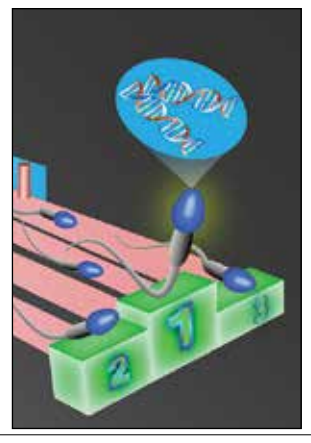
INSIDE STANFORD MEDICINE

Volume 10, No. 1 ■ January 16, 2018 ■ Published by the Office of Communication & Public Affairs



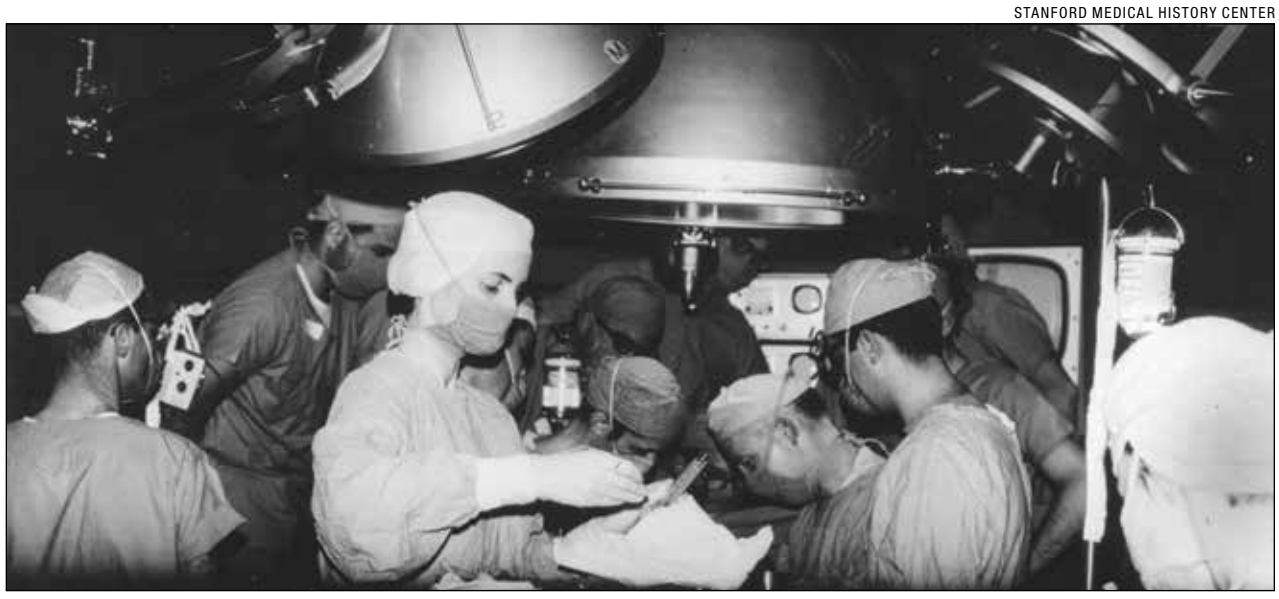
A new sperm-sorting device built at Stanford filters the unfit from the fit and could help improve infertility treatments.

Page 4

50 years ago, Stanford surgeons made history

By Tracie White

STANFORD MEDICAL HISTORY CENTER



Norman Shumway (seated, right center), helped by Edward Stinson (seated, left center), performed the first adult heart transplant in the nation.

For 30 seconds on the afternoon of Jan. 6, 1968, in an operating room at Stanford Hospital, two human hearts lay very still in two separate basins near the unconscious body of a 54-year-old patient, and time froze.

"We both stood there and stared into this huge, empty cavity for a good half a minute," said Edward Stinson, MD, chief resident at the time. "It was a magical moment." The young surgeon was assisting his mentor Norman Shumway, MD, PhD, chief surgeon, who had just removed Mike Kasperak's diseased heart in an effort to save the retired steelworker's life. It was the first attempted heart transplant in an adult in the United States.

"Do you think this is really legal?" Stinson asked Shumway.

"I guess we'll see," Shumway said.

One of the two hearts, diseased beyond repair, would never beat again. But the other, if transplanted into Kasperak's chest within the next hour or two, could possibly start up again and save his life. It was an outrageous act that was being followed with bated breath by the world as a frenzied press corps, camped out in the hallways of the hospital's basement, issued moment-by-moment reports.

"I just remember thinking the future was going to be different if they can transplant a heart," Tom Brokaw, the anchor and managing editor of *NBC Nightly News* for 22 years, said in a recent interview. On that day, he was one of the reporters at the hospital, waiting for the news to break.

The surgery that day 50 years ago captured a moment in history when the transplantation of a human heart was so hard to fathom, so bizarre, it was considered shocking, almost indecent. The heart, more than any other organ, holds a unique place in the public imagination, seen as the seat of the soul, the symbol of love and compassion. So, what happens if it's cut out and replaced with a stranger's? Does a man become a woman if transplanted with a woman's heart? Was it even legal? These types of questions hung over the surgery, as Shumway and Stinson paused for a moment to consider the enormity of their actions.

Today in the United States, death is defined by law as brain death — the cessation of electrical activity in the brain — although this definition is not without controversy. In 1968, the legal moment of death was murkier. Was it when the brain stopped working or when the heart stopped beating? For those pioneering surgeons and cardiologists intent on saving lives, using the still-beating heart of a brain-dead donor was just common sense if it gave a patient dying of heart disease a second chance at life. Sick hearts must be replaced with healthy hearts to save lives.

On that cold, bright winter day in 1968, the spell broke and the surgeons got back to work. There was no turning back.

Race to transplant

In the race to be the first to transplant a human heart — and a race it was — Shumway, a tall, lanky country boy from Michigan, was considered the leader of the pack. His decades-long research working with Richard Lower, MD, in dogs in the laboratory, ultimately led to what remains the standard surgical technique for heart transplantation.

The researchers' first big success occurred in 1959, when Shumway and Lower — a medical resident who later joined the faculty of the Stanford School of Medicine — successfully performed the first dog heart transplantation. Shumway, along with a gang of rotating residents, continued studies in the lab for eight more years, and in the process developed a method of preserving the donor heart by placing it in a solution of ice-cold saltwater to reduce its metabolism. They learned about the transplant-rejection response, which would become the key stumbling block to successful heart transplants.

Then, on Nov. 20, 1967, Shumway and his team announced that Stanford was finally ready to conduct the first human heart transplant, and the wait for a suitable patient and a donor began. A potential patient was identified in October, but died before a donor could be found. Two weeks after Shumway's announcement, on Dec. 3, 1967, South African surgeon Christiaan Barnard, MD, surprised not only Shumway, but also the entire world, by giving Louis Washkansky, a grocer dying of heart disease, a new

See TRANSPLANT, page 6

Drug blocks mosquito-borne viruses in cell cultures, researchers discover

By Sarah C.P. Williams

If there was a Mafia crime family of the virus world, it might be flaviviruses.

Dengue, Zika, West Nile and yellow fever virus — to name the more infamous public health gangsters of this clan — are all mosquito-borne flaviviruses, and they're notoriously hard to take out. Researchers struggle to find drugs to combat just a single flavivirus at a time.

Now, researchers at the School of Medicine have discovered a way to block a handful of members of the family at once. The approach, rather than killing the viruses directly, is akin to cutting off a crime family's bank accounts: It revolves around inhibiting access to a complex of proteins in mammalian cells on which the viruses rely when they invade.

PAUL SAKUMA

Jan Carette is the senior author of a paper that details how to shut off proteins in mammalian cells to keep viruses, including the Zika, dengue and West Nile viruses, from replicating in them.

"Generally, when you develop a drug against a specific protein in dengue virus, for instance, it won't work for yellow fever or Zika, and you have to develop new antivirals for each," said Jan Carette, PhD, assistant professor of microbiology and immunology and senior author of the paper, which was published Dec. 12 in *Cell Reports*. "Here, by targeting the host rather than a specific virus, we've been able to take out multiple viruses at once."

Flaviviruses are single-

See VIRUSES, page 7

Brain zap saps destructive urges

By Bruce Goldman

School of Medicine investigators have identified the smoking gun of a "moment of weakness": a signature pattern of electrical activity in a small, deep-brain region just a second or two before a burst of impulsive behavior.

The Stanford scientists discovered similar patterns in mice that had learned to binge-eat fatty food and in a human subject anticipating a large cash reward. The researchers also showed, in mice, that supplying a small electrical pulse to the brain region in question, called the nucleus accumbens, as soon as the electrical signature manifested prevented the mice from overindulging in fatty food, while not affecting their intake of normal food, their social behavior or other physical activity.

The findings were published online Dec.18 in the *Proceedings of the National Academies of Sciences*.

"We've identified a real-time biomarker for impulsive behavior," said Casey Halpern, MD, assistant professor of neurosurgery and the study's senior author. Postdoctoral scholar Hemmings Wu, PhD, and neurosurgery resident Kai Miller, MD, PhD, share lead authorship.

"Impulses are normal and absolutely necessary for survival," Halpern said. "They convert our feelings about what's rewarding into concrete action to obtain food, sex, sleep and defenses against rivals or predators."

Casey Halpern

Good impulses gone bad

But in some contexts, impulsive behavior can be pathological, manifesting as a marked tendency to make poor decisions and act on them. One need look no further than the recent rash of reports of sexual predators perched in powerful positions in Hollywood, the media, finance and politics to see examples of a fundamentally healthy drive — sexual appetite — taken to a pathological level.

