CenterTimes

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From gene discovery to a first-in-class drug

FDA approval of belzutifan culminates 25-year journey of scientific innovation at UT Southwestern

By Deborah Wormser

A first-in-kind kidney cancer drug developed from laboratory and translational studies conducted at UT Southwestern recently received approval from the Food and Drug Administration, providing a new treatment for patients with familial kidney cancer.

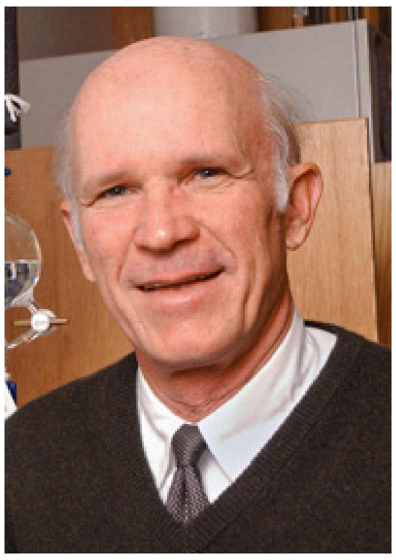
Merck's belzutifan grew out of the discovery at UT Southwestern of the protein hypoxia-inducible factor 2-alpha (HIF-2α), which was found to fuel the growth of kidney and other cancers. HIF-2α was discovered by Steven McKnight, Ph.D., Professor of Biochemistry.

"This is an exciting milestone for patients with inherited forms of kidney cancer who are in need of more effective therapies," said David Russell, Ph.D., Professor Emeritus of Molecular Genetics, who collaborated in the early stages of the research.

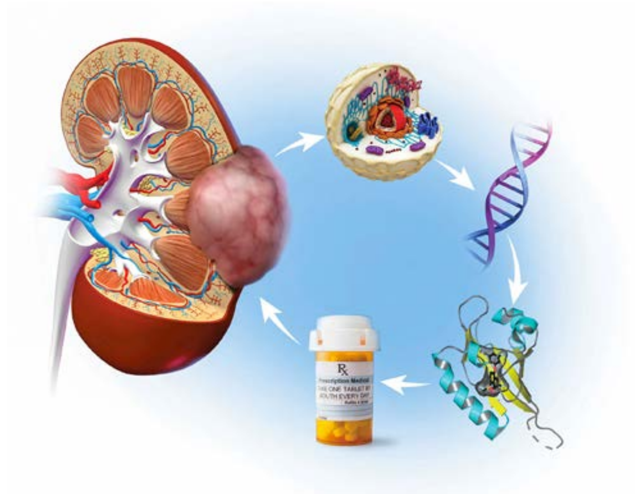
The drug, once called PT2977, was developed based on a UTSW discovery. Further drug development efforts were conducted by the spinoff company Peloton Therapeutics, which was launched on the UT Southwestern campus and eventually acquired by Merck. Drs. McKnight and Russell first identified HIF-2α in the 1990s.

For many years, HIF-2α was considered undruggable until two more UTSW scientists – Richard Bruick, Ph.D., former Professor of Biochemistry, and Kevin Gardner, Ph.D., former Professor of Biophysics, did the structural and biochemical work showing that the HIF-2α molecule contains a pocket that is potentially druggable. The two scientists then identified multiple compounds that fit into this pocket and inhibited the activity of HIF-2α.

Please see BELZUTIFAN on page 4



Steven McKnight, Ph.D.



The drug belzutifan was developed based on the discovery more than two decades ago at UT Southwestern of a protein that was found to drive the growth of kidney and other cancers.

Pioneering PULSAR-integrated radiotherapy with immunotherapy

Radiation oncology therapists help set up a patient on the treatment table of the Ethos adaptive radiotherapy machine prior to treatment.

From Staff Reports

Artificial intelligence, along with a $71 million expansion of Radiation Oncology services, is allowing UT Southwestern oncologists to pioneer a new PULSAR radiation-therapy strategy that improves tumor control compared with traditional daily therapy.

PULSAR, or personalized ultrafractionated stereotactic adaptive radiotherapy – detailed in the *International Journal of Radiation Oncology, Biology, Physics* – achieved better tumor control by giving α-PD-L1 therapy during or after radiation and by spacing fractions 10 days apart rather than daily.

In the PULSAR paradigm, patients receive only a few large dose "pulses," delivered with sophisticated, image-guided precision, at least a week, perhaps even months, apart. These "split treatments" are a radical break from the daily, long-course, conventional radiation treatments lasting six to nine weeks. They are less toxic and give oncologists time to fine-tune treatment after the new machines' imaging shows the tumor's changed shape, size, position, and its reaction to radiation.

Please see PULSAR on page 2

UTSW is a founding member of new sickle cell clinical trials network

By Patrick McGee

In a move that will increase access to clinical trials for patients with sickle cell disease, UT Southwestern has become a founding member of the new Sickle Cell Disease Clinical Trials Network (SCD CTN). The network's goal is to bring treatments and curative options to people suffering from this potentially life-shortening red blood cell disorder.

The American Society of Hematology (ASH), which created the network, is the world's largest professional society of clinicians and researchers focused on blood diseases. Under the leadership of Patrick Leavey, M.D., Professor of Pediatrics at UTSW, a collaborative North Texas clinical trial unit was developed and invited to be a participating site. The North Texas unit includes Children's Medical Center Dallas, William P. Clements Jr. University Hospital, Parkland Health & Hospital System, Medical City Dallas, and Cook Children's Health Care System in Fort Worth.

UT Southwestern's inclusion in the national network underscores its commitment as an academic medical center to bring the latest treatments to underserved populations. Sickle cell disease impacts Black Americans the hardest, with the genetic disease occurring in 1 out of every 365 African American births.

The 10-site Sickle Cell Disease Clinical Trials Network will coordinate patient enrollment in clinical trials at several academic medical

Please see NETWORK on page 4

Patrick Leavey, M.D.

Alecia Nero, M.D.

UT Southwestern is committed to offering opportunities and innovative support that allow employees to perform at their best and grow their careers. Photo taken pre-pandemic.

Forbes names UTSW top health care employer in Texas

By Patrick Wascovich

UT Southwestern has been recognized as the top health care employer in Texas, one of the top 10 employers across all industries in the state, and among the nation's best-in-state employers nationally by *Forbes*/Statista.

Recommendations from employees, as well as indirect recommendations from other workers within the same industries, are reviewed along with survey results that explore work conditions, salary, growth potential, and diversity among selection factors. The Best-In-State Employers 2021 is created through a survey of 80,000 U.S. employees across 25 industry sectors that consider employment opportunities at the local and national level. This is the second year UT Southwestern has been recognized.

Earlier this year, UTSW placed among the top 40 institutions *Forbes* honored as Best Employers for Women 2021 and was ranked No. 3 in the nation on *Forbes*' list of America's Best Employers For New Graduates, placing it in the top 1% and highest among academic medical centers.

UT Southwestern is committed to offering employees opportunities and innovative support to enable them to perform at their best and grow their careers. Among highlights, UTSW has established online and in-person training and mentoring programs for future management and leadership roles; technical skills training to adapt and master new software and technologies; and resources for employees in the areas of health and wellness, including

Please see BEST EMPLOYER on page 7

FACULTY PROMOTIONS

The following faculty promotions took effect Sept. 1 at UT Southwestern. (Where more than one department is listed, the first is the primary appointment.)

ANESTHESIOLOGY & PAIN MANAGEMENT
Professor: Mohammed Iqbal Ahmed, M.D., Pamela Ereckson Fox, M.D.
Associate Professor: Gijo Alex, M.D., Sreekanth R. Cheruku, M.D., Lyndsey Alison Grover, M.D., Jennifer L. Hernandez, M.D., Edgar Erold Kiss, M.D., Jaffer M. Odeh, M.D., Humair Rana, M.D., Bryan Tyler Romito, M.D., Austin D. Street, M.D., Alycia Wanat-Hawthorne, M.D.

BIOPHYSICS/BIOCHEMISTRY
Professor: Luke M. Rice, Ph.D.

BIOPHYSICS/CELL BIOLOGY
Associate Professor: Xiaochen Bai, Ph.D.

CELL BIOLOGY
Associate Professor: Marcel Mettlen, Ph.D.

CELL BIOLOGY/BIOPHYSICS
Associate Professor: William Michael Henne, Ph.D.

DERMATOLOGY
Associate Professor: Stephanie Savory, M.D.

DERMATOLOGY/EUGENE MCDERMOTT CENTER FOR HUMAN GROWTH AND DEVELOPMENT
Associate Professor: Donald A. Glass, M.D., Ph.D.

DERMATOLOGY/OBSTETRICS AND GYNECOLOGY
Associate Professor: Melissa Muszynski Mauskar, M.D.

EMERGENCY MEDICINE
Professor: Ava Edwana Pierce, M.D.
Associate Professor: Dazhe Cao, M.D., Jakub Furmaga, M.D.

FAMILY AND COMMUNITY MEDICINE
Professor: Nora Esther Gimpel, M.D.
Associate Professor: Sarah Woods, Ph.D.

IMMUNOLOGY/INTERNAL MEDICINE
Professor: Quan-Zhen Li, M.D., Ph.D.

IMMUNOLOGY/MICROBIOLOGY
Professor: Nan Yan, Ph.D.

