length of telomeres in chromosomes diminish with age, so too do the number of new neurons formed in the brain, especially with neurodegenerative diseases such as Alzheimer’s.

“When we get old, we lose cognitive abilities. The rate of new neuron formation in the hippocampus region of the brain declines with age,” said Dr. Steven McKnight, Chair of Biochemistry. “If we could enhance new neuron formation, would that help? We don’t know, but this is an idea we are pursuing.”

Studies in mice and rats indicate the hypothesis may be valid. A screen of 1,000 drug-like chemicals in the McKnight lab led to one promising compound called P7C3. Administration of P7C3 to rodents increased the production of neurons in the hippocampus, a region of the brain critical to learning and memory. Researchers are refining the compound and hoping to test it in clinical trials.

“Neurodegenerative diseases have no treatment now. If you could keep nerve cells from dying, you might extend life. P7C3 is not going to be a cure for those diseases, but treated patients might live a longer, healthier life,” Dr. McKnight said.

The research team is co-led by Dr. McKnight; Dr. Joseph Ready, Professor of Biochemistry; and Dr. Andrew Pieper, former Assistant Professor of Psychiatry and Biochemistry, now at the University of Iowa Carver College of Medicine. The researchers reported that the P7C3 compound boosted learning and memory in aged rats by protecting neurons from dying. Only about 30 percent of newborn nerve cells died in the drug-treated rats, versus 80 percent in the untreated animals.

“More newborn neurons survive and become wired into the hippocampus because not as many are dying. Our compound mitigates nerve cell death,” Dr. McKnight said. “If P7C3 is generally neuroprotective, that would be particularly gratifying because there is no such drug currently available.”

So far, the researchers have found that the compound prevents nerve cell death in mouse models of traumatic brain injury, Parkinson’s disease, and amyotrophic lateral sclerosis. One stumbling block, however, is pinning down just how P7C3 works.

**Evidence indicates that defects in expression or function of the *beclin 1* gene may contribute to aging, cancer, neurodegenerative diseases, and infectious diseases.**

“Discovering a drug is really hard, and sorting out the mode of action of a new drug is equally difficult. If we can pull off both tasks here in academia, that would be special,” said Dr. McKnight, whose expertise in early-stage drug discovery as founder of a San Francisco-based biotechnology company aided his UT Southwestern research.

When he joined the UT Southwestern faculty in 1995, Dr. McKnight set up a library of approximately 250,000 drug-like chemicals. This compound library is used by researchers campuswide. Dr. McKnight’s high-throughput screening laboratory uses robotic drug screening instruments and is critically dependent on support from UTSW chemists and pharmacologists.

“Our capabilities in early-stage drug discovery give us an advantage, and other universities are beginning to follow us,” Dr. McKnight said of his department’s combination of strengths in chemistry, pharmacology, and high-throughput drug screenings. “We were 10 years ahead of the curve in taking this leap into academia-based drug discovery.”

That’s also where investigators would like to be when it comes to important discoveries

in age-related research – ahead of the curve. With their expertise in basic and translational research, UT Southwestern researchers remain focused on deciphering the multiple cellular processes at work in aging and using that information to advance patient care.

“It is time for people to realize that aging is not a fixed process that we can’t do anything about. We now understand a lot about how it works, and over the next few decades, we hope to be able to slow the rate of aging in lots of different tissues,” Dr. Wright said.

*Dr. Levine holds the Charles Cameron Sprague Distinguished Chair in Biomedical Science.*

*Dr. McKnight holds the Sam G. Winstead and F. Andrew Bell Distinguished Chair in Biochemistry, and the Distinguished Chair in Basic Biomedical Research.*

*Dr. Ready is a Southwestern Medical Foundation Scholar in Biomedical Research.*

*Dr. Shay and Dr. Wright share the Southland Financial Corporation Distinguished Chair in Geriatrics.*



Dr. Steven McKnight (left) and Dr. Joseph Ready have found that the compound P7C3 prevents nerve cell death in mouse models of traumatic brain injury, Parkinson’s disease, and amyotrophic lateral sclerosis.

# FINDING YOUR

A team of UT Southwestern  
specialists restores once-vibrant  
voices lost due to overuse,  
neurological problems, age,  
trauma, and other conditions.

By Russell Rian



VOICIE

# W

Whether you're considered "chatty" or not, the amount of time you spend in conversation in a day – conducting business, conversing with co-workers, or catching up with friends and family – can take a toll on your voice. Quantifying just how much people talk isn't an exact science, but studies estimate that the average person speaks 16,000 words per day. A study in the *Journal of Communication* estimated that 50 percent to 80 percent of the workday is spent communicating, two-thirds of it talking.

All of this chatter likely accounts for why nearly 30 percent of people will experience a voice problem during their lifetime. A National Institutes of Health study noted that while singers are on the top 10 list of those seeking help from health professionals at voice centers, the majority of patients are teachers, retirees, homemakers, factory workers, executives, students, and nurses.

This difficulty with vocal cords often comes without warning or apparent reason. Voices erode and degrade or suddenly sound raspy, breathy, or strained. The erosion leaves those afflicted suffering more than just frustrating moments of conversation. Teachers, for instance, are forced to take time off from work for voice difficulties, at a taxpayer cost of more than \$2 billion a year. Seniors silently drift out of circulation simply because speaking has become too difficult or embarrassing. The daily details, triumphs, and tribulations of friends and family that are the celebration of life go unspoken.

An appreciation for these struggles and the people who live with them evolved into UT Southwestern's Clinical Center for Voice Care, a place where a team of specialists dedicated to restoring the lost voices of everyone from operators to opera singers works toward a common goal.

"Voice difficulties have a far greater effect on people than just the loss of voice," said Dr. Ted Mau, Assistant Professor of Otolaryngology–Head and Neck Surgery and Director of the Clinical Center for Voice Care.



UT Southwestern's Clinical Center for Voice Care team includes (from left): Dr. Lesley Childs; Laura Toles, Speech-Language Pathologist; Dr. Ted Mau; Amy Hamilton, Speech-Language Pathologist; Dr. Barbara Schultz; Janis Deane, Speech-Language Pathologist

## 'No need to live with it'

The American Academy of Otolaryngology–Head and Neck Surgery recommends that anyone who experiences vocal changes for more than two weeks be examined by an otolaryngologist, commonly referred to as an ear/nose/throat (ENT) physician. Those who specialize through fellowship training specifically in throat disorders are known as laryngologists.

Dr. Mau, along with Dr. Lesley Childs, Assistant Professor of Otolaryngology–Head and Neck Surgery, and Dr. Barbara Schultz, Associate Professor of Otolaryngology–Head and Neck Surgery, are the physicians on the Clinical Center for Voice Care team. In addition, an experienced team of speech-language pathologists who have particular expertise in voice disorders, including therapy and training techniques for professional singers, works with patients. Interestingly, the speech pathologists are classically trained singers as well.

"I was fortunate to recruit speech pathologists who were not only gifted in the area of voice therapy but who also have extensive musical backgrounds," said Janis Deane, Faculty Associate of Otolaryngology–Head and Neck Surgery and head of the speech-language pathology section for the Center.

Amy Hamilton, also a Faculty Associate in the department, has 20 years of singing experience and holds a vocology certification. Faculty Associate Laura Toles has worked exclusively with the Clinical Center for Voice Care since she began her career. Assistant Instructor Cristina Duran has experience in acting as well as singing.

"Our team approach to voice care makes all the difference in the world," said Dr. Schultz. "Our nurses and assistants are an important part of our team; they understand the urgency of various voice problems and help to coordinate the office visits.

"The physicians can do an initial evaluation and examine the vocal folds with our specialized scopes, which allow us to show the patients any pathology or problems we may find. We also are able to share this with the other physicians in our practice and with our speech pathologists."

Vocal problems can be somewhat vague: vocal fatigue; soreness in the jaw, throat, or even shoulders; a prolonged warm-up time for singers; a tickling or choking sensation when singing; or decreased vocal range. Other times, the symptoms are more obvious: breathiness, frequent coughing or throat clearing, hoarseness, a pain or tightness in the throat while singing.



## Calls for help

“A lot of times people live with problems with their voice because they don’t know what to do,” Ms. Deane said. “They get hoarse and think it’s just a sign of aging, or maybe they have a trauma and think their voice is just going to be raspy.”

Research from the American Academy of Otolaryngology–Head and Neck Surgery bears this out. Nearly three-quarters of seniors with voice problems do not seek help for problems that make it hard to talk, eat, or drink, and more than half do not realize that treatment is available.

“There’s no need to just live with it. We see many professionals who rely heavily on their voices, such as singers, teachers, and public speakers, but anyone with a voice problem can take advantage of our services,” Dr. Schultz explained.

Finding the right help is important because, according to a 2006 survey, the quality-of-life impact from voice disorders compares to chronic diseases such as sciatica (back pain), congestive heart failure, or chronic obstructive pulmonary disease.

Barbara Valentin understands. As a receiving coordinator for a large toy company, she talks on the phone frequently. But it was people on the other end of the line who first noticed something was amiss.

“I had always received comments about what a nice voice I had, but I started hearing comments like, ‘What’s wrong with your voice?’ and ‘Oh my, are you sick?’ My oldest sister was the first to notice the choppiness in



Dr. Ted Mau, wearing protective glasses, demonstrates pulsed potassium titanyl phosphate (KTP) laser therapy, an innovative procedure that allows physicians to treat vocal cord lesions in a minimally invasive fashion.



Barbara Valentin

my voice even when I didn't recognize anything was wrong," she recalled. "Gradually, it got worse. Rarely a day went by that I didn't have to explain to someone that no, I wasn't sick."

The slow erosion of her voice quickly turned into calls for help. Several MRIs and specialists later, the medical consensus was undecided.