The nucleus accumbens is the hub of the brain's reward circuitry, which evolution has engineered to reinforce survival-promoting actions

See IMPULSIVE, page 7

OBITUARY

Stanford innovator, imaging expert Juergen Willmann dies at 45

By Hanae Armitage

Juergen Willmann, MD, a professor of radiology at the School of Medicine, died Jan. 8 in a car accident in Palo Alto. He was 45.

Willmann honed an imaging tool known as targeted contrast microbubbles that, in combination with ultrasound, could be used to detect early tumors and target the delivery of drugs. Over a decade at the School of Medicine, his lab advanced the microbubble work from the bench to animals, all the way to the first clinical imaging trials in humans, in which microbubbles were used to detect breast and ovarian cancer.

Juergen Willmann

Described as both a brilliant clinician scientist and a compassionate family man, Willmann was known for his boundless energy and empathy. He loved music, played four instruments, was an accomplished pianist and considered becoming a professional musician before deciding on a medical career.

"He was as spectacular a person as he was a scientist. He just radiated this magnetism," said Brooke Jeffrey, MD, professor of radiology at Stanford. "He was never arrogant, never showed hubris, and he was always interested in how you and your family were doing — it was a compassion that's rare to find in someone who's so accomplished."

Native of Germany

Born in Germany, on May 24, 1972, Willmann earned his medical degree, summa cum laude, just 15 minutes from his childhood home in Buchenbach, at Albert Ludwig University of Freiburg. Willmann traveled between California and Zurich, training in diagnostic radiology at the University of California-San Francisco and in surgery at a teaching hospital of the University of Zurich as part of his education. He completed his residency at the University of Zurich, along with his wife Amelie Lutz, MD, whom he met in medical school. Lutz is currently an assistant professor of radiology at Stanford.

After completing his residency, Willmann became an assistant professor and clinical attending physician at the University of Zurich in 2003. He received tenure two years later. He and Lutz were both granted funding from the Swiss government to take a two-year leave and travel to Stanford for a research fellowship — quite a stroke of fate, considering both he and Lutz applied separately and were considered based on their independent merit. The two ended up together in the lab of Sanjiv Sam Gambhir, MD, PhD, professor and chair of radiology, where they worked on multimodality molecular imaging technologies and early cancer detection.

"Juergen was very interested in early cancer detection because he understood the value of long-term research and how impactful early cancer detection could be to humanity when eventually successful," Gambhir said. "He was exceptionally intelligent, highly driven, supremely organized and a wonderful leader, mentor, father and husband. I could not be more proud of anyone who I have had the opportunity to work with and learn from."

In 2008, shortly after the fellowship ended, Willmann and Lutz made a permanent move to the United States, and he became an assistant professor of radiology in the School of Medicine. In 2015, Willmann was promoted to the rank of professor. Although actively recruited by European universities, Willmann opted to make Stanford his home, won over by his strong, fruitful research collaborations.

"Though his life was tragically cut short, Dr. Willmann had already made extraordinary contributions to his field and touched countless lives through his warmth, leadership and compassion," said Lloyd Minor, MD, dean of the School of Medicine. "His death is a profound loss for the entire Stanford Medicine community."

'Just a dynamo'

Throughout his career, Willmann was generous in sharing his expertise with the students and postdoctoral scholars in his lab, and did so in a way that fostered what many deemed a family environment, Jeffrey said.

Outside of research, he assumed several administrative roles in the Department of Radiology, including clinical division chief of body imaging and executive vice chair of strategy, outreach and clinical trials. Jeffrey, the former clinical division chief, said that when he stepped down, Willmann was the unanimous choice. "In addition to his scientific accomplishments and his truly remarkable emotional intelligence, he was a real leader," he said. "His management style was very inclusive, low-key and effective at many levels."

Willmann's investigation into cancer detection and imaging technologies earned him the 2017 Distinguished Investigator Award from the Academy for Radiology & Biomedical Imaging Research.

"He was just a dynamo — people have used the term 'supernova' to describe him, and they're not wrong," Jeffrey said.

"He was a larger-than-life kind of person," Gambhir said.

Willmann was an elected fellow of the Society of Abdominal Radiology and of the American Institute for Medical and Biological Engineering.

He is survived by his wife and their two children, Alexander and Juliana Willmann; his parents, Elisabeth and Karl Willmann; and sister Sabine Willmann.

Arrangements for a memorial service are pending. **ISM**

New treatments, screening methods reduced breast cancer deaths

By Sarah C.P. Williams

In the last few decades, dozens of new breast cancer drugs — from chemotherapies to targeted compounds — have become available for clinical use, and mammogram technology has gone from film to digital. But are the changes making a difference in how many women die of breast cancer?

The answer to that question is a resounding yes, according to a multi-institutional network of researchers who have modeled the effect of breast cancer screening and treatment on mortality rates.

The researchers' models showed that screening and treatment reduced breast cancer mortality by 49 percent in 2012, compared with 37 percent in 2000.

"These numbers represent very positive news for breast cancer patients," said Sylvia Plevritis, PhD, professor of radiology and of biomedical data science at the School of Medicine and lead author of the paper, which was published Jan. 9 in *JAMA*. "Advances in screening and treatment are saving patients' lives, and this paper quantifies just how much of a difference these advances are making."

An international effort

In 2005, Plevritis and her colleagues in the Cancer Intervention and Surveillance Modeling Network used data from 1975 through 2000 to reveal the relative contributions of screening and treatment to reductions in breast cancer mortality rates. Using knowledge of how breast cancer advances, they developed models representing how many women would die of the cancer with no screening and no treatments, then simulated the effect of screening and treatment on those mortality numbers.

The decrease in mortality from the modeled baseline, they found, was about 50 percent due to screening and 50 percent due to treatment.

"Now, over 10 years later, a lot has happened in the field," said Plevritis, who heads the Stanford Center for Cancer Systems Biology. "We've moved from film-based mammography to digital; there are new molecularly targeted treatments and new types of chemotherapy regimens. We wondered whether these advances had changed the relative contributions of treatment and screening on breast cancer mortality."

So researchers in the network updated their models to reflect molecular subtypes of breast cancer. Six independent teams — including researchers from Stanford, the Dana-Farber Cancer Institute, Erasmus Medical Center, Georgetown University Medical Center, Albert Einstein College of Medicine, the University of Wisconsin, Harvard Medical School and MD Anderson Comprehensive Cancer Center — put together models representing the effect of current treatment and screening.

Sylvia Plevritis

The group added new data — spanning 2000 to 2012 — to the existing data and compared the conclusions of each model, calculating average effects on mortality of screening and of treatments, including chemotherapy, hormone therapy and the drug trastuzumab, which targets an epidermal growth factor receptor, ERBB2, overexpressed in some tumors. By comparing six models, the researchers were able to replicate the analysis, making the team more confident in results that were seen in all the models. Not only did they look at the effects on breast cancer as a whole, but on molecular subtypes of breast cancer, such as those that are ER positive, meaning that they grow in response to the hormone estrogen.

"This time around, it was important to look at molecular subtypes because more women are being treated based on the molecular subtype of their tumor," Plevritis said.

The researchers found that in 2012, screening and treatment together reduced breast cancer mortality by 49 percent. For all breast cancers together, 37 percent of that reduction was due to screening, and 63 percent was due to treatment.

Subtype matters

However, when they looked at some molecular subtypes of cancer, the numbers varied. For ER-positive/ERBB2-positive cancer, the most common type and the type for which the greatest number of new targeted treatments are available, only 31 percent of the mortality decline was associated with screening, with 69 percent associated with treatment. For ER-negative/ERBB2-negative cancer, which has fewer treatment options, 48 percent of the mortality decline was associated with screening and 52 percent with treatment, similar to results from 2000.

"Newer drugs, particularly ones that are molecularly targeted, are associated with a greater reduction in breast cancer mortality than screening," said Jeanne Mandelblatt, MD, MPH, professor of oncology and of medicine at Georgetown University and a senior author of the paper. "However, screening is still having a significant effect in reducing breast cancer deaths."

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

The study was funded by the National Institutes of Health. Data used in this study was supported by the National Cancer Institute. **ISM**

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/

Paul Costello
Chief communications officer
Susan Ipaktchian
Director of print & Web communications
John Sanford
Editor
Robin Weiss
Graphic designer

Send letters, comments and story ideas to John Sanford at 723-8309 or at jsanford@stanford.edu. Please also contact him to receive an e-mail version of *Inside Stanford Medicine*.

STANFORD MEDICINE

■ OBITUARY Ben Barres, who identified crucial role of brain's glial cells, dies

By Bruce Goldman

Acclaimed Stanford neuroscientist Ben Barres, MD, PhD, died on Dec. 27, 20 months after being diagnosed with pancreatic cancer. He was 63.

Barres' path-breaking discoveries of the crucial roles played by glial cells — the unsung majority of brain cells, which aren't nerve cells — revolutionized the field of neuroscience.

Barres was incontestably visionary yet, ironically, face-blind — he suffered from prosopagnosia, an inability to distinguish faces, and relied on voices or visual cues such as hats and hairstyles to identify even people he knew well. And there were many of them.

A professor of neurobiology, of developmental biology and of neurology, Barres was widely praised as a stellar and passionate scientist whose methodologic rigor was matched only by his energy and enthusiasm. He was devoted to his scholarly pursuits and to his trainees, advocating unrelentingly on their behalf. He especially championed the cause of women in the sciences, with whom he empathized; he was transgender.