INTERNAL MEDICINE
Professor: Kelly M. Chin, M.D., Sandeep Ram Das, M.D., M.P.H., Mark H. Drazner, M.D., Pradeep P. Mammen, M.D., Darren K. McGuire, M.D., Nilum Rajora, M.D., Anand Kumar Rohatgi, M.D.
Associate Professor: Marconi Abreu, M.D., Sadia Ali, M.D., Jaime Paul Almandoz, M.D., Faris G. Araj, M.D., Dian J. Cao, M.D., Ph.D., Uma Gunasekaran, M.D., Tamim Hamdi, M.D., Parag Joshi, M.D., Katy Lease Lonergan, M.D., Manish Mohanka, M.D., Siayareh Rambally, M.D., Navid Sadeghi, M.D., Shani Shastri, M.D., Kyaw K. Soe, M.D., Samira K. Syed, M.D., Julie B. Trivedi, M.D., Zhao Wang, Ph.D.

INTERNAL MEDICINE/MICROBIOLOGY
Professor: David E. Greenberg, M.D.

INTERNAL MEDICINE/MOLECULAR GENETICS/ CENTER FOR HUMAN NUTRITION
Associate Professor: Luke Engelking, M.D., Ph.D.

MOLECULAR BIOLOGY
Associate Professor: Vincent Scott Tagliabracci, Ph.D.

MOLECULAR GENETICS/BIOPHYSICS
Associate Professor: Xiaochun Li, Ph.D.

NEUROLOGICAL SURGERY/NEUROLOGY/ RADIATION ONCOLOGY
Associate Professor: Toral R. Patel, M.D.

NEUROLOGICAL SURGERY/ORTHOPAEDIC SURGERY
Professor: Carlos A. Bagley, M.D.

NEUROLOGICAL SURGERY/PEDIATRICS
Professor: Dale Matthew Swift, M.D.
Associate Professor: Bruno Braga, M.D., Angela Vivian Price, M.D.

NEUROLOGICAL SURGERY/PEDIATRICS/ RADIATION ONCOLOGY
Professor: Bradley Edward Weprin, M.D.

NEUROLOGY/NEUROSCIENCE/ PEDIATRICS/PSYCHIATRY
Associate Professor: Peter Tzu-shin Tsai, M.D., Ph.D

NEUROSCIENCE
Professor: Jay R. Gibson, Ph.D.

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Associate Professor: Matthew J. Carlson, M.D., David Bryan Nelson, M.D., Shivani R. Patel, M.D., Robert David Stewart, M.D.

OTOLARYNGOLOGY-HEAD & NECK SURGERY
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Associate Professor: Jacob Boston Hunter, M.D., Gopi Shah, M.D.

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Associate Professor: Nicole Kandalaft De Simone, M.D., M.P.H., Suntrea Teonta Goudeau Hammer, M.D., Allen Ross Hendricks, D.O., Alagarraju Muthukumar, Ph.D.

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Associate Professor: Samuel Zachary Davila, M.D., Jenny K. Rodriguez Francis, M.D., Veronica M. Meneses, M.D., Imran Nazir Mir, M.D., Julie Mirpuri Hathiramani, M.D., Devika R. Rao, M.D., Paul Kyungwon Sue M.D.

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PHYSICAL THERAPY
Associate Professor: Staci Shearin, M.P.T., Ph.D.

PLASTIC SURGERY
Professor: Sumeet Sorel Teotia, M.D.

POPULATION AND DATA SCIENCES
Professor: Jasmin A. Tiro, Ph.D.

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Associate Professor: Barry R. Ardolf, Psy.D., Joel Reed Baskin, M.D., Edward W. Clark, M.D., Nyaz Didehbani, Ph.D., Andrew Diederich, M.D., Meitra Doty, M.D., Brittany Hall, Ph.D., Jennifer Hughes, M.P.H., Ph.D., Heidi J. Koehler, Ph.D., Ben J. Lippe, Ph.D., Katherine Bellone Mount, Ph.D., Mona Angelique Robbins, Ph.D., Reed J. Robinson, Ph.D., Rachel A. Russo, M.D., Ladonna C. Saxon, Ph.D., Bo Wu, M.D.

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RADIOLOGY
Associate Professor: Lakshmi Ananthakrishnan, M.D., Oganes Ashikyan, M.D., Xinhui Duan, Ph.D., Matthew Ryan Hammer, M.D., Emily Eads Knippa, M.D., Li Liu, Ph.D., Jessica Huang Porembka, M.D., Stephen J. Seiler, M.D., Edward Justin Stehel, M.D.

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Associate Professor: Ananth J. Madhuranthakam, Ph.D.

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Professor: Avneesh Chhabra, M.D.

SURGERY
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Associate Professor: Kareem R. AbdelFattah, M.D., Deborah E. Farr, M.D., Sara A. Hennessy, M.D., Patricio M. Polanco, M.D., Thomas Schlieve, D.D.S., M.D., Rohit Ramesh Sharma, M.D.

SURGERY/MOLECULAR BIOLOGY/HAMON CENTER FOR THERAPEUTIC ONCOLOGY RESEARCH
Associate Professor: Michael T. Dellinger, Ph.D.

UROLOGY
Associate Professor: Douglas William Strand, Ph.D.

Pulsar Continued from page 1

These treatment models are being tested in multiple prospective clinical trials now open for enrollment or soon to launch.

"We unexpectedly found in these experiments that the time split between large, focused doses of radiotherapy will predict whether a certain class of immunotherapy drugs will work," said Robert Timmerman, M.D., Professor of Radiation Oncology and Neurological Surgery. "If they are 10 days apart, the drug therapy helps a lot for this model. If they are one to four days, it doesn't help. Yet many of the clinical trials that are being done right now with radiotherapy and immunotherapy are using radiation schedules a day apart or every other day apart – perhaps the exact wrong timing."

By allowing more time to assess changes for meaningful adaptation of an individual patient's course, the PULSAR paradigm fulfills the promise of personalized cancer care. Instead of marching through a course of standalone, daily radiotherapy without interruption, PULSAR can be spaced out to more thoughtfully integrate with surgery and drug therapy.

"Using artificial intelligence, the team can replan cancer treatment in 30 minutes instead of the typical five to seven days," said Dr. Timmerman, Interim Chair and Medical Director of Radiation Oncology and a member of the Harold C. Simmons Comprehensive Cancer Center. "The equipment and expertise under one roof should break new ground in fighting cancer."

Collaborating on the PULSAR project are faculty from the Departments of Radiation Oncology, Immunology, Pathology, and Neurological Surgery and members of the Peter O'Donnell Jr. Brain Institute and Simmons Cancer Center. PULSAR is being pioneered in a 71,000-square-foot expansion of Radiation Oncology services with seven new machines that image tumors and treat them with radiation. (See related story on page 3.)

Artificial intelligence experts from Radiation Oncology and the Lyda Hill Department of Bioinformatics developed machine-learning algorithms, while radiation oncologists use the machines' combined radiation and imaging abilities to make treatments as precise as possible, hitting the tumors and sparing healthy tissue.

Plans are underway to share expertise and data with other academic institutions, including Massachusetts General Hospital in Boston.

■

Dr. Timmerman holds the Effie Marie Cain Distinguished Chair in Cancer Therapy Research.

A radiation oncology MRI technologist helps set up a patient on the Elekta Unity MR-Linac prior to treatment.

PULSAR, a new radiotherapy for cancer, is customizable to the type and size of the cancer and also adapts dosage to how the tumor responds to treatment.

Findings

UTSW researchers discovered that PULSAR radiation could bolster systemic immunotherapy benefit, even in situations where immunotherapy alone was not effective.

In preclinical testing, they investigated one of the most common classes of immunotherapy, a PD-L1 checkpoint inhibitor, along with PULSAR radiation. This combination acted like a vaccination against tumors implanted in mice.

Splitting two pulses of radiation by 10 days was much more effective in combination with the checkpoint drug than the typical daily radiation schedule, researchers found. Next, the team will test this therapy strategy in patients through multiple open and pending clinical trials.

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

CENTERTIMES

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UTSW Radiation Oncology building expansion opens door to new therapies

From Staff Reports

UT Southwestern Medical Center recently completed its 71,000-square-foot expansion of Radiation Oncology services, heralding a new avenue of treatment to patients called adaptive therapy.

"For years, UT Southwestern has been a recognized leader in the field of radiation oncology, advancing research in stereotactic ablative radiotherapy, immunotherapy, and personalized patient care through the use of artificial intelligence, said Hak Choy, M.D., former Chair of Radiation Oncology. "With the opening of our expanded building, we're preparing to enter an exciting phase in the field of radiation oncology – adaptive therapy – which is not just the next iteration in care but a paradigm shift."

Adaptive therapy combines real-time, high-resolution imaging and modern radiation techniques to deliver ultra-precise treatment that can quickly be adapted to changes in patients' anatomy and tumor size.

"This distinctive facility with its unique technology opens the opportunity for our medical doctors to provide truly personalized adaptive radiation therapy to our patients," said Arnold Pompos, Ph.D., Associate Professor of Radiation Oncology and Director of Strategic Expansion Plans.

Radiation Oncology is a key component of UT Southwestern's Harold C. Simmons Comprehensive Cancer Center – one of 51 designated comprehensive cancer centers in the U.S. by the National Cancer Institute, a member of the elite 30-member National Comprehensive Cancer Network, with its cancer program nationally ranked among the top 25 by *U.S. News & World Report*.

