INSIDE STANFORD MEDICINE

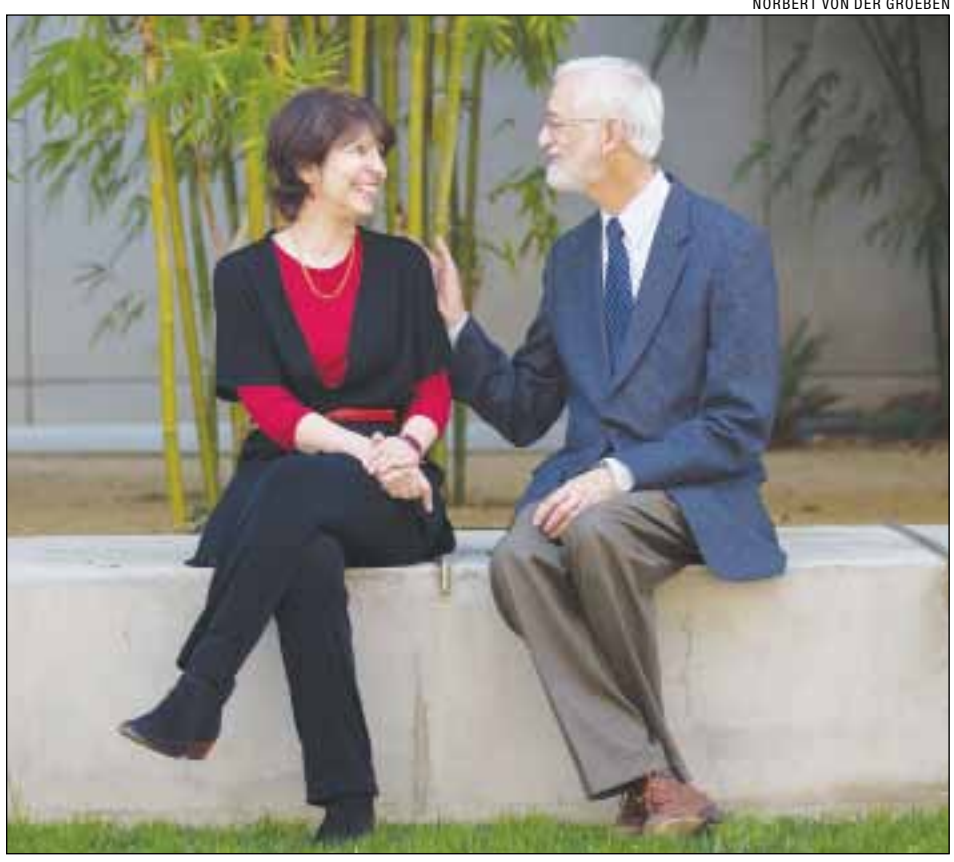
Volume 8, No. 22 ■ December 12, 2016 ■ Published by the Office of Communication & Public Affairs

Conjoined twins were successfully separated during a 17-hour surgery.
Page 5

For 30 years, duo has taught to make a lasting impression

By Kathy Zonana

NORBERT VON DER GROEBEN



Georgette Stratos and Kelley Skeff co-direct the Stanford Faculty Development Center for Medical Teachers, which prepares several faculty each year to lead a series of seven seminars in clinical teaching.

Kelley Skeff and Georgette Stratos were holding a two-day faculty development seminar at UCLA in September when one of the participants spoke up: "I didn't think this was going to be so fun," she said.

Teaching is embedded in medicine, Skeff said, perhaps more than in any other profession. But medical faculty are often anointed teachers without any real training in the subject, and they may not realize how they can improve. So he tries to tap into their innate desires for analytical challenge and self-improvement.

"We've not consistently capitalized on the idea of helping teachers do something they believe in, which is figuring out how to do things more effectively," said Skeff. "People get fed by the teaching that they do."

Skeff, MD, PhD, a professor of medicine, and Stratos, PhD, a senior research scholar in medicine, co-direct the Stanford Faculty Development Center for Medical Teachers. The center, which marked its 30th anniversary this year, brings a half-dozen medical faculty to Stanford for a month each autumn, preparing them to lead a series of seven seminars in clinical teaching when they return to their home institutions. Skeff and Stratos also host a follow-up course in basic-science teaching, and provide shorter teaching-improvement workshops throughout the world.

"I can say without hyperbole that it changed my life," said Bradley Sharpe, MD, a professor of medicine at UC-San Francisco, who took the clinical-teaching course in 2006. "It revolutionized the way I viewed my clinical teaching and the clinical teaching of others, mainly in having a structured, evidence-based approach to teaching, much as we do for other aspects of clinical medicine."

Skeff was a doctoral student at the Stanford Graduate School of Education in 1979, analyzing videotapes of medical teaching for his dissertation, when a colleague suggested he collaborate with Stratos, who was finishing her PhD in educational psychology at UC-Berkeley. "For me, meeting Georgette was such a gift," Skeff said. "She has brought to the program such a precise and analytical mind."

Keys to effective clinical teaching

After they completed their PhDs, Skeff and Stratos worked together to develop medical education courses and seek funding to support them. Their flagship, the monthlong clinical-teaching course, grew out of Skeff's dissertation. It provides instruction on seven facets of how to impart a good medical education to any trainee: learning climate, control of session, communication of goals, promotion of understanding and retention, evaluation, feedback and promotion of self-directed learning.

"It's amazingly timeless," said Sallie De Golia, MD, a clinical professor of psychiatry and behavioral sciences who teaches faculty development workshops at Stanford and nationally. "They developed it in

See TEACHING, page 6

Compound found to reduce tumor growth in mice

By Yasemin Saplakoglu

A baseball glove is typically made from leather. If a new design made gloves more attractive to baseballs — catching them at higher rates than the typical glove — would it be a game changer?

Researchers at the School of Medicine created such a glove at a microscopic scale. They developed a receptor — with a half-circle shape like that of a baseball glove — that attracted a key cancer-causing molecule called Gas6 and took it out of play, slowing the progression of pancreatic and ovarian cancer in mice.

The study was published online Nov. 28 in *The Journal of Clinical Investigation*.

When used alone or in combination with chemotherapy in mice, their "decoy receptor" showed a higher ability to reduce or stop cancer growth than other treatments did.

They also elucidated a previously unknown mechanism in the body. In mice, when the researchers inhibited Gas6 from binding to its native receptor, Axl, the cancer cells began to release DNA-damaging molecules, causing the cells to die. This suggests a potential method to improve current therapeutic approaches.

Amato Giaccia

"We were even able to get some

See TUMOR, page 6

Roeland Nusse wins $3 million Breakthrough Prize in Life Sciences

By Krista Conger

Roeland Nusse, PhD, the Virginia and Daniel K. Ludwig Professor in Cancer Research and a Howard Hughes Medical Institute investigator, was honored Dec. 4 with a 2017 Breakthrough Prize in Life Sciences.

NORBERT VON DER GROEBEN

Roeland Nusse was awarded the 2017 Breakthrough Prize in Life Sciences for his contributions to the understanding a signaling molecule called Wnt.

Nusse was awarded the $3 million prize for his contributions to the understanding of how a signaling molecule called Wnt affects normal development, cancer and the functions of adult stem cells in many tissues throughout the body.

"This is a complete surprise," said Nusse, who is professor and chair of developmental biology. "My gratitude goes out to many people — my past and present postdoctoral scholars and graduate students and my former mentors have all contributed to the success of my research. The research and collaborative environment at Stanford and the long-term support from the Howard Hughes Medical Institute have also been fantastic. I see this award as a great honor for the entire community."

The Breakthrough Prizes, initiated in 2013, honor paradigm-shifting research and discovery in the fields of life sciences, fundamental physics and mathematics. In total, about $25 million was awarded this year. A black-tie, red-carpet ceremony for the presentation of the prizes was held at the NASA Ames Research Center in Mountain View. The event was hosted by actor Morgan Freeman. The Grammy Award-winning pop star Alicia Keys provided entertainment.

"Roel's pioneering work has provided deep insights into an essential molecular signaling pathway that controls normal embryonic development and adult tissue repair, and that contributes to cancer when it is not properly regulated. His work has served as a model for many others in our field and accelerated further studies of these critical processes," said Stanford President Marc Tessier-Lavigne, PhD."We are grateful that the Breakthrough Prize recognizes the work of scientific leaders who are inspiring others to pursue discovery that is truly transformative, benefiting all of humanity."

Nusse's interest in Wnt began in the 1980s as a postdoctoral scholar in the laboratory of Harold Varmus, MD, who was then on the faculty of UC-San Francisco. In 1982, Nusse discovered the Wnt1 gene, which was abnormally activated in a mouse model of breast cancer. He subsequently discovered that members of the Wnt family of proteins also play critical roles in embryonic development, cell differentiation and tissue regeneration.