"Ben was a remarkable person. He will be remembered as a brilliant scientist who transformed our understanding of glial cells and as a tireless advocate who promoted equity and diversity at every turn," said Marc Tessier-Lavigne, PhD, president of Stanford University. "He was also a beloved mentor to students and trainees, a dear friend to many in our community and a champion for the fundamental dignity of us all."

Added Lloyd Minor, MD, dean of the School of Medicine, "Through courage and determination, Ben not only changed the course of neuroscience, he touched many lives. He was an inspiration, and I, like so many others, am a better person for having known him."

Nine of every 10 brain cells

Barres' research focused on the nine of every 10 cells in the human brain that aren't nerve cells, or neurons. They're called glial cells or, collectively, glia.

"Ben pioneered the idea that glia play a central role in sculpting the wiring diagram of our brain and are integral for maintaining circuit function throughout our lives," said Thomas Clandinin, PhD, professor of neurobiology, who assumed the role of departmental chair in April 2016 when Barres, who had held the position from 2008 until then, was first diagnosed with pancreatic cancer. "People had thought glia were mere passive participants in maintaining neural function. Ben's own work and that of his trainees transformed this view entirely."

When Barres first began studying them, glia, whose name comes from the Greek word for glue, were thought to be not much more than packing peanuts, supplying positional stability and various nutrients to the brain's much more talented neurons.

Ben Barres

But Barres and the numerous trainees who cycled through his lab showed otherwise.

Glial cells, they proved, are critical to sustaining the overall architecture of the brain's constellation of synapses, through which neurons pass signals to one another. Recent evidence from Barres' lab indicates that glia gone wrong may be to blame for many of the neurodegenerative disorders that vex humanity.

Born Sept. 13, 1954, Barres grew up in West Orange, New Jersey, one of four children in a not well-to-do family. He got his first taste of science in the West Orange Public Library, developed an affinity for microscopes and chemistry sets, and became a high school math star. Attending the Massachusetts Institute of Technology on a scholarship, he earned a bachelor's degree in life science there in 1976 and headed to medical school at Dartmouth, where he obtained an MD in 1979.

Motivated by a mystery

During his subsequent internship and residency in clinical neurology at Cornell, Barres grew increasingly frustrated at physicians' inability to provide cures or even to understand the causes of neuronal degeneration. He was struck by the observation, in pathologists' specimens of degenerating brain tissue, of irregular-appearing glial cells' ubiquitous presence near the lesions.

Bent on finding out why, Barres changed course. He returned to academia, enrolling in a graduate program in Harvard Medical School's neuroscience program in 1983, and published several research papers by the time he received his PhD in neurobiology in 1990. Then he embarked on a postdoctoral fellowship in the lab of Martin Raff, MD, a professor of biology at University College London who was using immunological techniques to tease apart the three classes of glial cells.

Working under Raff, Barres pushed forward and unearthed new insights concerning the best-known glial class: oligodendrocytes, cells stuffed with a fatty substance called myelin. These fat-filled cells were already understood to wrap themselves around neurons' lengthy projections, a process called myelination, providing electrical insulation and vastly increasing the transmission speed and reliability of neuronal impulses. Barres showed, among other things, that electrical activity in neurons was necessary for neurons' myelination.

Barres would routinely work in the lab until 2 or 3 a.m., said Raff. "He slept on the floor of my small office. Every morning when I arrived and opened the door, it would whack him in the head — he eventually learned to sleep facing the opposite direction."

Arriving at Stanford

In 1993, Barres moved from University College London to an assistant professorship in Stanford's Department of Neurobiology. He was promoted to associate professor of neurobiology and of developmental biology in 1998, and to a full professorship in 2001.

At Stanford, Barres turned his attention to a second class of glial cells known as astrocytes. These are the most common cells in the human brain, outnumbering neurons by a factor of four or so. Before Barres began focusing on them, nobody really had understood what astrocytes do for a living. With his colleagues, he discovered that they are crucial to the physical formation of synapses, as well as to those synapses' functional activation. He and his colleagues also discovered that astrocytes cooperate with microglia — a third glial-cell type that's become the object of much recent attention in Barres' lab — in pruning away excess synapses during fetal and neonatal development, in essence preserving brain circuitry that's proven itself to perform legitimate activities and clearing out the dead wood.

Beth Stevens, PhD, then a postdoctoral scholar in Barres' lab, led a 2007 study showing that the cooperation of astrocytes and microglia in synaptic pruning involves the coordinated secretion of molecules previously thought to be exclusive to the body's immune system. Stevens continues to focus on this phenomenon as an associate professor of neurology at Harvard Medical School.

"When I left Stanford for my new job," she said, "Ben told me, 'Take this work with you to your new lab, Beth. Nobody can do it better than you.' Mentors aren't always so generous about ceding areas of research initiated in their lab to trainees headed elsewhere. But Ben was a very special person. Not only was he an incredible scientist, but he also cared deeply about other people, especially his trainees. We were his kids."

Never losing sight of goal

Barres never lost sight of his original goal: to figure out the molecular and cellular causes of the brain tissue degeneration seen in Alzheimer's, Parkinson's and Huntington's diseases; multiple sclerosis; amyotrophic lateral sclerosis, or Lou Gehrig's disease; and glaucoma, an optic-nerve degenerative disease. Research in Barres' lab has strongly implicated inflamed or "reactive" astrocytes and microglia as drivers in all of these neurodegenerative disorders — most recently, in a 2017 *Nature* paper describing how certain reactive astrocytes secrete something that kills stressed or injured neurons.

In an interview about this study, Barres described these findings as "the most important discovery my lab has ever made."

Barres was an outspoken advocate for gender equity in the sciences, not infrequently digressing for a few minutes during his scientific talks to point out the differences he'd personally experienced in how other scientists treated him when they perceived him as a woman versus as a man.

Barres spent his last days and final hours making sure that the letters of recommendation he had written for others were ready. "In what time remains to me that will be my highest priority," he assured trainees in a letter he sent to them in early November.

Over the course of his career, Barres' published 167 peer-reviewed papers, organized and chaired numerous meetings, won many awards and served on the editorial boards of *Science*, *Neuron*, the *Journal of Neuroscience*, the *Journal of Cell Biology*, *Glia*, *Current Biology*.

"If you took the Barres lab out of the field of glial studies, there would be no field," Raff said. ISM

Use of chemotherapy for early stage breast cancer declines, study reports

By Krista Conger

A study of nearly 3,000 women with early stage breast cancer indicates a recent, significant decline in the use of chemotherapy despite the lack of any change in national treatment recommendations or guidelines, according to researchers at the School of Medicine and the University of Michigan.

The findings reflect a growing acknowledgement by oncologists and patients that for some women, the harms of chemotherapy may outweigh its potential benefits. The study also revealed that physicians are more likely to turn to tumor genomic testing when a patient expresses a treatment preference that doesn't match her physician's recommendations.

"For patients with early stage breast cancer, we've seen a significant decline in chemotherapy use over the last few years without a real change in evidence," said Allison Kurian, MD, associate professor of medicine and of health research and policy at Stanford. "This likely reflects a change in the culture of how physicians are practicing, and a move toward using tumor biology to guide treatment choices rather than solely relying on clinical measures."

Kurian is the lead author of the study, which was published online Dec. 11 in the *Journal of the National Cancer Institute*. Steven Katz, MD, MPH, professor of medicine and of health management and policy at the University of Michigan, is the senior author.

"Our study shows how breast cancer is a model for how doctors have driven advances in personalized medicine into the exam room to reduce overtreatment," said Katz.

Surveying women, oncologists

The researchers surveyed 5,080 women treated for early stage breast cancer between 2013 and 2015 in Georgia and Los Angeles. Among them, 2,926 had stage-1 or -2 breast cancers that were positive for estrogen receptor expression and negative for human epidermal growth factor receptor-2 expression. (Receptor expression status is often used to guide treatment recommendations for women with breast cancer.)

After categorizing the women based on the involvement of neighboring lymph nodes, the researchers asked them whether their oncologists had recommended chemotherapy and whether they had received it. The researchers also surveyed 504 of the oncologists treating these early stage breast cancer patients about how they decided whether to recommend chemotherapy for the patients.

Kurian and her colleagues found that from 2013 to 2015, there was a decrease from 34.5 percent to 21.3 percent in chemotherapy use in study participants. During the same period, the participants reported a decline in chemotherapy recommendations by their oncologists from 44.9 percent to 31.6 percent.

Chemotherapy use in patients with no lymph node involvement declined from 26.6 percent to 14.1 percent; in patients with lymph node involvement, it declined from 81.1 percent to 64.2 percent.

Finally, 67.4 percent of oncologists surveyed indicated they would order tumor genomic testing to estimate a lymph node-positive woman's risk of cancer recurrence if the woman disagreed with her doctor's recommendation to receive chemotherapy. In contrast, only 17.5 percent would order the test if the patient and doctor were in agreement about her course of treatment.