"I went to one doctor after another trying to find answers because, by this time, having a conversation was difficult and extremely aggravating for me," she said. "My words would come out of my mouth, but something was chopping them up, and I sounded a little as though I was being strangled while talking."

"I began to withdraw socially and wouldn't – and most of the time couldn't – engage in conversation. The look on people's faces as they would pretend to understand me but really just wanted to turn around and walk away was hurting me almost as much as the struggle to speak."

Eventually, a community ENT specialist referred her to the Clinical Center for Voice Care and Dr. Mau, who determined she had spasmodic dysphonia, a neurological problem in which muscles of the voice box spasm during speech. In Ms. Valentin's case, the recommended treatment was Botox injections, which helped loosen the muscles.

"Dr. Mau came highly recommended, and my doctor had already heard such good things about what he was doing at UT Southwestern," Ms. Valentin said. "When Dr. Mau saw me on my first visit, I felt comfortable and reassured that this was finally the right diagnosis."

"A couple of days after the Botox had settled into my vocal cords, I picked up the phone and called my sister. She was so excited that although she could barely hear the volume of my voice, she could understand every word I said. We were both in tears."

Ms. Valentin has since regained both her voice and her confidence. "I have additional help and support from my wonderful voice therapist, Amy Hamilton. She has taught me valuable techniques and exercises to help me get the most benefit out of my Botox injections," Ms. Valentin said.

A person's participation in his or her own recovery is crucial in voice care.

"Barbara was very diligent in practicing assigned voice exercises, and due to her perseverance, we were able not only to determine the definitive diagnosis of spasmodic dysphonia but also to help her optimize her vocal output in the presence of this frustrating disorder," Ms. Hamilton said.

## Difference makers

People's emotions are very much tied to their voices, Dr. Mau noted.

"Especially for those who depend on their voices for their professions and their livelihood, we are able to help and really make a difference in their lives."

For singers, the very mention of "nodule," for example, strikes a chord of fear. Nodules are benign vocal fold growths that can occur after overuse, marring the pure, clear tones singers demand. It is one of the more common problems that bring singers into the Clinical Center for Voice Care.

"It's your only set of vocal folds, so unlike a flute or guitar, you can't trade it in or upgrade it 10 years down the road," said Dr. Childs, a classically trained soprano who has recorded songs for Walt Disney Records. "People often think of nodules as a career-ending diagnosis, but it's not. Nodules are reversible."

Dallas-Fort Worth is home to a wide range of singers and serves as a popular concert stop for all genres of musicians who occasionally need expert care on the road.

“We see very high-level singers and performers who may be visiting Dallas and have an urgent voice issue, and we do our best to see these people rapidly so they may continue to perform,” said Dr. Schultz, a soprano with her church choir who has performed at the Morton H. Meyerson Symphony Center and with the Turtle Creek Chorale.

Even healthy singers and orators call on the Center to get an analysis of their voice while it is in good working order, for later tracking and comparison purposes.

To diagnose voice disorders, the team uses state-of-the-art videostroboscopy, which shows freeze frames of the vocal folds in action.

Overuse of the voice can cause polyps and cysts affecting voice quality, and some surgeries and viruses can lead to vocal fold paralysis. Muscle tension dysphonia can occur after a severe upper respiratory infection or as a result of allergies. The Clinical Center for Voice Care team also provides diagnosis and treatment for patients who develop a voice problem due to neurological disease, trauma, or other ailments.

Treatments may include microsurgery of the vocal folds, a minimally invasive procedure to remove polyps or cysts; Botox injections for problems such as spasmodic dysphonia; or laser surgery. Some of these can be done at the Center and don’t require a general anesthetic, so patients have much less downtime, Dr. Childs said. Thyroplasty and vocal fold injection augmentation also are available.

These procedures can strengthen weak vocal cords that are causing hoarseness or a breathy-sounding voice.

Regardless of the fix, voice therapy plays a critical role. Many voice problems can be resolved with therapy alone, and follow-up therapy is nearly always important after procedures, which makes coordination with voice therapists at the Center both crucial and convenient, Ms. Deane said.

Therapy can also be preventive, helping people optimize the efficiency of their voice production. For example, therapists can identify poor vocal habits, from excessive caffeine consumption to improper breathing techniques, which can lead to a recurrence of voice problems after surgery if not changed. Therapists also can identify preventive tactics such as proper nutrition and hydration, as well as offer practical tips such as vocal exercises to increase vocal endurance.

“Our mantra as laryngologists is to operate on the vocal cords as a last resort,” Dr. Childs said. “Even if the growth doesn’t go away with speech therapy, it will at least get smaller. This allows for a much less invasive surgical procedure, with less risk of permanent hoarseness from scarring.”

“We see many professionals who rely heavily on their voices, such as singers, teachers, and public speakers, but anyone with a voice problem can take advantage of our services.”



Dr. Barbara Schultz

## A ‘rich topic’ for research

While health care is at the heart of the Clinical Center for Voice Care, being part of an academic medical center means research is an integral component as well. Center members often team up with other researchers in otolaryngology to study vocal-fold biomechanics – how the folds move and are positioned to generate the wide range of sounds our voices produce.

“I started out as a scientist in biophysics, studying the atomic structure of proteins,” Dr. Mau said. “When I switched gears into medicine, I maintained the biophysics way of thinking about things. The voice box is fascinating because the human vocal fold tissue is unique. There’s nothing like it in other animals and nothing like it anywhere else on the body.”

Dr. Roger Chan, Associate Professor of Otolaryngology–Head and Neck Surgery, and Dr. Che Xu, Assistant Professor of Otolaryngology–Head and Neck Surgery, focus their research on studies of the human larynx.

Dr. Chan specializes in vocal-fold tissue mechanics and biorheology – the study of flow properties of biological systems – and their relationships with voice acoustics and laryngeal physiology. His current lab projects include quantification of key biomechanical characteristics of human laryngeal tissues, physical models, and computer models of the larynx.

Dr. Xu is working to unravel the anatomy and physiology of voice production and laryngeal biomechanics. His research includes development and testing of a vocal fold lamina propria tissue replacement for surgical applications. When the vocal fold is injured, whether from trauma, surgery, or resections due to vocal cord cancer, the scarring that occurs is often irreversible, creating the need for replacement tissue or an ability to regenerate healthy tissue.

“The complexity of the human vocal fold and the various possible tissue-engineering approaches make this a rich topic, but one with many challenges to solve,” Dr. Xu said.

In addition, the Clinical Center for Voice Care team is engaged in clinical studies, such as examining the effects of therapeutic injections,



the merits of different kinds of voice therapy, the care of the aging voice, and whether a device that helps patients communicate can improve their quality of life after voice surgery. Another study is assessing the impact of voice rest, which is sometimes prescribed to patients.

“Voice rest is much harder to do than you think,” Dr. Mau noted. Preliminary results suggest patient compliance with voice rest is much poorer than needed, yet the negative impact of failing to rest the voice is much greater than thought, he said.

That kind of understanding is critical to improving patient care, the ultimate goal for all of the Department of Otolaryngology’s research efforts.

“The voice is something that’s very precious,” Dr. Mau said. “With everyone on the team having a vocal background, I think we all share an appreciation of just how precious and valuable a clear voice is. That, in turn, provides a valuable understanding for where our patients are coming from so we can approach their challenges with that in mind and identify the best solution tailored particularly to them.”

Leading-edge technology and advanced expertise mean UT Southwestern’s Clinical Center for Voice Care can help with almost any type of voice problem, from minor irritations to major concerns.



## Transforming Medical Care Through Innovation and Compassion

Caregivers at UT Southwestern's new hospital will utilize innovative design, advanced technology, and best practices to deliver exemplary patient care that reflects UT Southwestern's strengths as an academic medical center dedicated to education, research, and patient care.

In late 2014, the William P. Clements Jr. University Hospital will open its doors, transforming medical care in North Texas and serving as a model for academic medical centers across the country.

"Our vision is to provide the very best care possible to all those who come to us for help, and to do so while training the next generation of caregivers and conducting research that addresses some of the most important challenges in medical science," said Dr. Daniel K. Podolsky, President of UT Southwestern Medical Center.

To that end, every aspect of the new hospital has been carefully considered. "We're bringing together innovative hospital design, state-of-the-art technology, and industry best practices to create an environment that seamlessly integrates patient care with leading-edge research and medical education. Everything we've done, and every decision we've made, has been to better serve our patients," Dr. Podolsky said.

To achieve these goals, the hospital planning team gathered input from patients, caregivers, faculty, and researchers. The team visited respected hospitals around the country to identify best practices. And work groups focused on specific aspects of hospital operations, developing innovative approaches to enhance patient care.

The architects for the facility also participated in the planning process, attending hundreds of

hours of work group meetings to listen to the discussions of the doctors, nurses, and staff who will be working in the new hospital. As a result, the architects were able to incorporate the best insights and ideas into the hospital's design.

"By listening to our stakeholders and evaluating best practices in the industry, we created a vision of what a patient-centered academic medical facility should offer," said Dr. John Warner, CEO of UT Southwestern University Hospitals. The result will be a 12-story, 460-room hospital that moves UT Southwestern toward its goal of being among the nation's top academic medical centers.

"Patients seek out UT Southwestern because of the strength of our science," said Dr. Bruce Meyer, Executive Vice President for Health System Affairs. "We are well-known for scientific discoveries that translate to the bedside. We also continuously track the latest clinical research and evaluate therapies that provide the best patient outcomes. We care about the *person* who is ill, not just his or her disease."

### Design promotes care, quality, and collaboration

One unique feature of the William P. Clements Jr. University Hospital is the W-shaped design, which is both distinctive and functional. This W design – which is a response to input from UT Southwestern nurses – will improve patient care and make it easier for patients, staff, and visitors to navigate the facility.

For staff, the W shape minimizes the distances that must be covered to perform routine duties. It will enable nurses to maintain closer interaction with patients and have better sight lines into each patient's room.