"Roel has devoted his career to identifying one of the major signaling molecules in embryonic development, and clarifying its role in cancer development and in tissue regeneration," said

See NUSSE, page 7

Drug interactions may reduce mortality in breast cancer patients

By Jennie Dusheck

Patient health records revealed two drug combinations that may reduce mortality rates in breast cancer patients, according to a study led by researchers at the School of Medicine.

The drugs involved were commonly used noncancer drugs that turned out to be associated with a longer average survival rate in breast cancer patients.

The study was published online Dec. 9 in the *Journal of the American Medical Informatics Association*. The lead author is Stanford postdoctoral scholar Yen Low, PhD. The senior author is Nigam Shah, MBBS, PhD, associate professor of medicine and of biomedical data science.

Nigam Shah

Often, when different drugs are taken together, they can have unexpected side effects. For example, some antibiotics and antifungal drugs can interfere with the effectiveness of birth control pills. It occurred to Shah and his team that the opposite could also be true — that some drug interactions might help patients.

"What if we looked for combinations of drugs that have an accidental beneficial effect?" Shah said.

Combing through records

The researchers decided to comb through a breast cancer database built at Stanford called Oncoshare, which takes de-identified patient information — including tumor and treatment information for each patient — from Stanford Health Care and from the Palo Alto Medical Foundation and links it to patient outcomes in the California Cancer Registry.

The team searched for noncancer drugs that patients just happened to be taking and that were statistically associated with better outcomes. "By integrating different kinds of data, we can ask questions we couldn't ask before. Usually, you don't find both survivorship data and all the different kinds of drugs and other treatments patients get all in the same place," said Allison Kurian, MD, associate professor of medicine and of health research and policy.

"We looked at all the noncancer drugs that breast cancer patients were on," said Shah. "People have other things going on in life. They might have hypertension, they might have high cholesterol or diabetes. They would be taking drugs for those as well. So the question we were asking was, do any of the drugs they are taking associate with better outcomes for breast cancer?"

The team looked at data from nearly 10,000 adult women diagnosed with breast cancer between 2000 and 2013, of whom about 12 percent died within five years of the diagnosis. The team examined 294 drugs in more than 43,000 pairwise combinations. Specifically, they looked for combinations of drugs in which the beneficial effect on survival was greater than the effect of either drug by itself.

"So we ran the analysis, and we found a few drug combinations that seemed to associate with better survival," said Shah.

'How do we know it's true?'

Specifically, there were three pairs of drug types: anti-inflammatory drugs, such as aspirin or naproxen, and blood-lipid modifiers, such as statins; lipid modifiers and drugs such as fluticasone used to treat asthma-like conditions; and anti-inflammatories and hormone antagonists — typically, drugs that suppress the synthesis of estrogen.

"But how do we know it's true, and not just an association?" said Shah.

The researchers needed to look for confirmation in a data set they had not yet examined. To do so, they turned to Shah's former student Andrew Radin, a co-author of the paper and co-founder of a company called twoXAR that searches for drug interactions using gene-expression data. Radin's company looks for common molecular pathways that might account for drug pairs with apparent synergistic effects, searching for drug-protein interactions in the company's database.

Said Shah, "So I asked Andrew, 'If I give you two drugs and a disease, can you tell me if there is any molecular-level evidence that would lead you to believe that, yes, these drugs might have a beneficial effect in treating this disease?'"

Radin's team set to work and independently came up with the same drug pairs. Two of the three pairs showed a likely molecular mechanism that a reasonable person might think had to do with survival in breast cancer, the study said. These were anti-inflammatories and lipid modifiers, and anti-inflammatories and anti-cancer hormone antagonists.

A joint effort

"This study is a nice example of an analysis spanning multiple data modalities. It's the kind of thing that can only happen at Stanford," said Shah, pointing out how his lab worked with Oncoshare, twoXAR, oncologists and statisticians to bring the study off.

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.

"It's a proof of principle that this kind of data mining has strong practical clinical applications," said Kurian. With electronic health records, she said, the challenge has been getting the data organized in a way that allows fruitful explorations like this one.

The key, said Shah, is to ask why these drugs and their protein targets have something to do with breast cancer and to leverage that information for better treatment. "This is a holistic look at the data — EHR, gene expression, protein targets of drugs — all in one analysis," he said.

Other Stanford co-authors are former research assistant William Chen; senior clinical data engineer Tina Seto; Susan Weber, PhD, director of informatics systems and software development for the Stanford Center for Clinical Informatics; former graduate student Michael Lim, PhD; Trevor Hastie, PhD, professor of statistics and of biomedical data science; biostatistician Maya Mathur; Manisha Desai, PhD, associate professor of medicine and of biomedical data science; research scientist Scarlett Gomez, PhD, MPH; and George Sledge, MD, professor of medicine.

Researchers at twoXAR Inc., the Palo Alto Medical Foundation Research Institute and the Cancer Prevention Institute of California were also co-authors of the study.

This research was supported by the National Institutes of Health, the National Science Foundation, the Susan and Richard Levy Give Fund, the Breast Cancer Research Foundation, the Regents of the University of California's Breast Cancer Research Program and the Stanford University Developmental Research Fund.

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

Stem cells police themselves to reduce scarring, researchers find

By Krista Conger

Treating mice with a compound that increases the expression of an inactive protein helped them heal from injury with less scarring, according to a study by researchers at the School of Medicine.

The researchers are hopeful that their findings could one day be used to help keep muscles supple during normal aging and to treat people with diseases like muscular dystrophy.

"Fibrosis occurs in many degenerative diseases and also in normal aging," said Thomas Rando, MD, PhD, a professor of neurology and neurological sciences. "It negatively impacts muscle regeneration by altering the stem cell niche and inhibiting the stem cell function. In addition, as more scarring occurs, muscles become stiff and can't contract and relax smoothly."

Rando, who is the director of Stanford's Glenn Center for the Biology of Aging, is the senior author of the study, which was published online Nov. 28 in *Nature*. Former graduate student Alisa Mueller, MD, PhD, is the lead author.

Self-policing stem cells

The researchers discovered that stem cells embedded in muscle fibers do some fancy gene-expression footwork in order to respond appropriately to injury, disease or aging. In particular, the cells toggle between producing a full-length, active version of a protein that responds to external signals to divide and a shorter, inactive version of the same protein that attenuates the growth signal and prevents an overly enthusiastic response that can lead to scarring or fibrosis.

The researchers studied a protein called platelet-derived growth factor receptor alpha, or PDGFR alpha, that sits on the surface of muscle-embedded stem cells called fibro-adipogenic progenitors, or FAPs. These stem cells are responsible for generating the connective tissue scaffolding necessary to support muscle development and regeneration.

PDGFR alpha straddles the cell membrane. The portion outside the cell serves as a landing pad for external signals that encourage the FAPs to begin dividing, or proliferating. The interior portion of the protein passes the signal along to other proteins inside the cell to get the ball rolling. Although some proliferation is necessary to repair an injury, an overly enthusiastic response can lead to scarring and fibrosis that inhibits its muscle function. So it's imperative the cells strike the right balance in their response.

Thomas Rando

The researchers found that the cells have devised a novel, unexpected way to police themselves. The cells found a way to generate a shortened version of the protein that is missing the interior portion of its structure. This shortened version hangs out on the cells' membranes and sequesters the growth signals away from the active form of PDGFR. Without the interior part of the protein, the message to grow is stopped in its tracks.

"We've found that the cells actively regulate the production of the inhibitory form of the protein, which is very surprising," said Rando. "If they make less, the degree of fibrosis increases; if they make more, it decreases."

The cells produce the shortened form of the protein by recognizing and using a specific series of nucleotides in the messenger RNA that encodes the instructions to make the PDGFR alpha protein. The nucleotide code tells the cell's messenger RNA-processing machinery to create a shorter-than-normal message. As a result, the protein that is made from that messenger RNA is also truncated.

Artificially increasing, decreasing expression

Mueller, Rando and their colleagues used a type of small molecule called a vivo-morpholino that can bind and block access to small sections of messenger RNA to artificially increase or decrease expression of the inhibitory version of the PDGFR alpha protein. They found that increasing the amounts of the inhibitory version allowed both young and old mice to heal from injury with less fibrosis and scarring. Conversely, decreasing the amount increased the severity of fibrosis.

"We'd like to test this approach in a mouse model of muscular dystrophy next," said Rando. "Interestingly, the vivo-morpholino we used is similar to a small oligonucleotide therapy currently being tested in clinical trials to stimulate the production of proteins missing in

See FIBROSIS, page 3

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

Study reveals extent of brain excited by specific dose of electricity

By Bruce Goldman

Researchers at the School of Medicine have determined the amount of human brain tissue that is excited by a given dose of electrical stimulation.

"We have, for the first time in humans, established a dose-response curve that applies to electrical stimulation rather than to drugs," said Josef Parvizi, MD, PhD, associate professor of neurology and neurological sciences.