"We believe this study indicates that physicians are attempting to be more selective in their recommendations and to spare patients toxicity when possible," said Kurian. "As personalized medicine becomes more widely available, doctors are using test results as part of their dialogue with patients about their preferences and overall treatment goals. But the long-term outcomes of these recent changes in chemotherapy use are uncertain." ISM

New device can quickly select healthy sperm, researchers say

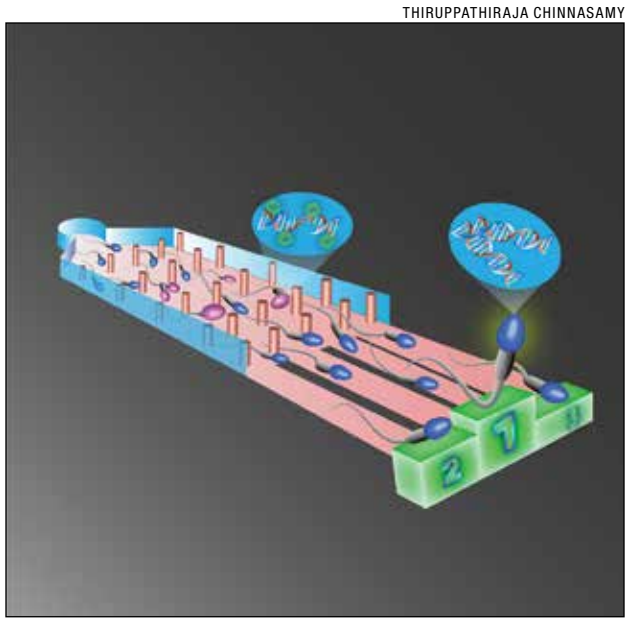
By Hanae Armitage

A device the size of your business card can separate the strong, healthy sperm cells from the duds, and it does so in about 10 minutes, according to a new study led by researchers at the School of Medicine and the Worcester Polytechnic Institute.

The sperm-sorting tool is called the Simple Periodic Array for Trapping and Isolation, or SPARTAN. It filters semen through rows and rows of pillars fitted for healthy sperm.

SPARTAN is not the only device of its kind, but its creators assert that it yields high-quality sperm more efficiently and effectively than others and hence could improve infertility treatments.

THIRUPPATHIRAJA CHINNASAMY



This illustration depicts how the SPARTAN device sorts unshapely and damaged sperm (in pink) from healthier sperm (blue). The unshapely sperm are diverted by the pillars in the device and don't emerge from the filtering system.

A paper detailing the work was published online Dec. 27 in *Advanced Science*. The study's senior authors are Utkan Demirci, PhD, professor of radiology at Stanford, and Erkan Tüzel, PhD, associate professor of physics, of biomedical engineering and of computer science at Worcester Polytechnic Institute. The lead authors are Stanford postdoctoral scholar Thiruppathiraja Chinnasamy, PhD, and graduate student James Kingsley at WPI.

"SPARTAN picks out the healthiest sperm, but it also allows us to ask deeper questions in the clinic in terms of how much sperm selection really matters for infertility treatments," Demirci said. Currently, many infertility treatments, like IVF, place emphasis on finding a healthy egg; the quality of the sperm cell is often secondary. But sperm carry critical heritable genetic elements, just like the egg does, and Demirci said sperm selection does play a big role in the quality of the embryo, so it warrants more careful selection. "Maybe SPARTAN can help change the paradigm in the field," he said.

Utkan Demirci

Simulate before you sort

Before SPARTAN's final form came to be, Demirci and Tüzel collaborated closely on computer models of the device. The researchers took many of their initial design cues from the female reproductive tract — the original filtering system — modeling some aspects of the tool, such as pH level, after the scrupulous screening system biology had already built. The main difference was the physical interior of the device, which comprises thousands of tiny, vertical pillars, painstakingly aligned and optimally spaced to best trap unshapely sperm. Those that were misshapen — a bent tail; too big of a head — or had low motility would either tucker out, or deflect in the wrong direction and never make it to the finish line.

"We're basically using microscale pillars as three-dimensional geometrical figures to capture poorly shaped cells while letting the morphologically normal through," Demirci said.

Compared to other standard clinical sperm-sorting methods — such as the swim-up method, in which semen is placed in a solution, and sperm unable to swim up into it are discarded — SPARTAN yields about twice as many morphologically sound sperm. Swim-up averages 24 percent, while SPARTAN averages 52 percent, the study said.

Over a period of about five years, Tüzel and Demirci tried out a variety of pillar alignments in their models. The arrangements tested patterns of different distances, both vertically and horizontally, and various sizes of pillars, until finally they landed on the most successful array, which they call "periodic structures," as the pillars stand in series, or periods.

Once the simulation showed the majority of strong, well-shaped swimmers reaching the end of the device, Demirci began to build it in his lab. To his delight, the device performed just as the simulation had predicted. Moreover, the researchers found that cells of the right shape and size could swim in a straight line the fastest and separate themselves from the rest of the pack. Upon further analyses, the strong swimmers also had lower rates of DNA damage.

Just keep swimming

SPARTAN separates the semen passively, meaning the cells swim through the device's maze on their own. The pillars sit in a fluid that naturally attracts sperm. The whole process takes about 10 minutes. It makes for a pretty easy user manual, Demirci said.

"It's basically a two-step process: pipette raw semen into one end of the box, then collect the filtered, healthy sperm cells at the other end," he said.

The ease of use is important for standardizing practices in the clinic; fewer steps mean fewer errors. But aside from the speedy sorting, Demirci said the passive nature of the device is crucial. Currently, many sperm-collection techniques use centrifuges, machines that spin samples of fluids and separate the components by density, to collect the sperm cells. The rapid, high-force motion is damaging to the cells, and actually induces destructive molecules called reactive oxygen species that harm the cells' DNA. Swim-up tactics yield a collection of sperm cells in which 13 percent show DNA fragmentation, a type of DNA damage; SPARTAN brings that number down to about 5 percent, the study said.

Demirci and Tüzel have a patent pending on the technology.

"SPARTAN offers a lot more advantages in terms of speed of sorting and fitness of the cells," Demirci said. "And I believe in the long run, we're going to see these types of devices replace the current centrifuge-based methods used in embryology labs."

The study's other Stanford co-authors are basic life science research associate Fatih Inci, PhD; and Barry Behr, PhD, professor of obstetrics and gynecology.

A researcher at the University of California-San Francisco also contributed to the work.

This study was funded by the National Science Foundation.

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

VA bests Medicare in end-of-life care for cancer patients, study reports

By Becky Bach

Cancer patients treated by the Department of Veterans Affairs are less likely to receive excessive end-of-life interventions than those treated through Medicare, according to a study led by researchers at the School of Medicine and Veterans Affairs Palo Alto Health Care System.

The study were published online Jan. 8 in *Health Affairs*.

"The findings are not just important for veterans and VA policy, but for anybody who needs medical care at the end of life, which is a majority of us," said Risha Gidwani-Marszowski, DrPH, a consulting assistant professor of medicine at Stanford. "We as a society need to ensure we are setting up the organization of health care and its financial incentives to ensure that the services patients receive are the ones that are in their best interests at the end of life."

Gidwani-Marszowski, the lead author, is also a health economist at the VA Health Economics Resource Center. The senior author is Steven Asch, MD, professor of medicine at Stanford.

Many Americans say they would prefer to die at home and forgo intensive medical care at the end of their lives. Yet in the last month of life, many studies have shown that the use and cost of health care accelerates. Approximately 4 percent of the entire federal budget is spent on care for Medicare patients in their last year of life, according to some estimates.

In addition, changes are afoot at the VA. Several efforts, including the proposed Veterans Empowerment Act, would change the VA so that it mostly funds medical services, along the lines of Medicare, rather than providing all the care itself.

Those changes could expose veterans to any effects a Medicare-like funding approach has on end-of-life care, Gidwani-Marszowski said.

Risha Gidwani-Marszowski

Testing a funding model

The researchers tested whether the way that care is organized affects the provision of end-of-life services for veterans dying of cancer. The study looked at 87,251 veterans older than 66 who had solid tumors and died between October 2009 and September 2014.

The researchers based the analysis of care quality on guidelines developed by the American Society of Clinical Oncology and the National Quality Forum, as well as on research that has shown patients consider some services undesirable or burdensome at the end of life. Specific criteria included whether patients received chemotherapy; whether they had two or more emergency department visits; whether they were admitted to the hospital and, if so, how many days they spent there; whether they died in the hospital; and whether they were admitted to intensive care. In the study, higher numbers of veterans receiving these services indicates lower quality of care.

The researchers then compared the use of these services by veterans with cancer who used VA health care with veterans with cancer who received their care through Medicare. More than 90 percent of older veterans are enrolled in Medicare as well as the VA, so the population that is eligible for both programs is ideal for evaluating differences in care due to health care system factors, Gidwani-Marszowski said. Researchers accounted for a variety of factors, including the distance patients live from health care facilities, which can affect which system they choose for care, Gidwani-Marszowski said.

The study showed that Medicare patients were more likely to receive unduly intensive care at the end of life, including chemotherapy, hospitalization, admission to the intensive care unit and longer stays in the hospital, and to die in the hospital, than those who received care through the VA.

Gidwani-Marszowski said the study's findings that Medicare patients receive lower-quality, higher-intensity end-of-life care make sense given the different financial incentives of the two systems. VA physicians are salaried, while Medicare-funded physicians bill according to the services provided, which is known as fee for service. Therefore, additional services provided through Medicare generate funds for physicians and health care organizations.

Emergency department use differs

The researchers also found that the VA patients were more likely than the Medicare patients to have two or more emergency department visits. One possible explanation, Gidwani-Marszowski said, is that extended hours or access to appointments are not available at all VA facilities and that veterans may instead need to go to the emergency department for their care. Another is that Medicare patients are more often hospitalized for care that VA patients get in the emergency department.

"The VA has long been a leader in providing patient-centered care at the end of life," Asch said. "Our study showed that veterans can expect appropriately lower-intensity care as they face late-stage cancer at VA facilities. If they choose instead to use their Medicare benefits outside the VA, they are at greater risk of getting chemotherapy, hospitalization and other services that will likely not help them in their last days."

