INSIDE STANFORD MEDICINE

Volume 8, No. 3 ■ February 8, 2016 ■ Published by the Office of Communication & Public Affairs

Child life specialists help young patients understand medical procedures, deal with fears and even have fun.

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In rebuilding noses, age-old practice lives on

By Tracie White

Gary Saxon has a nice nose. A gray beard covers his chin, and heavy eyebrows shade his eyes, but nothing hides his nose. It holds a position of prominence, sticking right out there in the middle of its owner's slightly grizzled face, like noses do. It's well-sculpted and well-proportioned — with a slightly turned-up tip that complements Saxon's positive perspective on life. And best of all, it works.

Saxon is lucky. A year ago, all he had was a bloody hole where his nose used to be.

"I was beat up, I'll admit," said Saxon, sitting between jam-packed rows of LPs at his record shop in Redwood City. "I had no nose. But my spirit was still there. I figured, well, I'm still alive, so now what?"

Part science, part architecture, part art, the surgical reconstruction of a missing nose is a most "compelling surgery," said Sam Most, MD, a facial plastic surgeon who has rebuilt nearly 1,000 severely damaged or destroyed noses over the past 15 years as chief of the Division of Facial Plastic and Reconstructive Surgery at the School of Medicine. For many of those noses, including Saxon's, the key to reconstruction was the use of an age-old surgical technique commonly called the "forehead flap."

Venerable technique

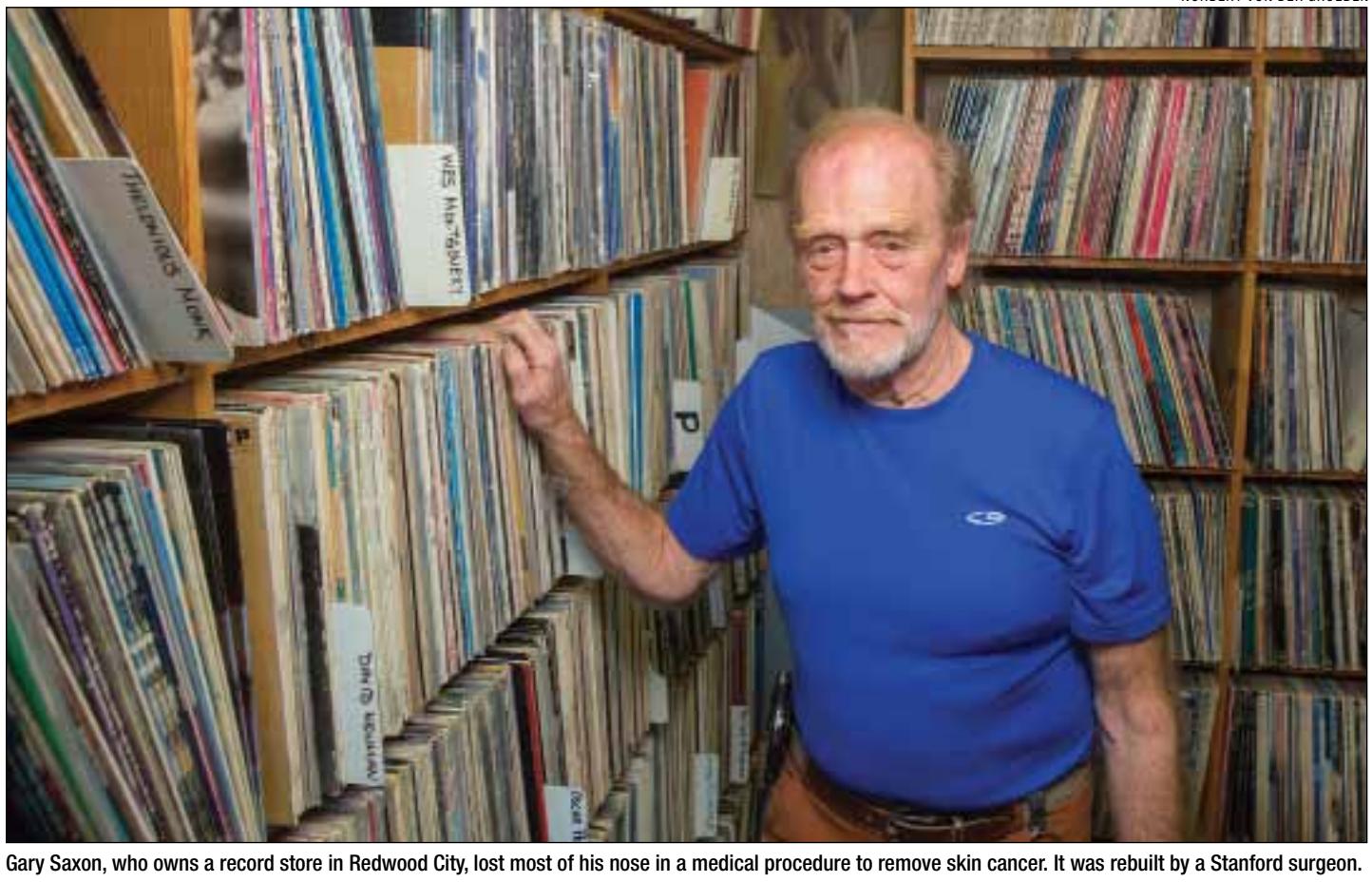
The forehead flap — so-named for the unsightly flap of forehead skin left plastered over a patient's nose for weeks following surgery — happened, by chance, to be the first surgical procedure Most ever witnessed. He observed it while a first-year medical student at Stanford, quietly standing at the back of the operating room. More than two decades later, a master craftsman of the technique himself, he has also published his own research to help improve upon it. He remains somewhat amazed that the success of these complex nose reconstruction surgeries still depends upon a technique that's probably older than Christianity or even the Roman Empire.

"I think it is just fascinating that we can take the skin from the forehead and create this outer-lining shape of the nose and make it turn into the shape of a nose," said Most, a professor of otolaryngology-head and neck surgery. Without the forehead flap, the reconstruction of a missing nose — perhaps the most challenging of facial reconstruction surgeries — would fail.

Most is quick to recount the historical significance of the forehead flap technique, which originated in India, probably before the birth of Christ, but wasn't widely known to Western medicine until 1794, with the publication of a letter to the editor in *The Gentleman's Magazine*

See NOSE, page 6

NORBERT VON DER GROEBEN



Gary Saxon, who owns a record store in Redwood City, lost most of his nose in a medical procedure to remove skin cancer. It was rebuilt by a Stanford surgeon.

Wearable device detects, analyzes real-time changes in sweat composition

By Jennie Dusheck

A team of researchers has combined two separate technologies to create a health-monitoring device that is noninvasive, doesn't interfere with strenuous outdoor activities and can continuously track a user's health at the molecular level.

The two-part system of flexible sensors and a flexible circuit board sticks to the skin and then detects and analyzes a profile of chemicals in sweat.

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The device is described in a paper published online Jan. 27 in *Nature*.

The project, led by senior author Ali Javey, PhD, professor of electrical engineering and computer sciences at the University of California-Berkeley, is a collaboration with researchers at the Stanford School of Medicine.

"This wearable device provides more information than the currently commercialized wearable sensors. It provides insight about an individual's physiological state at molecular levels," said Sam Emaminejad, PhD, a joint postdoctoral scholar at Stanford and at UC-Berkeley, who is the co-lead author with UC-Berkeley postdoctoral scholar Wei Gao, PhD.

Other noninvasive sweat biosensors either monitor only a single molecule at a time or lack signal processing that can adjust for temperature effects or interactions among different molecules. The new device, tested on a team of sweaty volunteers, is a fully-integrated "perspiration analysis system" that binds to the skin and measures certain sweat metabolites and electrolytes, and can calibrate its readings based on skin temperature.

In the future, this kind of wearable biosensor could be able to alert athletes and patients to fatigue, dehydration, overheating and other health problems.

Emaminejad said that when he first came to Stanford several years ago, he wanted to earn a doctorate in electrical engineering and to work with renowned scientist Ron Davis, PhD, professor of biochemistry and of genetics and director of the Stanford Genome Technology Center. Over a 50-year career, Davis has been the originator, with others, of a series of disruptive technologies, such as a way to map RNA, a technique for splicing fragments of DNA together, the first DNA microarray for profiling the expression of genes and a method for mapping genes

See SWEAT, page 5

Many malpractice claims linked to small number of physicians, study finds

By Beth Duff-Brown

A substantial share of all malpractice claims in the United States is attributable to a small number of physicians, according to a study led by researchers at Stanford University and the University of Melbourne.

The team found that just 1 percent of practicing physicians accounted for 32 percent of paid malpractice claims over a decade. The study also found that claim-prone physicians had a number of distinctive characteristics.

"The fact that these frequent flyers looked quite different from their

See MALPRACTICE, page 6

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OBITUARY

Herbert Abrams, pioneering radiologist, anti-nuke activist, dies at 95

By Elaine Ray

Renowned radiologist Herbert Leroy Abrams, MD, who co-founded the Nobel Prize-winning organization International Physicians for the Prevention of Nuclear War, died Jan. 20 at his Palo Alto home. He was 95.

Abrams was a professor emeritus of radiology at the Stanford University School of Medicine, a senior fellow at Stanford's Freeman Spogli Institute for International Studies and an affiliated faculty member at the Center for International Security and Cooperation.