The findings, described in a study published online Dec. 8 in *Neuron*, may guide the therapeutic application of electrical brain stimulation via surgically implanted, current-emitting devices.

Parvizi is the senior author of the study. The lead author is former Stanford postdoctoral scholar Jonathan Winawer, PhD, now an assistant professor of psychology at New York University.

Devices delivering defined therapeutic doses of electricity to structures within the brain are now in widespread commercial use for countering the tremors of Parkinson's disease and controlling seizures in epilepsy patients, and are approved for some patients with obsessive-compulsive disorder. Similar devices are undergoing clinical testing for other conditions, including depression and Tourette's syndrome.

"We often try to correct a problem occurring in some tiny part of the brain's complicated circuitry by administering a drug," said Parvizi. "However, instead of reaching the cells you want to target, much or most of the drug may wind up in the skin, bone, muscle, liver and elsewhere, not to mention brain cells you don't want to target." That can cause all kinds of side effects.

'Immense potential'

"Electrical brain stimulation, targeting only a specific malfunctioning brain circuit, has immense potential to change medical practice," Parvizi said. "But figuring out just how much current will be effective without recruiting unwanted brain circuitry and inducing side effects has been largely guesswork."

To get a more accurate picture, the new study focused on part of the brain's surface called the primary visual cortex, one of the most well-studied regions of the human brain. Located in the back of the brain on the facing inner surfaces of that organ's two hemispheres, the primary visual cortex is the first docking station for visual information from the retina.

Each nerve cell in the primary visual cortex receives its information from a fixed location in the retina and responds to an object observed at a given position in a person's visual field. The precision with which this correspondence has already been mapped out makes the primary visual cortex an ideal place to examine just how far the effects of a given electrical input propagate along the brain's surface.

Josef Parvizi

Jonathan Winawer

Parvizi, who directs Stanford's Human Intracranial Cognitive Electrophysiology Program, was taking care of four adult patients under his evaluation at Stanford Health Care to determine the point of origin of their recurring, drug-refractory epileptic seizures. In this procedure, a portion of the skull is temporarily removed and a grid of electrodes is placed on the brain's surface in order to record seizure activity and pinpoint the spot in the brain where it begins.

Each of these four patients' primary visual cortex, while perfectly healthy, was partially covered by the electrode grids.

Mapping phosphenes

Investigators showed them geometric forms moving across a computer screen while they stared at the center of the screen. Using brain-imaging techniques, the researchers mapped which areas of the participants' primary visual cortex these displays activated.

Once electrode grids were in place, the team used them to stimulate and to record activity in the participants' primary visual cortex. After each stimulation, they asked the participants to chart the location and size of the hallucinatory phenomena, or phosphenes, they experienced in their visual field in response to electrical stimulation.

A phosphene is a visual sensation in the absence of light. Some phosphenes look like a flickering, fractured formation composed of small zigzagging lines of color dancing at a specific location in the field of vision. (For people prone to migraines, such apparitions often herald the onset of a painful headache.) Others may just be a burst of light or color. (People often "see" phosphenes when they rub their closed eyes.) It's long been known that activating the primary visual cortex by direct electrical stimulation can produce phosphenes, which persist for the duration of the stimulation and then vanish.

The investigators, always taking care to adhere to strict safety limits, pulsed electrical current from one or another electrode at varying frequencies, pulse widths, amplitudes and durations while the participants stared at the center of the computer screen. After each instance of stimulation, they were asked to draw on the computer screen, using its trackpad, the outline of the phosphene they saw in its perceived location. Then, using the imaging-derived maps of the individuals' primary visual cortexes they'd constructed earlier, the researchers were able to connect points on the observed phosphenes to corresponding points on participants' primary visual cortex, and to infer from phosphenes' sizes and locations just how much brain-surface area in that brain region had been excited by each electrode-delivered stimulation.

"The resulting dose-response relationship can be used now in clinical trials of electrical brain stimulation," Parvizi said.

Scientists have tried to establish this relationship in rodents, said Winawer. "But you can't easily extrapolate from rodent studies, both because our brains are quite different from theirs and because the recording and stimulating instruments used in rodent experiments are 1,000-fold different from those used in humans."

Nor have connections between the physiologically measureable outcome and perceptual outcome been previously mapped to any extent. (Animals can't report what they see.)

"Notably, we observed a clear correspondence between the amount of electricity applied and the size and intensity of the ensuing visual phenomena subjects reported experiencing," said Parvizi, who has long been fascinated by the question of how manipulating the brain's strictly material components alters subjective consciousness.

How well the dose-response relationship as measured at the cortical surface holds up in deep-brain structures remains to be further tested, he added.

The study was funded by grants from the National Eye Institute, National Institute of Neurological Disorders and Stroke, the National Institute of Mental Health and the National Science Foundation.

Stanford's Department of Neurology and Neurological Sciences also supported the work. ISM

Fibrosis

continued from page 2

patients with Duchenne muscular dystrophy. Perhaps we could also use this approach to reduce fibrosis in this disease."

Other Stanford co-authors of the study are postdoctoral scholar Cindy van Velthoven, PhD; former undergraduate student Kathryn Fukumoto; and former postdoctoral scholar Tom Cheung, PhD.

The research was supported by the Glenn Foundation for Medical Research, the National Institutes of Health, the California Institute for Regenerative Medicine and the Department of Veterans Affairs.

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

Remembering Norbert von der Groeben

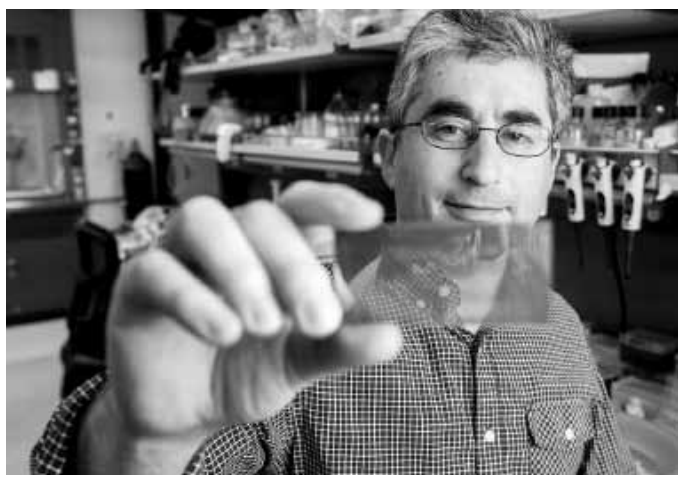
At 6 feet 4 inches tall, and with a camera slung around his neck, Norbert von der Groeben was hard to miss. And yet somehow when he was taking photos, he managed to become part of the background.

For nearly 10 years, von der Groeben was a regular presence on the Stanford Medicine campus, taking shots of faculty members, staff, students and patients. The freelance photographer was deeply familiar with the campus' buildings and grounds, and could find just the right spot to capture an image. His laidback demeanor and quick laugh instantly put people at ease, allowing him to produce portraits that captured their personalities.

Norbert von der Groeben

On Dec. 4, von der Groeben died at his Palo Alto home of an apparent heart attack.

As we look back on the hundreds of images he produced for the School of Medicine, Stanford Health Care and Lucile Packard Children's Hospital, we wanted to share a few of our favorites. ISM



(Top left) In 2014, von der Groeben took this photo of Brian Feldman, one of the inventors of a microchip-based test for diagnosing Type 1 diabetes. (Top right) In 2015, von der Groeben was photographing the start of the school year for new medical students. In this photo, Xylen Washington, 5, tries out the stethoscope belonging to his father, Gabriel Washington. (Right) In 2013, von der Groeben shot this portrait of Gwen McCane, who was initially told the cancer that reached her liver was incurable. But a Stanford doctor provided a solution: using microwave ablation to heat and destroy the tumors.

Stanford patient was first to receive lifesaving drug as an infant

By Erin Digitale

In 2013, Zoe Harting became the first baby in the world to receive an experimental drug that her doctors hoped would save the lives of thousands of infants like her.

Zoe has spinal muscular atrophy type 1, a degenerative neuromuscular disease that kills most patients by their second birthday.

Before she began receiving the drug, 7-month-old Zoe was quite weak. She couldn't sit up or roll over. She couldn't move her legs at all, or lift her arms when she was lying down. She struggled to swallow. Her parents, John and Eliza Harting, knew that without an effective treatment, she would soon struggle to breathe. But no treatment had ever succeeded against SMA-1. So when the Hartings got a call from Stanford pediatric neurologist John Day, MD, PhD, asking if they would consider enrolling Zoe in a phase-2 clinical trial of an experimental drug called nusinersen, they agreed.

"I've seen so many kids die with this disease," said Day, who directs the Neuromuscular Disorders Clinic at Lucile Packard Children's Hospital Stanford and is a professor of neurology and of pediatrics at the Stanford University School of Medicine.