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. ISM

Drug boosts speed, safety of treatment for multiple food allergies

By Erin Digitale

In a randomized, controlled phase-2 clinical trial, an asthma medication increased the speed and safety of a protocol used to treat children for several food allergies at once, according to a study by researchers at the School of Medicine.

The study was published online Dec. 11 in *The Lancet Gastroenterology & Hepatology*.

About 30 percent of people who have food allergies are allergic to more than one food. Doctors tell them never to eat foods that trigger their allergies — the consequences can be deadly — but this requires constant vigilance.

"Patients find it very hard to live with multiple food allergies," said the study's senior author, Sharon Chinthrajah, MD, director of the Clinical Translational Research Unit at the Sean N. Parker Center for Allergy and Asthma Research at Stanford University. "It puts a huge social and economic burden on families." The trial was conducted at the Parker Center.

"Having food allergies separates you from everyone else," said Kristen Geller, the mother of 14-year-old Joshua Geller, who participated in the trial. Before Joshua enrolled in the trial, ordinary childhood and family activities, such as birthday parties and restaurant meals, were a constant source of anxiety for the Geller family.

The new trial examined oral immunotherapy, an allergy treatment in which patients are dosed daily with tiny amounts of the foods that cause their allergic reactions. Over time, the dose is gradually increased until the patient can tolerate normal quantities of the food. In the trial, the oral treatment was combined with omalizumab, an antibody medication that ramps down the allergic response.

The new trial used a placebo-controlled, randomized design to determine whether omalizumab made it safer and faster for children to receive oral immunotherapy to desensitize them to multiple foods simultaneously. At the end of the nine-month trial, 83 percent of children who had received omalizumab could tolerate at least 2 grams of two different food allergens, whereas only 33 percent receiving placebo reached the same level of tolerance.

'Excited to see the clinical efficacy'

"We were excited to see the clinical efficacy of this combination approach using omalizumab and multiple foods," said Chinthrajah, who is also a clinical assistant professor of medicine and of pediatrics at Stanford. "This could be a very promising way to decrease the burden of living with food allergies."

"The study showed significant efficacy and safety improvements in multi-allergic patients treated with omalizumab and food immunotherapy," said co-author Kari Nadeau, MD, PhD, director of the Parker Center and professor of medicine and of pediatrics. "Multi-allergic patients are at much higher risk for anaphylactic reactions since they are allergic to more foods, and omalizumab can help change the course of therapy by making it safer and faster."

The study included 48 children ages 4-15. Thirty-six children were randomly assigned to receive omalizumab, and 12 children to receive placebo, during oral immunotherapy. The drug or placebo was given for eight weeks before oral immunotherapy began, and also for the first eight weeks of oral immunotherapy. Immunotherapy continued without the medication or placebo for the next 20 weeks. The oral immunotherapy was tailored to patients' individual allergies, with each child being treated for two to five of their food allergens. The foods included in the study were almond, cashew, egg, hazelnut, milk, peanut, sesame, soy, walnut and wheat, all of which are common causes of food allergies.

> "It's completely changed our lives."

Children taking omalizumab were desensitized significantly faster than those dosed with placebo. They also had fewer gastrointestinal side effects during therapy, such as nausea and abdominal pain, and fewer respiratory side effects, such as shortness of breath. Twenty-two percent of oral immunotherapy doses in omalizumab patients and 54 percent of doses for placebo patients caused gastrointestinal side effects, while 0 and 1 percent of doses caused respiratory side effects in the omalizumab and placebo groups, respectively. None of the patients in the study experienced serious side effects, such as anaphylactic shock.

Sharon Chinthrajah

Kari Nadeau

To maintain success of treatment for their food allergies, patients continued to eat each food daily after the study was completed. The trial found that after the nine-month immunotherapy procedure, patients continued to be able to eat the foods safely. Larger and longer clinical trials are needed to understand how tolerance develops after someone stops eating the food every day and what makes the benefits of treatment last, the researchers said. The Parker Center is now engaged in such studies.

The successful therapy made a big difference for children who participated in the trial, Chinthrajah said.

That's certainly the case for Joshua Geller and his family. During the trial, Joshua became tolerant to milk, eggs, cashew and pistachio. (Although pistachio was not administered in the trial, some individuals who are desensitized to one nut allergen, such as cashew, develop tolerance to other nuts, such as pistachio, the study found.) Joshua is now trying many foods that he couldn't eat in the past, according to his mom. "He's loving everything, and he seems a lot healthier," Kristen Geller said. "It's completely changed our lives."

"Patients and families say they're so grateful," Chinthrajah said. "They can broaden their food variety and participate in more social activities without fear of a bad allergic reaction. Kids say things like 'I no longer sit at the allergen-free table at lunch; I can sit with my usual friends.' These tiny things that others take for granted can open their social world."

The team's 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.

Other Stanford co-authors of the study are Sandra Andorf, PhD, director of computational biology at the Parker Center; biostatistician Natasha Purington; nurse practitioner Whitney Block; staff pharmacist Andrew Long, PharmD; research data analyst Dana Tupa; Manisha Desai, PhD, professor of medicine and of biomedical data science; and Stephen Galli, MD, professor of medicine, of pathology and of microbiology and immunology.

The research was funded by the National Institute of Allergy and Infectious Diseases Asthma and Allergic Diseases Cooperative Research Centers, the Sean N. Parker Center for Allergy & Asthma Research at Stanford University, the Simons Foundation, the Myra Reinhard Foundation, and the Food Allergy Research and Education Center of Excellence. Genentech provided omalizumab and placebo omalizumab for the research at no cost.

Stanford's departments of Pediatrics and of Pathology also supported the work. ISM

Study: Higher blood sugar in early pregnancy raises baby's heart-defect risk

By Erin Digitale

Higher blood sugar early in pregnancy raises the baby's risk of a congenital heart defect, even among mothers who do not have diabetes, according to a study led by researchers at the School of Medicine.

The study was published online Dec. 15 in *The Journal of Pediatrics*.

For many years, physicians have known that women with diabetes face an increased risk of giving birth to babies with heart defects. Some studies have also suggested a link between nondiabetic mothers' blood sugar levels and babies' heart defect risk. However, the new study is the first to examine this question in the earliest part of pregnancy, when the fetal heart is forming.

James Priest

"Most women who have a child with congenital heart disease are not diabetic," said the study's senior author, James Priest, MD, assistant professor of pediatric cardiology. "We found that in women who don't already have diabetes or develop diabetes during pregnancy, we can still measure risk for having a child with congenital heart disease by looking at their glucose values during the first trimester of pregnancy."

The study's lead author is Emmi Helle, MD, PhD, an affiliate in pediatric cardiology and former postdoctoral scholar.

A research challenge

One challenge associated with conducting the research was the fact that maternal blood glucose is not routinely measured in nondiabetic pregnant women. Instead, women typically receive an oral glucose tolerance test halfway through pregnancy to determine whether they have gestational diabetes, but this test is performed well after the fetal heart has formed.

The research team studied medical records from 19,107 pairs of mothers and their babies born between 2009 and 2015. The records included details of the mothers' prenatal care, including blood test results and any cardiac diagnoses made for the babies during pregnancy or after birth. Infants with certain genetic diseases, those born from multiple pregnancies and those whose mothers had extremely low or high body-mass-index measures were not included in the study. Of the infants in the study, 811 were diagnosed with congenital heart disease, and the remaining 18,296 were not.

> "We could use blood glucose information to select women for whom a screening of the fetal heart could be helpful."

When risk is elevated

The scientists analyzed blood glucose levels from any blood sample collected from the mothers between four weeks prior to the estimated date of conception and the end of the 14th gestational week, just after the completion of the first trimester of pregnancy. These early blood glucose measurements were available for 2,292, or 13 percent, of women in the study. The researchers also looked at the results of oral glucose tolerance tests performed around 20 weeks of gestation, which were available for 9,511, or just under half, of the women in the study.

After excluding women who had diabetes before pregnancy or who developed it during pregnancy, the results showed that the risk of giving birth to a child with a congenital heart defect was elevated by 8 percent for every increase of 10 milligrams per deciliter in blood glucose levels in the early stages of pregnancy.

The next step in the research is to conduct a prospective study that follows a large group of women through pregnancy to see if the results are confirmed, Priest said. If researchers see the same relationship, it may be helpful to measure blood glucose early in pregnancy in all pregnant women to help determine which individuals are at greater risk for having a baby with a heart defect, he said.

"We could use blood glucose information to select women for whom a screening of the fetal heart could be helpful," Priest said, adding that modern prenatal imaging allows for detailed diagnoses of many congenital heart defects before birth. "Knowing about defects prenatally improves outcomes because mothers can receive specialized care that increases their babies' chances of being healthier after birth."

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 study's other Stanford co-authors are Joshua Knowles, MD, PhD, assistant professor of medicine; data analyst Wei Yang; Gerald Reaven, MD, emeritus professor of medicine; and Gary Shaw, DrPH, professor of pediatrics.

Priest is a member of the Stanford Child Health Research Institute, the Stanford Cardiovascular Institute and the Stanford Neurosciences Institute. ISM

Transplant

continued from page 1

heart. Using Shumway's surgical technique, Barnard forever cemented himself into the annals of history as the first to transplant an adult human heart. Washkansky lived 18 days.

Shock to the program

It was a shock to the Stanford program. Everyone had expected Shumway to be the first. But work at Stanford continued, and on Jan. 5, 1968, both a donor and a transplant recipient were found.

At 2 p.m. Jan. 5, Kasperak had a massive heart attack at his home in East Palo Alto. He'd been living with heart disease for several years, and the prognosis wasn't good.