UTSW's Radiation Oncology facility, with total combined space of more than 130,000 square feet, features a collection of the most sophisticated treatment machines. Coupled with image-guided therapy, the equipment is versatile and capable of treating an array of cancer malignancies under one roof. The additional "smart" treatment technologies provide a personalized patient experience through artificial intelligence-assisted radiation therapy adaptable to changes in the patient's anatomy, tumor size, and position, along with the ability to monitor treatment progress due to biological and functional changes.

"The adaptive machines not only provide precise image-guidance to tumors, they can realign and reshape radiation beams to the borders of the tumor as it changes, meaning we'll be able to better target tumors and avoid healthy tissue," said Robert Timmerman, M.D., Professor and Interim Chair of Radiation Oncology.

> "This distinctive facility with its unique technology opens the opportunity for our medical doctors to provide truly personalized adaptive radiation therapy to our patients."
> – Arnold Pompos, Ph.D.,
> Associate Professor of Radiation Oncology

The expanded Radiation Oncology building contains two Ethos machines, which incorporate CT scans and artificial intelligence with radiotherapy.

UT Southwestern has plans to take the technology further by combining it with a "big data" approach enhanced by artificial intelligence to create even more effective and highly personalized treatments called PULSAR, now being investigated through multiple clinical trials at UT Southwestern. (See related story on page 1.)

Adaptive therapy today is focused on conforming radiation to changing anatomy to make treatment more precise, said Steve Jiang, Ph.D., Professor and Vice Chair of Radiation Oncology.

"In the near future, we'll have more intelligent adaption based on biomarkers," said Dr. Jiang. "We'll be able to prescribe different levels of radiation to patients based on their unique response to treatment and what models and past data for similar conditions suggest are optimum."

■

Dr. Jiang holds the Barbara Crittenden Professorship in Cancer Research.

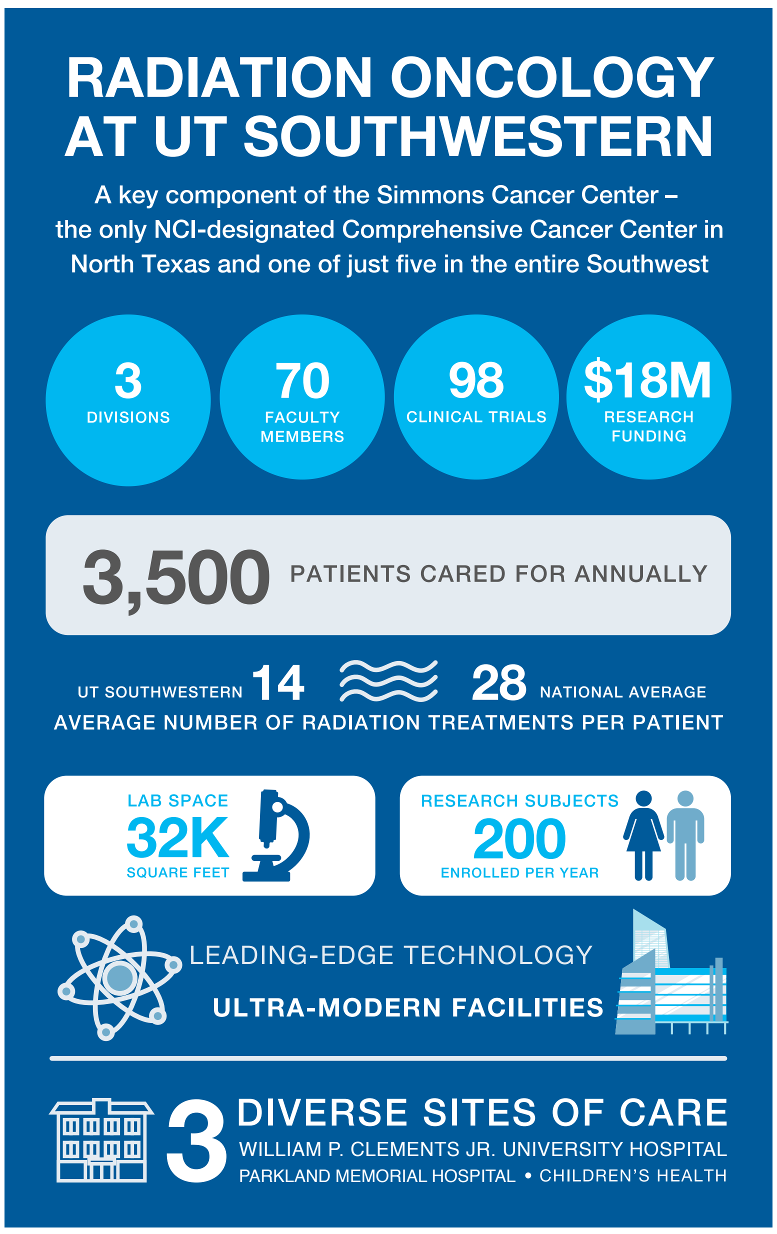
Dr. Timmerman holds the Effie Marie Cain Distinguished Chair in Cancer Therapy Research.

More online: Read the full story on *Center Times Plus* at **utsouthwestern.edu/ctplus**, which includes a video highlighting the new space and radiation oncology technology.

Take a look inside

The Radiation Oncology expansion includes 49 exam rooms, procedure rooms, patient support rooms, two children's areas, a quick-serve cafe, and more than a dozen advanced imaging/treatment machines including:

- Two Ethos machines, which incorporate CT scans and artificial intelligence with radiotherapy
- Two Elekta Unity machines, which incorporate MRI imaging with radiotherapy
- Two Halcyon machines, which incorporate cone-beam CT imaging with radiotherapy
- One RefleXion machine, which incorporates PET imaging with radiotherapy
- Two CT simulators/AIRO
- One MR simulator
- One high-dose-rate brachytherapy suite
- One Xstrahl treatment machine
- One GammaPod treatment machine for breast cancer



A master gear in the circadian clock

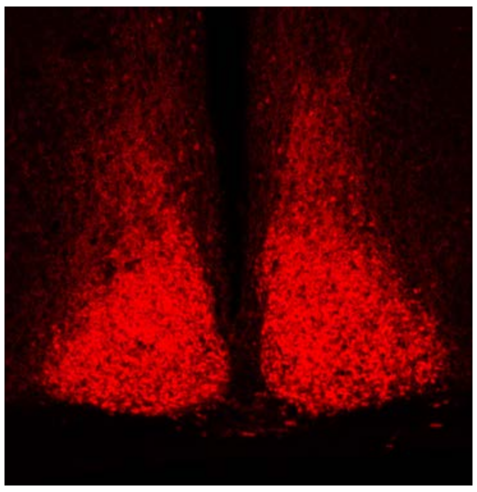
Scientists identify gene that appears to influence hundreds of others for timekeeping in the brain

By Christen Brownlee

A gene called *Npas4*, already known to play a key role in balancing excitatory and inhibitory inputs in brain cells, appears to also be a master timekeeper for the brain's circadian clock, new research led by UT Southwestern scientists suggests. The finding, published in *Neuron*, broadens understanding of the circadian clock's molecular mechanisms and could eventually lead to new treatments for managing challenges such as jet lag and sleep disorders.

"To reset the circadian clock, you ultimately need to reset its molecular gears," said study leader Joseph S. Takahashi, Ph.D., Professor and Chair of Neuroscience and a Howard Hughes Medical Institute Investigator. "This study suggests that *Npas4* might be one of the most important components for resetting the clock to light."

For decades, researchers have known that a brain region called the suprachiasmatic nucleus (SCN) controls circadian rhythms, the various cycles of activity that typically run on a 24-hour basis. These rhythms are entrained by light, Dr. Takahashi explained; cells in the SCN respond to signals relayed by the retina, the eye's light-sensitive tissue. However, the molecular basis of this phenomenon is not well understood.



Microscopic image of the mouse suprachiasmatic nucleus, the brain region responsible for controlling circadian rhythms.

To learn more about how the SCN sets circadian rhythms, the researchers used a technique called single nucleus sequencing to examine gene activity in cells in mice after the animals were exposed to light. Dr. Takahashi and his colleagues found that three different subpopulations of SCN neurons respond to light stimulation. A common thread tying these subtypes together was increased activity in genes that respond to Neuronal PAS Domain Protein 4 (NPAS4), the protein made by the *Npas4* gene.

Joseph S. Takahashi, Ph.D.

When the research team exposed mice engineered to lack *Npas4* to light, it dampened the response of hundreds of circadian clock genes. In addition, the animal's circadian period lengthened about an extra hour, to nearly 25 hours instead of the normal 24. Together, Dr. Takahashi said, these results suggest that *Npas4* is a master regulator of many light-induced genes, a key piece in the puzzle of how the circadian system works.

The more researchers learn about the molecular underpinnings of the circadian clock, Dr. Takahashi added, the more they may be able to manipulate it to improve health and well-being – for example, to ease jet lag or help shift workers stay awake to match their work cycles. It could also lead to new treatments for disorders marked by abnormal sleep/wake cycles.

This work was a collaboration with the laboratory of Genevieve Konopka, Ph.D., Associate Professor in the Department of Neuroscience and Director of the UTSW Neurogenomics Core.

■

Dr. Konopka is a Jon Heighten Scholar in Autism Research.

Dr. Takahashi holds the Loyd B. Sands Distinguished Chair in Neuroscience.

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

Belzutifan Continued from page 1

"The history of belzutifan's development demonstrates the value of cross-disciplinary collaborations at academic medical centers and how that can translate to new treatments for diseases," said Dr. Russell, former Vice Provost and Dean of Research. "It also underscores the value of investing in basic science discoveries at the core of advancements in medicine."