The design also supports operational quality, protecting patients from infections and exposure, since most materials will be moved directly from supply elevators to storage areas – bypassing patient hallways and creating a cleaner, quieter environment. Dedicated trash and linen chutes also will contribute to a healthier environment by removing items quickly from the building.

Promoting collaboration is another priority, and related specialties will be co-located on certain floors. This will allow cardiologists and cardiovascular surgeons, for example, to easily consult on cases. There also will be designated areas for doctors and students to confer and for clinical research to take place.

### The power of technology

Along with the innovative design, the new hospital incorporates the most advanced technology. Secure mobile devices, for example, will enable physicians and nurses to maintain, track, and share up-to-date electronic medical records. RFIDs (radio frequency identification devices) and bar coding of equipment and medications will promote proper tracking and administration – reducing the potential for errors.

In patient rooms, monitors will enable caregivers and patients to review charts and images (such as X-rays, CT scans, and MRIs) at the bedside, while videoconferencing capability – one of the most innovative features of the hospital – will allow patients to stay connected with their caregiving team, family, and friends. Surgeons also will have similar videoconferencing capabilities in the operating rooms, enabling real-time discussions with pathologists and other colleagues during surgery.

Looking to the future, the hospital is designed for maximum flexibility. This will enable new equipment and technology to be quickly integrated, with minimal downtime for renovations.

### Putting patients and families first

To support healing and comfort, the hospital will provide a variety of amenities for patients and their loved ones.

The physical environment is an important consideration. Patient rooms will be spacious and private, with large windows that bring in natural light. Patients will have more control over their space, with controls for calling for assistance, as well as for Wi-Fi, TV, lighting, drapes, and temperature, easily accessible from their bed. Restaurant-quality food will be available around the clock, with the patient's dietary restrictions already factored into the menu options. And outdoors, beautiful gardens will serve as a sanctuary, while still allowing patients to be carefully monitored.

Recognizing the important role of family and friends in a patient's recovery, the hospital is designed to accommodate them as well. Patient rooms will have ergonomically designed sleeper sofas, allowing family members to stay overnight. Private cellphone rooms will be available in waiting areas, offering a quiet place to make calls without disturbing others. Dining areas will provide nutritious meals and snacks 24 hours a day, along with alcoves for private conversation. And a Patient Information Center with kiosks will enable patients, friends, and family to research and better understand diseases, diagnoses, treatment options, and clinical trials.

Even long-standing hospital procedures have been re-evaluated to provide a better patient experience. For example, rather than separating newborns from their parents, whenever possible, newborns will stay with their parents in labor and delivery suites, as well as in individual Neonatal Intensive Care Unit rooms. This allows more time for bonding, which research shows can positively influence a baby's weight gain and growth rate, reduce time in the hospital and future complications, improve breastfeeding capability, and (especially important for premature infants) promote better body temperature regulation.

### Building the future

Building a hospital of this quality and magnitude is a massive undertaking. Bringing the new hospital from vision to reality is possible because of the generous support of friends in the community and of UT Southwestern physicians, through their commitment of revenues from the Faculty Practice Plan.

The hospital is named in honor of former Texas Gov. William P. Clements Jr., who in 2009 made a landmark \$100 million contribution to the Southwestern Medical Foundation, the largest single gift in the Foundation's history. The funds were unrestricted, meaning they could be used for any purpose. But there was one stipulation – the gift must be used for something that would be “transformational” for UT Southwestern. The new hospital will indeed have the transformative impact Gov. Clements envisioned.

“This new hospital is critical to North Texas,” said William T. Solomon, who serves as Chairman of Southwestern Medical Foundation and of the *Building the Future of Medicine* capital campaign, which has been working to raise \$200 million in private funds. “The hospital will significantly enhance both the availability of care and the quality of life in our community. It will provide the absolute best in patient care, innovative facilities, and leading-edge science ... and that benefits everyone we serve.”



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

*Dr. Warner holds the Jim and Norma Smith Distinguished Chair for Interventional Cardiology, and the Audre and Bernard Rapoport Chair in Cardiovascular Research.*

(special section)

## Predicting your cardiac health and risk

By Lisa Warshaw

Is there a medical equivalent of a crystal ball that can offer a glimpse into the future of your heart health? That's what researchers at UT Southwestern Medical Center have set out to discover, as they seek sophisticated ways to predict cardiology-related catastrophes in patients who are otherwise healthy.

"We're trying to figure out who is going to develop heart attacks, strokes, and even death from cardiovascular disease," said Dr. Amit Khera, a preventive cardiologist and Associate Professor of Internal Medicine who holds the Dallas Heart Ball Chair in Hypertension and Heart Disease.

To do that, Dr. Khera and researchers have been using data mined from UT Southwestern's ongoing Dallas Heart Study – a large-scale, multiethnic population-based study that is evaluating heart health. As part of the study, more than 2,200 healthy Dallas County residents underwent magnetic resonance imaging (MRI) of their abdominal region to assess the aorta – the candy cane-shaped artery that carries blood from the heart and distributes it throughout the entire body. One of this year's more prominent findings could have implications for the ability to predict cardiac health.

Researchers, led by Dr. Khera, found two subtle but highly significant differences in two distinct measurements of aortic atherosclerosis: aortic plaque buildup and thickness of the aortic walls.

"Both measurements are predictors of cardiovascular events, but there's an important difference between accumulation of plaque and the thickness of the aortic walls," Dr. Khera said.

"Accumulation of plaque tells us there is an increased risk for peripheral vascular occlusion, stroke, and abdominal aortic aneurysms, that is to say cardiovascular issues that occur either above or below the heart, rather than events that directly take place in the heart, such as heart attacks," noted Dr. Khera. "In contrast, a thickening of the aorta walls is more likely to be predictive of all forms of cardiovascular disease."

Even when researchers adjusted for other risk factors, such as smoking, which is known to have adverse effects on the aorta, the study concluded that people with the thickest aortic walls had a twofold higher risk of future cardiovascular events.

While the relationship between coronary atherosclerosis and adverse cardiovascular events has long been established, much less is known about atherosclerosis in the aorta. This study is one of the first to undertake imaging of the aorta in healthy individuals and link it to future cardiovascular events.

According to Dr. Khera, this cutting-edge research demonstrates the biological uniqueness of individual blood vessels. Each one, he says, gives researchers more insight into vessels' inner workings and their link to future cases of cardiovascular disease.

### 'Unique information'

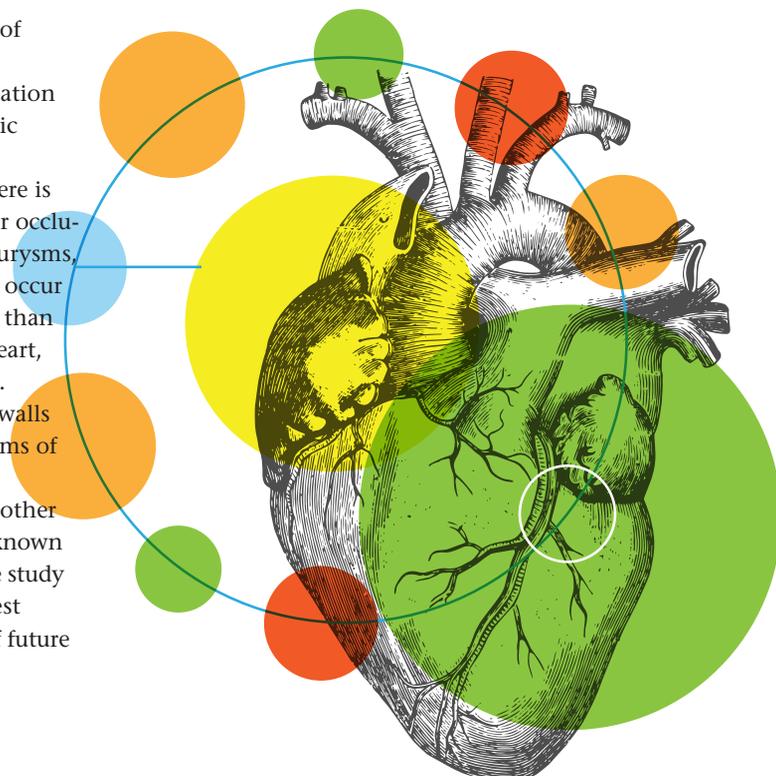
"Some patients are at highest risk for stroke, some for heart attack, and others for blockages in their leg arteries," said Dr. Khera. "We're exploring how different tests can provide unique information specific to each individual patient and thus an opportunity to prevent those specific problems."

Although the findings are novel and relevant, Dr. Khera cautioned they don't necessarily mean that health care providers should begin using aortic MRIs routinely to screen for cardiovascular risks. Instead, he said, findings of aortic thickening or plaque buildup in patients currently undergoing the exams could provide important information for the future.

"We're focusing on the future of cardiovascular prevention," said Dr. Khera. "We're going beyond cholesterol and blood pressure and looking at more sophisticated markers of cardiovascular risk."

"We're trying to figure out who is going to develop heart attacks, strokes, and even death from cardiovascular disease."

—Dr. Amit Khera



# Breast reconstruction goes natural

By Jan Jarvis

After a mastectomy in 2010, Dallis Parker tried wearing a prosthetic. But when the breast cancer survivor looked in the mirror, the image she saw did not match the one in her mind's eye.

Three years later, breast reconstructive surgery gave her a new vision of herself.

"When I look in the mirror now, I see my femininity restored," Mrs. Parker said.

Mrs. Parker underwent "double DIEP flap" surgery, using her own abdominal tissue to create a soft, natural-looking breast. DIEP flap, which stands for deep inferior epigastric perforator flap, represents the gold standard in autologous breast reconstruction. It is one of several highly complex procedures UT Southwestern plastic surgeons perform to restore a woman's breast after a mastectomy.