"He had been referred to me," said Don Harrison, MD, a Stanford cardiologist. "He had end-stage heart disease and was not going to live very long. I remember talking to his wife about this transplant surgery. I explained to her that this was a new procedure that had only been done once in the world before. I had to explain to her that her husband was terminally ill, and there was nothing we could do." According to news reports, Kasperak asked his wife, Ferne, if he should go ahead with the operation.

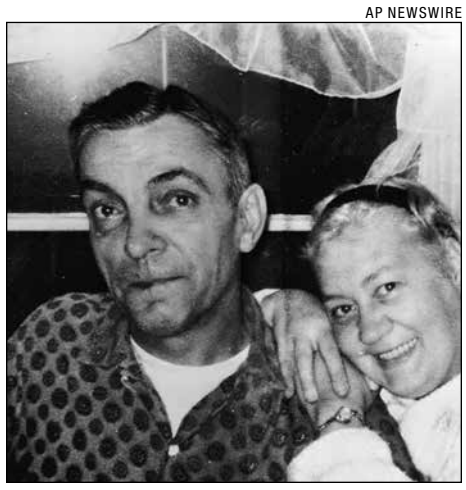
"Go ahead," she said. "I want you alive with me."

Just four hours after Kasperak's heart attack and 7 miles west of his home, another tragedy occurred. Virginia-Mae White, a 43-year-old housewife and mother of two from Mountain View, suffered a brain hemorrhage that left her in a coma at nearby El Camino Hospital. Physicians had confirmed that she was brain-dead by the time they placed her on a respirator, which pumped air in and out of her lungs and kept her heart beating.

Part of the pathos surrounding the drama of each of the 2,000 heart transplants routinely done each year in the United States comes from the reality that for one person to live, another must die. Today, more than 4,000 people in the United States are waiting for a donor heart at any given time. Each case evokes the same emotional quandary that Shumway felt when he picked up the phone just before noon Jan. 6, 1968, to call Bill White, Virginia's husband, to ask him for his wife's heart.

The couple lived in a modest home and had two children, an 18-year-old daughter and a 12-year-old son. They had recently celebrated their 25th wedding anniversary. Shumway was typically light-hearted and quick-witted. In his lab, the professor of cardiothoracic surgery was upbeat, confident, somewhat irreverent and brilliant. His team members loved him. For him, as for anyone, this wasn't going to be an easy conversation to have.

AP NEWSWIRE



Retired steel worker Mike Kasperak with his wife, Ferne. He was the first adult to get a heart transplant in the United States.

In his book *Every Second Counts: The Race to Transplant the First Human Heart*, author Donald McRae describes the conversation between Shumway and Bill White that day:

"Once Shumway had explained the mechanics of transplantation and discussed the concept of brain death, White revealed that his wife had been fascinated by the South African transplant. She and Bill had recently talked to friends about Edward Darvall — who had allowed his daughter's heart to be used for the Washkansky transplant. 'How marvelous,' Virginia White said, 'to give someone else a chance to live.'

"White needed only 30 minutes to discuss the transplant with his children. His answer to Shumway was decisive. They wanted him to proceed."

"Knowing that she is helping another is easing our grief," Bill White said, according to news reports. "I've got two of the proudest children you ever knew."

It was time to round up the surgical team.

Bringing the donor to Stanford

That afternoon, Stinson was sent to pick up Virginia White at El Camino Hospital in an ambulance and deliver her, with her heart still beating, to Stanford Hospital at 3:30 p.m. Shumway received a neurologist's confirmation of brain death in order to proceed, and the surgery began.

Two surgical teams were set up in two adjoining rooms on the second floor of the east wing of the hospital. Stinson removed White's heart in Room 12, then walked it over in a basin filled with cold saltwater to Room 13, where Shumway was waiting.

Kasperak was connected to a heart-lung machine that kept his blood circulating to keep him alive while Shumway cut out his diseased heart.

White's heart, just a third the size of Kasperak's, which was swollen by disease, was then lifted out of its basin and placed inside the empty chest cavity. Shumway sutured White's heart into Kasperak's chest, connecting the major heart vessels — the vena cava, the aorta, the pulmonary artery — and the left atrium

In all, the surgery took about 3½ hours. White's heart had been motionless for two hours. Now, there was nothing to do but wait and see if it would beat again.

It generally takes about 20 or 30 minutes for a transplanted heart to begin to beat after surgery. The surgeon triggers the electrical system of the heart with a single shock from a defibrillator, then waits for it to "pink up" as blood flows back into it. The recipient remains attached to the heart-lung machine until the heart starts to beat effectively again and can take over to keep the blood circulating.

"The excitement was palpable," Harrison said. Ten, 20 minutes passed. At 25 minutes, the new heart faintly pulsed and then grew stronger. "We were all elated."

STANFORD MEDICAL HISTORY CENTER

Shumway (left) and cardiologist Ed Harrison spoke to the media following the historic transplant surgery.

'A three-ring circus'

Downstairs, all hell broke loose. Fifty or so journalists had arrived even before surgery began, according to an article in *Stanford Report* by Spyros Andreopoulous, director of the medical center's news office at the time. He had converted two classrooms into an impromptu press room.

"The tip actually came from a reporter from the *San Jose Mercury News* who was at a wedding reception with members of the transplant team," Andreopoulous wrote. "When they received an emergency call from the hospital, he deduced that the transplant operation was imminent." The news spread fast. Television reports aired that night.

"My friends and I were on the phone that night saying, 'Oh my gracious, did you hear they did the transplant?'" said Joan Miller, RN, a nurse who was at home after finishing her shift on the third floor of the hospital, just above the surgical rooms.

"When I arrived at work it was chaos. It was like a three-ring circus. People were everywhere. It was just great fun and exciting. On break, we'd race down to the basement to see it all — the cameras, the equipment, the news anchors."

By the time the operation was complete and Kasperak was moved on a gurney down the hall to the intensive care unit, reporters were literally scaling the hospital walls trying to snap photos of him through the window of his hospital room.

"I remember thinking they were going to break their necks!" said Stinson, who saw them climbing when he stepped outside. Kasperak's nurses, though, were quick to close the curtains, preventing any photos, and the defeated reporters climbed back down.

The next morning, Shumway, with Harrison by his side, stood with arms folded over a wrinkled, white lab coat and faced the crowd of several hundred reporters at an impromptu news conference

See TRANSPLANT, page 7

Celebration planned for 50th anniversary of the first U.S. adult heart transplant

By Tracie White

Fifty years ago, Norman Shumway, MD, PhD, a cardiothoracic surgeon at Stanford, performed the first successful human heart transplant in the United States at Stanford Hospital.

To celebrate that landmark event, a daylong conference is set for Jan. 22 at the Li Ka Shing Center for Learning and Knowledge at Stanford. Heart experts from Stanford and other institutions will speak, including Shumway's daughter Sara Shumway, MD, a professor of surgery and vice chief of cardiothoracic surgery at the University of Minnesota; and Edward Stinson, MD, professor emeritus of surgery at Stanford, who assisted Shumway during the operation.

The operation, which took place Jan. 6, 1968, sparked a flurry of heart transplantations worldwide, but most institutions and cardiac surgeons quickly desisted because of the high rate of post-surgical deaths. Shumway and his team at Stanford persevered, however, ultimately leading to the success of the operation today.

'Radical innovation'

"Norman Shumway not only introduced a lifesaving procedure but also made sure that the operation became widespread practice," said Lloyd Minor, MD, dean of the School of Medicine. "We are honored to celebrate the anniversary of this unforgettable moment in Stanford Medicine's history, and to recognize Dr. Shumway's radical innovation and perseverance."

For nearly a decade following that first surgery, Stanford was virtually the only major institution moving ahead with heart transplant research and continuing to perform operations. The research led to the use of the drug cyclosporine to help prevent the body's rejection of a donor heart, and to an innovative biopsy technique that helps doctors assess whether a heart transplant is failing before it's too late. These advances greatly improved patient survival rates.

In 1981, Shumway and Bruce Reitz, MD, who is now a professor emeritus of cardiothoracic surgery, performed the world's first heart-lung transplant at Stanford.

Shumway died in 2006 at the age of 83.

"We are eternally grateful for Dr. Shumway's scientific and academic contributions to the field of cardiac surgery," said Joseph Woo, MD, professor and chair of cardiothoracic surgery. "It is upon these foundational values that we seek to build upon our understanding to better care for patients while striving to continue the momentum he sparked toward discovering novel solutions to combat the No. 1 killer in America, heart disease."

The total number of heart transplants performed at Stanford reached 1,933 in December.

More than 60,000 successful heart transplants have been performed around the world. Today, 80 percent of patients who receive a heart transplant survive the first year.

The event is free and open to the public. Registration is required. More information is available at: http://med.stanford.edu/ctsurgery/shumway-50th-anniversary.html. SM

Viruses

continued from page 1

stranded RNA viruses which, combined, are responsible for widespread morbidity and mortality throughout the world. Some flaviviruses, including dengue, Zika, West Nile and yellow fever virus, are spread by mosquitos, while others are spread by ticks. Existing drugs that work against flaviviruses often target parts of the viruses themselves.

Carette and his colleagues, however, study the components of host cells — cells which viruses infect, such as human cells — that flaviviruses depend on. In a previous study, they found that the viruses are especially dependent on their hosts' oligosaccharyltransferase complex, which is normally responsible for adding sugar molecules, called glycans, to proteins. When Carette's team genetically engineered cells to lack OST, which is made up of multiple protein subunits, the cells could no longer be infected by flaviviruses.

In the new work, Carette and lead author Andreas Puschnik, a former Stanford graduate student who now works at the Chan Zuckerberg Biohub, teamed up with Yale University researchers who had developed a drug, NGI-1, that blocked the activity of the OST complex.