SMA-1 is the most common genetic cause of death in infants. It's triggered by a gene mutation that is carried by 1 in 40 people. The disease, which occurs when a child inherits the mutated gene from both parents, is diagnosed in about 250 babies per year nationwide. In the past, pediatric neurologists could help make patients comfortable as their health declined, but that was all. "We would have to tell the parents, 'I'm sorry, we don't have anything that will stop the progression of the disease,'" Day said.

COURTESY OF THE HARTING FAMILY

Zoe, now 4, was the first in the world to receive the drug nusinersen as a baby.

The drug nusinersen is changing that.

Improvement in meeting motor milestones

On Dec. 6, the results of the phase-2 trial that Zoe Harting helped to launch were published in *The Lancet*. Day is a co-author of the study, which was led by pediatric neurologist Richard Finkel, MD, of Nemours Children's Hospital in Orlando, Florida. Nusinersen is safe and well-tolerated, the study reports. Although the multisite trial included only 20 children and was intended primarily as a safety test, the investigators report significant improvements in patients' ability to achieve motor milestones, as well as better motor function and increased function of nerves that are attacked by the disease.

"She continues to slowly gain motor skills; it's quite unexpected and rewarding."

The drug is quickly progressing through the regulatory approval process. In addition to the phase-2 trial in which Zoe participated, nusinersen has been evaluated in a phase-3 trial of SMA-1 patients, which was stopped early in August because it was obvious that infants receiving the drug were achieving significantly more motor milestones than those in the control group. The phase-3 trial is now an open-label study, meaning that all participants can receive nusinersen.

The drug is expected to receive approval from the FDA within the next two months, and in the interim is available under an expanded access program at a few sites around the country, including Lucile Packard Children's Hospital Stanford.

"This drug completely turns things around for SMA," Day said. "It's a definite game-changer." An even larger discovery is that drugs with the same mechanism of action may help treat other genetic diseases, he added. Nusinersen is an antisense oligonucleotide, which works by sticking to a specific piece of genetic material. Trials of antisense oligonucleotide drugs are now underway for other neurological diseases, including myotonic dystrophy, Huntington's disease and amyotrophic lateral sclerosis.

A painful diagnosis

When Zoe was born, in October 2012, the El Granada, California, infant seemed healthy. But after several weeks, John and Eliza suspected she might be weakening, and a Christmas visit with Eliza's extended family solidified their worries. Zoe was moving much less than her baby cousin, who was a week younger.

"It was really noticeable that they were very different," John Harting said. "Her cousin was rolling over and Zoe was almost immobile."

Their pediatrician referred Zoe to a neurologist, who diagnosed SMA-1.

"It was really, really hard," John said. "That neurologist basically told us she would not live past 2, and that we could only hold her, love her and let her die."

The Hartings are both involved in scientific research: John is a bioinformatician, and Eliza a statistician. They began searching for clinical trials Zoe could join, and found a new pediatrician who connected them to Day. Though the nusinersen trial had not yet enrolled any patients, doctors at four sites in the United States and Canada were looking for infants with recently diagnosed SMA-1 who might be good candidates. The drug had already been given to older children with a milder form of spinal muscular atrophy to test its safety, but physicians needed to try it in babies with SMA-1 to discern if it caused a measurable improvement in symptoms. Day asked the Hartings to let Zoe be the first.

John Harting read some of the scientific papers explaining how nusinersen was expected to function. "What I read suggested it was a good bet, and the only one available at the time," he said. "We decided we had to take this chance."

What goes wrong in SMA-1

SMA-1 develops in babies who inherit two faulty copies of the SMN1 gene, which encodes a protein called survival motor neuron. The protein maintains nerves that carry signals from the spinal cord to muscles; without it, these nerves degenerate. Muscles atrophy to the point that, eventually, the patients can't move, swallow or breathe.

However, most people have a second gene called SMN2, which is 99 percent identical to the SMN1 gene but makes very little functional protein.

"SMN2 doesn't work well," Day said. "It's like you've got a spare tire, but it's flat."

Nusinersen can, in effect, inflate the spare tire. Compared to SMN1, there is a difference of just one base pair in the genetic code of SMN2 that greatly reduces its production of full-length messenger RNA, the molecule needed to carry genetic information from DNA to the cells' protein-making machinery. Nusinersen binds to the faulty RNA, allowing it to be constructed correctly and increasing the production of functional SMN protein.

Day and his colleagues hoped nusinersen would provide SMA-1 patients with enough survival motor neuron protein to reduce the impact of the disease.

"It was anxiety-producing for all of us at the outset," Day said. "What kept me awake at night was that I wondered if we were going to create this bad situation where we might keep Zoe's diaphragm working but she would otherwise be devastated." Day told the Hartings that he couldn't be sure about the results, and he worried Zoe might improve just enough to stay alive, but that her quality of life would be poor. "We talked about it, and they were willing to give it a try and see what happened," he said.

Gaining strength

In June 2013, Zoe began receiving doses of nusinersen. To reach the nerves where it is needed, the drug is injected into the spinal fluid once every few months.

The next year was difficult. Because SMA-1 had hurt Zoe's nerves so much before the drug trial began, her breathing and coughing were weak. Several colds landed her in the intensive care unit with pneumonia, and whenever she seemed to grow stronger, another bout of illness weakened her again.

Finally, near Zoe's second birthday, everyone was convinced that she was gaining strength. Remarkably for a toddler with SMA-1, she could lie on her back, lift her legs and play with her toes.

COURTESY OF THE HARTING FAMILY

Zoe Harting was born with spinal muscular atrophy type 1, a deadly neuromuscular disease. Her condition has improved since she began receiving an experimental drug at Lucile Packard Children's Hospital Stanford.

"She started picking up milestones and doing things that were totally unexpected," Day said. "It was incredible."

Soon afterward, Zoe started speaking. Her ability to cough improved, helping her fight off respiratory germs. She gained control over her head, then got strong enough to sit if someone helped her up into a seated position.

Today, 4-year-old Zoe is still making gradual improvements. She can eat, talk, yell and tussle with her little sister. She has learned to scoot around in a motorized wheelchair. She goes to preschool. She likes to play catch with her dad. Her parents recently bought her a recumbent bicycle, which they hope will help strengthen her legs, a step that once seemed far too much to hope for.

"She continues to slowly gain motor skills; it's quite unexpected and rewarding," said Day.

"It's a world of difference," added John Harting.

The outlook for SMA-1 patients who receive nusinersen soon after their diagnosis is even better than for patients like Zoe, who was already weak when she began getting the drug, Day said.

"If we identify children early on, before they become symptomatic, we can be optimistic that it will effectively cure them," he said. But he still sees families who lose valuable time because the doctor who diagnoses their baby is not aware that a treatment can help the disease. "Our goal is to get the word out so that no patient experiences that delay," Day added. "It's critical."

Children with SMA-1 who receive nusinersen also continue to need neurological and pulmonary care, as well as extensive support — such as physical, occupational, speech and swallowing therapies — to ensure they continue to develop normally, he said.

The phase-2 trial of nusinersen was funded by Ionis Pharmaceuticals Inc. and Biogen, and the SMA program at Stanford is supported by the SMA Foundation, the Muscular Dystrophy Association and the Pierce Marshall Heritage Foundation. Day serves as a consultant for Biogen and received grants from Biogen and Ionis Pharmaceuticals during the conduct of the study. He serves as a consultant to AveXis, Cytokinetics and Ionis Pharmaceuticals, and serves on advisory boards for the Muscular Dystrophy Association and the SMA Foundation.

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

Conjoined twins successfully separated at Packard Children's

By Erin Digitale

Conjoined twins Erika and Eva Sandoval were successfully separated at Lucile Packard Children's Hospital Stanford in a 17-hour surgery that began Dec. 6 and stretched into the early morning hours of Dec. 7. Prior to separation, the two-year-old twins of Antelope, California, shared much of their lower body.

"They did very well," said lead surgeon Gary Hartman, MD, a clinical professor of surgery at the School of Medicine. "I'm very pleased with the outcome."

The Sandoval girls are the seventh pair of conjoined twins Hartman has separated and the fifth separation surgery he has done at Stanford. The last separation at Packard Children's was performed in 2011.

"It's amazing how strong these girls are, and it's amazing what their team performed," said Aida Sandoval, the twins' mother.

Erika and Eva are now in stable condition in the pediatric intensive care unit, where they are expected to recover for about two weeks. Their physicians anticipate that they will spend an additional two weeks in the hospital before they go home. They are sharing a hospital room but are in separate beds.

Prior to separation, Erika and Eva were thoraco-omphalo-ischiopagus twins, positioned facing each other and joined from the lower chest and upper-abdomen level down. They had separate hearts and lungs but shared their diaphragm muscle and some anatomical structures below the diaphragm. They had one liver, one bladder, two kidneys and three legs. They each had a stomach.

"Before separation, you could think of their anatomy as two people above the rib cage, merging almost into one below the bellybutton," said plastic and reconstructive surgeon Peter Lorenz, MD, professor of surgery at the School of Medicine, who led the reconstructive phase of the twins' separation.