Abrams' illustrious, multi-faceted career embraced what he called the "four dimensions of bio-medicine" — patient care, research, teaching and advocacy.

"For as long as I have known him, I could only describe Herb Abrams as a class act," said Sanjiv Sam Gambhir, MD, PhD, professor and chair of radiology at Stanford. "It is upon the shoulders of giants such as Herb that we ourselves stand today at the cutting edge of radiology."

Former U.S. Secretary of Defense and CISAC colleague William Perry praised Abrams for his "wisdom and carefully chosen words" in his advocacy for better control of nuclear weapons.

"The forces maintaining nuclear weapons and creating the danger that we might use them are very powerful and very hard to stop, and Herb and the International Physicians for the Prevention of Nuclear War were an early voice of sanity in this field," Perry said.

Visionary pioneer in radiology

Born in 1920 in New York to immigrant parents, Abrams declined to go into the family hardware business. He graduated from Cornell University in 1941 and earned a medical degree from Long Island College of Medicine in 1946.

According to his family, Abrams had planned to become a psychiatrist until he was captivated by radiological imaging, which provided the road map for virtually all surgical and many medical therapies.

Abrams, his wife, Marilyn, and daughter, Nancy, moved to the West Coast in 1948. Their son, John, was born a year later. Abrams completed his residency in radiology at Stanford in 1952 and joined the faculty as an assistant professor in the department in 1954.

While Abrams rose to become director of diagnostic radiology at Stanford, he and Marilyn raised their children in the Bay Area during what his children say he often called "the golden years" — rich with deep friendships, youthful exuberance, guitar-playing, family adventures and professional success.

Abrams was an internationally known authority on cardiovascular radiology and wrote more than 190 articles and seven books on cardiovascular disease and health policy.

For many years he served as editor-in-chief of *Postgraduate Radiology*, and he was founding editor-in-chief of the journal *Cardiovascular and Interventional Radiology*.

In 1961 he published *Angiography*, the first comprehensive volume on the subject, which now is in its fourth edition (edited by Stanley Baum) under the title *Abrams' Angiography: Vascular and Interventional Radiology*.

"Under his guidance, Stanford pioneered in the fields of coronary artery imaging and the diagnosis of adult and congenital heart diseases, as well as vascular diseases, such as renal artery narrowing as a cause of hypertension," said Lewis Wexler, MD, professor emeritus of radiology at Stanford, who was a resident under Abrams.

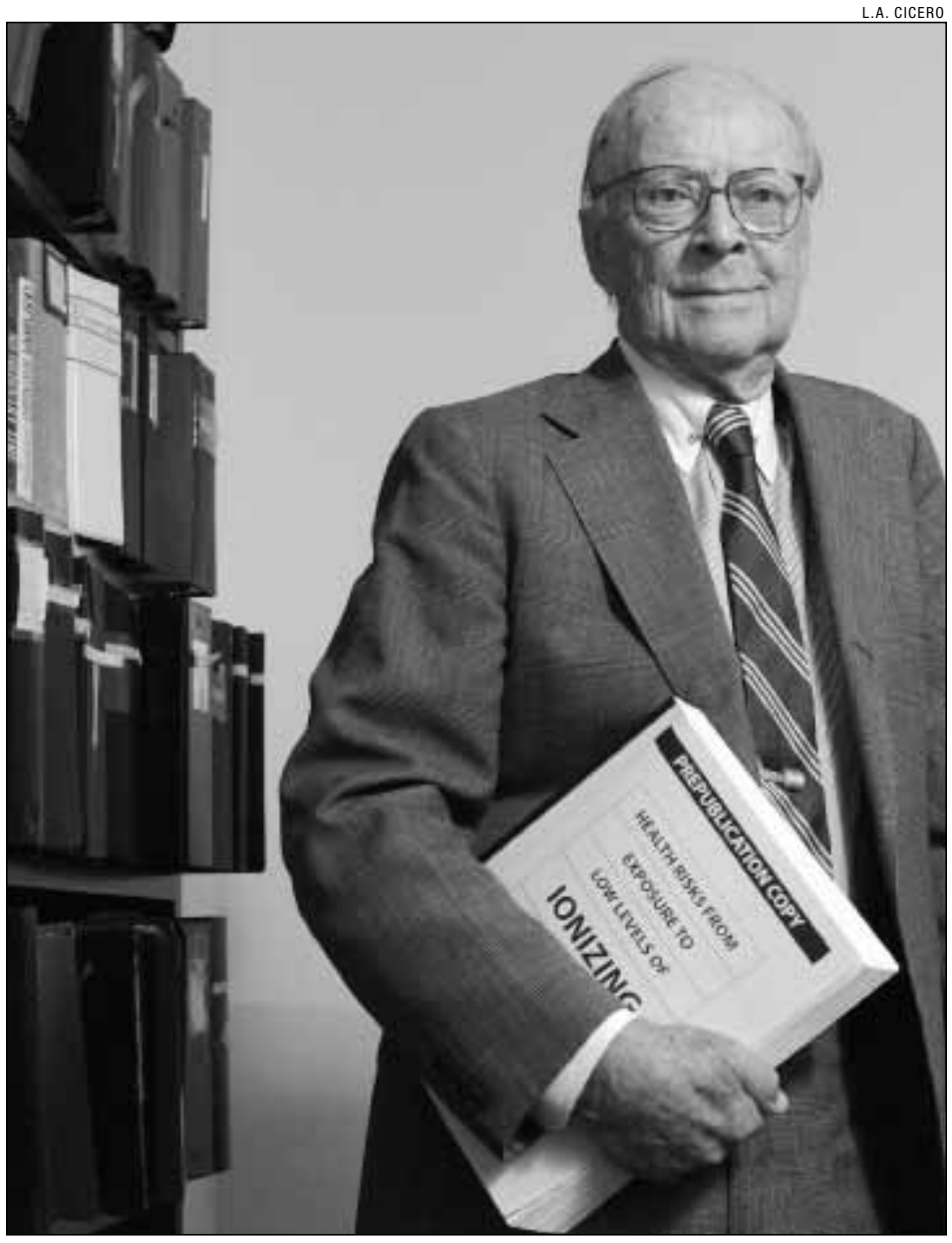
"For many years, I referred to him as 'Dr. Abrams,' even though he requested a less formal address," Wexler added. "I think I waited until I was a full professor before I called him 'Herb.' His wife and a number of his old friends from San Francisco called him 'Hoppy,' an endearment that aptly describes his energy, excitement and ability to jump effortlessly from discussing radiology [to discussing] health policy, politics, religion, art and music."

The Boston years

In 1967, with their children pursuing their own paths, Abrams and his wife moved to Boston, where he became the Philip H. Cook Professor of Radiology at Harvard Medical School and radiologist-in-chief at Brigham and Women's Hospital and at the Dana Farber Cancer Center. During their time in Boston, he and Marilyn also began a long love affair with Martha's Vineyard, where they built a house in 1975.

> "For as long as I have known him, I could only describe Herb Abrams as a class act."

L.A. CICERO



Herbert Abrams co-founded International Physicians for the Prevention of Nuclear War. He said that for physicians, nuclear weapons and nuclear war were "the central health issue of the 20th century."

Steven Seltzer, MD, chair of radiology at Brigham and Women's Hospital, who holds the the same professorship Abrams previously held, remembers his longtime mentor as a visionary who helped broaden the scope of radiology as a discipline.

When Seltzer arrived at Brigham and Women's in 1976 to do his radiology residency in what was then a very small department, he recalled being "incredibly impressed with the professional growth opportunities and the values and quality of the program that Abrams was building." He added that radiology was "still growing up" at that time and that Abrams had a vision that began during his years at Stanford and developed during his years in Boston.

"He was a very determined man. I fully bought into that vision. I thought this is a good person to have as a mentor and a role model, because I also aspired to live in a world that had similar characteristics that Herb had dreamed of," Seltzer said.

Anti-nuclear advocacy

Toward the end of the Boston years, in the early 1980s**,** Abrams developed a keen interest in the effects of ionizing radiation and nuclear weapons and the problems of accidental or inadvertent nuclear war, which led to the next phase of his career as an anti-nuclear activist.

"He leveraged his training in radiology to become one of the leading experts on the health effects of low-dose radiation," said David Relman, MD, professor of medicine at Stanford and current co-director of CISAC.

"It's a problem that doesn't get as much attention as the catastrophic effects of a nuclear blast, but the long-term consequences of low-dose radiation was something that Herb … helped promote as a serious issue, worthy of attention and study," Relman added.

Abrams discussed the threats posed by radiation in a story published in the spring 1986 issue of *Stanford Medicine* magazine. He said that, for physicians, nuclear weapons and nuclear war were "the central health issue of the 20th century."

He was founding vice president of International Physicians for the Prevention of Nuclear War, which won the Nobel Peace Prize in 1985, just five years after the organization was established. He also served for many years on the national board of directors and as national co-chair of Physicians for Social Responsibility, a U.S. affiliate of IPPNW.

"His contributions were huge," said Scott Sagan, PhD, professor of political science at Stanford. Sagan added that under Abrams' leadership the IPPNW "did yeoman's work to try to educate the public and world leaders about the consequences of nuclear war at a time when many, including some in the Reagan administration, were minimizing the consequences of nuclear weapons use."

Abrams returned to Stanford in 1985 as a professor of radiology, but spent most of his time in research at CISAC, working to link various disciplines and philosophies in the political, international and academic arenas to create a better understanding of international security during the nuclear age.