"The goal with surgery is to reconstruct a breast that looks as normal as possible," said Dr. Sumeet Teotia, Assistant Professor of Plastic Surgery and Director of the Breast Reconstruction Program at UT Southwestern. "Women can feel feminine again; they don't have to live their lives feeling disfigured."

For the more than 230,000 women in the United States who will be diagnosed with breast cancer this year, reconstructive surgery can restore a natural silhouette and enhance their quality of life. It also gives those at high risk for breast cancer a viable option following a prophylactic mastectomy.

## Active genetics program

Today, women from their 20s to their 80s – with all stages of breast cancer or no cancer at all but who are genetic carriers – are turning to UT Southwestern for help. Many come to UT Southwestern initially because of an active genetics program based at the Mary L. Brown Breast Cancer Genetics and Risk Assessment Clinic. More than 12,000 women have been seen at UT Southwestern for the evaluation of hereditary breast cancer since the program's establishment in 1992, making it one of the largest cancer genetics programs in the country. It also is the only one in North Texas that uses patient whole-genome germline sequencing to make discoveries for the development of new ways to treat or prevent cancer.

Women who choose surgery at UTSW look for guidance in making the best decision regarding reconstruction. Increasingly, they are opting to use their own tissue because it produces a very natural look that lasts a lifetime, Dr. Teotia said.



The surgery that Mrs. Parker underwent was a rare combination of procedures in which her entire lower abdomen was used to reconstruct one breast.

A "double DIEP" or "stacked DIEP" flap breast reconstruction can be performed at the time of the mastectomy or delayed until later. During the surgery, tiny arteries and veins are linked together to make a new breast that matches the unaffected one.

"The 'double DIEP' is one of the innovative procedures that UT Southwestern offers patients who want reconstruction with their own tissue but have undergone radiation or have a large breast on the other side," Dr. Teotia said. "These are rare operations, and our team at UT Southwestern has tremendous experience with them to make them successful."

Women without a history of radiation treatment and who have adequate skin have the option of getting silicone or saline implants. Such implants have significantly improved over time and are great for women who lack enough tissue for flaps, Dr. Teotia said.

Implants are often the preferred choice for young women who opt for a prophylactic mastectomy.

"Women who have this at the time of their prophylactic nipple-sparing mastectomy can wake up with a breast in many instances," Dr. Teotia said. "Many combinations of procedures

"The goal with surgery is to reconstruct a breast that looks as normal as possible."

—Dr. Sumeet Teotia

(special section)

exist to potentially save the nipple if it is oncologically safe, and UT Southwestern offers these latest procedures."

One of the newest options for patients is a form-stable, cohesive silicone gel implant that keeps its shape and doesn't leak, Dr. Teotia said. Dubbed "gummy bears" because their texture is similar to the candy, these implants feel more natural than others, he said.

With the help of their surgeon, women can consider the many options and choose the surgery that is best suited for them.

"We see many wonderful patients, from those with no cancer but a high risk, to those with Stage 4 metastatic stable disease," Dr. Teotia said. "For every patient, our ultimate goal is a best attempt to give them the results that look natural and beautiful."

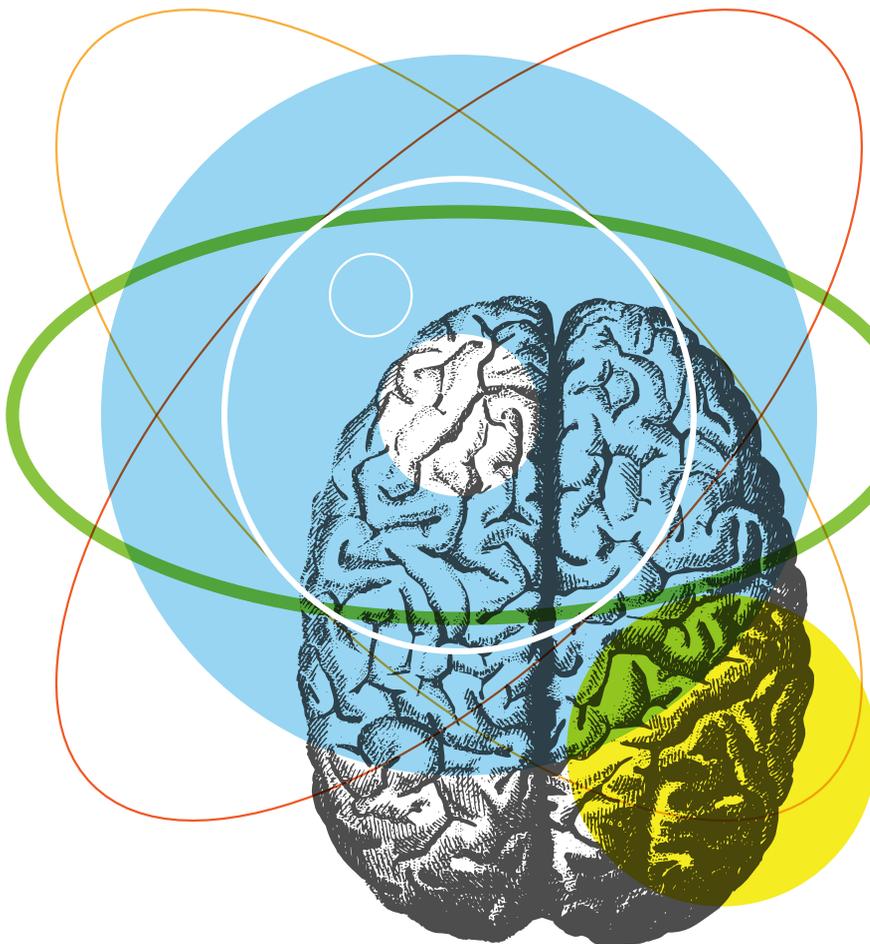
Reconstruction is not safe for all women with metastatic disease.

Mrs. Parker feared that having metastatic cancer would limit her choices regarding reconstruction. But after several clean scans, her physicians gave her the OK for reconstruction.

"I have no regrets," she said. "Mentally and physically, I have been restored."

"Mentally and physically, I have been restored."

—Dallis Parker



## Depression: New insights into the mind's eye

By Russell Rian

The depths of depression run far and wide.

The U.S. Centers for Disease Control and Prevention estimates 1 in 10 adults meets criteria for depression. But even that estimate fails to capture the personal toll on each of the roughly 19 million individuals struggling with the disease and its effect on their friends and family.

Julie Hersh understands. Her depressive episodes over the years included three suicide attempts before she successfully underwent two rounds of electroconvulsive therapy at Zale Lipshy University Hospital to take back her life. Mrs. Hersh, a board member of Southwestern Medical Foundation and numerous other Dallas institutions, boldly detailed her struggles in the highly regarded book *Struck by Living: From Depression to Hope*.

She became a national advocate to highlight the need to better understand depression, and she took a hands-on approach by serving on the advisory board for UT Southwestern's Depression Center, which studies the neurobiology and psychology of depression, bipolar disorder, and related disorders. The Depression Center is led by Dr. Madhukar Trivedi, Professor of Psychiatry, who holds the Betty Jo Hay Distinguished Chair in Mental Health.

"Each time I speak about my experience, I find people are often one step removed from the devastation of mental illness or even suicide," Mrs. Hersh, who is married with two children, writes in the leaf of her book. "Stories about mothers, fathers, brothers, sisters, spouses, and children all make me wonder: Could we have stopped these deaths? If we are more aware, can we see the signs earlier and save a life? I think we can."

Dr. Trivedi shares that view, and for decades he has been actively pursuing remedies. He helped launch a national effort to find the best treatments for depression, serving as Co-Principal Investigator for what at the time was the largest study on depression treatments – STAR\*D, or Sequenced Treatment Alternatives to Relieve Depression – a \$35 million, six-year study that initially included more than 4,000 patients from clinics across the country. The groundbreaking STAR\*D study served as the first benchmark investigation to implement specific step-by-step medication treatment guidelines based on patients' symptoms and medication side effects.

His current research is building upon that foundation.

Based on the STAR\*D findings, Dr. Trivedi developed a computerized treatment system using algorithms developed and refined by UT Southwestern researchers over decades. The computer software provides a step-by-step guide to assist doctors as they are treating patients.

"It's like walking with someone learning to ride a bike, versus just sitting there and telling them how to ride," he said. His team created a similar algorithm for suicide risk.

Dr. Trivedi is now heading up a national clinical trial to find biomarkers that can better predict how people suffering from depression will respond to medications so that physicians eventually can personalize treatments. The EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care) study, funded by the National Institute of Mental Health, is using existing state-of-the-art technologies and pioneering its own innovative approaches to examine carefully selected clinical and biological markers. Participants initially undergo magnetic and electroencephalographic brain imaging and blood, DNA, hormonal, chemical, cognitive, and behavioral tests.

"Early indicators of whether a treatment is going to work are imperative," said Dr. Trivedi, EMBARC's Principal Investigator. "Which medication is taken makes a big difference to success, but there's nothing to guide physicians in making that choice. We are aggressively seeking the biological indicators that can help us rapidly guide patients to the best treatment for their depression, and these latest findings give us further hope that we're on the right track."

### Tracking messenger proteins

Dr. Trivedi also leads a national trial called TREAD (Treatment with Exercise Augmentation for Depression), which is trying to determine if a simple blood test could eventually determine whether exercise would help reduce symptoms of depression better than antidepressant medications. UTSW psychiatrists track specific cytokines – messenger proteins in blood cells that tell the cell what to do and generally boost the body's immune response. Researchers have found that people with higher levels of certain cytokines have greater decreases in depression symptoms after exercising. They also found that other cytokines predict a poor response to antidepressant medications.

Other research by Dr. Trivedi has revealed another light at the end of the dark tunnel. A 2013 study showed that workplace productivity improved when depressed individuals received treatment early for their depression but continued to decline with late-stage treatments, underscoring the importance of his efforts

aimed at finding biological indicators that could permit quicker diagnoses.