The separation team included about 50 people. By the time the twins go home, more than 100 hospital caregivers will have helped with their case, including many physicians and nurses who took care of Aida during her high-risk pregnancy and who cared for the twins as newborns.

"The results are as good as we could have asked for."

Separation day

The girls were wheeled into the operating room shortly after 7 a.m. Dec. 6, where they were carefully anesthetized by a team of six anesthesiologists, three per twin, led by Gail Boltz, MD, clinical professor of anesthesiology, perioperative and pain medicine at the School of Medicine. Once the twins were anesthetized, the team placed central and arterial lines to enable blood transfusions and deflated the three saline-filled tissue expanders that had been used to generate new skin to help cover their separation site. The first incision was made at 11 a.m.

Erika and Eva had received comprehensive CT and MRI scans as part of the preparation for surgery, and these were used to print 3-D models of their pelvic bones and blood vessels to help plan the division. But there were still questions about details of the girls' shared anatomy, which the team spent about an hour resolving at the beginning of the surgery.

"We had amazing information from our radiology colleagues, but even with that there were some surprises," Hartman said. "There was only one large intestine. It appeared that it all belonged to Eva but had some blood supply from Erika, so we had to do some testing in the operating room to clarify that." During surgery, the team also found that the girls shared a single pericardial sac around their separate hearts, and that each child had her own gallbladder.

Once the exploratory phase was complete, the team divided the twins' liver and split their gastrointestinal and urinary tracts. The girls' single bladder was divided and made into two bladders, and each child received a colostomy. The pelvic bones were then divided.

The biggest risk that the surgical team had anticipated prior to separation was excessive bleeding from small, diffuse blood vessels and from the pelvic bones, but fortunately the twins did not experience excess blood loss. The final incision that officially separated Eva and Erika was made by James Gamble, MD, professor of orthopedic surgery, and Matias Bruzoni, MD, assistant professor of pediatric surgery, at 4:34 p.m. Dec. 6.

For the first time, separate rooms

After the girls were separated, Eva was wheeled to an operating room across the hall, marking the first time in their lives the twins were in separate rooms. Lorenz led the team that performed Eva's reconstructive surgery, which took until 12:30 a.m. Dec. 7. Erika's reconstructive surgery, led by pediatric plastic and reconstructive surgeon Rohit Khosla, MD, assistant professor of surgery at the School of Medicine, was completed an hour later. Eva had enough skin from the tissue expanders to completely close her surgical site. To help complete Erika's reconstruction, the bones from the girls' third leg were removed, and skin and muscle from the leg were used to close Erika's abdominal wall. The surgeons had considered keeping the leg with Erika if it was not needed for reconstruction, but it would likely not have been useful for walking because of its abnormal anatomy.

Throughout the surgery, the team used a 3-D, virtual-reality imaging system that was recently introduced at Packard Children's. The imaging system allows the surgeons to put on 3-D glasses and view an image that can be rotated and manipulated to better see the anatomy detected in prior radiology scans. Pediatric radiologist Frandics Chan, MD, associate professor of radiology at the School of Medicine, assisted the surgeons with the new technology.

"When it became clear that we needed to use the third leg for reconstruction, Dr. Chan came in to the operating room and showed the team exactly where the blood vessels supplying the leg were located so that they could plan how to protect the blood supply to the leg," Hartman said.

Now that Eva and Erika are separated, each child has one kidney and one leg. As the children heal and grow, the team will assess whether any further reconstructive surgeries would be helpful for either child. "We set them up so that if everything heals well, they may not need any further surgery," Hartman said.

The expertise of many Stanford pediatric specialists contributed to the separation's successful outcome, with surgeons specializing in gastrointestinal, orthopedic, urologic and plastic and reconstructive surgery all contributing. "We have both the subspecialist surgeons we needed and the appropriate anesthesia and nursing expertise to take care of Eva and Erika during and after their separation," Lorenz said. "We do high-risk surgical cases often, and our experience counts a great deal for a case like this."

"The results are as good as we could have asked for," Hartman concluded. ISM

PHOTOS BY DAVID HODGES

Two-year-old twin sisters Erika and Eva Sandoval were thoraco-omphalo-ischiopagus twins, positioned facing each other and joined from the lower chest and upper-abdomen level down.

Surgeons operate on the twins Dec. 6 at Lucile Packard Children's Hospital Stanford to separate them.

Case history: Monitoring twins in utero, preparing for their birth

Conjoined twins are rare. They occur in 1 in 30,000 to 1 in 200,000 births. When Aida Sandoval was referred to Packard Children's midway through her 2014 pregnancy with Erika and Eva, the hospital's Fetal and Pregnancy Health Program immediately brought together physicians from high-risk obstetrics, neonatology, radiology, surgery, pediatric urology, and other specialties to form an expert group that could care for Aida and both babies. Aida had high blood pressure, which further complicated an already difficult pregnancy.

"In addition to our multidisciplinary team's very close monitoring of Aida and our vigilant evaluation of fetal health, we had to create a detailed delivery plan that included simulation of potential delivery scenarios," said Susan Hintz, MD, professor of neonatal and developmental medicine and medical director of the Fetal and Pregnancy Health Program. After performing fetal MRI scans to investigate the babies' anatomy, the team brought in Louis Halamek, MD, professor of neonatal and developmental medicine and director of the Center for Advanced Pediatric and Perinatal Education at Packard Children's, who made a specialized conjoined mannequin that resembled the twins as closely as possible to facilitate realistic simulations.

"Because the girls were situated facing each other, we knew that if they were delivered prematurely and had respiratory issues, the physical constraints of how they were connected could pose challenges to successful resuscitation, including intubation," said Hintz, who is also the Robert L. Hess Family Professor. The team practiced potential delivery scenarios with the mannequin, including intubating, or inserting breathing tubes. Fortunately, when the girls were delivered by cesarean seven weeks early on Aug, 10, 2014, they were able to breathe without intubation, instead requiring positive pressure and oxygen via face masks. Nevertheless, Eva and Erika were fragile. They were hospitalized at Packard Children's for their first 6 months of life, and then followed by several physicians as they grew big enough to be separated. ISM

Teaching

continued from page 1

the mid-'80s, and it's so relevant today."

Medical teachers who have taken the course say it endures because it equips participants with widely applicable behavioral techniques, rather than a bag of content-specific teaching tricks. "It isn't prescriptive," said Dana Dunne, MD, associate professor of medicine at Yale. "You get more buy-in from participants when they realize it's not about wrong or right ways to teach; it's more about introducing a variety of teaching behaviors to increase their versatility," so they can more effectively teach different types of learners in varying situations.

"There's something really special about the relationship between a teacher and a student," said Skeff, the George DeForest Barnett Professor in Medicine. "There have been a tremendous number of changes in medical education, and yet the potential power of the relationship between a teacher and a student never changes."

"At the heart of the Stanford program is essentially a learner-centered approach," said Louis Pangaro, MD, professor and chair of medicine at the Uniformed Services University of Health Sciences, the federal health-professions academy. "A learner-centered approach means not only that the teacher feels good about knowing their material, mastering knowledge of cardiology or whatever it is, but that their purpose is to help someone else become independent. It depends on the teacher — the person of presumed superior authority and power — orienting their work toward the learner. I'm not sure we do this as well as we should, but I think the Stanford program is a milestone in doing this."

Participants are grateful that Skeff and Stratos provide methods of giving feedback that their students won't dread. "I have been groomed to be kind, caring and compassionate to patients," said Debra Litzelman, MD, professor of medicine at Indiana University. "But Kelley and Georgette absolutely reinforced in me the need to be kind, caring and compassionate to our learners. You can't go into a room and be kind, caring and compassionate to your patient and then come out and yell at your medical students. And I still see that happening. I still see people who finish up a two-week rotation with a student and don't know their name."

Always learning

Course participants are taught that one key to successfully implementing clinical-teaching techniques is to cultivate the attitude that everyone is there to learn and improve — faculty included. "One of my favorite things about the Stanford course is the acknowledgment that effective teachers admit the limits of what they know and of what the science is, and that engenders a sense of curiosity in other people," said Michael Barnes, MD, associate professor of medicine at the Oakland University William Beaumont School of Medicine. In that kind of environment, he said, learners may be more motivated to admit their own limitations.

> "I can say without hyperbole that it changed my life."

"A lot of clinical teaching is questioning," said Lisa Coplit, MD, the associate dean for faculty development at Quinnipiac University's Frank H. Netter MD School of Medicine. Until she took the course in 2003, however, "I never had any insight into the types of questions I was asking and why," she said. "Now I look at questions as an unbelievably valuable tool. Being deliberate about the questions I ask, I can really zero in on one piece of a learner's performance. So if I think this person is struggling with differential diagnoses, I need to ask them analysis/synthesis-type questions. It's also such a great way to model for learners the types of questions they should be asking themselves. If all we're asking are recall questions, we're teaching them that that's what's important. More important is, how do you think? How do you inquire? How do you self-assess? Those are the really big questions in medicine."