While high concentrations of NGI-1 stop the OST in human cells from carrying out its normal function, the group found that much lower concentrations of NGI-1 were needed to block flaviviruses from replicating inside the cells. Therefore, low concentrations of the drug could be used to block the viruses without harming host cells.

When Carette and Puschnik treated Zika- or dengue-infected cells with NGI-1 immediately after infection, they saw a 99 percent decrease in infection; when the treatment was administered 24 hours after initial infection, the decrease was 80 percent. Additional experiments showed antiviral activity against all four dengue types and multiple strains of Zika, as well as against West Nile and yellow fever virus.

The researchers went on to show it's unlikely that viruses will develop resistance to NGI-1 because it would require four specific and separate changes to their RNA.

"When you target a host function rather than a viral protein, it's usually much more difficult for a virus to develop resistance," said Carette.

A better antiviral

To understand exactly what makes NGI-1 such an effective and broad antiviral drug, the researchers worked to determine which part of the OST complex was required for flaviviruses to replicate. When they inactivated the section of the complex that allows OST to add sugar to proteins, a process known as glycosylation, OST still enabled viral replication.

"This means whatever OST is doing for the viruses is really unrelated," said Carette. "It also means we may be able to develop a drug that can more specifically inhibit the viral complex."

While NGI-1 blocks both viral activity and protein glycosylation, the team is now working to uncover other compounds that will act more specifically against flaviviruses without impacting protein glycosylation at all.

At the same time, they're continuing to study NGI-1, testing the drug in small animal models of dengue infection.

"This work highlights how cell components can be used as antiviral drug targets," said Puschnik. "We hope this leads to a new generation of antiviral drugs." **ISM**

Impulsive

continued from page 1

by inducing pleasure in anticipation or performance of those actions. The study's findings offer the promise, Halpern said, of an implantable device that monitors the nucleus accumbens for the telltale signal preceding a burst of impulsivity and immediately delivers a measured dose of electricity. This intervention may prevent impulsive and sometimes life-threatening actions by high-risk people for whom all noninvasive therapies have failed.

The findings could also lead to less invasive methods of countering obesity, substance-abuse disorders, pathological gambling, sexual addiction or intermittent explosive disorder, a psychiatric condition marked by impromptu outbursts of inappropriate ferocity.

"Imagine if you could predict and prevent a suicide attempt, a heroin injection, a burst of binge-eating or alcohol intake, or a sudden bout of uncontrolled rage," said Halpern.

Clinically, Halpern focuses on deep-brain stimulation, whereby devices deliver electrical pulses to targeted brain regions in which they've been implanted. DBS is now approved by the Food and Drug Administration for treating symptoms of Parkinson's disease and essential tremor, and is currently in clinical trials for depression, obsessive-compulsive disorder and multiple other disorders of the brain.

But the tens of thousands of DBS devices in current use are inflexible in the timing, duration and intensity of the pulses they deliver; they simply fire away on a preprogrammed basis, 24/7. New-generation devices can respond to feedback from the brain region they target, or even a distant one, so pulses get delivered only when necessary and at appropriate intensities. These so-called responsive neurostimulation devices have so far been approved for partial-onset epilepsy. Because they fire only after sensing specific electrical-activity signatures, they may actually deliver as little as five minutes per day of total stimulation, which neuroscientists such as Halpern view as greatly advantageous from the standpoint of avoiding side effects and optimizing the behavioral specificity of the treatment.

"There's no available responsive neurostimulation intervention for dangerous impulsive behavior yet, because until now no one's been able to document a characteristic signature in the brain that could be used for triggering pulse delivery by the device," he said.

From mouse to man

The Stanford scientists discovered this signature in experiments with mice. Typically, laboratory mice are fed pellets of a standard chow that's nutritious without being highly caloric. In the study, mice were given special high-fat food pellets for one hour every day for 10 days. During that hour, they were allowed to eat as much as they wanted.

The novel food took some getting used to, but by day 10 the mice became habituated to it and pretty much ate it nonstop. The researchers had implanted electrode arrays in the mice's brains in order to monitor electrical activity in the nucleus accumbens, where a pattern of heightened electrical activity — restricted to a particular low-frequency band called delta — emerged immediately prior to binge-eating, peaking about one second before a mouse took a bite of the high-fat food pellet. Notably, this uptick didn't occur when that mouse was about to bite into standard lab chow. Nor was it seen in other typically rewarding activities, such as interactions with younger mice.

Halpern and his colleagues then programmed their electrode arrays to deliver 10-second pulses of electrical current — the typical regimen in approved DBS therapies — to the nucleus accumbens whenever the arrays sensed a sizeable increase in delta intensity there. This substantially reduced the mice's high-fat binges. But it didn't affect their social lives, or their general physical behavior.

Further experiments compared responsive neurostimulation with standard DBS, random pulse delivery and manual delivery whenever an experimenter saw a mouse preparing to stuff itself. Both manual and responsive-neurostimulation pulse delivery proved superior to either random or DBS delivery, despite delivering far fewer electrical pulses daily than DBS.

Next, the Stanford researchers took advantage of a rare opportunity to perform a similar experiment on a human subject: a patient with obsessive-compulsive disorder, a condition for which DBS to the nucleus accumbens is in clinical trials. This participant was resistant to all other treatments for his OCD and had opted for surgical implantation of a DBS device.

The investigators received the participant's consent to intervene briefly once electrical leads had been introduced to the participant's nucleus accumbens but prior to their hookup with the DBS pulse generator. In the interim, the participant was asked to perform computerized tasks that generated cash rewards if completed successfully. As with the mice, once the participant got acclimated to the near-certainty of receiving a reward upon completing the task, a receiver to which the implanted electrical leads were temporarily hooked was able to detect the characteristic "high-delta" electrical signature in his nucleus accumbens just before he commenced the tasks.

"The fact that we saw a similar signal prior to two different behaviors, both intended to obtain rewards — food in the case of mice, money in the case of the human subject — to which the individuals had become hypersensitized by their repeated exposure suggests that this signal may be common to many impulsive behaviors, making them amenable to treatment along similar lines," said Halpern.

Unlike newer parts of the brain, such as the cerebral cortex, the more deeply seated reward system's components have largely been conserved among vertebrates. So Halpern thinks the behavior-altering results his team observed in mice are likely to apply to humans, although further study will be needed to confirm these findings in a single human subject.

Halpern, Wu and study co-author Robert Malenka, MD, PhD, professor of psychiatry and behavioral sciences, are co-authors of a provisional patent filed by Stanford's Office of Technology Licensing on intellectual property associated with these findings. **ISM**

Transplant

continued from page 6

held in one of the medical school's amphitheaters.

"We have reached first base, so to speak, but our work is just beginning," Shumway said, cameras clicking. "The heart transplant patient, Mike Kasperak, awakened in satisfactory condition." Harrison, the patient's cardiologist, presented diagrams of cardiac functioning measurements collected through the night showing that the heart was functioning well.

Shumway, known to be shy of the media, would later turn down offers to appear on *Face the Nation, Meet the Press* and the *Today Show*, but that morning he appeared calm and in high spirits.

"Shumway looked just a little bit like a guy who had just got off the gridiron," Brokaw said. "Exhausted, but pleased with himself. He looked the part — handsome, white jacket, just a built-in charisma. Here was this monumental moment, and he handled it with such modesty."

The patient's condition

During the next few weeks, Stinson, who later joined the School of Medicine faculty, led the fight to keep Kasperak alive. The first five nights post-surgery, Stinson remained sleepless by his patient's side. Meanwhile, the Stanford press office issued daily bulletins on Kasperak's condition.

"The patient, Mike Kasperak, 54 years old, was reported to be awake and alert," *The New York Times* reported three days after surgery. "He was allowed a first visit with his wife yesterday evening and slept during the night." Two days later, it followed up with: "Mr. Kasperak managed to scribble an 'I love you' note and hand it to his wife."

For the first few days post-surgery, Kasperak's condition remained hopeful, but then he slipped into a semi-comatose state. Extensive bleeding of the stomach led to worries that his liver and kidneys had been too severely damaged by years of heart disease to keep him alive.

"In retrospect, he was too ill at the time of surgery," Stinson said. "His lungs, liver, kidneys, GI tract weren't functioning well. His body didn't tolerate the stress of the operation well." Fifteen days after the surgery, Kasperak died of severe hemorrhaging. Stinson, making certain he was given enough morphine that he was never in pain, was there by his side.

In the aftermath of the Stanford transplant, the world hit near-hysteria in its fascination with heart transplants. Nearly 100 medical institutions jumped in to attempt the operation. The surgery itself proved fairly simple, but the inability to prevent recipients' bodies from rejecting foreign hearts quickly led to alarming death rates. Sensationalized accounts of these operations appeared in newspapers like the *National Enquirer*. One paper ran with this headline: "Docs give her a man's heart — now she puffs stogies and rants and raves at TV wrestlers."

In 1970, on the third anniversary of Barnard's first transplant, exhausted by this near-madness and frightened by the soaring death rates, the medical establishment, led by the American Heart Association, called for a moratorium on heart transplants. All major institutions complied, except for one: Stanford.

Refining the work

The Stanford physician-scientists continued to methodically publish scientific papers and conduct heart transplants, slowly establishing new protocols for the selection of patients and for measuring and treating rejection.