In the 1990s Abrams began to focus on presidential disability and its potential impact on decision-making.

In 1992, he published *The President Has Been Shot: Disability, Confusion and the 25th Amendment*, which brought together important issues at the intersection of medicine, politics and humanism.

A vibrant family life

Always at the core of Abrams' life was bringing together his family to travel, to ski, to play tennis and to celebrate birthdays and holidays.

On his 95th birthday Abrams played four-generation tennis with his son, grandson and great-grandson on Martha's Vineyard, where his family spent summers for 45 years. Until the last month of his life, he played doubles three times a week.

In addition to Marilyn, to whom he was married for 73 years, daughter Nancy (Richard Eilbert), of Lincoln, Massachussetts, and son John (Christine) of West Tisbury, Massachussetts, Abrams is survived by three grandchildren and three great-grandchildren.

Memorial donations in memory of Abrams may be made to Physicians for Social Responsibility, 1111 14th St. NW, Suite 700, Washington, DC, 20005, or by visiting that organization's website at www.PSR.org.

A service to celebrate his life will be held on the Stanford campus on March 19; details will be announced. **ISM**

Writers Steve Fyffe and Susan Ipaktchian contributed to this report.

INSIDE STANFORD MEDICINE

Inside Stanford Medicine is published monthly in July and December and semi-monthly the rest of the year.

is produced by
Office of Communication & Public Affairs
Stanford University
School of Medicine
3172 Porter Drive
Palo Alto, CA 94304
Mail code 5471
(650) 723-6911
http://med.stanford.edu/news/

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STANFORD MEDICINE

OBITUARY

Oleg Jardetzky, visionary in magnetic resonance imaging, dies at 86

By Rosanne Spector

Oleg Jardetzky, PhD, a pioneer in the use of nuclear magnetic resonance to understand the structure and dynamics of proteins, died Jan. 10 at his Stanford home after a period of declining health. He was 86.

Jardetzky, a professor emeritus of molecular pharmacology at the School of Medicine, founded and served as the original director of Stanford's Magnetic Resonance Laboratory, one of the world's first and premier facilities dedicated to using nuclear magnetic resonance for biological research.

"Oleg basically started the field of protein NMR spectroscopy," said Stanley Opella, PhD, a former graduate student and now a professor of chemistry and biochemistry at UC-San Diego. "He was a true pioneer. Many of his innovations are still being used in the field. In short, he was way ahead of his time in research."

Nuclear magnetic resonance is a phenomenon, discovered in 1938, in which the nuclei of atoms in a magnetic field absorb and re-emit electrochemical radiation. Another Stanford professor, Felix Bloch, PhD, won the Nobel Prize in 1952 for his contributions to developing NMR. Soon researchers realized they could use the pattern of radiation emitted from a substance to extrapolate its structure. Researchers began using the technique to analyze chemicals, but it wasn't until the mid-1950s and 1960s that Jardetzky and a few others with a biological bent applied the technology to biochemical molecules, like proteins.

COURTESY OF TED JARDETZKY

Oleg Jardetzky, who died Jan. 10, founded and served as the original director of Stanford's Magnetic Resonance Laboratory.

Burning the midnight oil

Over his more than 40 years of research, Jardetzky became an internationally known authority on applying the technology to biology. He served terms as leader of the field's several major scientific societies, co-authored more than 250 scientific articles, was named a fellow of the American Association for the Advancement of Science and was awarded an honorary medical degree from the University of Graz, in Austria, and an honorary doctorate from the University of the Mediterranean (now Aix-Marseille University). He also established an international NMR conference, held every summer in Erice, Italy, and co-founded the annual International Conference on Magnetic Resonance in Biological Systems.

Jardetzky was born in Belgrade, Yugoslavia, the son of Russian immigrants. His father, Wenceslas Jardetzky, PhD, was a well-known geophysicist and authority on celestial mechanics, and his mother, Tatiana, was a professor of French, German, Russian and comparative literature. After his early education, which was in Yugoslavia and Austria, Oleg Jardetzky attended two years of medical school at the University of Graz. In 1949, a scholarship to Macalester College in St. Paul, Minnesota, led him to move to the United States. He graduated from Macalester in 1950, married his first wife, Christine Drakakis, PhD, in 1952, and earned an MD in 1954 and his PhD in 1956 from the University of Minnesota.

Jardetzky spent the following year at Caltech as a National Research Council Fellow, working with Nobel laureate Linus Pauling, PhD, studying the structure of water. He burned the midnight oil to pursue his own research: nuclear magnetic resonance studies on amino acids and proteins, using a chemistry professor's NMR machine from 10 at night until 2 in the morning.

In 1957, Jardetzky joined the Harvard Medical School faculty and founded the first NMR laboratory dedicated to biological research. He worked there for 10 years, establishing the foundation for future research in this field.

'Forceful presence'

"We came in with the idea of possibly using it [NMR] for determination of protein structures, which proved to be absolutely impossible at the time," Jardetzky said in a March 2015 interview for the Stanford Historical Society. "The resolution was not good enough. At that time, you could just study the structure of amino acids in small peptides and nucleotides and the interactions between them. You *could* look at the spectrum of a protein — but it was a big mess."

He married his second wife, Norma Gene Wade, in 1964, and in 1967 they moved to New Jersey so he could work for Merck, Sharp and Dohme Laboratories, first as director of the biophysics department, then as executive director of the Merck Institute.

In 1969 he joined the Stanford faculty as a professor in the Department of Pharmacology (renamed the Department of Chemical and Systems Biology in 2006). "He loved the academic freedom to explore scientific questions independently," said one of his sons, Theodore (Ted) Jardetzky, PhD, a professor of structural biology at Stanford. Oleg founded the Stanford Magnetic Resonance Laboratory and directed it from 1972 to 1997. At Stanford, he trained and inspired students to push the boundaries of science, and many went on to leadership roles in the field.

"Oleg was a very forceful presence, and he used that to motivate the group and tackle entire new areas for the first time," said Opella. "He certainly prepared his students and postdocs for academic life and what was needed to succeed."

Ribonucleases and the tryptophan repressor

In 1975, he married Erika Albensberg, PhD, who had been a close friend in Austria. Together, they enjoyed visiting friends and family there, traveling the world and having guests at their home.

"My wife, Rina, and I were so sad to hear of Oleg's passing," said Nobel laureate Michael Levitt, PhD, professor of structural biology at Stanford. "He was a close family friend from the time when we moved to Stanford in 1987. He was so wonderfully 'European' in the best sense of the word, and we loved to visit his home on campus. Oleg is no longer with us but his tradition lives on."

Jardetzky continued developing NMR technology methods until they were useful for imaging proteins and nucleic acids. "It took us 20 years, but we did it," he said in the 2015 interview.

Beyond laying the foundation for NMR methodology, he made important discoveries about the structures and dynamics of proteins. In the 1960s, he proposed a model for membrane protein transport that was validated decades later. He contributed pioneering studies of enzyme mechanisms, investigating a ribonuclease protein that breaks down RNA into smaller components, and the regulation of gene expression by the tryptophan repressor.

Awed by nature

Jardetzky was awed by nature, not only at the molecular level, but at the macro, too, Ted said. "He found nature comforting, and especially loved being close to the ocean," he said. "He found peace in the beauty of the ocean and the mountains, and felt a spiritual connection to the world there." Jardetzky owned a beach house on the south shore of Massachusetts and spent as much time as he could there with his family, swimming in the ocean, clamming, going out in a boat to fish and watching fireworks on the Fourth of July.

"He also loved history and being surrounded by the 'old stones' of European cities and towns — things that had survived and helped to keep us connected to the past meant a lot to him," Ted said. "He enjoyed celebrating his Russian traditions, exploring different cultures, listening to classical music — and also smoking his pipe, voicing his opinions, painting, dabbling in ceramics and collecting historical books of significance." He published two history books, and one of these, on the history of the Polish clan Ciolek, received a prize of the International Union of Heraldry and Genealogy in 1998.

Jardetzky retired and closed his Stanford laboratory in 2006 but continued to attend seminars and departmental functions for several more years. He also continued to publish, mostly historical articles, on the early history of NMR and on the Russian emigration due to the revolution of 1917.

"It's an overwhelming experience to be confronted with an entire life all at once. I see my students and former students," he said at a 1994 international symposium on nuclear magnetic resonance held at Stanford in honor of his birthday. "But it's a great comfort to realize precious friendships and how many conversations have emerged trying to lead a simple scientific life."

His wife, Erika, died in 2008. In addition to Ted, he is survived by sons Alexander Jardetzky and Paul Jardetzky, PhD, four grandchildren and two step-grandchildren.

Donations in memory of Oleg Jardetzky may be made to Macalester College (the Engel-Morgan-Jardetzky Distinguished Lecture on Science, Culture and Ethics), Davis and Elkins College (Tatiana Jardetzky Scholarship for Foreign Languages and Cultures), or the Lamont-Doherty Earth Observatory at Columbia University (the W.S. Jardetzky Lecture). ISM

Stanford Medicine and Intermountain Healthcare to collaborate

By Ruthann Richter

Stanford Medicine and Intermountain Healthcare, an integrated healthcare system based in Utah, have formed a new collaboration to support innovative projects in research, patient care and medical education, it was announced Jan. 27.