The dissemination model

Behind course participants' dedication to improving their teaching is, ultimately, their devotion to patient care. "There is often somebody at the end of the line for whom the stakes of this type of teaching are extraordinarily important, and everyone knows that," Stratos said.

Pangaro said, "If you believe that our role as physicians is to serve patients, then anything that enhances the humanity, the other-centeredness of a physician, is good."

By design, course participants pass along what they have learned to other medical educators, who do the same in turn. Pangaro, for example, has trained almost 1,000 physicians in clinical-teaching techniques.

More than 200 faculty members, hailing from more than half of U.S. medical schools and several international institutions, have completed the Faculty Development Center's clinical-teaching course. Stratos estimates the curriculum has been taught to 10,000-15,000 medical educators, and Skeff quickly revises that estimate upward to 25,000. Both of them know they're underestimating.

In addition to disseminating their educational precepts worldwide, each year Skeff and Stratos instruct 200 Stanford School of Medicine teaching assistants, postdoctoral scholars, fellows, residents and faculty, often in collaboration with colleagues who have taken the clinical-teaching course. "It makes our faculty better teachers so we can provide better medical education to our learners," said associate professor of medicine Lars Osterberg, MD, who directs Educators-4-CARE, a mentoring program designed to foster the development of Stanford medical students as skilled and compassionate physicians. "Kelley and Georgette's thinking about an organized way of teaching has helped our faculty provide peer feedback."

In class, Skeff and Stratos deliberately model the methods they teach, as do their students when teaching others. "If you're pursuing an approach to education and modeling it, the hope is that that also educates the future physician in modeling to the next generation," said De Golia. "If we become humanistic, respectful teachers, hopefully the next generation will too."

Skeff and Stratos "have 'kids' all around the world, who look to them as mentors for the rest of their life," said Barnes. Several have made careers out of faculty development. "Everyone talks about medical students having that aha moment," said Coplit. "I do get great joy from that, but I also have great joy when I get to witness a colleague have an aha moment about their teaching."

"I'm never going to publish an article in a peer-reviewed journal that revolutionizes and changes patient care," said Sharpe. "But clinical teaching is a way you can have the same exponential impact. If I work with 20 interns, and in each encounter with a patient there's a way they say a word or a way they examine the heart, I've now touched as many as 100,000 patients in my teaching. If five of them teach their interns the same thing, then there are 500,000 I've touched in some small way."

"I talk about this as the merging of two noble professions," said Skeff. "The noble profession of medicine and the noble profession of education become synergistic in their societal impacts. The synergy then has an impact on every physician whom that teacher touches, and then every patient whom that physician touches. It's an exponential impact. That's why medical teachers teach." ISM

Tumor

continued from page 1

animals cured, even those that started out with widespread and aggressive metastatic disease," said Amato Giaccia, PhD, professor of radiation oncology and lead author of the study.

The problem with current treatment

The researchers wanted to test their molecule in animal models of ovarian and pancreatic cancer, which are hard to detect in early stages. Current treatment options for ovarian and pancreatic cancer patients are limited and usually require a combination of surgery, radiation and chemotherapy. The therapies can have toxic side effects and rarely lead to a complete cure. So researchers have been increasingly turning to other medications, such as antibiotics or small compounds called tyrosine kinase inhibitors, to use with them. But those medications also have drawbacks: They're toxic, so they can't be delivered in large quantities, and they are unable to beat the strong attraction between Gas6 and Axl. Although they can sometimes stop tumor growth, they rarely result in complete eradication of cancer.

"A lot of treatments out there are very toxic because they are not specifically targeting the cancer cells, and they have a huge burden on the liver and kidney," said Rebecca Miao, PhD, a Stanford research associate who shares lead authorship of the study. "Our decoy receptor seems in mice to not only to be very efficacious but also safe."

Giaccia said, "We basically came up with a better glove, with a much stronger ability to catch the baseball — in this case, Gas6."

Axl a key player in different forms of cancer

Gas6 is a molecule that binds and activates Axl, the surface receptor that plays a key role in cell survival, growth and migration. In many forms of cancer, Axl is over-expressed and binds Gas6 very strongly, which makes it difficult for the development of therapeutics to target this complex.

However, Giaccia and his team developed a decoy receptor that binds to Gas6 around 350 times better than Axl does. When given to mice, the decoy took out the Gas6 molecules from the system and blocked them from activating Axl, suppressing cell growth and migration and stopping cancer growth.

"Our molecule has a higher affinity for Gas6, so it is more effective in taking it out," said Giaccia.

To create the decoy receptor, called MYD1-72, they used yeast as a vessel to express different mutations of the Axl protein. They then labeled Gas6 with a fluorescent molecule so that they could detect which mutated Axl protein it best bound with.

Once they found the most effective mutation, they tested it against other promising therapies that target the Axl pathway and that are currently in clinical trials: BGB324 and foretinib. MYD1-72 and foretinib were both able to reduce tumor size and metastasis, but foretinib showed toxicity in the mice. BGB324 showed little in the way of harmful effects on the mice, but did not reduce tumor burden.

The researchers further tested their new decoy receptor on pancreatic and ovarian cancer in mice.

In ovarian cancer models, they tested the efficacy of MYD1-72 both alone and in conjunction with a DNA-damaging agent called doxorubicin that is commonly used for treatment. They found that alone, MYD1-72 reduced tumor burden by 95 percent. In combination with doxorubicin, most mice ended up with almost complete tumor reduction. In mice with more aggressive forms of ovarian cancer, MYD1-72 alone decreased tumor weight by 51 percent, whereas doxorubicin decreased tumor weight by 91 percent. When used together, the researchers measured a 99 percent reduction of tumor weight.

In pancreatic cancer, they also found that MYD1-72 in combination with a DNA-damaging agent called gemcitabine showed greater tumor reduction. Alone, MYD1-72 did not make any impact on the mice's tumor burden. Mice treated with MYD1-72 and gemcitabine together had a three times higher survival rate than mice not on any treatment.

These results suggested that a combination therapy of their decoy receptor and DNA-damaging agents could result in significantly lower levels of tumor burden.

Hoping to bring therapy to clinic

"We are actively working to push this into clinical trials," said Miao. "But we are also interested in looking at how our molecule affects other types of cancers." They hope to continue studies on how this decoy receptor could enhance treatments for other types of cancer, such as leukemia.

"These pre-clinical models in mice are pretty robust as we've shown in a number of different tumor settings and now in ovarian cancer and pancreatic cancer," said Giaccia. "But we need to ultimately test this in human cancers."

The paper's other lead author is Mihalis Kariolis, PhD, a former postdoctoral scholar at Stanford who is now a staff scientist at Denali Therapeutics.

Other Stanford co-authors are postdoctoral scholars Monica Olcina, PhD, and Shiven Kapur, PhD; graduate student Anh Diep; Douglas Jones II, PhD, a former PhD student now at Torque Therapeutics; Shannon Nash, a former summer research fellow; Dadi Jiang, PhD, instructor in radiation oncology; Irimpan Mathews, staff scientist at SLAC; Albert Koong, MD, PhD, professor of radiation oncology; Erinn Rankin, PhD, assistant professor of radiation oncology; and Jennifer Cochran, PhD, associate professor of bioengineering.

Stanford University holds a patent for the decoy receptor. Giaccia and Koong formed a company, Aravive Biologics, that has licensed the patent.

This research was supported by the Wallace H. Coulter Translational Research Grant Program, Stanford ChEMH, Stanford Bio-X, the ARCS Foundation, the National Cancer Institute, the National Institutes of Health, a Siebel Graduate Fellowship, the Cancer Research Institute, the Silicon Valley Foundation, the Kimmelman Fund and the Skippy Frank Foundation.

Stanford's Department of Radiation Oncology also supported the work. ISM

Jon Mulholland is honored with 2016 Marsh O'Neill Award

By Kathleen J. Sullivan

Over the last 15 years, Jon Mulholland has transformed the Cell Sciences Imaging Facility into a world-class center by working tirelessly to keep Stanford at the leading edge of the revolution in technological advances in light and electron microscopy.

That was one of many accolades bestowed by faculty members on Mulholland, winner of the 2016 Marsh O'Neill Award for Exceptional and Enduring Support of Stanford University's Research Enterprise.

The award was established in honor of Marshall D. O'Neill, who worked at Stanford from 1952 to 1990, when he retired as associate director of the W.W. Hansen Laboratories. He was the first recipient of the award.

When Mulholland became director of the imaging facility in 2001, it had two confocal microscopes and an annual budget of less than $165,000. Today, its technologies include advanced light microscopy, electron microscopy and scanning microscopy, and its budget exceeds $1 million.