James Brugarolas, M.D., Ph.D., Director of the UTSW Kidney Cancer Program

In 2011, several researchers spun off Peloton Therapeutics, and by 2019, when Merck acquired the company, at least three HIF-2α agents were under investigation.

James Brugarolas, M.D., Ph.D., Director of the Kidney Cancer Program at UT Southwestern's Harold C. Simmons Comprehensive Cancer Center, showed that the drug was effective against kidney cancer. With funding from a prestigious National Cancer Institute SPORE award, his team reported in *Nature* in 2016 that the drug could inhibit HIF-2α in human kidney tumors transplanted into mice and stop the cancer's growth.

This and other studies led to the first clinical trial of PT2385, a precursor to PT2977, which became belzutifan. The trial, which was led by the UTSW Kidney Cancer Program, showed that the drug was well-tolerated and effective.

"The approval of belzutifan represents a new paradigm in the treatment of kidney cancer," said Dr. Brugarolas, also Professor of Internal Medicine. "By exclusively targeting HIF-2α, which is essential for kidney cancers but dispensable for normal processes, belzutifan specifically disables cancer cells while sparing normal cells. Belzutifan is the best-tolerated kidney cancer drug today and one suitable for patients with familial kidney cancer. It is a testament to the prowess of designer drugs and carefully chosen targets of which it is a prime example."

Disclosures: UT Southwestern and some of its researchers will receive financial compensation, through prior agreements with Peloton, based on belzutifan's FDA approval.

■

Dr. Brugarolas holds the Sherry Wigley Crow Cancer Research Endowed Chair in Honor of Robert Lewis Kirby, M.D.

Dr. McKnight holds the Distinguished Chair in Basic Biomedical Research.

TIMELINE: The path to developing a HIF-2α inhibitor

1997
UT Southwestern biochemist Steven McKnight, Ph.D., and molecular geneticist David Russell, Ph.D., report the discovery of the HIF-2α gene, which they call *EPAS1*. The team shows that HIF-2α binds to another protein, HIF-1α. The HIF-2 partner functions like a pair of tweezers to grab DNA. HIF-2 binds DNA at specific places to initiate the production of other proteins such as VEGF, which support kidney cancer growth.

2003
Richard Bruick, Ph.D., and Kevin Gardner, Ph.D., uncover aspects of the atomic blueprint of HIF-2α. They show how HIF-2α docks with HIF-1α to assemble into a functional HIF-2 complex. They identify a cavity within the HIF-2α protein, hypothesizing that it may offer a foothold for a drug. Working with UT Southwestern's High-Throughput Screening laboratory, the researchers develop a test to identify chemicals among 200,000 drug-like molecules that bind to the HIF-2α cavity, preventing HIF-2α from binding to HIF-1α. By interfering with HIF-2α binding to HIF-1α, these compounds block HIF-2 action. The most promising chemicals undergo a refinement process by UTSW medicinal chemists.

2010
Peloton Therapeutics is founded by UTSW researchers, via the UTSW Office of Technology Development, to develop the HIF-2α-blocking chemicals into drugs. Peloton scientists create libraries of related compounds, ultimately identifying PT2385 and PT2977 to test in humans. A related drug, PT2399, is identified for laboratory work.

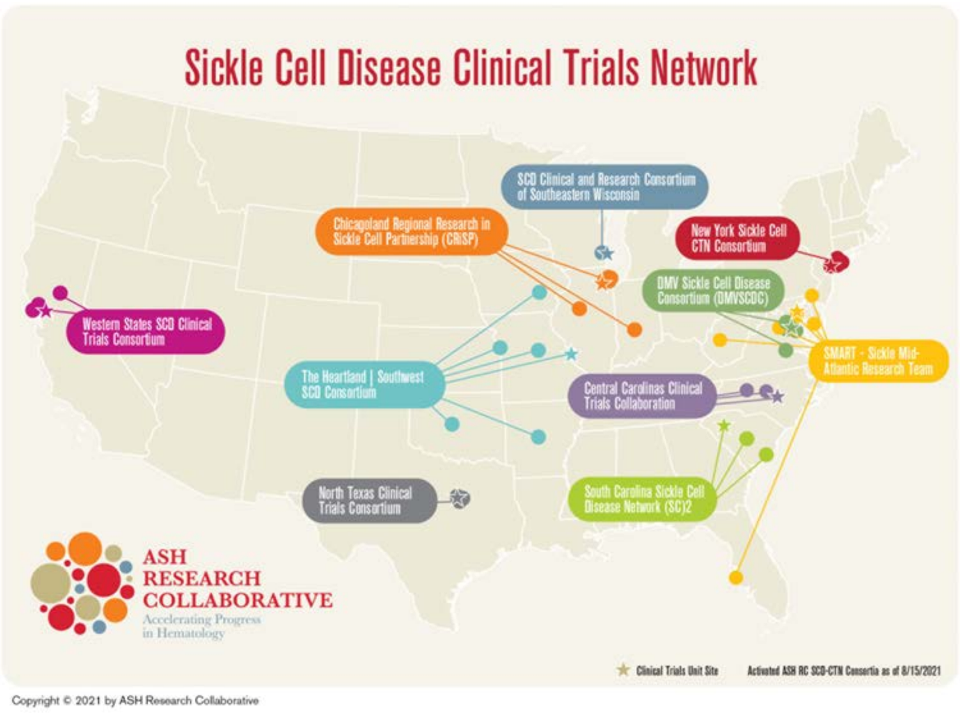
2016
James Brugarolas, M.D., Ph.D., validates HIF-2α as a target in kidney cancer. In experiments involving mice transplanted with human kidney tumors, researchers show that PT2399 blocks HIF-2α while not affecting related proteins, is active against 50% of human kidney tumors, and has more activity and is better tolerated than sunitinib (the most commonly used drug for renal cancer treatment at the time).

2018
Kevin Courtney, M.D., Ph.D., Associate Professor of Internal Medicine, reports the results of a phase one clinical trial testing PT2385 in humans. The trial represents the first-in-human study of a first-in-class inhibitor of HIF-2α. The trial demonstrates that PT2385 is safe, well-tolerated, and active against kidney cancer in humans. More than 50% of patients see their cancer regress or stabilize.

2019
U.S. drug manufacturer Merck acquires Peloton Therapeutics for $1.05 billion, with an additional $1.15 billion contingent on sales and regulatory milestones.

2020
Through studies of tumor biopsy samples from patients who participated in the phase one clinical trial, Drs. Courtney, Brugarolas, and Ivan Pedrosa, M.D., Ph.D., report the identification of drug resistance mutations in patients, establishing HIF-2α as the first-known core dependency of kidney cancer.

Network Continued from page 1



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centers nationwide, attracting enough patients to make the trials feasible, expanding treatment options, and growing medical science knowledge to fight the disease.

Alecia Nero, M.D., Associate Professor of Internal Medicine and Pediatrics, said the push to bring clinical trials to new heights is severely needed. Currently, there are just four drugs used to treat sickle cell disease; three have only been available since 2017.

"Sickle cell disease, being a relatively rare disease, struggles with keeping significant trials open because it takes so long to get patients. By creating these networks, you can then enroll the patients to get the answer that you're after," Dr. Nero said.

Dr. Nero, who treats pediatric sickle cell patients at Children's Medical Center, is Director of the Transition Sickle Cell Program that helps patients successfully transfer from pediatric to adult care. Young adult patients are at increased risk of death during this critical period, making transition of care a high priority. She is also the adult sickle cell program Medical Director and cares for patients at Clements University Hospital and Parkland.

Dr. Leavey, a member of the Harold C. Simmons Comprehensive Cancer Center, said he hopes the network will bring significant advances against the disease by opening up new collaborations with pharmaceutical companies. Dr. Nero said there are 30 to 40 new drugs that pharmaceutical companies would like to bring to clinical trials for sickle cell disease. Her highest hopes are for new treatments involving gene therapies.

A description of the program was part of UT Southwestern's application to the Washington D.C.-based ASH to become a founding member of the network.

"This was very competitive. It speaks to our institution and the leadership and ASH seeing all the things we can do at UT Southwestern," Dr. Nero said.

Dr. Leavey said UT Southwestern's leadership in sickle cell clinical research and its data resources also helped, along with an advisory board that includes community members. Other founding members of the Sickle Cell Disease Clinical Trials Network include The Johns Hopkins University School of Medicine, the University of Chicago, and Weill Cornell Medicine.

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

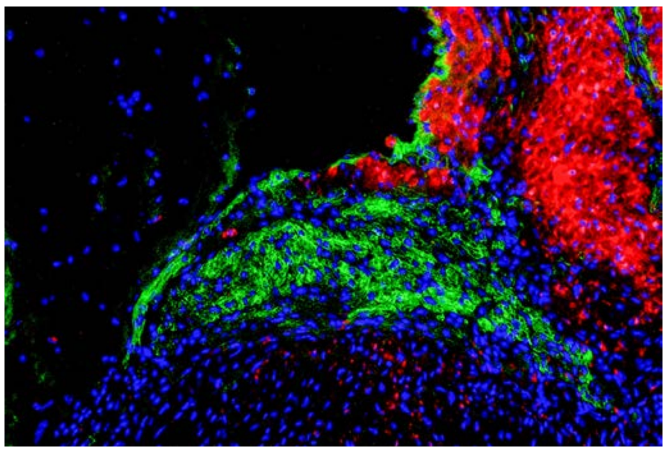
Cells that keep the heart beating can regenerate, study reveals

By Christen Brownlee

Specialized cells that conduct electricity to keep the heart beating have a previously unrecognized ability to regenerate in the days after birth, a new study in mice by UT Southwestern researchers suggests. The finding, published online in the *Journal of Clinical Investigation*, could eventually lead to treatments for heart rhythm disorders that avoid the need for invasive pacemakers or drugs by instead encouraging the heart to heal itself.