As a first part of the effort, Intermountain will provide a $1.25 million grant to Stanford Medicine to support clinical research projects, particularly in the areas of heart disease and cancer, as well as novel methods to improve healthcare delivery and clinician training.

The Stanford School of Medicine will provide $1.25 million to match the grant to bring total research funds to $2.5 million. In addition, Intermountain will commit another $1.25 million for operational expenses and additional projects, for a total $3.75 million investment by the two institutions across five years.

Stanford already has a number of research and educational collaborations under way with Intermountain and has appointed several Intermountain physicians to Stanford's clinical faculty.

"Intermountain Healthcare is an internationally respected delivery system that has achieved consistently excellent patient outcomes," said Lloyd Minor, MD, dean of the Stanford School of Medicine. "They have done this through a long-term investment in sophisticated medical information systems and system-wide programs that advance consistent use of best practices that produce excellent clinical outcomes at sustainable pricing for patients and payers. We are very pleased to embark on an even closer relationship with Intermountain that will be strengthened in the years ahead, for the benefit of our patients and the physicians we are training for the future."

"We will work with colleagues at Stanford to more rapidly assess new treatment modalities and move these into the care of our patients," said Charles Sorenson, MD, president and CEO of Intermountain Healthcare.

Researchers at Stanford and Intermountain already are working together on several projects, including research in cancer genomics, clinical studies of atrial fibrillation and cognitive function, and studies in applied clinical informatics. In addition, Intermountain has served as a pilot site for a Stanford project on "ambulatory care ICUs," a new form of outpatient care to prevent costly and dangerous health crises among patients with severe, chronic illnesses. The project is led by Arnold Milstein, MD, director of Stanford's Clinical Excellence Research Center, who serves on the board of Intermountain.

Clinician-researchers at the two institutions are also sharing work on other methods to improve care, such as expanded use of clinical pathways, which are science-based guidelines that help reduce variability in care and improve patient outcomes. Intermountain, a longtime pacesetter in educating healthcare leaders about these concepts and methodologies, has collaborated in establishing a similar program at Stanford.

Other proposed initiatives include trainee exchanges, in which residents and fellows will do rotations at collaborating institutions, and sharing approaches to reduce blood utilization. ISM

Un-medical care: Child life program helps children handle stre

By Erin Digitale

It was a young girl with epilepsy who made Susan Kinnebrew certain she'd chosen the right career.

The girl was scheduled to undergo surgery for her seizure disorder. She was scared. To get through the procedure, she wanted something beyond the expert ministrations of her brain surgeon, anesthesiologist and operating room nurses. She wanted to bring her favorite doll.

Kinnebrew was just starting her career at a Florida hospital as a child life specialist, an expert in helping children and their families handle the stresses of illness and the hospital environment. She understood the importance of that security object.

She and the other caregivers made a plan: Kinnebrew and the doll would accompany the girl into the operating room, where the doll could stay on the girl's bed until she was anesthetized. Kinnebrew would then take the doll and make sure it was back on the girl's bed before she awoke.

"Going to the OR with her, I knew this was for me," Kinnebrew said. She saw how much the doll's presence — and her own — eased the child's fear. "She eventually had a total of four surgeries, and even at the last one, at age 18, she said, 'I need you with me.'"

Supportive role

Today, Kinnebrew directs Child and Family Life Services at Lucile Packard Children's Hospital Stanford, where she took over the director's role in November. Her team works with patients and their families to help kids be kids, even when they're hospitalized.

"The family supports their child in a different capacity than we do," Kinnebrew said. "The parent is there to be the parent, to provide the love and comfort kids need from their mom or dad. We're there to help the child understand the medical side of the process on their own developmental level, and to give psychological support to the entire family."

"Many of our families come in to the hospital with a high level of anxiety because their child is ill," said Anne McCune, the hospital's chief operating officer. She has seen countless instances in which child life specialists eased that anxiety. "They make very deep connections very quickly with children," she said, adding that the child life specialist is often the person a child remembers most fondly after going home from the hospital, a fact reflected in comments on patient satisfaction surveys. "From the feedback we get, we know they make a tremendous difference," McCune added.

NORBERT VON DER GROEBEN

Lucia Ruiz, who is being treated for acute lymphoblastic leukemia, talks with child life specialist Jake Lore.

On a typical day, Kinnebrew's team can be found at patients' bedsides, educating hospitalized kids about medical procedures and giving them opportunities to have fun. They staff the Forever Young Zone, a recreational area in the hospital that is free of white coats and medical procedures; facilitate pet therapy and play therapy; and assist the entire family, including healthy siblings who may feel left out by the focus on their ill brother or sister.

As part of their training, child life specialists earn a bachelor's or master's degree in child development or a related field, including specific coursework set by the Child Life Council, the profession's national accrediting body. They also must complete a minimum of 480 hours of clinical work under the supervision of a certified child life specialist and pass a certification exam.

Refreshingly un-medical

On a recent afternoon, child life specialist Jake Lore checked on 18-year-old Lucia Ruiz, who was spending four hours at Packard Children's to receive infusions of medication and fluid for her acute lymphoblastic

Individuals' medical histories predicted by noncoding genomes

By Krista Conger

Identifying mutations in the control switches of genes can be a surprisingly accurate way to predict a person's medical history, researchers at the School of Medicine have found.

When the scientists used the technique to analyze the whole genome sequences of five individuals, they found that a person with narcolepsy had mutations in the regulatory regions of genes controlling alertness; a person with a family history of sudden cardiac death had mutations in regions controlling genes associated with cardiac output; and a person with high blood pressure had mutations in regions controlling circulating sodium levels in the blood.

"The beauty of having whole genomes available for study is that you can then ask completely agnostic questions," said Gill Bejerano, PhD, an associate professor of developmental biology, of pediatrics and of computer science at Stanford. "We set out to find hidden layers of susceptibility in the regulatory regions of these genomes. We were very pleased that our analysis gave such clear and significant associations between the mutations and medical histories."

Bejerano, a genomicist who is a member of the Stanford Artificial Intelligence Lab, Child Health Research Institute, Neurosciences Institute, Cancer Institute and Bio-X, is the senior author of a paper describing the research, which was published Feb. 4 in *PLOS Computational Biology*. The first author is Harendra Guturu, PhD, a former Stanford graduate student who is now a research associate in pediatrics at the university.

Importance of regulatory regions

The researchers focused their analyses on a relatively small proportion of each person's genome — the sequences of regulatory regions that have been faithfully conserved among many species over millions of years of evolution. Proteins called transcription factors bind to regulatory regions to control when, where and how genes are expressed. Some regulatory regions have evolved to generate species-specific differences — for example, mutating in a way that affects the expression of a gene involved in foot anatomy in humans — while other regions have stayed mostly the same for millennia.

Gill Bejerano

"In these cases, evolution has given a clear signal that these regions are important to key biological pathways, and it's important for them to stick around," said Bejerano.

All of us have some natural variation in our genome, accumulated through botched DNA replication, chemical mutation and simple errors that arise when each cell tries to successfully copy 3 billion nucleotides prior to each cell division. When these errors occur in our sperm or egg cells, they are passed to our children and perhaps grandchildren. These variations, called polymorphisms, are usually, but not always, harmless.

GREAT work

Guturu looked for what are called single nucleotide polymorphisms, or SNPs, in the DNA of five people who have made their genomes and information about their own or their family's medical history publicly available for use by researchers worldwide. SNPs are places along a chromosome where the DNA sequence varies from a composite human DNA reference sequence by one letter, or nucleotide.

Rather than search through the whole genome, Guturu focused on SNPs in evolutionarily conserved regulatory regions. Even within these regions, each person had many SNPs. So Guturu used a software program, Predicting Regulatory Information of Single Motifs, developed in the Bejerano lab, to predict which nucleotide changes were likely to disrupt the conserved binding of a transcription factor.

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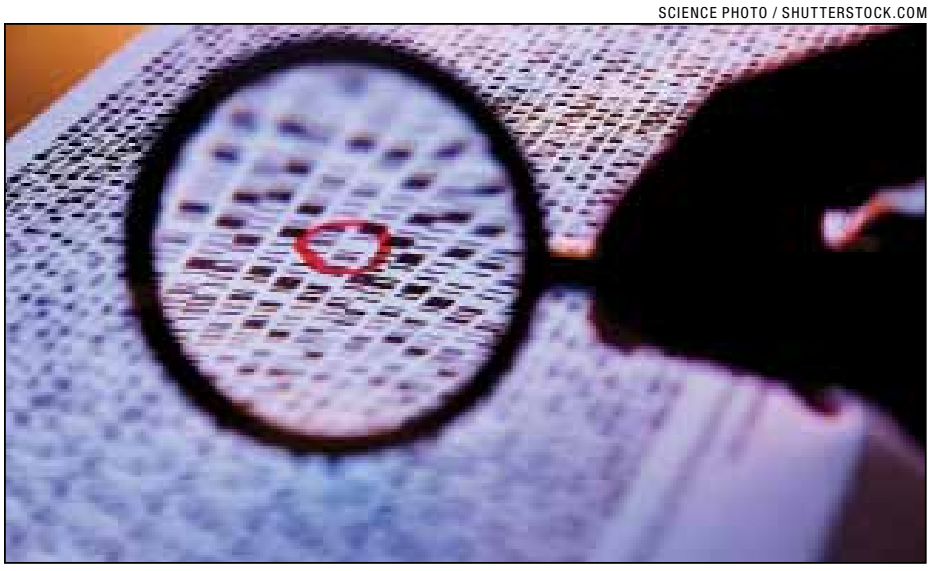


Guturu then turned to software called Genomic Regions Enrichment of Annotations Tool to determine whether the disrupted binding sites were likely to perturb the expression of groups of genes that together control a particular biological function. GREAT, which was also developed in the Bejerano lab, curates knowledge about the diverse functions of thousands of different groups of genes. For any set of genomic regions a user inputs, GREAT determines the most common set or sets of nearby genes.