Today, Stanford Medicine's reputation is cemented as the research center responsible for leading to the thousands of successful transplants carried out annually around the world. But that first surgery remains a magical moment, for Stinson at least, and an essential one, along the journey toward making heart transplantation a standard operation. **ISM**

Paul Yock wins National Academy of Engineering's Gordon Prize

By Stacey McCutcheon

Paul Yock, MD, professor of medicine and of bioengineering at Stanford and the founder and director of the Stanford Byers Center for Biodesign, will receive the National Academy of Engineering's 2018 Bernard M. Gordon Prize for Innovation in Engineering and Technology Education.

The academy said Yock was chosen for "the development and global dissemination of Biodesign, a biomedical technology training program that creates leaders and innovations that benefit patients." The prize is the academy's top honor for teaching and carries a $500,000 award.

Yock, who holds the Martha Meier Weiland Professorship and was the founding co-chair of Stanford's Department of Bioengineering, is known internationally for his work inventing and testing new medical devices in the field of interventional cardiology. Motivated to help other aspiring innovators succeed in developing devices to improve health care, he founded Stanford Biodesign in 2001. Reflecting its roots in both engineering and medicine, Biodesign is part of Bio-X, Stanford's interdisciplinary biosciences institute.

Focus on need-driven innovation

Stanford Biodesign was a pioneering innovation training program dedicated exclusively to the design and development of medical devices, and was revolutionary in its focus on need-driven innovation — identifying and characterizing important, unmet clinical needs as the essential first step in successful inventing.

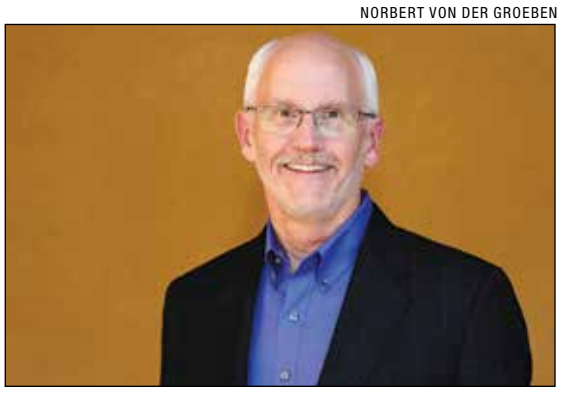
"There are different innovation processes that make sense for different technology domains," said Yock. "Unlike the situation for consumer products, health care has a complex landscape of stakeholders — from doctors and patients to regulators and insurers — all of whom have a say in whether a new technology is adopted into patient care."

Not only do innovators need to satisfy all of these stakeholders, but given the multiyear timeline and millions of dollars required to develop, test and obtain regulatory approval for a new medical device, it's essential that innovators get it right the first time. "This is why our trainees spend three to four months screening needs and understanding the problem they ultimately choose to solve before they ever invent anything," Yock said.

Doctors, engineers work together

Stanford Biodesign was also among the first academic training programs to formalize a mechanism for bringing together talented engineers and physicians to collaborate on project-based learning experiences. Josh Makower, a serial inventor and entrepreneur, had experimented with this approach previously in a corporate setting. As co-founder of the program, Makower worked with Yock to define and implement a multidisciplinary learning model. "To create meaningful new health technologies, innovators need to understand everything from biology and medical care delivery to engineering and health care economics," Yock said. "No one individual can cover that waterfront; you need a team to be effective."

NORBERT VON DER GROEBEN



Paul Yock is being honored for his work in founding and directing Stanford Biodesign, which is dedicated to aspiring innovators who want to design and develop medical devices.

Since the program's founding, its trainees have created 45 companies based on technologies invented during their time in the program, and these new products have been used in the care of nearly 1 million patients. The program has been emulated by universities throughout the world, and the Stanford Biodesign textbook and open-source video library have become the premier international teaching resources on the topic of need-driven innovation.

"Winning the prestigious Gordon Prize is a well-deserved achievement for Paul, as he has had a tremendous influence on the biomedical innovation process both here in the United States and around the world," said Lloyd Minor, MD, dean of the School of Medicine. "By bringing people from a range of backgrounds together to develop predictive and preventive health solutions, Paul and Stanford Biodesign have introduced the kind of out-of-the-box thinking that's crucial to advancing our vision for precision health."

Jennifer Widom, PhD, dean of the School of Engineering, said Yock's emphasis on bringing students together from across disciplines is key to solving the kind of real-world problems they are tackling, as well as a critical element of Biodesign students' education. "By helping students apply their diverse expertise and resources to develop solutions, we are creating confident leaders with the ability to tackle important problems around the globe," she said. **ISM**

Novel technique could reveal immunotherapy targets, researchers find

By Hanae Armitage

Researchers at the School of Medicine and their colleagues have developed a way to pinpoint potential targets for cancer therapies that rely on the body's immune system.

Those targets are molecules called antigens, which appear on the surface of tumor cells and other malignant or damaged cells. Antigens are cumbersome to identify but critical to developing cancer immunotherapies, a type of treatment in which the host's own immune system is trained to seek out and fight harmful or mutated cells. And while cancer vaccines are still largely a thing of the future, new antigens are key to nudging progress forward.

Christopher Garcia

The researchers exploited years of structural and protein engineering studies by the laboratory of Christopher Garcia, PhD, professor of molecular and cellular physiology and of structural biology, to better understand how the immune system "sees" antigens. Based on this knowledge, they developed a technique to identify them. What's more, the technique could serve to identify potential antigens relevant to other immunotherapies, such as those that combat autoimmune or infectious diseases.

A paper describing the work was published online Dec. 21 in *Cell*. Stanford graduate student Marvin Gee and postdoctoral scholar Arnold Han, MD, PhD, share lead authorship of the paper. Garcia, who holds the Younger Family Professorship, is the senior author.

"The whole foundation of immunotherapy depends on immune cells recognizing specific antigens on tumor cells. That's the basis of the actual killing event — where the rubber hits the road," Garcia said. "But currently we know very few tumor antigens, and there's just been no good way of discovering them." Here, he said, is where he sees potential for a new biochemical screen to expedite the identification process.

A game of odds

A type of immune cell known as a T cell patrols the body for foreign invaders or mutated cells poised to cause harm. On their surface, T cells have receptors that bind to one or more specific antigens of a tumor or other harmful cell. When a receptor finds its match, the antigen acts as the T cell's molecular directive to infiltrate and kill the unhealthy cell. But because matched receptor-antigen pairs are difficult to come by experimentally, many receptors remain unidentified. They're called orphan receptors.

"This screen is a completely unbiased way of taking a random T cell receptor that's infiltrated a tumor and interrogating it to find out exactly what antigen it is actually seeing," said Garcia, who is a Howard Hughes Medical Institute investigator.

The screen he and his colleagues devised pulls data from two resources: orphan T cell receptors found on colon cancer tumors, and a hefty repository of antigen sequences of white blood cells. Using yeast as a vehicle, the team scanned some 400 million of these antigen sequences, all possible matches to 20 orphan receptors derived from the colon cancer tissue samples. Four of the 20 receptors found matches.

The somewhat modest ratio is a product of chance. The receptors are restricted by genotype, and will only bind to antigens of a matching genotype. Between that and the enormous variability of possible antigens, pegging a receptor-antigen match is "a bit like winning the lottery," Garcia said. "The key to increasing the odds is to increase the throughput of the experiments, kind of like putting more coins into the slot machine."

What's in the screen, and what's getting screened, Garcia explained, are mimics of the original receptors and antigens — accurate, but not 100 percent identical. So, after the initial screen, the four receptors that bound antigens were then sequenced and run through an algorithm, which ultimately figured out the correct corresponding identity of the human antigen. With this technique, the team unambiguously identified two human antigens of the four receptors that found matches in the yeast-based library, and they're currently in the process of identifying a third one.

Neo versus self

There's an ongoing debate, Garcia said, about the most important types of antigens that T cells "see" and attack in tumors. One currently popular notion is that T cell receptors react with neoantigens, or antigens that are mutated or uniquely part of a cancer, rather than self-antigens, which both cancerous and healthy cells can have in common. Unexpectedly, however, evidence from the new study suggests otherwise, as one of the two antigens was "self." In addition, the self-antigen turned out to be shared between two patients — a key to developing immunotherapies.

"It was a huge surprise to find that one of the antigens was a non-mutated, shared self-antigen, and the implications are that if you screen many more T cell receptors, you'll likely find a lot of shared antigens," Garcia said. "So in theory, you could have one immunotherapy that targets this antigen, and it'd be effective for multiple patients." But this, he said, brings us to the million-dollar question: How do we generate antitumor immunity against an antigen that is attached to both healthy and cancerous cells?

"Right now, we don't have an answer, but there are a lot of efforts going into that problem, and it's something that I'm very interested in," Garcia said. **ISM**

OF NOTE

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

Euan Ashley

EUAN ASHLEY, FRCP, DPhil, has been promoted to professor of medicine, effective Sept. 1, 2017. His research develops methods to use genome sequencing data to improve the diagnosis of genetic disease and to personalize the practice of medicine. Ashley directs the Clinical Genome Program and the Center for Inherited Cardiovascular Disease at Stanford, and is principal investigator of the MyHeart Counts study.

Dimitri Augustin

DIMITRI AUGUSTIN, MD, a postdoctoral scholar in nephrology and an innovation fellow with the Stanford Byers Center for Biodesign, was named a diversity and inclusion fellow for the American Society of Nephrology. The one-year position offers the opportunity to contribute to the society's diversity and inclusion initiatives.

Manisha Desai

MANISHA DESAI, PhD, professor of medicine and of biomedical data science, has received the Outstanding Mentorship Award from the American Statistical Association's Section on Statistical Consulting. The honor recognizes leadership in the mentoring and career development of students, statisticians and statistical investigators. **ISM**