"Patients with arrhythmias don't have a lot of great options," said study leader Nikhil V. Munshi, M.D., Ph.D., a cardiologist and Associate Professor of Internal Medicine, Molecular Biology, and in the Eugene McDermott Center for Human Growth and Development. "Our findings suggest that someday we may be able to elicit regeneration from the heart itself to treat these conditions."

Dr. Munshi studies the cardiac conduction system, an interconnected system of specialized heart muscle cells that generate electrical impulses and transmit these impulses to make the heart beat. Although studies have shown that nonconducting heart muscle cells have some regenerative capacity for a limited time after birth – with many discoveries in this field led by UTSW scientists – conducting cells called nodal cells were largely thought to lose this ability during the fetal period.



The mouse atrioventricular (AV) node. Green staining indicates AV node cells, while red staining highlights neighboring atrial muscle cells. All cell nuclei are stained blue.

Nikhil V. Munshi, M.D., Ph.D.

Previous research had suggested that neonatal nodal cells lose stem cell-like qualities before birth, giving them negligible regenerative properties. However, Dr. Munshi explained, their regenerative abilities had never been directly tested because there was no way to eliminate only nodal cells in animal models to spur regeneration.

To solve this problem, Dr. Munshi and his colleagues used genetic engineering to develop mice whose atrioventricular (AV) node cells – located near the intersection of the heart's four chambers – did not respond well when they were fed the breast cancer drug tamoxifen. In adult mice of this strain that were given tamoxifen, tissue samples and electrocardiograms revealed progressive heart damage stemming from the loss of AV node cells in the following weeks and months. However, when neonatal mice were dosed, heart function appeared to be completely normal in one-third of the animals a month later.

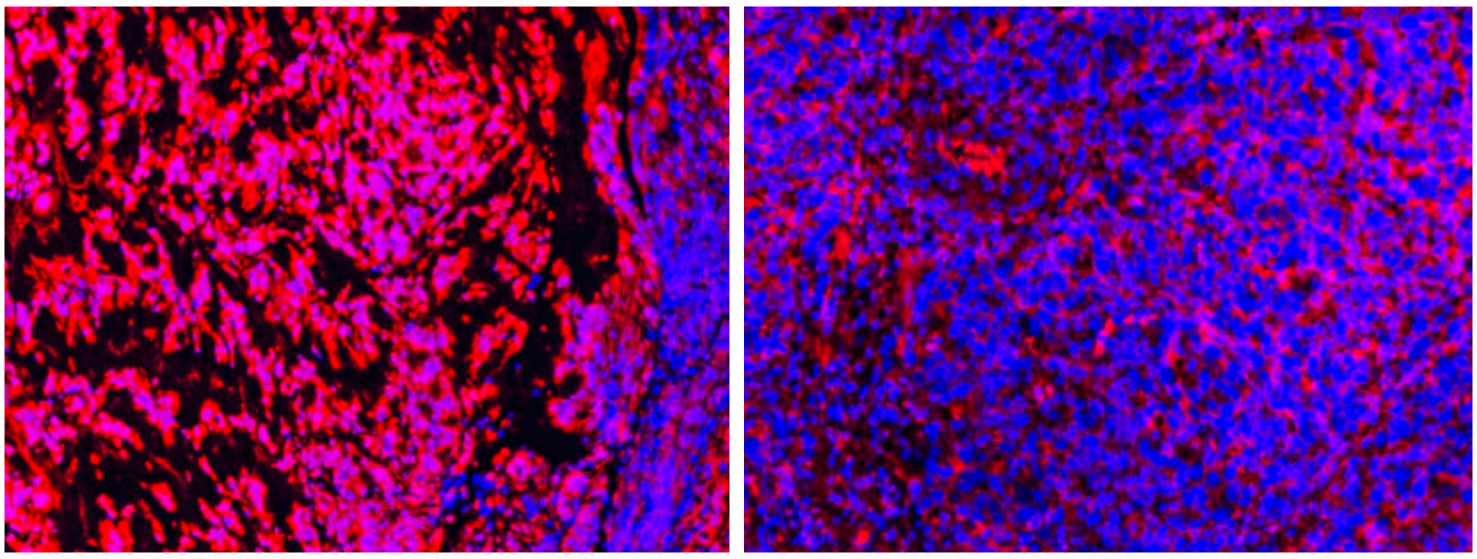
Taking a closer look, the researchers performed electrocardiograms on newborn mouse models of AV node failure every couple of days after tamoxifen treatment. These tests revealed an initial injury to the heart that gradually healed itself in many of the animals. Although tissue examination showed that this healing didn't result in a completely normal heart in adulthood, it was sufficient for the mice to have regular heart rhythms.

Intriguingly, further investigation showed that nonmuscle heart cells were the predominant cell type that proliferated after the nodal cells died. These cells appeared to modulate production of proteins that help heart cells make electrical connections.

The reasons why these proteins increased and why only about one-third of the animals showed regeneration remain unclear, Dr. Munshi said. He and his colleagues plan to continue studying the molecular mechanisms behind this phenomenon to gain more knowledge that could eventually lead to a drug that can stimulate the regeneration pathway on demand to regrow damaged nodes in arrhythmia patients.

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

Scientists find new molecular mechanisms and biomarkers in ovarian cancer



Ovarian cancer patient samples show high levels of protein aggregates in magenta (left), which coincides with low levels of mono(ADP-ribose) (MAR), compared with low levels of protein aggregates (right) and high levels of MAR. The study found that high levels of MAR and low levels of protein aggregates enhance ovarian cancer cell survival.

By Patrick McGee

UT Southwestern researchers have discovered what appears to be an Achilles' heel in ovarian cancers, as well as new biomarkers that could point to which patients are the best candidates for new treatments.

The finding, published in *Cell*, was made in part using a research tool invented in a UTSW lab in the Cecil H. and Ida Green Center for Reproductive Biology Sciences. The research was led by W. Lee Kraus, Ph.D., Professor of Obstetrics and Gynecology and Pharmacology.

"Many researchers are trying to find dependencies in cancers by asking why a cancer cell amplifies a gene, increases the levels of a protein, or upregulates a critical cellular pathway. These changes give that cancer a selective advantage, but at the same time they can become an Achilles' heel – something that, if the alteration was blocked, would kill the cancer or stop its growth," said Dr. Kraus, also Director of the Cecil H. and Ida Green Center for Reproductive Biology Sciences and a member of the Harold C. Simmons Comprehensive Cancer Center.

W. Lee Kraus, Ph.D.

The research team, including lead author Sridevi Challa, Ph.D., a postdoctoral researcher in Dr. Kraus' lab, found that ovarian cancers massively amplify the enzyme NMNAT-2, which makes NAD+. NAD+ is the substrate for a family of enzymes called PARPs, which chemically modify proteins with ADP-ribose from NAD+. In this study, the team found that one PARP family member, PARP-16, uses NAD+ to modify ribosomes, the protein synthesizing machines of the cell.

In collaboration with UTSW clinicians, led by Jayanthi Lea, M.D., Professor of Obstetrics and Gynecology and a member of the Simmons Cancer Center, Dr. Kraus and his team screened ovarian cancer patient samples using a synthetic mono(ADP-ribose) detection reagent to identify those with low or high levels of mono(ADP-ribose). The study identified mono(ADP-ribose) and NMNAT-2 as potential biomarkers for ovarian cancers, enabling clinicians to determine which cancer patients may respond well to treatment. Ovarian cancer patients might also benefit from an inhibitor for PARP-16, which blocks ribosome mono(ADP-ribosyl)ation.

Dr. Kraus, an expert in PARPs, said medical science has had great success in developing FDA-approved PARP-1 inhibitors, and an inhibitor for PARP-16 is likely.

"No PARP-16 inhibitors are currently in clinical trials, but labs in academia and the pharmaceutical industry are developing specific and potent inhibitors of PARP-16. Such a drug could be an effective therapeutic for treating ovarian cancers," he said.

"Dr. Kraus' research is not just a great advance in basic science. It has real promise for clinician investigators and cancer care practitioners because it shows a biomarker and a pathway a future drug could target. The fact that technology developed in his laboratory helped make these findings shows how our faculty builds on their findings to break new ground," said Carlos L. Arteaga, M.D., Director of the Simmons Cancer Center

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Dr. Arteaga holds The Lisa K. Simmons Distinguished Chair in Comprehensive Oncology.

Dr. Kraus holds the Cecil H. and Ida Green Distinguished Chair in Reproductive Biology Sciences.

Dr. Lea holds the Patricia Duniven Fletcher Distinguished Professorship in Gynecological Oncology.

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

RedBird project on target to open in mid-2022

Progress continues on construction of UT Southwestern Medical Center at RedBird, a two-story, 150,000-square-foot center in the redeveloped RedBird Mall in southern Dallas County that is scheduled to open in summer 2022. Here are some highlights:

- Exterior walls recently were finished, with construction targeted for completion next summer.
- Outpatient clinical and support services will include primary care, diabetes management, cardiology, neurology/memory loss, cancer, culinary medicine, mammography, advanced imaging, infusion therapy, laboratory services, and a pharmacy.
- Pediatric services, provided through Children's Health by members of the UT Southwestern Pediatric Group, are being evaluated, with an anticipated opening date in 2023.
- RedBird serves as an anchor for Reimagine RedBird, a revitalization initiative converting the historic RedBird Mall into a mixed-use development bustling with restaurants, businesses, and luxury apartments.