Lucy Shapiro, PhD, professor of developmental biology and director of the Beckman Center for Molecular and Genetic Medicine, described Mullholland's decision to take the helm of the imaging center in 2001 as "a turning point" that has benefited the entire Stanford community.

"Jon's professional, collaborative and innovative approach to working with faculty, staff and trainees has benefited the entire research community, brought in numerous federal shared-equipment grants, and enabled the expansion of the facility beyond the Beckman Center into additional dedicated space in the School of Engineering," Shapiro said.

She said Mulholland also dedicated "an extraordinary amount of time and resources" to training faculty, postdoctoral scholars, technicians, and graduate and undergraduate students in advanced microscopy techniques in courses, guest lectures and hands-on demos.

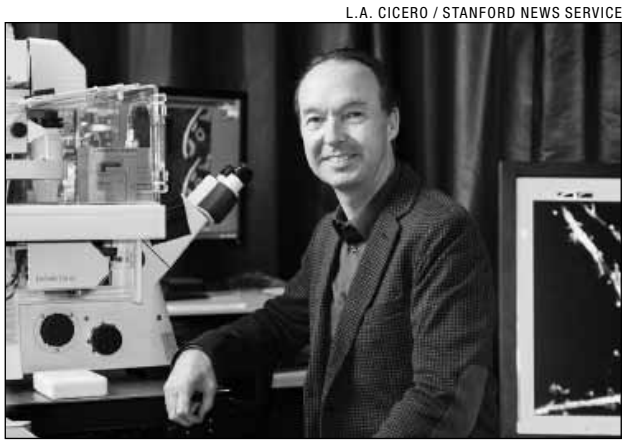
The facility has two sites — one at the Beckman Center and another in the Shriram Center at the School of Engineering — and an expert staff of five people: two electron microscopy specialists, a light microscopy specialist, an array tomography specialist, and an imaging specialist who also manages the facility's satellite site in the School of Engineering.

Trained as a molecular biologist

The facility serves 400 researchers working in 30 departments in the schools of Medicine, of Engineering and of Humanities and Sciences. Its team conducts more than 150 training sessions a year for faculty, postdoctoral scholars and graduate students. Since taking the helm, Mulholland has brought $7.4 million in grant funding to the facility.

Mulholland, who grew up in Lunenburg, Massachusetts, earned a bachelor's degree in biology and philosophy at Clark University in Worcester, Massachusetts. After graduating, he joined the lab of David Botstein, PhD, a pioneer of modern human genetics at the Massachusetts Institute of Technology, where he gained experience in molecular biology and genetics, as well as in light and electron microscopy. For Mulholland, the job was meant to be a means to an end — a stepping stone to becoming a pharmaceutical sales representative. But working alongside Botstein and other scientists doing groundbreaking research set him on a new career path.

L.A. CICERO / STANFORD NEWS SERVICE



Jon Mulholland, director of the Cell Sciences Imaging Facility, is this year's winner of the Marsh O'Neill Award.

One day, Botstein asked him if he was having fun.

"It really took me aback," Mulholland said, recalling a seminal conversation that took place 30 years ago. "Having fun? I mean, this is work. Then I realized — yeah, I really am having fun."

Later, when Botstein was considering moving across the country to California to become vice president of science at Genentech, he asked Mulholland if he wanted to join him.

"Absolutely," Mulholland replied.

At Genentech, Mulholland set up Botstein's lab and helped establish the company's new electron microscopy facility. Later, he moved with Botstein to Stanford's Genetics Department and continued doing research there, using yeast genetics and electron and fluorescence microscopy. While working for Botstein, Mulholland went back to school, earning a master's degree in molecular cellular biology at San Francisco State University.

"The research component for my thesis was what I was already working on at Stanford, so it was a joint master's program," he said. "It really worked out well."

When Botstein became director of a genomic institute at Princeton University, Mulholland decided to remain at Stanford. When the position at the Cell Sciences Imaging Facility opened up, faculty members at the Beckman Center encouraged him to apply.

"It was a huge step for me," Mulholland said. "At that time I was working at the bench, doing research and writing papers. I took care of David's lab in terms of keeping things up and running, but I wasn't in charge of everything."

As director of the facility, a service center that must recover its operating costs, Mulholland is an imaging expert and scientist as well as a business manager, supervisor, budget chief and grant writer.

"Setting up, expanding and operating the imaging facility has been, and continues to be, one of the most challenging and at the same time the most satisfying thing I have done," Mulholland said. "I feel very fortunate to be in a position that supports the research of so many outstanding scientists."

'A treasure'

Margaret Fuller, PhD, a professor of developmental biology and of genetics and of obstetrics and gynecology, described Mulholland as "a treasure." She said one of Mulholland's most important contributions was his proactive leadership role in bringing the most cutting-edge imaging technology to Stanford.

"Jon is constantly abreast, indeed ahead of the game, in the latest technical advances in microscopy, and he works tirelessly and with much advance planning to make sure that we have the instruments to apply these new developments to our work," she said.

Fuller said Mulholland's hard work, organizational talents, deep technical knowledge and forward-looking planning have supported and catalyzed the research programs of many faculty, postdoctoral scholars and graduate students.

Alexander Dunn, PhD, an associate professor of chemical engineering, said Mulholland and his team keep the facility's complex equipment in excellent working order, with little down time. He said the team has greatly contributed to the education of several generations of graduate students.

"In part this stems from a real passion for the research itself," Dunn said. "Jon is wonderfully curious about any biological and technical problem you set before him. My personal experience is that he will work tirelessly to get researchers the data they need, even if it means substantially rebuilding an instrument, or staying up late at night to get a tricky experiment to work. This kind of passion and dedication is very rare." **ISM**

Nusse

continued from page 1

Lloyd Minor, MD, dean of the School of Medicine. "The importance of Wnt signaling in these processes cannot be overestimated. His work has been the foundation of much of modern developmental biology, and we are very proud of his contributions."

Nusse's more recent work has focused on understanding how Wnt family members control the function of adult stem cells in response to injury or disease. In 1996, he identified the cell-surface receptor to which Wnt proteins bind to control cells' functions, and in 2002 he was the first to purify Wnt proteins — an essential step to understanding how they work at a molecular level.

"My work has shifted significantly over the years due to the influence of my Stanford colleagues, although it has always been focused on Wnt," said Nusse. "When I arrived at Stanford, I was studying the involvement of the Wnt proteins in mouse development and cancer. I then switched to fruit flies, and then to the study of adult stem cells. Stanford has supported me during this evolution of my research career."

Nusse's lab is currently devoted to understanding how Wnt signaling affects the function of adult stem cells in the liver to help the organ heal after injury, as well as what role Wnt signaling might play in the development of liver cancer.

"The Breakthrough Prizes are a sign of the times," said Nusse. "Together with the recently announced Chan Zuckerberg Initiative, they show how the wealth of Silicon Valley is now making an impact not just in the field of computer science, but also in biomedical fields. This is very exciting."

> "The Breakthrough Prizes are a sign of the times."

Nusse is a member of the Ludwig Center for Cancer Stem Cell Research and Medicine at Stanford, of the Stanford Cancer Institute and of the Stanford Institute for Stem Cell Biology and Regenerative Medicine. He was awarded the Peter Debye Prize from the University of Maastricht in 2000. He is a member of the U.S. National Academy of Sciences, the European Molecular Biology Organization and the Royal Dutch Academy of Sciences. He is also a fellow of the American Academy of Arts and Sciences.

Seven $3 million Breakthrough Prizes — five in the life sciences, one in fundamental physics and one in mathematics — were awarded to 12 recipients. In addition, a special Breakthrough Prize in fundamental physics was awarded to the more than 1,000 researchers who proved the existence of gravitational waves in February of 2016.

Probing for dark matter

In addition, three $100,000 New Horizons in Physics Prizes were awarded at the ceremony.Peter Graham, PhD, an assistant professor of physics at Stanford, shared one of them with Asimina Arvanitaki of the Perimeter Institute in Ontario, Canada, and Surjeet Rajendran of the University of California-Berkeley, for "pioneering a wide range of new experimental probes of fundamental physics."

Graham earned a PhD at Stanford and completed postdoctoral studies at the Stanford Institute for Theoretical Physics before joining the Stanford faculty in 2010. In 2014, he received an Early Career Award from the Department of Energy.

Graham has developed new experiments to detect particles known as dark matter, which physicists have reason to believe exist but haven't yet been able to detect. Physicists have theorized about what dark matter might be, and based on that work have designed experiments to detect those theorized particles. However, those experiments would miss one possible variant of what dark matter might be, known as an axion.

"It was a scary scenario that this might be what dark matter is and our current experiments wouldn't detect it," Graham said.

Graham designed new experimental approaches that would detect axions if they turn out to be what make up dark matter. "This prize is a huge honor," Graham said. "It's great to get recognition from the community for this new direction; it will really help this emerging field."

Three $100,000 New Horizons in Mathematics Prizes were also presented at the Breakthrough Prize ceremony.