Using this approach to study the genomes of the five individuals, Guturu, Bejerano and their colleagues found that one of the individuals who had a family history of sudden cardiac death had a surprising accumulation of variants associated with "abnormal cardiac output"; another with hypertension had variants likely to affect genes involved in circulating sodium levels; and another with narcolepsy had variants affecting parasympathetic nervous system development. In all five cases, GREAT reported results that jibed with what was known about that individual's self-reported medical history, and that were rarely seen in the more than 1,000 other genomes used as controls.

'Exciting avenue for study'

The researchers would like to create a web portal that would allow others to easily conduct similar studies. However, they concede that, for some diseases, the results may not be so clear-cut.

"We are the sum of billions of transcription-factor-binding events in thousands of cell types throughout our bodies," said Bejerano. "Not every disease will be amenable to this type of analysis. But this study shows that nature, even the noncoding genome, can be very benevolent when you ask the right questions. And it may help us begin to combine our knowledge about variations, or mutations, that occur throughout the genome. It's a very exciting avenue for study."

The research is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford co-authors of the paper are graduate student Sandeep Chinchali and former graduate student Shoa Clarke, MD, PhD.

The research was supported by the National Institutes of Health, the National Science Foundation, the Howard Hughes Medical Institute, a Stanford graduate fellowship and the King Abdullah University of Science and Technology.

Bejerano and Guturu have filed a patent application on the algorithm used in this study.

Stanford's Department of Developmental Biology also supported the work. **ISM**

ess, have fun at Lucile Packard Children's Hospital Stanford

leukemia. Sitting on a hospital bed connected to an IV was boring. Ruiz asked Lore to bring her some things to do.

Lore left and returned with two mystery novels and some art activities. He knelt next to Lucia's bed to show her the painting supplies and a set of small cardboard boxes with matching lids for her to decorate.

"Do you like art?" Lore asked.

"Yes, I took it in high school," Ruiz said.

"Oh, maybe these are too easy for you!" Lore said.

Soon they fell to chatting about whether they considered themselves dog or cat people. Ruiz loves dogs; when she was hospitalized for several days after her cancer diagnosis last summer, she especially enjoyed visits from two of the hospital's pet therapy dogs, Guinness and Cici. Lore began describing the antics of his own dog; Ruiz listened eagerly. He wasn't fixing her IV or explaining her prognosis, and he wasn't rushing off to the next thing; the whole interaction was refreshingly un-medical.

Lore and his colleagues have also assisted Ruiz in difficult moments, bringing books to explain leukemia and how her body would respond to treatment, for instance. "They're a big help for you to cope with everything and get a sense of having a support system," she said.

Importance of play, creativity

Patients like Ruiz also benefit from many events the child life team organizes, including recreational outings for kids with cancer, hospital visits by local pro athletes and annual festivities such as the hospital's Halloween Trick or Treat Trail and other holiday parties.

NORBERT VON DER GROEBEN

Susan Kinnebrew, who directs Child and Family Life Services at Packard Children's, meets with members of her staff.

"Play is a crucial part of how children develop," Kinnebrew said. "You can't lose that aspect when kids are in the hospital." The opportunity to visit with a therapy dog, play video games with friends or express themselves creatively through art projects isn't a luxury for sick kids, she adds; it's a significant part of how the hospital helps them get well.

And, just as she did for that young epilepsy patient having surgery, Kinnebrew and her colleagues help kids handle medical experiences in ways that are tailored to the child's developmental stage. To help a preschooler prepare for an MRI scan, a child life specialist uses dolls and toy versions of medical equipment to demonstrate, through play, everything that will happen during the scan. The explanation uses simple, nonthreatening terms that focus on what the patient will see, smell and hear. For a teenager getting ready for the same scan, the specialist gives a more detailed explanation of the procedure, encourages the patient to ask questions and may take the patient to visit an MRI machine in advance.

During a procedure, child life specialists can also help make it easier for a child to hold still or cooperate. For example, Kinnebrew vividly remembers using guided imagery — verbal cues that enable the listener to use their imagination to relax — so that she could help her own toddler cope with getting stitches for a minor injury. While the sutures were going in, she talked him through the plot of his favorite movie, *Toy Story*, distracting him so successfully that the medical team did not need other techniques to immobilize him.

Research demonstrates that all these efforts make a difference for hospitalized kids and their families. Child life programs have been shown to reduce children's postoperative pain, lower parents' anxiety about their kids' hospital stays and decrease the emotional distress children feel about being at the hospital.

"There is so much you can do if you are able to be the voice that is helping a child get through a hard time in the hospital," Kinnebrew said. "That's what makes the field of child life so powerful and effective." **ISM**

Sweat

continued from page 1

that led to the Human Genome Project. His work has repeatedly changed the face of biomedical research and earned him membership in the National Academy of Sciences.

"For personalized medicine," said Davis, "we need sophisticated biosensors that can collect data continuously from individuals."

When a patient goes for an appointment, said Emaminejad, the physician can take a blood sample and measure any of hundreds of molecules. But at best, the physician typically gets only one measurement every few months. There's no telling what's happening between patient visits. To monitor health continuously, a new technology was needed. "We wanted to move from the kind of cumbersome equipment used in a clinic to a light, wearable device that could deliver continuous measurements," he said.

Devices like the Fitbit already monitor people's activity levels and heart rate, but the researchers needed far more information. They wanted to be able to noninvasively map the molecular physiology of an individual's body. The answer, they realized, was sweat.

What's more personal than sweat?

"Sweat is hugely amenable to wearable applications and a rich source of information, so our first step in developing wearable biosensing technologies was to think about how to analyze sweat," said Davis.

Sweat is loaded with physiological information about what's happening in the body, with hundreds of different constituents — from simple ions to metabolites and protein molecules.

Until now, sweat studies have collected perspiration off the body in containers and then analyzed it in the lab. Sweat can be used to diagnose certain diseases, to detect drug use and to optimize athletic performance. But the resulting data aren't real-time or continuous. It's like watching 10 seconds of a football game and trying to guess how the rest of the game went.

Designing the device

After earning a PhD in electrical engineering at Stanford, Emaminejad became a postdoctoral scholar jointly at Stanford and UC-Berkeley. The result of the collaboration between researchers at the two universities is the new sensor technology that can detect the chemical constituents of sweat in real time. The research team tested the device on a group of men and women who pedaled indoors on stationary bikes or ran outdoors.

The prototype device consists of two parts: a set of five sensors and a flexible circuit board for signal processing and wireless transmission of data. Sticking to the skin is a flexible plastic bandage with sensors that can measure skin temperature and four constituents of sweat: sodium ions, potassium ions, glucose and lactate.

The soft, flexible sensor bandage feeds data from the skin to the second part of the device, a wireless circuit board of interconnected chips, called a flexible printed circuit board, which comes as a wristband or headband.

The circuit board's job is to amplify, filter, calibrate and transmit the signal. After processing the information from the sensors, the circuit board beams it to a nearby smartphone or other device for storage and further analysis. The flexible sensor array that binds to the skin is disposable and might last a few days at most, while the less-flexible printed circuit board is reusable.

Complementary technologies

Neither the sensor nor the circuit board could have done the job by itself. "Each technology has strengths and weaknesses," said Javey. "If you were just using silicon integrated circuits, you would not have been able to do this work. Silicon integrated circuits are too small and too rigid to come in good contact with the skin. It's just not realistic to use them for the sensing part."

On the other hand, a flexible integrated sensor array can be printed onto a large surface area that conforms to the body. It makes a great sensor but isn't as good for doing computation, signal processing or transmission, said Javey. Together, the two technologies complement one another and create a lightweight biosensor.

DER-HSIEN LIEN AND HIROKI OTA / UC-BERKELEY

This wearable sensor measures skin temperature in addition to glucose, lactate, sodium and potassium in sweat. Integrated circuits analyze the data and transmit the information wirelessly to a smartphone or other device.

The *Nature* paper describes how the flexible sensors detect the presence of different molecules and ions based on their electrical signals, said Emaminejad. "The more glucose or lactate in your sweat, the more electrical current is generated at the sensor's surface. And the more sodium and potassium, the larger the voltage."

"Both the current and the voltage generated are themselves affected by temperature," Gao said. When your skin temperature goes up, the generated signal from the glucose sensor appears larger, making it look like you are releasing more glucose in your sweat than you actually are. As a result, it's important to measure both temperature and molecules at the same time to calibrate the device.

"Sweat is hugely amenable to wearable applications."

The device could open up new fields of research. "With continuous, real-time monitoring of populations of people," said Davis, "we'll be able to mine the collected data for patterns that can guide clinically oriented investigations and deliver personalized medicine."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Emaminejad said the device will enable researchers to conduct science experiments that couldn't be done before. "I think we will learn a lot about sweat itself and what its composition is telling us about our health," he said.

Another Stanford-affiliated co-author of the paper is PhD student Samyuktha Challa.