"No one treatment is perfect, so it is crucial to examine depression from more than a single viewpoint. If you have diabetes, no one says, 'Just take insulin. Just improve diet.' People do diet, insulin, and exercise," he said. "We need to consider all the modalities, as well as some novel approaches for depression, and then use our best science to find the best therapy for each individual. We also have to engage our communities in making it a national priority to understand these devastating illnesses if we are to make major strides."

## Finding the sweet spot for diabetes treatments

By Russell Rian

There's no sugarcoating it.

An estimated 26 million adults and children in the United States have diabetes. The disease affects both males and females – roughly 13 million of each gender – and hits more than a quarter of those over age 65. Another 79 million people have prediabetes and are at risk for developing type 2 diabetes.

Estimates now project that as many as one in three American adults may have diabetes by 2050.

UT Southwestern Medical Center's commitment to arresting the proliferation of diabetes is well established; the Medical Center has demonstrated leadership for decades, in large part through the Touchstone Center for Diabetes Research.

Founder Dr. Roger Unger, Professor of Internal Medicine who holds the Touchstone/West Distinguished Chair in Diabetes Research, has played a pivotal role investigating diabetes, obesity, and insulin resistance for more than 50 years. His laboratory introduced the concept of lipotoxicity – the accumulation of lipids in inappropriate locations – as a potential cause of diabetes and other metabolic diseases, such as insulin resistance and fatty liver.

The Touchstone Center, now under the direction of Dr. Philipp Scherer, Professor of Internal Medicine and Cell Biology, who holds the Gifford O. Touchstone, Jr. and Randolph G. Touchstone Distinguished Chair in Diabetes Research, continues to focus needed resources on the basic science and clinical aspects of type 1 and type 2 diabetes, hoping to answer questions about the impact of diabetes and obesity on cardiovascular disease outcomes, cancer incidence, and related health problems such as eye disease.

Estimates now project that as many as one in three American adults may have diabetes by 2050.

(special section)

In 2013, UT Southwestern's William T. and Gay F. Solomon Division of General Internal Medicine was recognized for excellence in diabetes care by the Blue Cross and Blue Shield of Texas and Health Care Incentives Improvement Institute's Bridges to Excellence program.

As a leading medical center, UT Southwestern has been able to offer its patients additional benefits, such as participation in national clinical trials to help caregivers determine the best treatments.

Dr. Philip Raskin, Professor of Internal Medicine who holds the Clifton and Betsy Robinson Chair in Biomedical Research, is leading UT Southwestern's part of one major national trial to determine the best combination of diabetes treatments. The study is making a head-to-head comparison of the four top diabetes medications often used in combination with metformin, the most common first-line diabetes medication. It will compare the long-range effect on blood-sugar (glucose) levels, complications, and overall quality of life over a five-year span.

"We need to know which combination of medications works best and has fewer side effects so that we can recommend the best choice for our patients," explained Dr. Raskin, part of UT Southwestern's Division of Endocrinology, which was recognized by *U.S. News & World Report* in its 2012-2013 "Best Hospitals" annual issue.

That National Institutes of Health-funded study is just one reflection of UT Southwestern's prevention and intervention efforts.

Dr. Raskin also serves as Principal Investigator for the Type 1 Diabetes TrialNet, a worldwide network of 18 select centers that offer unique opportunities to help scientists identify the best causes, prevention strategies, and therapies. TrialNet physicians are screening relatives of people with type 1 diabetes to find out if family members are at risk of developing the disease, using a simple blood test to look for the presence of diabetes-related antibodies. In addition, the network's researchers are developing studies to determine whether therapies can delay or prevent the onset of diabetes as well as designing intervention studies to try to preserve insulin secretion in people newly diagnosed with type 1 diabetes.

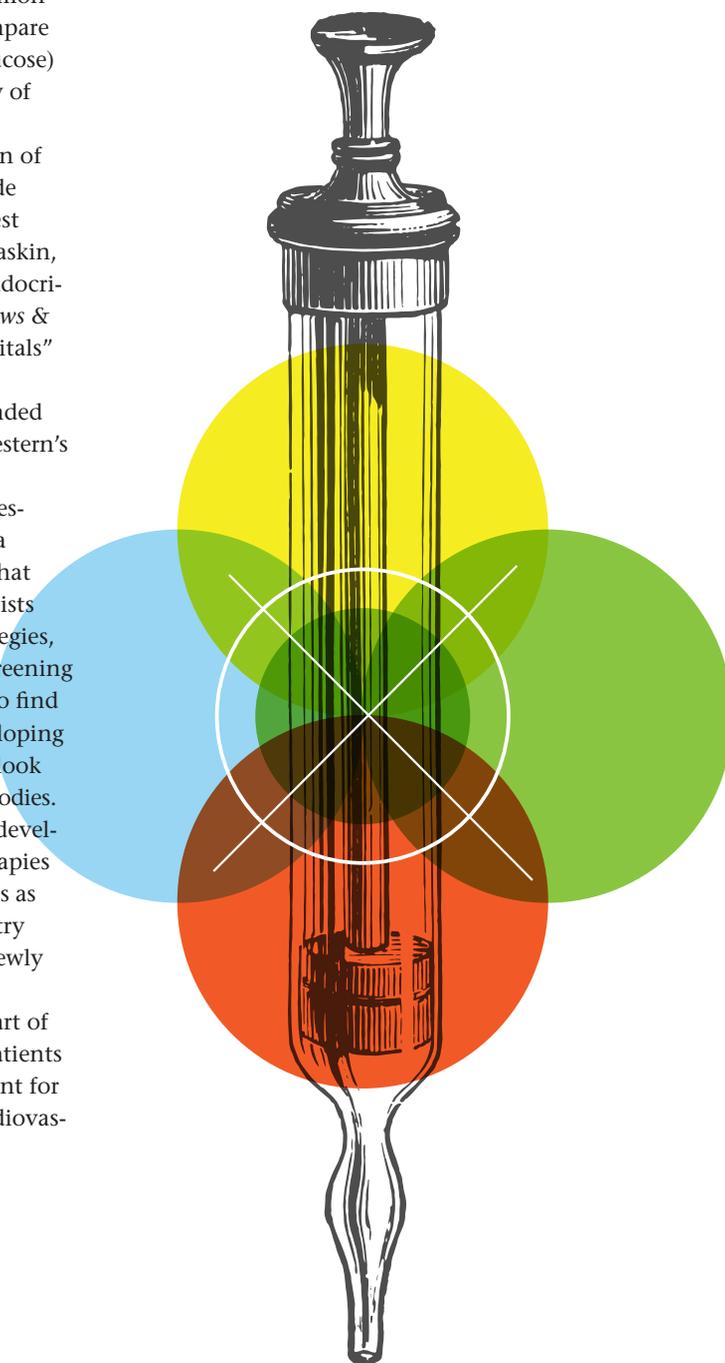
Researchers at UT Southwestern, as part of a 27-institution study, also found that patients who receive early and aggressive treatment for diabetes reduced their risk of serious cardiovascular disease by almost 60 percent.

Dr. Ildiko Lingvay, Associate Professor of Internal Medicine and Clinical Sciences, and her colleagues were the first in the U.S. to use magnetic resonance spectroscopy to measure the amount of pancreatic fat in humans, which may ultimately serve as an effective clinical tool to identify those at high risk of diabetes and to monitor interventions designed to prevent the disease. Drs. Raskin and Lingvay also found that intensive early treatment of type 2 diabetes slows progression of the disease by preserving the body's insulin-producing capacity, in stark contrast to the stepwise approach recommended in standard guidelines.

"We have shown that this treatment approach preserves beta-cell function, and that's the key in changing the course of the disease," Dr. Lingvay noted.

"We have shown that this treatment approach preserves beta-cell function, and that's the key in changing the course of the disease."

—Dr. Ildiko Lingvay



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# HIGHLIGHTS

of the year

FALL 2012

## STUDY PROVIDES POSSIBLE BRAIN TUMOR TARGET

Researchers at UT Southwestern have revealed new insights into why the most common, deadly kind of brain tumor in adults recurs and have identified a potential target for future therapies.

Glioblastoma multiforme (GBM) currently is considered incurable. Despite responding to initial therapy, the cancer almost always returns. GBM is a fast-growing, malignant brain tumor that occurred in 15 percent of the estimated 22,000 Americans diagnosed with brain and nervous system tumors in 2010. The median survival rate is about 15 months.

In a study published in *Nature*, scientists led by Dr. Luis Parada identified a subset of brain tumor cells that are



DR. LUIS PARADA

slower-growing or remain at rest and appear to be the source of cancer recurrence after standard therapy. Dr. Parada, Chairman of Developmental Biology and Director of the Kent Waldrep Center for Basic Research on Nerve Growth and Regeneration, holds the Diana K. and Richard C. Strauss Distinguished Chair in Developmental Biology, and the Southwestern Ball Distinguished Chair in Nerve Regeneration Research.

“Current therapy targets fast-growing tumor cells but not those responsible for new tumors. To the best of our knowledge, this is the first identification of a cancer stem-like cell

in a spontaneously forming tumor inside a mammal,” he said. “We are trying to better understand these cells. The important point is that we now are faced with technical obstacles, not conceptual ones.”

## UTSW SELECTED FOR NATIONAL NEURO NETWORK

UT Southwestern’s expertise in neurology has placed the Medical Center in an innovative national clinical trials network that will make it easier to test promising treatments for patients with brain, muscle, and nerve disorders.

One of 25 sites selected for the National Institute of Neurological Disorders and Stroke’s (NINDS) new Network for Excellence in Neuroscience Clinical Trials, UT Southwestern is the only participating medical center in Texas and its bordering states.

Known as NeuroNEXT, the network represents a unique clinical trials model for brain diseases. By creating a shared infrastructure and institutional review board, institute officials said they expect to minimize the time and expense of studies while making new treatments available to patients more quickly.