– By Remekca Owens

Exterior wall construction was recently finished at UT Southwestern Medical Center at RedBird.

Grad student studying neurotransmitters receives Ida M. Green Award

By Carol Marie Cropper

Karolina Stepien, who studies how the brain's neurotransmitters are released from one neuron to send a signal to another, has been named winner of the 2021 Ida M. Green Award. This honor is given each year by Southwestern Medical Foundation to a female student in UT Southwestern's Graduate School of Biomedical Sciences based on her scientific accomplishments and commitment to the UTSW community.

Ms. Stepien said she was extremely happy to receive the award, which is one of the most prestigious for UTSW graduate students.

"I like that there is an award that specifically recognizes a scientist who is a woman. In general, women have had fewer chances than men in the sciences," she said.

Her basic research into how powerful neurotransmitter chemicals housed within vesicles, or tiny bubbles, inside nerve cells are released outside the cells could one day help scientists understand the mechanisms involved in and devise treatments for neurodegenerative, emotional, and movement disorders such as Alzheimer's disease, depression, and epilepsy.

Ms. Stepien, a Fulbright Scholar from Poland, is working toward her doctorate in molecular biophysics as a graduate student researcher in the lab of Jose Rizo-Rey, Ph.D., a Professor of Biophysics, Biochemistry, and Pharmacology. She initially came to UTSW in 2014 as an exchange student in the BioLAB program, which provides Polish master's and doctoral students in the biological sciences a one-year paid internship to study at UT Southwestern or other American institutions.

Karolina Stepien, winner of the 2021 Ida M. Green Award, studies how brain neurotransmitters work in hopes of uncovering new treatments for neurodegenerative disorders.

At the time, Ms. Stepien was focused on biotechnology, the subject she received her undergraduate degree in from the Wroclaw University of Science and Technology. But she became fascinated with Dr. Rizo-Rey's biophysics research into neuronal function and was impressed by UTSW's supportive and collaborative atmosphere. After returning to Poland and completing her master's in 2016, she came back to UT Southwestern to pursue doctoral studies in molecular biophysics.

"This is the process that underlies everything that we do – our emotions, feelings – basically who we are as humans," she said, explaining her attraction to research about how nerve cells in the brain communicate.

"Karolina Stepien has a brilliant intellect and enormous curiosity that drives her to tackle multiple projects in parallel," Dr. Rizo-Rey said. "She has a combination of talent and effort that I have seen in very few students over my 32 years at UT Southwestern."

"We are honored and delighted to celebrate Ms. Karolina Stepien as the 2021 winner of the Ida Green Award," said Kathleen M. Gibson, President and CEO of Southwestern Medical Foundation. "Ms. Stepien has served the UT Southwestern community and the Graduate School with distinction across a broad spectrum, both in leadership and in service. Her scientific contributions have advanced the understanding of the mechanisms of neurotransmitter release and embody the innovative spirit and rich legacy of Ida Green."

The Ida M. Green Award was established by Southwestern Medical Foundation in honor of Mrs. Green, who died in 1986. Her husband, Cecil Green, who died in 2003, worked at General Electric and later co-founded Texas Instruments. Mrs. Green provided unrestricted gifts to many community organizations, including a major bequest to Southwestern Medical Foundation. The award includes a $2,000 prize.

In 2019, Ms. Stepien's work led to publication in *Nature Communications* of a study that explained the competition between two neuronal proteins – Munc18-1 and αSNAP – to bind to a protein in the membrane of the neuron called syntaxin-1. Depending on which protein wins this competition, membrane fusion and then release of the neurotransmitters outside the cell is either helped or inhibited, Ms. Stepien said. This was her first study as lead author.

In 2021, she was the first author of a *PNAS* study that focused on recapitulating the process of neurotransmitter release in the test tube with purified proteins. She also has been an author on six additional papers in high-impact journals.

During her time at UTSW, Ms. Stepien served as President of Quest for Careers, an organization that helps Ph.D. students learn about career options, and she volunteered as chair in the science area for United to Serve, which organizes an annual health fair in Dallas. Working with a friend who is also a Fulbright Scholar and a UTSW graduate student, Martyna Kosno, Ms. Stepien founded a local chapter of the Fulbright Scholar organization for those in the Dallas area. In addition, she chairs the Molecular Biophysics Program's social committee, arranging monthly get-togethers.

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Dr. Rizo-Rey holds the Virginia Lazenby O'Hara Chair in Biochemistry.

Batjer, Niederkorn named UT Southwestern Professors Emeritus

From Staff Reports

Two UT Southwestern faculty – one an internationally recognized cerebrovascular surgeon and the second a leader in the field of ocular immunology – have been appointed Professors Emeritus.

Former Chair of Neurological Surgery Hunt Batjer, M.D., retired at the end of 2020 after a nearly 40-year career. In his new role as Professor Emeritus, he looks forward to mentoring faculty, residents, and students and assisting with recruitment and program development.

Dr. Batjer's UT Southwestern journey began in 1973 as a medical student. He completed his medical degree, general surgery internship, and neurological surgery residency at UTSW, followed by a neurology fellowship at the University College London and a cerebrovascular disorders fellowship at the University of Western Ontario. He served on the UTSW faculty for 13 years before leaving to become Chair of Neurological Surgery at the Northwestern University Feinberg School of Medicine. In 2012, he returned to UT Southwestern as the third Chair of Neurological Surgery.

Dr. Batjer's academic pursuits and research in ischemic and hemorrhagic stroke and brain injuries have resulted in nine books and 467 peer-reviewed publications and book chapters. He also has presented 53 endowed lectureships and served as a visiting professor in 63 medical institutions worldwide. In addition, as co-Chair of the NFL Head, Neck, and Spine Committee for eight years, he helped develop the league's concussion protocol.

Hunt Batjer, M.D.

Jerry Niederkorn, Ph.D.

Among his many accolades, Dr. Batjer is the 2020 recipient of the Harvey Cushing Medal, the highest honor bestowed by the American Association of Neurological Surgeons. Now Treasurer of the Accreditation Council for Graduate Medical Education (ACGME), he previously served as Chair of the ACGME's Residency Review Committee for Neurological Surgery and as Director and Chair of the American Board of Neurological Surgery.

"I am fortunate to have trained at UTSW under great neurosurgeons," Dr. Batjer said. "I benefited immensely from that training and look forward to being able to give back to the organization that gave me so much."

The second appointee, Jerry Niederkorn, Ph.D., is recognized as a leader in infectious diseases of the eye. A faculty member since 1977 who retired in August, Dr. Niederkorn was Professor of Ophthalmology and Microbiology. He also served as Chair of the Immunology Graduate Program.

Dr. Niederkorn's efforts have earned multiple international awards, including the Alcon Research Institute Award, an award given to a handful of international scientists each year. He also was selected for the Association for Research in Vision and Ophthalmology's Proctor Medal Award in 2019, a prestigious honor for scientists conducting vision and ophthalmic research.

For more than 35 years, Dr. Niederkorn has maintained continuous National Institutes of Health funding and has served as Principal Investigator on three research grants that were simultaneously funded for 28 years. His productivity as a scientist is reflected in the publication of 273 articles in peer-reviewed journals and 50 book chapters and articles.

Cornea transplantation was especially intriguing to him.

"It is the most successful transplant surgery that is done, but why?" he asked.

Answering that question has been the focus of much of his research. In 2015, he identified why secondary corneal transplants are rejected at triple the rate of first-time corneal transplants, which have a success rate of 90%. He uncovered an immune process that led to the rejection.

As much as he has enjoyed research, he has also found working with students to be especially rewarding. Dr. Niederkorn has mentored 20 graduate students who earned their Ph.D.s in his laboratory and has served on the dissertation committees for 60 Ph.D. students at UT Southwestern. He continues to serve in multiple capacities for the University, including assisting with medical student interviews and as a member of the Steering Committee for the Immunology Graduate Program.

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

NEWS MAKER

Cunningham receives lifetime achievement honor

Gary Cunningham, M.D., has received the American College of Obstetricians and Gynecologists' Luella Klein Lifetime Achievement Award, which honors an obstetrician and gynecologist who has dedicated his or her life in a significant way to women's health.

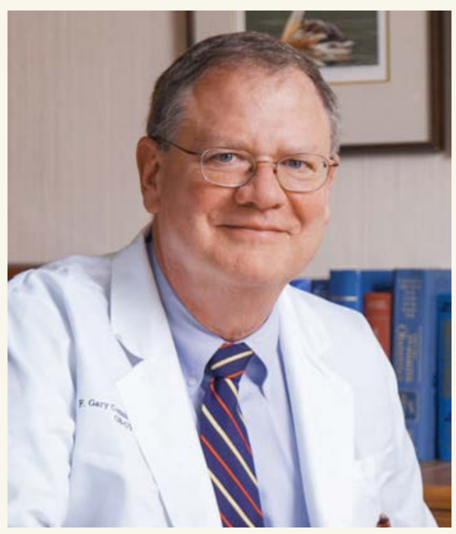
"The award is especially meaningful because it comes from my peers and it reaffirms in my mind that I have made a contribution to our specialty of obstetrics and gynecology and the care of all women," said Dr. Cunningham, Professor of Obstetrics and Gynecology.