This research was supported by the National Institutes of Health, the Berkeley Sensor & Actuator Center and the U.S. Department of Energy.

Stanford's departments of Electrical Engineering, of Biochemistry and of Genetics also supported the work. **ISM**

Nose

continued from page 1

of London. The letter provided the first account in English literature of the procedure.

Rewards for noses

At the time, the British East India Company ruled parts of India. A sultan, angry at the occupation, offered bounties for the amputated ears, noses and hands of British sympathizers. The letter describes the nasal reconstruction of an Indian bullock driver who, imprisoned by the sultan, had his nose and one of his hands cut off as punishment for delivering supplies to British troops. It goes into detail how the driver's nose was rebuilt 12 months later, after he joined the Bombay Army of the East India Company:

First, a piece of wax was sculpted to the stump of his nose, then flattened out to create a nose template. Next, this template was laid on the forehead and outlined. An incision was made along the outline, and the skin was peeled away, while remaining attached at a point near the top of the nose. The flap was then twisted over to keep the outward skin facing on top, pulled down over the face and molded around the area of the nose. For several weeks, the flap remained attached by a bridge of skin on the forehead to maintain a blood supply. After blood vessels from the nose began to nourish the flap, the ugly connection to the forehead was cut, and a normal-looking nose emerged. This same basic procedure remains the most popular method of nose reconstruction today.

More than 200 years later, Most, working with 21st-century surgical tools at his disposal, used pretty much the exact same procedure to rebuild Saxon's nose — with a few additions.

Saxon, like the bullock driver, had most of his nose removed, but in his case it was cut off piecemeal by a dermatological surgeon trying to root out an invasive case of squamous cell carcinoma.

Skin cancer

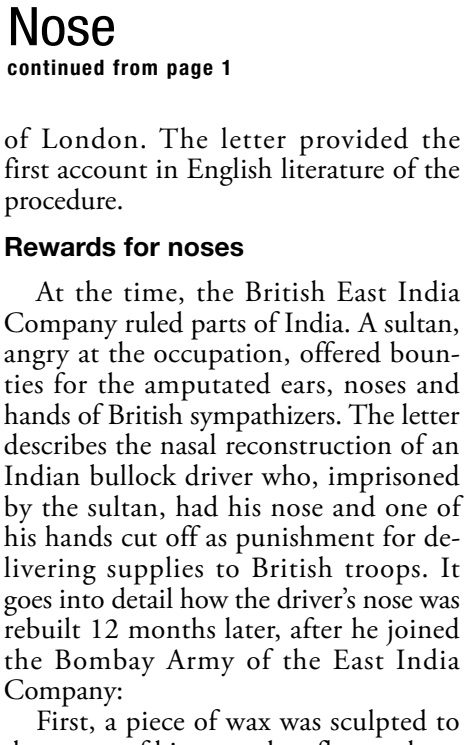
Skin cancer has replaced bounty hunting as the most common cause of major nose deformities that require forehead flap procedure reconstruction, Most said.

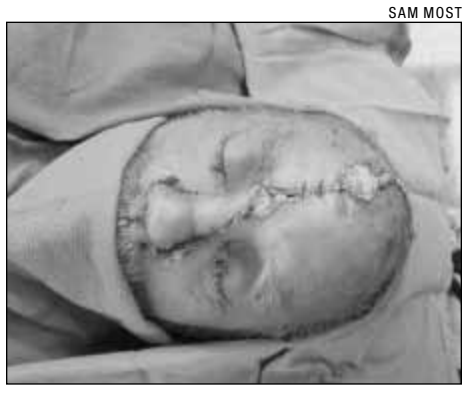
"Unfortunately we are seeing skin cancers in younger and younger patients," Most said. "We get patients in their late 30s, early 40s who need total nasal reconstruction."

The 72-year-old Saxon said his own nose story began more than 40 years ago, with a dog bite.

"When I was 30 years old, a dog bit off the tip of the nose," Saxon said. "It was a mama Dalmatian who'd just had pups. I bent down to pat her and boom, boom, snap." Three nips later, the tip of his nose was gone.

"It healed up, but I had a sore on the tip of the nose for years that kept festering and coming back for decades," he said. Finally, two years ago, he had it biopsied, and it came back positive for cancer. The dermatologist scheduled him for a surgical procedure called Mohs, which is a way of precisely removing the cancerous tissue. The patient sits in the waiting room while the tissue that's been removed is examined for cancer to determine whether all of the diseased cells have been cut out. If not, the patient returns to the operating room for additional tissue removal.





SAM MOST

An illustration, left, that appeared in *The Gentleman's Magazine* in 1794 shows an Indian bullock driver after rhinoplasty with the forehead flap method. Saxon, right, after his rhinoplasty operation.

Sam Most

'I had no nose left'

"I was there for nine hours," said Saxon. "By that point, I had no nose left. I was stunned." In addition, he learned that he was still not cancer-free; the disease was traveling to his brain, and he'd need radiation therapy to treat it.

Most performed the nose reconstruction surgery the very next day, before Saxon really even had time to miss the protuberance. "When he arrived, there was a very extensive hole all the way to the base of the lip," Most said. "They had chopped off most all of the nose." Before the flap procedure could be performed, Most had to rebuild the missing cartilage with cartilage taken from Saxon's ear.

"When you reconstruct a nose, you have to worry about nasal function and create the nasal skeleton both to make it look good and so that it doesn't collapse, so the person can still breathe," Most said. To recreate the aesthetic component of the nose, the surgeon attempts to recreate the nose in subunits, dividing it into sections where the natural shadow lines of a nose should fall. The nose is rebuilt into these subunits with the intention of hiding the scars or stitches along these shadow lines.

"For Mr. Saxon, his entire cartilage framework of the septum in the front of the nose and the cartilage that formed the tip of the nose were gone," Most said. "The cartilage structure of the septum and the tip had to be rebuilt in order to give him a tip again, to make it look like a natural-looking nose."

Creating the template

After the primary reconstruction, the forehead flap was cut out and brought down to form the nose.

Most used a piece of sterile pad dressing to create a template of the nose. He drew an inked outline around the nose defect, placed the pad on top to create an inked negative and then placed that on Saxon's forehead. The flap was incised along this inked on line, the skin peeled away, turned over and placed over the area of the nose, where tiny stitches molded it into place.

"It's not pretty," Most said, describing what it looks like to wear a forehead flap over your face for the typical three- to four-week period. "People have a horrible time with it. They walk around with this giant bridge of skin sticking down. It's scary looking. They can't go to work."

In an effort to decrease this length of time, Most has published two studies in medical journals showing evidence that new imaging techniques can allow surgeons to see exactly when the nose's blood vessels are supplying the skin graft.

"The accepted dogma is — there is no real evidence out there — that you have to wait three to four weeks or longer before you can cut that umbilical cord," Most said. By using laser-assisted angiography, the surgeon can actually see, rather than guess, when the new vessels are supplying blood to the graft.

A natural-looking nose

For Saxon, the new technology didn't reduce the amount of time he lived with the attached flap. The damage to his nose was too extensive. For more than a month, he walked around with the flap while undergoing radiation therapy for his remaining cancer. After the umbilical cord was cut, it took six months for the swelling to go down and for a natural-looking nose to emerge.

"I wore that forehead flap for about six weeks," Saxon said. "I went to work. I wasn't going to hide out." When you are a small business owner, that's just the way it is, he said. You have to work; you can't stay home.

It hasn't been easy, and he's still at risk for a return of the cancer. But he said he's extremely grateful for his new nose.

"My nose looks really different to me, but other people don't notice," he said. For the six-month recovery period, the nerve regeneration made his nose itch like crazy, and he would feel sharp pains rip through it. But his new nose is a nice nose. He's finished radiation therapy, and he's been given a second chance at life.

"I'm satisfied, and I'm grateful," he said, scratching his new nose as naturally as could be. **ISM**

Malpractice

continued from page 1

colleagues — in terms of specialty, gender, age and several other characteristics — was the most exciting finding," said David Studdert, LLB, ScD, MPH, professor of medicine and of law at Stanford. "It suggests that it may be possible to identify high-risk physicians before they accumulate troubling track records, and then do something to stop that happening."

Studdert, who is also a core faculty member at Stanford Health Policy, is the lead author of the study, which was published Jan. 28 in *The New England Journal of Medicine*.

'Concentrated among a small group'

"The degree to which the claims were concentrated among a small group of physicians was really striking," added Studdert, an expert in the fields of health law and empirical legal research.

The researchers analyzed information from the U.S. National Practitioner Data Bank, a data repository established by Congress in 1986 to improve health-care quality. Their study covered 66,426 malpractice claims paid against 54,099 physicians between January 2005 and December 2014.

Almost one-third of the claims related to patient deaths; another 54 percent related to serious physical injury. Only 3 percent of the claims were litigated to verdicts for the plaintiff. The remainder resulted in out-of-court settlements. Settlements and court-ordered payments averaged $371,054.

"The concentration of malpractice claims among physicians we observed is larger than has been found in the few previous studies that have looked at this distributional question," said Michelle Mello, JD, PhD, MPhil, a co-author of the study and professor of law and of health research and policy at Stanford.

"It's difficult to say why that is," Mello added. "The earlier estimates come from studies of single insurers or single states, whereas ours is national in scope. Also, the earlier numbers are more than 25 years old now, and claim-prone physicians may be a bigger problem today than they were then."