In addition, two teenagers — one from Peru and one from Singapore — each won the 2017 Breakthrough Junior Challenge. They will each receive $400,000 in educational prizes.

The Breakthrough Prizes are funded by grants from the Brin Wojcicki Foundation, established by Google founder Sergey Brin and 23andMe founder Anne Wojcicki; Mark Zuckerberg's fund at the Silicon Valley Community Foundation; Alibaba founder Jack Ma's foundation; and DST Global founder Yuri Milner's foundation. Recipients are chosen by committees comprised of prior prizewinners. **ISM**

Amy Adams, director for science communications at the Stanford News Service, contributed to this article.

Faculty members appointed to endowed professorships

MARY LEONARD, MD, professor of medicine and professor and chair of pediatrics, was appointed the Arline and Pete Harman Professor and Chair of Pediatrics, effective Oct. 18. She is the physician-in-chief at Lucile Packard Children's Hospital Stanford, the director of the Child Health Research Institute at Stanford and a co-leader of Spectrum Child Health. Her research has focused on the effects of chronic diseases on nutrition, physical function and bone health throughout life.

The professorship was established in 2000 by Leon W. "Pete" and Arlene Harman, and is intended for the chair of the department. The Harmans, who are now deceased, managed restaurants, including Kentucky Fried Chicken franchises, and were longtime supporters of Lucile Packard Children's Hospital Stanford.

THOMAS MONTINE, MD, PhD, professor and chair of pathology, was appointed the Stanford Medicine Pathology Professor, effective Oct. 18. His research examines the structural and molecular bases of cognitive impairment, with the goal of identifying therapeutic targets.

The professorship was established this year with funds from the Department of Pathology and is intended to support a member of the department.

MARK NICOLLS, MD, professor of medicine, was appointed the Stanford University Professor in Pulmonary and Critical Care Medicine, effective Oct. 18. He is the director of lung immunology, chief of pulmonary and critical care medicine, and chairman of the board of the Palo Alto Veterans Administration Institute for Research. His research focuses on the relationship between the immune response and lung disease, as well as on lymphedema.

The professorship was established with funds from the School of Medicine in 2004 and is intended to support the chief of pulmonary and critical care medicine. ISM

Mary Leonard

Thomas Montine

Mark Nicolls

OF NOTE

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

STEVEN CHU, PhD, the William R. Kenan Jr. Professor of Humanities and Sciences and professor of physics and of molecular and cellular physiology, received his 30th honorary doctorate in November from the University of Massachusetts-Lowell, where he delivered the Tripathy Memorial Lecture, titled "Climate Change and a Path to Clean Energy." Chu is a Nobel laureate and former U.S. energy secretary. His current research interests include the development of imaging techniques, the synthesis and characterization of rare-earth nanoparticles for molecular optical and electromagnetic imaging, and battery research.

WENDY DEMARTINI, MD, was appointed professor of radiology, effective Sept. 1. She is the chief of breast imaging. Her research examines the appropriate use of imaging to detect and evaluate breast cancer, with a particular focus on breast magnetic resonance imaging. In 2017, she will serve as the president of the Society of Breast Imaging.

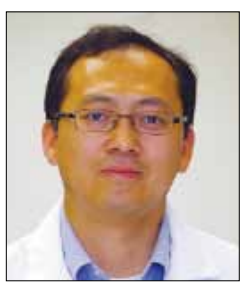
Steven Chu

Neir Eshel

James Ford

May Han

Robert Harrington

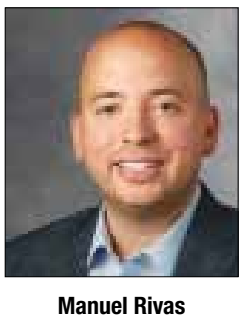


Yang Hu

Bruce Ling

Amanda Miguel

Robert Negrin



Manuel Rivas

Nirao Shah

Christina Smolke

José Vilches-Moure

Taia Wang

NEIR ESHEL, MD, PhD, a resident in psychiatry, has won the *Science* & SciLifeLab Prize for Young Scientists, which includes a $30,000 prize and a trip to Stockholm, Sweden, for the Nobel Prize lectures. His winning paper, "Trial and error: Optogenetic techniques offer insight into the dopamine circuit underlying learning," appeared in *Science*. His research focuses on the brain mechanisms of learning and decision-making, and how they break down in neuropsychiatric disease.

JAMES FORD, MD, was promoted to professor of medicine and of genetics, effective Oct. 1. He is director of the Stanford Clinical Cancer Genetics Program and of the director of clinical cancer genomics. His research focuses on the role of genetic changes that affect the risk of and development of cancer.

ANDREW GENTLES, PhD, was appointed assistant professor (research) of medicine, effective Nov. 1. His research focuses on computational systems biology, particularly cancer.

JASON GOTLIB, MD, was promoted to professor of medicine, effective Oct. 1. He directs the hematology fellowship training program. His research focuses on the clinical development of therapies for myeloproliferative neoplasms, including systemic mastocytosis, myelofibrosis and eosinophilic leukemias.

MAY HAN, MD, was appointed associate professor of neurology and neurological sciences, effective Oct. 1. Her clinical focus is on multiple sclerosis, neuromyelitis optica and central nervous system autoimmune conditions, and her research aims to understand central nervous system autoimmunity.

ROBERT HARRINGTON, MD, the Arthur L. Bloomfield Professor, professor and chair of medicine and director of clinical investigation in the Stanford Cardiovascular Institute, delivered the Laennec Clinician/Educator Lecture at the American Heart Association Council on Clinical Cardiology Scientific Sessions in November. His address was titled "Rethinking Randomized Clinical Trials." He is an interventional cardiologist who specializes in improving the design and execution of clinical trials and in incorporating research findings into clinical care.

YANG HU, MD, PhD, was appointed assistant professor of ophthalmology, effective Dec. 1. His research focuses on neuroprotection and axon regeneration in the central nervous system after neural injury.

SCOTT LAMBERT, MD, was appointed professor of ophthalmology, effective Oct. 1. His clinical focus is on treating children and adults with strabismus, and his research interests include improving care for children with congenital cataracts.

HENRY LEE, MD, was promoted to associate professor of pediatrics, effective Oct. 1. He is the director of research for the California Perinatal Quality Care Collaborative. His research focuses on perinatal and neonatal epidemiology, including the assessment of quality of care for mothers and newborns.

BRUCE LING, PhD, was appointed assistant professor (research) of surgery, effective Sept. 1. His research uses big-data techniques to translate work in genomics, proteomics and metabolomics into clinically useful forms and to explore the biological mechanisms of disease.

AMANDA MIGUEL, a graduate student in bioengineering, was named a 2016-17 scholar by the Achievement Rewards for College Scientists Foundation Northern California Chapter. She will receive an award of more than $30,000. Her research focuses on understanding how changes in bacterial cell morphology are controlled.

ROBERT NEGRIN, MD, professor of medicine and chief of the blood and marrow transplant program, has been named editor-in-chief of a new digital, open-access journal, *Blood Advances*, published by the American Society of Hematology. The new journal will feature multimedia and discussion forums. Negrin's research focuses on understanding graft-versus-host disease and the graft-versus-tumor reaction.

ERIC OLCOTT, MD, was promoted to professor of radiology, effective Oct. 1. His research and clinical interests include body imaging using computed tomography, ultrasound and magnetic resonance imaging, as well as imaging of appendicitis and of pancreatic and biliary tumors.

WILLIAM PATRICK, a fourth-year medical student, received the Southern Thoracic Surgical Association's George Daicoff President's Award, which includes a $500 prize, for his paper "Major aortopulmonary collateral arteries in patients with anatomy other than pulmonary atresia with ventricular septal defect," which he also presented at the associations' November meeting in Florida.

MANUEL RIVAS, DPhil, was appointed assistant professor of biomedical data science, effective Sept. 1. He is a biostatistician whose research interests include linking genetic variants with clinical outcomes.

NIRAO SHAH, MD, PhD, was appointed professor of psychiatry and behavioral sciences and of neurobiology, effective Sept. 1. His research focuses on understanding the molecular and neural network mechanisms underlying complex social behaviors that differ between the sexes.

CHRISTINA SMOLKE, PhD, was promoted to professor of bioengineering, effective Sept. 1. Her research interests include engineering RNA-based control systems, developing technologies to measure biochemical processes and creating microbial biosynthesis platforms for plant-derived compounds.

JOSÉ VILCHES-MOURE, DVM, PhD, was appointed assistant professor of comparative medicine, effective Oct. 1. He directs the Comparative Medicine Animal Histology Service Center. He specializes in experimental pathology, comparative pathology and pathology of laboratory animal species.

TAIA WANG, MD, PhD, was appointed assistant professor of medicine, effective Nov. 1. Her research interests include human susceptibility to viral pathogens, vaccine responses and immunoglobulin-G-mediated disease. ISM