A 1968 graduate of Louisiana State University School of Medicine in New Orleans, Dr. Cunningham came to UT Southwestern in 1972 as a postdoctoral fellow and joined the faculty in 1973. He was an attending physician at Parkland Memorial Hospital before becoming Chief of Obstetrics in 1981. He served as UTSW Chair of Obstetrics and Gynecology from 1983 to 2004 and as Chief of Obstetrics and Gynecology at Parkland from 1982 to 2006.

A world-recognized authority on the hematological and hypertensive disorders of pregnancy, he was the chief author/editor of the *Williams Obstetrics* textbook from the 18th through the 25th editions.

"Working over the years with a host of talented and dedicated people, we have continued to serve the indigent women in the Dallas area for Ob/Gyn care through Parkland Hospital. Our program has trained hundreds of Ob/Gyn residents and fellows who are now community practitioners – many in Dallas – and providing expert care for women in gynecology, obstetrics, gynecological oncology, family planning, and pelvic medicine and reconstructive surgery," he said.

"Our Department was so pleased to learn that Dr. Cunningham was selected to receive this prestigious honor," said Steven Bloom, M.D, Associate Dean for Clinical Sciences and former Chair of Obstetrics and Gynecology. "Through his bedside teaching, his authorship of major textbooks and scientific papers, and his mentorship, Dr. Cunningham has made so many of us – both at UT Southwestern and beyond – better physicians."



Gary Cunningham, M.D.

Parikh joins UT Southwestern as Chief of Nephrology Division

Samir Parikh, M.D.

By Jan Jarvis

Samir Parikh, M.D., had one eye on the rich history of UT Southwestern and the other on its promising future when he accepted the position of Chief of the Division of Nephrology in the Department of Internal Medicine.

"This institution has a reputation for being dedicated to research, serving the needs of the patient population, and being a unique environment for biomedical education," he said. "Very few places look far into the future, but I think this is one of those places. That is exciting and something I wanted to be a part of."

"Dr. Parikh is an outstanding physician-scientist who reflects the ideals of the clinical scholar exemplified by the late Donald Seldin, M.D.," said Thomas Wang, M.D., Chair of Internal Medicine.

Dr. Seldin led the Department of Internal Medicine from 1952 until 1988 and is viewed as the intellectual father of UT Southwestern.

"We have an outstanding and historic Nephrology Division, and I am excited to see it continue to advance under Dr. Parikh's leadership," Dr. Wang said.

Dr. Parikh, also Professor of Internal Medicine and Pharmacology, brings an enthusiasm for research, teaching, and clinical care to his new role and has focused on kidney disease throughout his career.

"Kidney disease is extremely common, but it's also complex and silent," he said. "Other than transplantation, there's really no magic bullet for our patients."

To date, Dr. Parikh's research has emphasized mechanisms underlying acute kidney injury and sepsis. His work has sought to understand how patients with kidney disease survive major stressors such as surgery or severe infection.

Dr. Parikh was recruited to UT Southwestern from Harvard Medical School, where he was Professor of Medicine and Associate Vice Chair for Research in the Department of Medicine at Beth Israel Deaconess Medical Center. He graduated magna cum laude from Harvard with a degree in chemistry and later received the Founder's Medal for highest academic standing from Vanderbilt University School of Medicine. Dr. Parikh, who completed residency and fellowship training in nephrology at Beth Israel Deaconess and Harvard, has mentored more than 10 trainees who have attained the job title of Assistant Professor or higher.

The pandemic was among the factors in his decision to join UTSW. Like many people, he chose to focus more on his long-term goals because of COVID-19 and its worldwide impact.

"I started asking myself, 'How can I find a way to make more of an impact?'" Dr. Parikh said.

He found his answer at UT Southwestern.

"We have truly distinguished faculty in Nephrology, and our fellows are among the best in the nation. It is a privilege to join this dedicated group as we try to improve the health of North Texas kidney patients," he said.

"We have people here thinking about what comes next and how medicine will look in five, 10, 20 years."

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Dr. Parikh holds the Robert Tucker Hayes Distinguished Chair in Nephrology, in Honor of Dr. Floyd C. Rector, Jr., and the Ruth W. and Milton P. Levy, Sr. Chair in Molecular Nephrology.

Dr. Wang holds the Donald W. Seldin Distinguished Chair in Internal Medicine.

NEWS MAKER

Levine receives award for NASA research

Benjamin Levine, M.D., Professor of Internal Medicine and Director of the Institute for Exercise and Environmental Medicine (IEEM), has been awarded the 2021 Jeffrey P. Sutton Scientific Achievement Award for his work with NASA studying spaceflight's effect on the human body. The IEEM is a partnership between UT Southwestern and Texas Health Presbyterian Dallas.

The annual award from the Space Medicine Association recognizes an individual or team for research with significant scholarship, innovation, and impact for space medicine. The award was presented by Jeffrey Sutton, M.D., Ph.D., Director of the Center for Space Medicine at Baylor College of Medicine.

"As a clinical cardiologist and expert in space physiology, Ben has been a valuable resource to NASA in evaluating and managing cardiovascular problems in astronauts," Dr. Sutton said, noting Dr. Levine also has mentored countless students and served in substantial scientific leadership roles. "However, it is in space biomedical research where Dr. Levine has truly excelled, making him most deserving of this award."

Over three decades ago, Dr. Levine applied to be a NASA astronaut. Being disqualified – he's colorblind – was a good thing. It gave Dr. Levine the opportunity to ask key questions as a researcher.

As a young physician-scientist, Dr. Levine placed the first invasive central venous pressure catheters in astronauts, demonstrating that central venous pressure decreases rather than increases in space, as had been previously thought. He also defined the concept of cardiac atrophy as it applies to bedrest and spaceflight – and identified specific interventions to prevent it.

Dr. Levine's ambitious series of experiments in the Shuttle era found that sympathetic nerve activity is increased in space – findings that pointed the scientific community toward the mechanisms of reduced stroke volume. In addition, his team discovered that adequate exercise aboard the International Space Station could prevent cardiac atrophy and orthostatic intolerance, Dr. Sutton noted.

"Some of the most exciting and rewarding work I have done in my career has been to address the critical research questions regarding the cardiovascular adaptations to spaceflight," Dr. Levine said. "This research effort has also led to one of my areas of clinical expertise, which is taking care of patients with 'gravity diseases' – that is, those who can't stand up on Earth, or faint. The ability to merge my research focus with an important clinical application is one of the true joys of academic medicine, and I am grateful to NASA and my colleagues in space medicine for this opportunity and recognition."

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Dr. Levine holds the Distinguished Professorship in Exercise Sciences.

Benjamin Levine, M.D.

Best Employer Continued from page 1

stress and financial management.

UT Southwestern partners with diverse professional organizations within the community, including the National Association of Black Accountants, National Black MBA Association Inc., National Society of Hispanic MBAs, and the Association of Latino Professionals For America to assure that members are aware of the numerous employment opportunities available at UT Southwestern. Career development is supported by initiatives such as the President's Council on Diversity and Inclusion, Business Resource Groups, the Women in Science and Medicine Advisory Committee, the Committee on the Advancement of Women, the Office of Faculty Diversity and Development, and the Office of Women's Careers.

UT Southwestern is committed to an educational and working environment that provides equal opportunity to all members of the University community. In accordance with federal and state law, the University prohibits unlawful discrimination, including harassment, on the basis of race; color; religion; national origin; sex, including sexual harassment; age; disability; genetic information; citizenship status; and protected veteran status.

Technical skills training to adapt and master new software and technologies are part of employment opportunities at UTSW. Photo taken pre-pandemic.

A growing legacy of workplace excellence

Other recent workplace honors for UT Southwestern include:

- Best Places to Work Postdocs from *The Scientist*
- *Hospital Careers*' Top 100 Best Hospitals to Work For
- Top Veteran-Friendly Company from *U.S. Veterans Magazine*
- Top Healthcare Company in Best of the Best Awards for *Hispanic Network Magazine* and *Black EOE Journal*
- 2020 Health Professions Higher Education Excellence in Diversity (HEED) Award from *INSIGHT Into Diversity* magazine, the oldest and largest diversity-focused publication in higher education
- Top LGBTQ+ Company from three publications, *Professional Woman's Magazine, Black EOE Journal*, and *Hispanic Network Magazine*
- Top Mother-Friendly Worksite from the Texas Department of State Health Services
- Lex Frieden Employment Award from the Texas Governor's Committee on People with Disabilities
- Magnet Recognition from the American Nurses Credentialing Center
- Start! Fit-Friendly Worksite Award from the American Heart Association
- Employer of the Year from the Association for Independent Living
- Top 10 Best Organizations for Leadership Development Award from the National Center for Healthcare Leadership
- Corporate Citizen Award from LaunchAbility

UTSW has established online and in-person training and mentoring programs for future management and leadership roles. Photo taken pre-pandemic.

Innovative 3D modeling advances surgical and medical training

By Carol Marie Cropper

Dr. Daniel Scott, left, works with Rahm Heymann at the Simulation Center to create a laparoscopic surgery training tool.

A few years ago, Kirk Atkinson served as a Navy corpsman in Afghanistan, where he trained medics how to respond to catastrophic injuries seen on the battlefield. Often, he had to use fake body parts and wounds he had fashioned from plastic to familiarize soldiers with what they might face.

Today, Mr. Atkinson, a Senior Operations Specialist in UT Southwestern's Simulation Center, uses sophisticated 3D printers to create simulated body parts and training tools for the hundreds of physicians, medical students, and other health care professionals who train here.