David Studdert

Encouraging greater awareness

The authors recommend that all institutions that handle large numbers of patient complaints and claims develop a greater awareness of how these events are distributed among clinicians.

"In our experience, few do," they write in the paper. "With notable exceptions, fewer still systematically identify and intervene with practitioners who are at high risk for future claims."

The most important predictor of incurring repeated claims was a physician's claim history. Compared to physicians with only one prior paid claim, physicians who had two paid claims had almost twice the risk of another one; physicians with three paid claims had three times the risk of recurrence; and physicians with six or more paid claims had more than 12 times the risk of recurrence.

"Risk also varied widely according to specialty," the authors noted. "As compared with the risk of recurrence among internal medicine physicians, the risk of recurrence was approximately double among neurosurgeons, orthopedic surgeons, general surgeons, plastic surgeons and obstetrician-gynecologists."

The lowest risks of recurrence occurred among psychiatrists and pediatricians.

Male physicians had a 40 percent higher risk of recurrence than female physicians, and the risk of recurrence among physicians younger than 35 was about one-third the risk among their older colleagues, the study found.

"If it turns out to be feasible to predict accurately which physicians are going to become frequent flyers, that is something liability insurers and hospitals would be very interested in doing," Studdert said.

"But institutions will then face a choice," he added. "One option is to kick out the high-risk clinicians, essentially making them someone else's problem. Our hope is that the knowledge would be used in a more constructive way, to target measures like peer counseling, retraining, and enhanced supervision. These are interventions that have real potential both to protect patients and reduce litigation risks."

Stanford's Department of Medicine helped to support the work. **ISM**

Spectrum awards more than $1 million in pilot grants to 30 projects

By Kris Newby

Thirty biomedical projects at Stanford have received a total of $1.1 million in research funding through the Spectrum pilot grant program.

Spectrum, the Stanford Center for Clinical and Translational Research and Education, is focused on accelerating the translation of medical research from bench to bedside. Its pilot grants are awarded to investigators with bold ideas that address health-care problems through novel approaches and multidisciplinary teams.

This year, Spectrum awarded grants in five areas: medical technologies; therapeutics; population health; community engagement; and predictive tools and diagnostics. Awardees are mentored by teams of experts in each of these areas.

Seven additional grants were awarded through the Stanford Learning Health Care Innovation Challenge for projects that improve the health of patient populations served by Stanford Health Care. These grants are funded by Stanford Health Care in partnership with Spectrum.

The principal investigators and projects receiving funds are:

Medical technologies

• "Automated real-time monitoring of differentiated stem cells for quality assurance in regenerative medicine applications." Bertha Chen, MD, professor of obstetrics and gynecology; and Thomas Baer, PhD, executive director of the Stanford Photonics Research Center.

• "Passive home monitor for early detection of asthma exacerbations in children." David Cornfield, MD, professor of pediatrics.

• "A novel device for treating chronic wound infections." Peter Lorenz, MD, professor of surgery.

• "Targeted topical therapy to treat inflammatory bowel disease using a novel thermosensitive delivery platform." Sidhartha Sinha, MD, instructor of medicine; Aida Habtezion, MD, MSc, assistant professor of medicine.

• "A low-cost, rapid, point-of-care nucleic-acid-based detection system." Stephen Quake, PhD, professor of bioengineering and of applied physics; and Nate Cira, graduate student in bioengineering. (The investigators on this project also will be mentored by a "predictives and diagnostics" team.)

Therapeutics

• "Development of a therapeutic and companion diagnostic for TREM1." Katrin Andreasson, MD, professor of neurology and neurological sciences.

• "Development of p300/CBP histone acetyltransferase inhibitors for treatment of cancer." Peter Jackson, PhD, professor of microbiology and immunology and of pathology.

• "Topical delivery of MRTF/SRF inhibitors in resistant basal cell carcinoma." Ramon Whitson, PhD, dermatology fellow; and Anthony Oro, MD, PhD, professor of dermatology.

• "Evaluation of novel medical treatment for interstitial cystitis: an unmet clinical need." Amandeep Mahal, MD, urology fellow; and Craig Comiter, MD, professor of urology.

Population health sciences

• "Assessment of novel outcomes in the Women's Health Initiative using Medicare claims: An exploration of a new administrative and clinical trial data linkage opportunity at Stanford." Jacqueline Baras Shreibati, MD, cardiology fellow; and Mark Hlatky, MD, professor of medicine and of health research and policy.

• "Post-traumatic stress disorder, deployment stress and pregnancy outcomes among active duty U.S. Army soldiers." Lianne Kurina, PhD, associate professor of medicine; and Jonathan Shaw, MD, MS, clinical assistant professor of medicine.

• "Curating National Health and Nutrition Examination Survey genetic data for sociogenomic modeling." David Rehkopf, ScD, MPH, assistant professor of medicine; and Benjamin Domingue, PhD, assistant professor of education.

• "Designing cluster-randomized trials that are less susceptible to interference across levels of the treatment: with application, data sharing and software." Michael Baiocchi, PhD, assistant professor of medicine; and David Rogosa, PhD, associate professor of education.

• "Health insurance design and international differences in health at older ages." Maria Polyakova, PhD, assistant professor of health research and policy; and Petra Persson, PhD, assistant professor of economics.

• "Using anthropometrics to assess the impact of a novel multidisciplinary social enterprise intervention on population health in the Democratic Republic of Congo." Yvonne Maldonado, MD, professor of pediatrics and of health research and policy; and Marcella Alsan, MD, PhD, MPH, assistant professor of medicine.

• "Desmoid tumors for big data linkage." Shivaani Kummar, MD, professor of medicine; and Ann Hsing, PhD, professor of medicine.

Community engagement

• "Muslim Community Association of Santa Clara and Stanford Muslims and Mental Health Research Lab: Strengthening an emerging community-based participatory research collaboration." Rania Awaad, MD, clinical instructor of psychiatry and behavioral sciences.

• "Patient provider race concordance and the preventive health-seeking behavior of black men." Marcella Alsan, MD, assistant professor of medicine.

• "Community first-responder training for medical emergencies: Empowering Bay Area high school students." Henry Curtis, MD, clinical instructor of emergency medicine.

Predictives and diagnostics

• "Prospective validation of a three-gene set for diagnosis of tuberculosis and prognosis of treatment response." Purvesh Khatri, PhD, assistant professor of medicine; and Jason Andrews, MD, assistant professor of medicine.

• "Improving early HIV detection with an ultrasensitive oral fluid antibody test." Carolyn Bertozzi, PhD, professor of chemistry; and Mark Pandori, PhD, associate clinical professor of laboratory medicine at UC-San Francisco.

• "Point-of-care diagnostics for resource-poor settings: An ultra-low-cost portable centrifuge." Manu Prakash, PhD, assistant professor of bioengineering; and Saad Bhamla, PhD, bioengineering research fellow.

• "Sentry AI: Harnessing machine learning for the early detection and diagnosis of melanoma." Roberto Novoa, MD, clinical assistant professor of dermatology and of pathology; and Sebastian Thrun, PhD, professor of computer science.

Stanford Learning Health Care Innovation Challenge

• "Accuracy of weekly self-reporting of healthcare utilization, infectious disease and antibiotic use among pregnant women and their infants." Julie Parsonnet, MD, professor of medicine and of health research and policy; and Jon Krosnick, PhD, professor of communication.

• "Electronic patient portal-enabled clinical decision support to improve health maintenance: A randomized evaluation." Lance Downing, MD, fellow in clinical informatics; and Paul Heidenreich, MD, professor of medicine.

• "Creation and use of decision aids fueled by patient-reported outcomes: Building the bridge between doctor and patient for improved shared decision-making." Cindy Kin, MD, assistant professor of surgery; Kate Bundorf, PhD, MPH, associate professor of health research and policy.

• "Data-driven mammography decision support: Analyzing images and reports to improve breast cancer diagnosis." Daniel Rubin, MD, assistant professor of radiology and of medicine; and Francisco Gimenez, PhD, bioinformatics fellow.

• "Precision surgical care: Risk and treatment stratification using a novel learning health system." Sean Mackey, MD, PhD, professor of anesthesiology, perioperative and pain medicine.

• "Low cost accelerometers for profiling early mobilization progress following spinal surgery." Allen Ho, MD, neurosurgery resident; Arjun Pendharkar, MD, neurosurgery resident; Eric Sussman, MD, neurosurgery resident; and Atman Desai, MD, clinical assistant professor of neurosurgery.

• "A population-wide analysis of emergency department length of stay for patients undergoing interfacility transfer for severe psychiatric illness." Suzanne Lippert, MD, MS, clinical assistant professor of emergency medicine; and Nancy Ewen Wang, MD, professor of emergency medicine.

Spectrum pilot grants are administered by Stanford Biodesign (medical technologies), SPARK (therapeutics), Population Health Sciences, the Office of Community Health (community engagement) and the Stanford Predictives and Diagnostics Accelerator (predictives and diagnostics). Primary funding comes from Spectrum's $45.3 million Clinical and Translational Science Award (UL1TR001085) from the National Institutes of Health. ISM

Stanford Cancer Institute symposium to feature young researchers

The Stanford Cancer Institute is sponsoring its second annual symposium to highlight the work of young cancer investigators.