“We want to bring the fruits of discovery in the laboratory as quickly as we can to the patients who need them,” said Dr. Mark Goldberg, Chairman of Neurology and Neurotherapeutics at



DR. MARK GOLDBERG

UT Southwestern and a Co-Principal Investigator for the project. “It is more efficient to

have a well-organized team in place, allowing us to test one therapy after the next.” Dr. Goldberg holds the Linda and Mitch Hart Distinguished Chair in Neurology.

UT Southwestern is expected to receive \$1.4 million in NINDS support over the next seven years for its role in the network.

## FAT TYPE, LOCATION PLAY ROLE IN RISK FOR TYPE 2 DIABETES

Obese individuals with excess visceral fat (abdominal fat that surrounds the body’s internal organs) have an increased risk for the development of type 2 diabetes, according to a new study by investigators at UT Southwestern. By contrast, people with excess abdominal subcutaneous fat (fat underneath the skin) were not at higher risk for the onset of the disease.

The study, published in *The Journal of the American Medical Association*, is one of the largest of its kind to assess a multi-ethnic population of obese people in the U.S. using extensive imaging of adipose tissue.

“Among obese individuals, it is not necessarily how much fat a person has, but rather where the fat is located on a person that leads to diabetes,” according to the paper’s senior author, Dr. James de Lemos, Professor of Internal Medicine, who holds the Sweetheart Ball - Kern Wildenthal, M.D., Ph.D., Distinguished Chair in Cardiology.

The study, which collected information from UT Southwestern’s Dallas Heart Study, sampled 732 obese adults – those with a body mass index of 30 or greater – between the ages of 30 and 65, without diabetes

or cardiovascular disease. Researchers utilized magnetic resonance imaging and dual-energy X-ray absorptiometry to determine where fat was stored in the body.



DR. JAMES DE LEMOS

When participants returned for a follow-up after seven years, researchers found that 11 percent of the people sampled had developed diabetes. Among the participants who had normal glucose at baseline testing, 39 percent developed prediabetes or diabetes. Those who developed diabetic conditions had higher amounts of visceral fat and greater insulin resistance compared to those who remained healthy.

#### STAYING ACTIVE INCREASES CHANCE OF LIFETIME HEALTH

Being physically fit during your 30s, 40s, and 50s not only helps extend life span, but it also increases the chances of aging healthily, free from chronic illness, investigators at UT Southwestern have found.

For decades, research has shown that higher cardiorespiratory fitness levels lessen the risk of premature death, but it previously had been unknown just how much fitness might affect the burden of chronic disease in the most senior years – a concept known as morbidity compression.

“We’ve determined that being fit is not just delaying the inevitable, but it is actually lowering the onset of chronic disease in the final years of life,” said Dr. Jarett Berry, Assistant Professor of Internal Medicine

and senior author of the study in the *Archives of Internal Medicine*. Dr. Berry is a Dedman Family Scholar in Clinical Care.

Researchers, working with the Cooper Institute, examined the patient data of 18,670 participants in the Cooper Center Longitudinal Study, research that contains more than 250,000 medical records maintained over a 40-year span. Analyses showed that when patients increased fitness levels by 20 percent in their midlife years, they decreased their chances of developing chronic diseases – congestive heart failure, Alzheimer’s disease, and colon cancer – decades later by 20 percent.

#### HORMONAL BOOST EXTENDS LIFE SPAN UP TO 40 PERCENT

Scientists at UT Southwestern have shown that a starvation hormone markedly extends life span in mice without the need for calorie restriction.

The study defined average life span as the point at which half the members of a given test group remained alive. While none of the untreated mice lived longer than about three years, some of the female mice that overproduced FGF21 were still alive at nearly four years, the researchers reported.

“Restricting food intake has been shown to extend life span in several different kinds of animals,” said senior author

Dr. Steven Kliewer, Professor of Molecular Biology and Pharmacology, who holds the Nancy B. and Jake L. Hamon Distinguished



DR. STEVEN KLIEWER

Chair in Basic Cancer Research. “In our study, we found transgenic mice that produced more of the hormone fibroblast growth factor-21 (FGF21) got the benefits of dieting without having to limit their food intake. Male mice that overproduced the hormone had about a 30 percent increase in average life span, and female mice had about a 40 percent increase in average life span.”

FGF21 seems to provide its health benefits by increasing insulin sensitivity and blocking the growth hormone/insulin-like growth factor-1 signaling pathway. When too abundant, growth hormone can contribute to insulin resistance, cancer, and other diseases, the researchers said.

#### PATIENT CARE AT ZALE LIPSHY GETS NATIONAL PRAISE

UT Southwestern was one of only two academic medical centers in the country to receive two major patient satisfaction awards – the Patient Voice Award and the Summit Award for inpatient services – from Press Ganey, a national consulting firm specializing in health care performance.

Both awards recognize outstanding care provided to patients at Zale Lipshy University Hospital. UT Southwestern is the nation’s only academic medical center to win both awards in each of the past two years.

The Patient Voice Award honors the achievement of outstanding patient satisfaction scores. The Summit Award is given to hospitals that sustained consistently high levels of excellence in patient satisfaction over a three-year period.



ZALE LIPSHY EARNED TWO MAJOR PATIENT SATISFACTION AWARDS FROM PRESS GANEY.

Dr. Bruce Meyer, Executive Vice President for Health System Affairs, said the awards signify the high level of consistency and quality delivered throughout the entire patient-care process.

Just seven academic medical centers received a Patient Voice Award, up from three recognized in 2011. Hospitals had to score an overall rating in the 90th percentile or higher to be considered. UT Southwestern earned the Summit Award for its inpatient services by ranking in at least the 95th percentile every quarter for three consecutive years. The consulting firm evaluated data from April 2009 through March 2012. In all, 100 Summit Awards were presented out of more than 1,000 eligible hospitals.

**MONCRIEF INSTITUTE DEDICATION FULFILLS FORT WORTH VISION**

The UT Southwestern-affiliated Moncrief Cancer Institute in Fort Worth was dedicated during a ceremony attended by building fund donor W.A. “Tex” Moncrief Jr. and officials from Tarrant County, the city of Fort Worth, UT Southwestern,

Moncrief Cancer Foundation, and the Institute.

Dr. Daniel K. Podolsky, President of UT Southwestern, said the Medical Center is proud to be associated with the Institute and looks forward to playing an important role in its future.

“The programs offered at the new Moncrief Cancer Institute in collaboration with UT Southwestern will provide cancer patients with vitally important care and services that would not be available otherwise,” Dr. Podolsky said. “The center will provide new hope to untold thousands, now and in the future.”

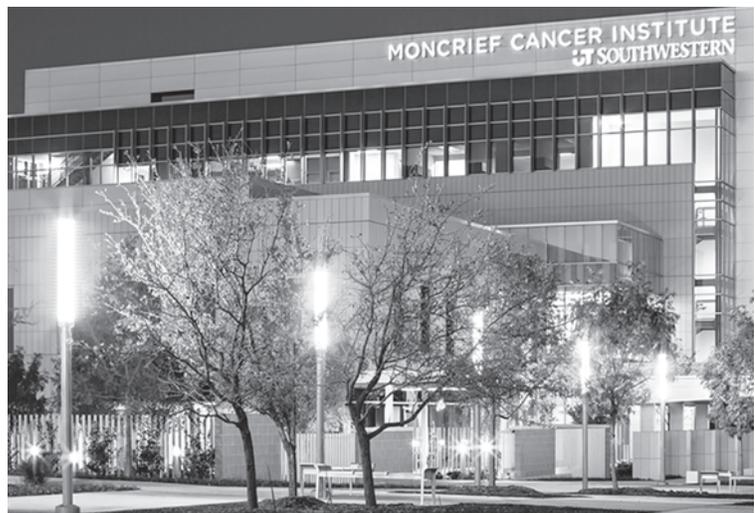
Located on a 3.4-acre site on West Magnolia Avenue, the \$22 million facility was designed from the ground up to serve North Texas cancer survivors, especially medically underserved adults, in a very special way by focusing on prevention, research, and survivorship programs. The new 60,000-square-foot center offers services that include genetic counseling, mammography screening, nutritional counseling, and cooking classes, said Dr. Keith Argenbright, Medical Director of the Institute.

**MELANOMA MODEL SHOWS PROGRESSION OF SKIN CANCERS**

UT Southwestern scientists led by Dr. Sean Morrison, Director of the Children’s Medical Center Research Institute at UT Southwestern, developed an innovative model for predicting the progression of skin cancer in patients.

In a study published in *Science Translational Medicine*, Stage III human melanoma cells from 20 patients were implanted into specially selected mice with compromised immune systems. Using a xenograft model, in which tissue is transplanted from one species to another, the Institute’s team observed reproducible differences in the rate at which the cancer spread, or metastasized, in the mice that correlated with clinical outcomes in patients.

Dr. Morrison said human melanomas that metastasized efficiently in the mice eventually progressed to advanced, Stage IV disease in patients – spreading to distant organs, such as the brain, liver, or lungs. When the melanoma did not metastasize efficiently in the mice, it also did not form



UT SOUTHWESTERN-AFFILIATED MONCRIEF CANCER INSTITUTE IN FORT WORTH

distant metastases in patients. The researchers said they hope their system will lead to new prognostic markers that identify patients at highest risk of disease progression, as well as new therapies.

“We believe this is the only time in cancer biology that anyone has developed a xenograft model in which disease progression correlates with what happens in the patient,”

said Dr. Morrison, senior author of the study and a Howard Hughes Medical Institute Investigator at UT Southwestern. He holds the Mary McDermott Cook Chair in Pediatric Genetics.