UT Southwestern is one of the few medical schools in the U.S. with such an expansive 3D model development operation, allowing creation of specialized plastic body parts and tissue – simulated bones, ears, hands, and more – using six 3D printing machines.

In Afghanistan, explained Mr. Atkinson, a former Navy Petty Officer 2nd Class, the goal was to make medics intimately familiar with war injuries so that they could perform effectively while treating amputated limbs and bullet wounds as gunfire exploded around them.

While most UT Southwestern graduates and physicians will never face such conditions, honing their expertise on sophisticated manikins and stitching wounds in silicone suture molds benefits both them and the people they treat, said Daniel Scott, M.D., Assistant Dean, Simulation and Student Integration, Graduate Medical Education, and Professor of Surgery.

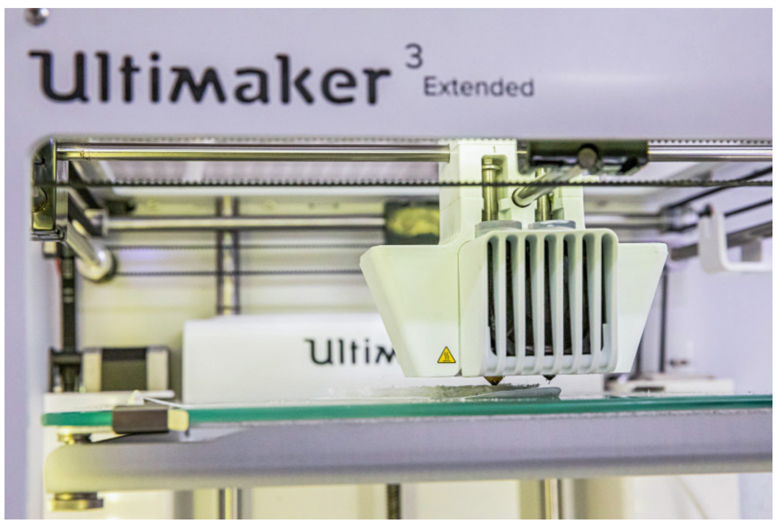
"Training people in the Simulation Center translates into better patient care without having to practice in the clinical environment," Dr. Scott said.

In fact, an early study examining this issue, published in 2000 in the *Journal of the American College of Surgeons* with Dr. Scott as first author, determined that such training improved laparoscopic surgery skills of surgery residents during actual operations.

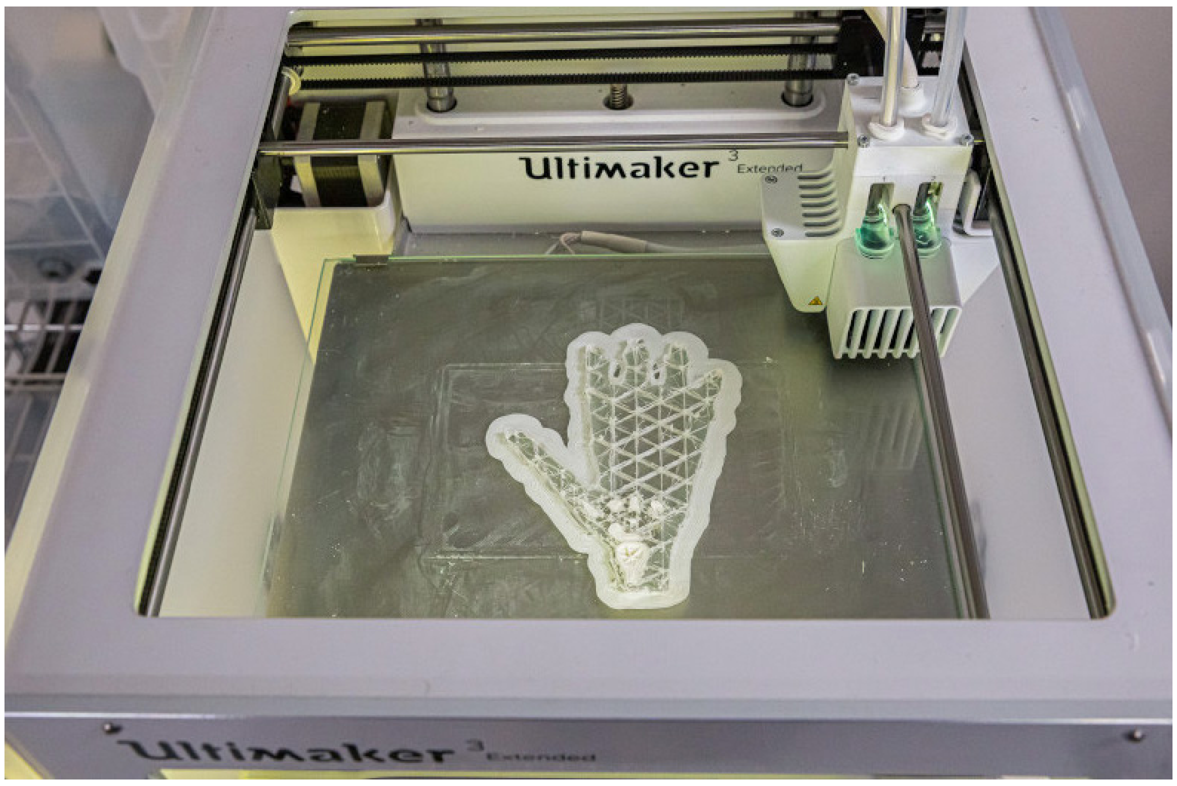
Mr. Atkinson, along with fellow 3D expert and Senior Clinical Simulation Educator Rahm Heymann, now are working on an advanced suture pad for training in laparoscopic surgery. The pad will enable learners to practice suturing while using the less-invasive equipment of laparoscopic surgery, which relies on tiny cameras and surgical tools to operate through small incisions. The pad is a 5-inch strip of flesh-colored silicone with two rows of dots to provide practice targets for learners to place laparoscopic sutures.

Dr. Scott, past President of the Association for Surgical Education, is working with the 3D team to develop the pad for possible use in the Association's Advanced Training in Laparoscopic Suturing (ATLAS) program. The goal, Dr. Scott said, is to create a training device that will be more durable and lifelike than the suture pads trainees now use.

The 3D team already makes the suture pads available for medical students to practice conventional suturing. Holding a pad with its simulated wounds ready for stitching, Mr. Atkinson points out the four separate layers – two simulated skin layers atop a sticky "fat" layer, with a "muscle" layer at the base. UT Southwestern used to purchase similar pads from vendors, but they were less durable, less realistic, and had only three layers, he said. Plus, they cost more than it costs the 3D team to make them, Mr. Atkinson added.



The printer's extruder (right) pushes plastic out in a preprogrammed design.



One of the Simulation Center's six 3D printers works to create a plastic hand with visible bones.

The 3D team also created an "ear" to train students on how to suture that tricky body part, said Krystle Campbell, Director of Simulation Center Operations.

"It's challenging to suture on a patient's ear," she said.

While difficult to treat, ear lacerations occasionally show up in the Emergency Department as patients come in from traffic accidents and other mishaps, thus it is important that UTSW trainees have an opportunity to practice this delicate skill on a simulated ear prior to suturing on real patients.

Joseph Martinez, M.D., a Professor of Emergency Medicine who helped lead the development of the ear model, said he values the Simulation Center's 3D capabilities – in particular the Center's ability to create training models for procedures that might occur rarely but where proficiency is very important.

The suture pad created from 3D printing allows learners to practice suturing wounds using less-invasive techniques.

"The 3D models created at the Sim Center provide precise models for the specific skills being taught," he said, which is something outside vendors cannot always do.

Mr. Atkinson said UT Southwestern's 3D machines can make higher-quality models at lower cost and also repair some of the sophisticated, lifelike manikins used for training in the Simulation Center.

The boxlike metal machines – ranging in size from less than 2 feet tall to one almost 4 feet long, large enough to build a human torso – line the walls of the Simulation Center's Innovation Lab. Containers of different plastics and color pigments cover a table. Melted plastic is fed into the printers, then pushed out into a preprogrammed shape, much like a baker would push decorative icing onto a cake.

The Center is pursuing marketing some of its creations, said Ms. Campbell.

"We have unusual models that you don't see on the market," she said.

The ATLAS mold is one possibility, she said. A second is a novel simulation being developed with Jeffrey Kenkel, M.D., Chair of Plastic Surgery, that is designed to solve a clinical problem facing those in the field.

"We had a concept that required design, materials consideration, and implementation with the experts at the Simulation Center," said Dr. Kenkel. "Our group is top-notch, from administration and implementation of a plan to design and production."

Dr. Scott recalls the days when he was training to become a surgeon and needed a way to practice suturing. He jury-rigged a device by twisting two rubber exam gloves and pinning them inside a wooden box.

"I sutured two gloves together," he said

As a clinician and a researcher, he has helped transform such training for today's students.

"We're much further along than where we started a mere 20 years ago," he said of simulation training in general. And when it comes to 3D work, "not too many are doing what we're doing in creating our own models."

"It all translates to better patient care," he said of the end result.

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Dr. Kenkel holds the Betty and Warren Woodward Chair in Plastic and Reconstructive Surgery and the Rod J. Rohrich, M.D. Distinguished Professorship in Wound Healing and Plastic Surgery.

Dr. Scott holds the Frank H. Kidd, Jr., M.D. Distinguished Professorship in Surgery.