Graduate students, postdoctoral scholars and other junior researchers will convene from 12:30-6 p.m. Feb. 23 at the Li Ka Shing Center for Learning and Knowledge to share their latest research projects and hear advice from established cancer scientists. The event is free and open to the Stanford Medicine community. Lunch will be provided.

For more information or to register, visit http://med.stanford.edu/cancer/research/sci-trainees-symposium.html. Registration is required to attend.

"Part of our mission is to train and prepare the next generation of outstanding cancer researchers and clinicians," said Beverly Mitchell, MD, institute director and the George E. Becker Professor in Medicine. "This symposium is a terrific forum for young investigators to network with their peers and receive guidance from accomplished mentors."

The symposium will feature a keynote address from Tito Fojo, MD, PhD, who served as director of the National Cancer Institute Medical Oncology Fellowship Program from 2006 through 2015. An expert on neuroendocrine tumors, Fojo is now a professor of medicine at Columbia University.

Beverly Mitchell

Participants will also hear about cancer research career paths from Stanford faculty members Sean Bendall, PhD, assistant professor of pathology; Ami Bhatt, MD, PhD, assistant professor of medicine and of genetics; and Allison Kurian, MD, McS, assistant professor of medicine and of health research and policy.

The symposium will include a poster session highlighting the work of young researchers, six of whom will also give oral presentations on their research projects. The topics span the breadth of cancer-related science, including basic, translational, clinical and population-based research. (The deadline for abstract submission has passed.)

The Stanford Cancer Institute coordinates and supports all aspects of cancer-related research and treatment conducted or provided through Stanford Medicine. ISM

Researchers develop fast and accurate cystic fibrosis test

By Erin Digitale

Researchers at the School of Medicine have developed a fast, inexpensive and highly accurate test to screen newborns for cystic fibrosis. The new method detects virtually all mutations in the CF gene, preventing missed diagnoses that delay babies' ability to begin receiving essential treatment.

A paper describing the new test was published online Feb. 1 in *The Journal of Molecular Diagnostics.* Cystic fibrosis, which causes mucus to build up in the lungs, pancreas and other organs, is the most common fatal genetic disease in the United States, affecting 30,000 people. To develop the disease, a child must inherit two mutated copies of the CF gene, one from each parent. Newborns in every U.S. state have been screened for CF since 2010, but the current tests have limitations.

"The assays in use are time-consuming and don't test the entire cystic fibrosis gene," said the study's senior author, Curt Scharfe, MD, PhD. "They don't tell the whole story." Scharfe was a senior scientist at the Stanford Genome Technology Center when the study was conducted and is now associate professor of genetics at the Yale School of Medicine.

"Cystic fibrosis newborn screening has shown us that early diagnosis really matters," said Iris Schrijver, MD, a co-author of the study and professor of pathology at Stanford. Schrijver directs the Stanford Molecular Pathology Laboratory, which has a contract with California for the state's newborn CF testing.

Early diagnosis, medical attention

Prior studies have shown that newborn screening and prompt medical follow-up reduce symptoms of CF such as lung infections, airway inflammation, digestive problems and growth delays. "When the disease is caught early, physicians can prevent some of its complications, and keep the patients in better shape longer," Schrijver said. Although classic CF still limits patients' life spans, many of those who receive good medical care now live into or beyond their 40s.

Curt Scharfe

In the current test, babies' blood is first screened for immunoreactive trypsinogen, an enzyme that is elevated in CF cases but also can be high for other reasons, such as in infants with one mutated copy and one normal copy of the CF gene. Since the majority of infants with high trypsinogen will not develop CF, most U.S. states follow up with genetic screening to detect mutations in the CF gene. California, which has the most comprehensive screening process, tests for 40 CF-causing mutations common in the state. (More than 2,000 mutations in the CF gene are known, though many are rare). If one of the common mutations is identified, the infant's entire CF gene is sequenced to try to confirm whether the baby has a second, less common CF mutation.

The process takes up to two weeks and can miss infants who carry two rare CF mutations, particularly in nonwhite populations about whose CF changes scientists have limited knowledge.

DNA from dried blood spots

The Stanford-developed method greatly improves the gene-sequencing portion of screening, comprehensively detecting CF-causing mutations in one step, at a lower cost and in about half the time now required. Stanford University is exploring the possibility of filing a patent for the technique.

To enable these improvements, the team developed a new way to extract and make many copies of the CF gene from a tiny sample of DNA — about 1 nanogram — from the dried blood spots that are collected on cards from babies for newborn screening. "These samples are a very limited and precious resource," Scharfe said. The entire CF gene then undergoes high-throughput sequencing. This is the first time scientists have found a way to reliably use dried blood spots for this type of sequencing for CF, which typically requires much more DNA.

"In our new assay, we are reading every letter in the book of the CF gene," Schrijver said. "Whatever mutations pop up, the technique should be able to identify. It's a very flexible approach."

Iris Schrijver

In order for the new test to be adopted, the molecular pathology lab needs to train its staff on the new procedure and run thorough validation studies as part of regulatory and quality requirements to show that the reliability of the test in a research setting will be maintained in the larger-scale clinical laboratory. California newborn screening officials will then have the opportunity to decide whether they want the new test to replace the current method. Schrijver expects the process will take less than a year. "Regardless of how the state decides, the new technique can be widely adopted in different settings," she said, noting that the technique could also be used for carrier and diagnostic testing and to screen for other genetic diseases, not just CF.

"Ultimately, we would like to develop a broader assay to include the most common and most troublesome newborn conditions, and be able to do the screening much faster, more comprehensively and much more cheaply," Scharfe said.

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

The lead authors of the paper are Martina Lefterova, MD, PhD, a former molecular genetic pathology fellow at Stanford; Peidong Shen, PhD, research associate; and Justin Odegaard, MD, PhD, instructor in pathology. Other Stanford-affiliated co-authors are Eula Fung, MS; Tsoyu Chiang, PhD; and Ronald Davis, PhD, professor of biochemistry and of genetics.

Researchers at the University of Texas and the California Department of Public Health also contributed to the paper.

The research was funded by a grant from the National Institutes of Health.

Stanford's Department of Pathology also supported the work. ISM

ST. VALENTINE PRODUCTION / SHUTTERSTOCK.COM

Researchers have developed a method that allows them to extract DNA from tiny drops of blood — like those taken during newborn screenings — in order to look for genetic mutations that cause cystic fibrosis.

OF NOTE

reports on significant honors and awards for faculty, staff and students

Mary Chen

Stanley Cohen

Peter Marinkovich

Robert Ohgami

Jochen Profit

TARA CHANG, MD, was appointed assistant professor of medicine, effective Oct. 1. Her research focuses on the treatment of cardiovascular disease in patients with chronic kidney disease.

MARY CHEN, MS, MBA, was appointed assistant dean of maternal and child health research. She helped launch the Child Health Research Program to support clinical and translational research, now known as Spectrum Child Health. In her new role, she will develop and administer programs to support maternal and child health researchers at Stanford.

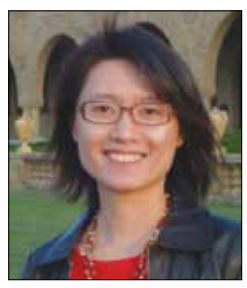
STANLEY COHEN, MD, professor of medicine and of genetics, and **PETER MARINKOVICH**, MD, associate professor of dermatology, have received 2016 Harrington Scholar-Innovator Awards from the Harrington Discovery Institute at University Hospitals in Ohio. Each award includes up to $700,000 in financial support and mentoring from pharmaceutical industry leaders to facilitate drug development. Cohen, who is the Kwoh-Ting Li Professor, aims to develop a treatment for Huntington's disease and mechanistically related inherited neurodegenerative or neuromuscular disorders. Marinkovich studies the extracellular matrix, composed of molecules outside a cell that support surrounding cells, in epithelial tissues for applications in the treatment of blistering diseases such as epidermolysis bullosa. He also examines the pathogenesis and therapy of human psoriasis.

ROBERT OHGAMI, MD, PhD, was appointed assistant professor of pathology, effective Oct. 1. His clinical work focuses on the diagnosis of hematopoietic diseases. His research uses sequencing technologies to understand the molecular pathogenesis of leukemias and lymphomas.

JOCHEN PROFIT, MD, assistant professor of pediatrics, has received two R01 grants from the National Institutes of Health. He received $2.2 million to test a program at six hospitals that is intended to reduce burnout among health workers in the high-stress environment of the neonatal intensive care unit. He also received $3.1 million to track racial and ethnic disparities in care provided to very-low-birth-weight infants at 700 NICUs across the country, with the goal of providing feedback that could be used to eliminate such disparities.

Derrick Wan

Gerlinde Wernig



Fan Yang

DERRICK WAN, MD, was promoted to associate professor of surgery, effective Sept. 1. He focuses on pediatric craniofacial and adult reconstructive surgery. His research interests include using adipose-derived stromal cells for soft-tissue reconstruction.

GERLINDE WERNIG, MD, was appointed assistant professor of pathology, effective Oct. 1. Her research focuses on discovering drivers of fibrotic diseases, including primary myelofibrosis and preleukemia, in patients and mouse models.

FAN YANG, PhD, assistant professor of orthopaedic surgery and of bioengineering, has received the 2016 Young Investigator Award from the Society for Biomaterials. The award will be presented at the World Biomaterials Conference in Montreal. Yang's research focuses on developing biomaterials to enhance tissue regeneration and on deciphering how extracellular cues regulate cell fate during normal development or disease progression. ISM