DR. SEAN MORRISON

WINTER 2012-2013

TOPPING OFF EVENT  
A CELEBRATION OF  
CLINICAL MILESTONE

The UT Southwestern campus celebrated a mid-December Topping Off ceremony – a milestone for the new William P. Clements Jr. University Hospital, signaling that construction had reached full height.

Several hundred employees and students gathered at the construction site for the Topping Off tradition of placing a tree atop a newly constructed building, symbolizing growth and good luck. Members of the crowd also signed a concrete panel that will be incorporated into the facility, which opens in late 2014.

“We’re really celebrating a milestone for us as an institution and in our commitment to provide the

very best care possible to all those who come to us for help, and to do so while training the next generation of caregivers and providing the answers to the yet-unmet medical needs of the worldwide community,” UT Southwestern President Dr. Daniel K. Podolsky told the enthusiastic gathering.

Many in the crowd had contributed ideas as part of the interactive design process that involved more than 600 members of the campus community, as well as patients and families. The 460-bed hospital broke ground in March 2011 and is named to honor legendary Texas Gov. William P. Clements Jr., in recognition of his 2009 gift of \$100 million to the Southwestern Medical Foundation, the largest single gift for the benefit of UT Southwestern in the institution’s history.



A TREE WAS RAISED TO THE TOP OF THE WILLIAM P. CLEMENTS JR. UNIVERSITY HOSPITAL IN A TOPPING OFF CEREMONY ATTENDED BY HUNDREDS OF EMPLOYEES AND STUDENTS.

MEDICAL CENTER  
OPENS SATELLITE  
COMMUNITY CLINICS

UT Southwestern patients and employees living in the Richardson, Plano, and Park Cities areas are now able to get world-class health care close to home, as the Medical Center opened neighborhood Clinical Centers. UT Southwestern opened its first center in late 2012 across from UT Dallas in north Richardson. A second center opened in January 2013 in the Park Cities.

Both Clinical Centers offer a mix of primary and specialty care. They operate on patient-centered medical home principles, a holistic approach to health care that focuses on the management of chronic illnesses and the coordination of care so individuals stay healthier while avoiding costly hospitalizations.

“We recognized that in order to effectively serve our community, we needed to have more services placed off campus where they can be more accessible,” said Dr. Bruce Meyer, Executive Vice President for Health System Affairs. “At the same time, it improves efficiency and promises a more comprehensive way of taking care of patients.”

The Richardson/Plano center provides adult primary care and women’s services. Rotating specialists in sports medicine, cancer, and behavioral health also are available. The Park Cities clinic provides adult primary care, ob/gyn care, and cardiology care. Mammography and general radiology services also are offered, along with other internal medicine specialties, based upon demand.



DR. LORA HOOPER AND DR. YOUXING JIANG

**TAMEST SELECTS  
HOOPER, JIANG FOR  
O'DONNELL AWARDS**

**D**r. Lora Hooper, Professor of Immunology and Microbiology, and Dr. Youxing Jiang, Professor of Physiology, received 2013 Edith and Peter O'Donnell Awards from the Academy of Medicine, Engineering, and Science of Texas (TAMEST).

The annual awards honor outstanding achievements by early-career investigators in science, medicine, engineering, and technology innovation. Both Dr. Hooper and Dr. Jiang are accomplished Howard Hughes Medical Institute Investigators, and Dr. Hooper also has an appointment in UT Southwestern's Cancer Immunobiology Center. In addition, she is the Nancy Cain and Jeffrey A. Marcus Scholar in Medical Research, in Honor of Dr. Bill S. Vowell.

Dr. Hooper was honored in medicine for her discovery of immune mechanisms that promote host-bacterial interactions. These discoveries in

part explain how beneficial bacteria can safely exist in the intestinal tract and may ultimately reveal what to do when illness-causing bacteria predominate.

The award in science recognized Dr. Jiang's efforts to elucidate the atomic structures of membrane-bound ion channels, which are cell-surface proteins that allow specific charged particles like sodium and potassium ions to pass through or be blocked by cell membranes. Dr. Jiang is the W.W. Caruth, Jr. Scholar in Biomedical Research.

**SCIENTISTS COLLABORATE  
TO PROBE HEART'S  
REGENERATIVE POTENTIAL**

**U**T Southwestern researchers pinpointed a molecular mechanism needed to unleash the heart's ability to regenerate, a critical step toward developing eventual therapies for damage suffered following a heart attack.

Cardiologists and molecular biologists at the Medical Center teamed up to study in mice how

heart tissue regenerates. They found that microRNAs – tiny strands of RNA that regulate gene expression – contribute to the heart's ability to regenerate up to one week after birth. Soon thereafter, the heart loses the ability to regenerate.

By determining the fundamental mechanisms that control the heart's natural regenerative on-off switch, researchers have begun to better understand the No. 1 hurdle in cardiovascular research – the inability of the heart to regenerate following injury. Their findings were published in the *Proceedings of the National Academy of Sciences*.

"It is a fresh perspective on an age-old problem," said Dr. Eric Olson, Director of the Nancy B. and Jake L. Hamon Center for Basic Research in Cancer. "We're encouraged by this initial finding because it provides us with a therapeutic opportunity to manipulate the heart's regenerative potential."

Dr. Olson, Chairman of Molecular Biology, holds the Pogue Distinguished Chair in Research on Cardiac Birth Defects, the Robert A. Welch Distinguished Chair in Science, and the Annie and Willie Nelson Professorship in Stem Cell Research.

**SPRING 2013**

**LEVINE JOINS  
RANKS OF UTSW'S  
NAS MEMBERSHIP**

**T**he National Academy of Sciences elected Dr. Beth Levine, Professor of Internal Medicine and Microbiology and a Howard Hughes Medical Institute Investigator at UT Southwestern, to membership. NAS membership represents one of the highest honors attainable by an American scientist.

Dr. Levine, Director of the Center for Autophagy Research in Internal Medicine and holder of the Charles Cameron Sprague Distinguished Chair in Biomedical Science, said, “I appreciate the freedom I have enjoyed throughout my career to pursue new scientific ideas, as this freedom has been at the root of our discoveries.



DR. BETH LEVINE

We hope to use our discoveries to improve the prevention and treatment of human disease.”

Dr. Levine’s research explores a cellular process called autophagy, in which cells devour their own damaged or unneeded components. Her laboratory identified the first known gene in mammals that is responsible for autophagy. Her research has since shown that defects in the expression or function of this specific gene, called *beclin 1*, may contribute to cancer, aging, neurodegenerative diseases such as Alzheimer’s, and infectious diseases. Conversely, *beclin 1* activity and the autophagy pathway appear to be important for protection against breast, lung, ovarian, and perhaps other cancers, as well as for fighting off viral and bacterial infections and for protecting individuals from neurodegenerative diseases and aging.

**SCIENTISTS RECEIVE PRC DISTINGUISHED AWARDS**

The President’s Research Council (PRC) presented its 2013 Distinguished Young Researcher Awards to a pair of outstanding UT Southwestern investigators. The recipients –

Dr. Deepak Nijhawan, Assistant Professor of Internal Medicine and Biochemistry, and Dr. Rhea Sumpter Jr., Instructor of Internal Medicine – each received a \$65,000 award.

Dr. Nijhawan, a Chicago native, graduated from Northwestern University and earned his M.D./Ph.D. in 2005 from UT Southwestern. He then completed an internship and residency in internal medicine at Massachusetts General Hospital in Boston, followed by fellowships at Dana-Farber Cancer Institute in Boston and the nearby Broad Institute of Harvard and MIT.

He returned to UT Southwestern in 2012 to launch an ambitious research program in the Department of Biochemistry that uses chemistry to identify new targets for lung cancer treatment.

Dr. Sumpter, a *magna cum laude* biochemistry graduate of Rice University, completed a Fulbright Fellowship in Argentina prior to arriving at UT Southwestern in 1998. A 2006 M.D./Ph.D. graduate, he is a member of the Alpha Omega

Alpha medical honor society, completed his internship and residency in internal medicine at UT Southwestern, and was a Fellow in infectious diseases and in the Physician Scientist Training Program concurrently.

In 2009, he joined the laboratory of Dr. Beth Levine, Director of the Center for Autophagy Research. In 2012 the National Institutes of Health awarded Dr. Sumpter a highly competitive Mentored Clinical Scientist Research Career Development Award for a multiyear project he proposed to investigate novel host factors in the selective autophagy of viruses. That same year, he was promoted from postdoctoral Fellow to Instructor.

The Distinguished Young Researcher Award is presented annually by the PRC, which is made up of community leaders who are interested in learning about and advancing medical research at UT Southwestern. The PRC was founded 28 years ago through the vision and generosity of UT Southwestern supporters Cece Smith and Ford



DR. RHEA SUMPTER JR. (LEFT) AND DR. DEEPAK NIJHAWAN RECEIVED 2013 DISTINGUISHED YOUNG RESEARCHER AWARDS FROM THE PRESIDENT’S RESEARCH COUNCIL.

Lacy and has awarded more than \$2.4 million in research funds contributed by its members.

**SUMMER 2013**

**THREE SCHOOLS  
CONFER 464 DEGREES**

Diplomas were conferred to 221 UT Southwestern Medical School students and 111 UT Southwestern Graduate School of Biomedical Sciences students in early-June commencement ceremonies.

In mid-December 2012, the UT Southwestern School of Health Professions awarded 132 students their degrees. The graduates included students from physical therapy, physician assistant studies, clinical nutrition, medical laboratory sciences, prosthetics-orthotics, and radiation therapy.

Dr. Darrell G. Kirch, President and CEO of the Association of American Medical Colleges, delivered the keynote address to the Medical School graduates and guests. Southwestern Medical Foundation's Ho Din Award, the top honor for graduating medical students,

was presented to Dr. David Leverenz.

The Graduate School's address was delivered by Dr. David Mangelsdorf, Chairman of Pharmacology. Yuxiao Wang received the Nominata Award, given to the outstanding Graduate School student.

**APPOINTMENTS  
FOR 2012-2013**

The following individuals were appointed to endowed positions or to major leadership positions at UT Southwestern during the past fiscal year.

- Dr. James Amatruda, to the Nearburg Family Professorship in Pediatric Oncology Research.

- Dr. Michael Choti, to Chairman of Surgery, to the Hall and Mary Lucile Shannon Distinguished Chair in Surgery, and, when the hospital opens in 2014, to Surgeon-in-Chief of the William P. Clements Jr. University Hospital.

- Frank Grassler, to Vice President for Technology Development.

- Dr. Frederick Grinnell, to the Robert McLemore Professorship in Medical Science.

- Kimel Hodges, to Assistant Vice President for Diversity & Inclusion and Equal Opportunity.

- Dr. Amit Khera, to the Dallas Heart Ball Chair in Hypertension and Heart Disease.

- Dr. Erik Knudsen, to the Dr. Charles T. Ashworth Professorship in Pathology.

- Dr. Elizabeth Maher, to Director of the Crystal Charity Ball Center for Pediatric Brain and Neurological Diseases.

- Dr. Kim Orth, to the Earl A. Forsythe Chair in Biomedical Science.

- Dr. Julio Perez-Fontan, to Chairman of Pediatrics, and to the Robert L. Moore Chair in Pediatrics.

- Dr. Dinesh Rakheja, to the John Lawrence and Patsy Louise Goforth Distinguished Professorship in Pathology.

- Dr. Cynthia Rutherford, to the Drs. Cynthia and John Rutherford Distinguished Chair in Hematology-Oncology.

- Nimisha Savani, to Vice President for Communications, Marketing, and Public Affairs.

- Dr. Jay Schneider, to the Dallas Heart Ball Chair in Cardiac Research.

- Dr. Michael Story, to the David A. Pistenmaa, M.D., Ph.D. Distinguished Chair in Radiation Oncology.



UT SOUTHWESTERN MEDICAL SCHOOL GRADUATES (FROM LEFT) DR. AIMEE LAM, DR. ANNE KIRK, AND DR. ATHRA KAVIANI RECITE THE PHYSICIAN'S OATH AT THE 2013 COMMENCEMENT EXERCISES, WHERE 221 GRADUATES RECEIVED DEGREES.

**MAJOR GIFTS  
IN 2012-2013**

**Philanthropists continued to demonstrate their commitment to UT Southwestern in 2012-2013, providing support for a variety of research, clinical, and educational programs.**

**Major new pledges and gifts received in the fiscal year 2012-2013 were:**

- \$5,000,000 from an anonymous donor to support the development of a genetic mutations database.
- \$4,293,750 from an anonymous donor to support molecular genetics research, the Center for Human Nutrition, and the establishment of the Scott Grundy Director's Chair.
- \$4,116,243 from Dr. Solomon B. Margolin, through a bequest to Southwestern Medical Foundation, to support cancer research.
- \$3,504,028 from Mrs. Eugene McDermott to Southwestern Medical Foundation to support UT Southwestern's new William P. Clements Jr. University Hospital.
- \$3,400,000 from Jeanne Fields Shelby, through a bequest, to support cancer research and scholarships for medical students.
- \$3,000,000 from the C.J. Thomsen Separate Property Trust to support programs in medical education, research, and clinical care.
- \$2,400,000 from the Harry S. Moss Heart Trust to support cardiology programming at the Harry S. Moss Heart Center.
- \$1,829,921 from proceeds of the 2012 Sweetheart Ball to Southwestern Medical Foundation in support of cardiology research at UT Southwestern.

- \$1,498,220 from Mr. and Mrs. Robert D. Rogers to Southwestern Medical Foundation to establish the Robert D. Rogers Stroke Center at UT Southwestern.

- \$1,070,000 from the David M. Crowley Foundation to support research in the areas of pathology and cancer, peripheral nerve and pain management, spinal cord injury, and digestive diseases, as well as to support the construction of UT Southwestern's new William P. Clements Jr. University Hospital.

- \$1,000,000 from anonymous donors to Southwestern Medical Foundation to create the Drs. Cynthia and John Rutherford Distinguished Chair in Hematology-Oncology.

- \$1,000,000 from the Eugene McDermott Foundation to Southwestern Medical Foundation to support UT Southwestern's new William P. Clements Jr. University Hospital.

- \$1,000,000 from Louis Dorfman Sr., and Dr. Samuel Y. Dorfman Jr., to Southwestern Medical Foundation to support the construction of UT Southwestern's new William P. Clements Jr. University Hospital.

- \$1,000,000 from Mr. and Mrs. Harry Crutcher III to Southwestern Medical Foundation to support the construction of UT Southwestern's new William P. Clements Jr. University Hospital.

- \$1,000,000 from Mrs. Ute Schwarz Haberecht and Dr. Rolf R. Haberecht to Southwestern Medical Foundation to support research, education, and clinical care at UT Southwestern.

- \$954,907 from the Howard Hughes Medical Institute for laboratory equipment.

- \$900,000 from the Ernest & Bonnie Beutler Foundation and Mrs. Ernest Beutler to support research activities.

- \$702,572 from the Rust Testamentary Trust, through a bequest, to support genetics research.

- \$600,000 from the Cain Foundation to support programs in vision loss, hearing loss, and diagnostic imaging, as well as to support Alzheimer's disease research.

- \$550,000 from NCH Corp., including gifts in kind and a gift to Southwestern Medical Foundation to support the construction of UT Southwestern's new William P. Clements Jr. University Hospital.

- \$500,000 from Mr. and Mrs. Jeffrey M. Heller to Southwestern Medical Foundation to support the construction of UT Southwestern's new William P. Clements Jr. University Hospital.

- \$500,000 from the Hoblitzelle Foundation to Southwestern Medical Foundation to support the construction of UT Southwestern's new William P. Clements Jr. University Hospital.

- \$500,000 from the M.B. & Edna Zale Foundation and the Abe Zale Foundation to Southwestern Medical Foundation to support capital improvements at Zale Lipshy University Hospital.

- \$486,745 from the Moody Foundation for flow cytometry support.

- \$485,284 from Dr. Harvey A. Birsner, through a bequest to Southwestern Medical Foundation, to establish the Duke Samson Chair of Neurological Surgery.

- \$400,000 from the Lupe Murchison Foundation to Southwestern Medical Foundation to support Alzheimer's disease research.

- \$250,000 from the Kent & JoAnn Foster Family Foundation to support genetics research.

- \$250,000 from Dr. and Mrs. Charles A. Sanders to Southwestern Medical Foundation to establish the Charles A. and Elizabeth A. Sanders and Harold Barefoot Sanders Fund for Distinguished Professors in Medical Jurisprudence.

- \$250,000 from Torchmark Corp. to support activities in the Department of Family and Community Medicine.

**Generous contributions and pledges of \$100,000 to \$249,999 were received from a number of additional donors, including the following new commitments from:**

- An anonymous donor to Southwestern Medical Foundation to support the construction of UT Southwestern's new William P. Clements Jr. University Hospital.

- An anonymous donor to support lung cancer programs in honor of Drs. Hak Choy, J. Michael DiMaio, Jonathan E. Dowell, and David A. Pistenmaa.

- An anonymous donor to support multiple sclerosis research.

- Rosemarie Bouley, through a bequest, to support lung cancer research.

- Drs. Debra L. Caudy and Clay M. Heighten to support Shank 3 genetic research.

- Mr. and Mrs. Edwin R. Daniels to Southwestern Medical Foundation to support the Lyra B. and Edwin R. Daniels Fund honoring Marnie Wildenthal and UT Southwestern wives.

- Mr. and Mrs. Peter J. Denker to Southwestern Medical Foundation to support the construction of UT Southwestern's new William P. Clements Jr. University Hospital.

- Gayden Family Foundation to Southwestern Medical Foundation to provide unrestricted support for UT Southwestern.

- Dr. and Mrs. Adi F. Gazdar to support cancer research.

- Mr. and Mrs. Mark Gibson, through The Melchizedek Fund of Communities Foundation of Texas, to Southwestern Medical Foundation to support research, education, and clinical care.

- Dr. Myron G. Glidewell, through a bequest, to support resident educational activities in the Department of Orthopaedic Surgery.

- J.M. Haggar Jr. Family Foundation to St. Paul Medical Foundation to support the construction of UT Southwestern's new William P. Clements Jr. University Hospital.

- David C. Haley to support diabetes research.

- The Hartwell Foundation to support the Individual Biomedical Research Award and Foundation Fellowship.

- Mr. and Mrs. Donald P. Kivowitz to support the Department of Urology, the Women's Health Symposium, and cancer research.

- David M. Marshall, through a bequest, to support cancer research and clinical activities.

- Mrs. J. Frank Miller III to St. Paul Medical Foundation to support the construction of UT Southwestern's new William P. Clements Jr. University Hospital.

- William A. and Elizabeth B. Moncrief Foundation to Southwestern Medical Foundation to support research, education, and clinical care.

- National Multiple Sclerosis Society to support continuing education.

- Ted Nash Long Life Foundation to support Alzheimer's disease research.

- Perkins-Prothro Foundation to support programs in medical education, research, and clinical care.

- Mr. and Mrs. David A. Ridley to support liver disease research.

- Mary R. Saner Charitable Trust to support patient care.

- Mrs. King Terry Jr., to Southwestern Medical Foundation to establish the Drs. Malone V. Hill and John W. Pate Professorship in Family Medicine.

- West Endowment to support bone marrow transplantation and follicular lymphoma research.

- Mrs. Michael H. Winter to support programs in physical medicine and rehabilitation.

- The Ivor and Mildred Wold Charitable Fund to Southwestern Medical Foundation to support the Mildred Wyatt and Ivor P. Wold Center for Geriatric Care.

- Mr. and Mrs. Sam Wyly to support research, education, and patient care.