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

By Kathy Zonana

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 DeGolia, MD, a clinical professor of psychiatry and behavioral sciences who teaches faculty development workshops at Stanford and nationally. “They developed it in a way that is so precise and analytical.”

Compound found to reduce tumor growth in mice

By Yasemin Sapakaloglu

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 NAMs — damaging molecules, causing the cells to die. This suggests a potential method to improve current therapeutical approaches.

“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.

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 who 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, benefitting all of humanity.”

Nusse’s interest in Wnt began in the 1980s as a post-doctoral 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, together, are associated with a longer average survival rate in breast cancer patients.

The study was published online Dec. 9 in the *American Medical Informatics Association*.

"Some we were asking, do any of the drugs they are taking associated 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 their 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 ibuprofen and 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 combinations of drugs in which the beneficial effect on survival is greater than the effect of either drug by itself. "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 these drugs might have a beneficial effect in treating this disease?,'" said Shah.

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

A joint effort

"This is a nice study that is an 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 the Pathology, Omics, and Statistics to bring the study off.

It's a proof of principle that this kind of data mining has strong practical clinical utility," 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.

The researchers of twoXAR Inc., the Palo Alto Medical Foundation Research Institute and the Cancer Prevention Research 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 Foundation. Stanford's Department of Medicine also supported the work.

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 neuroscientific sciences. "It negatively impacts muscle regeneration by altering the stem cell niche and inhibiting the stem cell function. In addition, fibrosis is occurring, 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 footwear 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 cues to divide and a shorter, inactive version of the same protein that attenuates the growth signal and prevents overgrowth of the muscle 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 cells. They found that muscle cells called fibro-adipogenic progenitors, or FAPs, These stem cells are responsible for generating the support tissue for muscles, called connective tissue, and foldy 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 previous research has suggested that PDGFR is necessary to repair an injury, an overly enthusiastic response can cause fibrosis and fibrosis that inhibits its muscle function. So it's imperative the cells strike the right balance in their response.

The researchers found that the cells have devised a novel, unexpected way to police themselves. The cells found a way to produce 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 their 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 PDGFR alpha. The nucleotide code tells the cell's messenger RNA-processing machinery to create a shorter-than-normal message that the protein that is made from that messenger RNA is also truncated.

"Artificially increasing, decreasing expression," said Mueller. Rando and their colleagues used a type of small molecule called a 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 they could increase or decrease the amounts of the inhibitory version allowed both young and old mice to heal from muscle injury," said Rando.

Conversely, decreasing the amount increased the severity of fibrosis.

"This study is a nice example of a mouse model of muscular dystrophy," said Rando. "Interestingly, the two-protein manipulation that we used here, the small oligomucleotide therapy currently being tested in clinical trials to stimulate the production of proteins missing in muscular dystrophy patients..."
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 even 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 counteracting the tremors of Parkinson’s disease and controlling seizures in epilepsy patients, and are approved for some patients with drug-resistant 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.

‘Immensely 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.

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 patients’ 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 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, into the 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 measurable 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.

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Fibrosis continued from page 2

patients with Duchenne muscular dysrophy. 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.

Remembering Norbert von der Groeben

Norbert von der Groeben was hard to miss. And yet somehow familiar with the campus’ faculty members, staff, students and patients.

The freelance photographer was known for his laidback demeanor and quick laugh. He was a presence on campus, always engaging with those he met.

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.

Norbert von der Groeben

(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 took this photo of the school year for new medical students. In this photo, Xylen Washington, 5, tries out the stethoscope he bought from his father, Gabriel Washington. (Right) In 2013, von der Groeben shot this portrait of Owen McCane, who was initially told the cancer that reached his liver was incurable. But a Stanford doctor provided a solution: using microwave ablation to heat and destroy the tumors.

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By Bruce Goldman
In 2013, Zoe Harting became the first baby in the world to receive an experimental drug that her doctors hoped would save her 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.

“We’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 two copies of the faulty 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.

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 multi-dose 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.

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 results of this study, which are under review by the FDA, are scheduled to be released in 2017. “The results of the multi-dose trial strongly mean that all participants can receive nusinersen,” Day said.

The drug is expected to receive FDA approval 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, for a toddler with SMA-1, she could lie on her back, lift her legs and play with her toys. “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 in her ability to sit and 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 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 are not only expected to 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 receives research support from Ionis Pharmaceuticals during the conduct of the study. He serves as a consultant to AveXis, Cytokinetiks 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.
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 and umbilical cord. “Think of them 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 care, including bringing in many physicians and nurses who took care of Aida during her high-risk pregnancy and who cared for the twins as newborns.

**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 Bolzt, 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 some 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 separated their gastrointestinal and urinary tracts. The girls’ single bladder was divided and made into two bladders, and in 2014, the girls’ single appendix was divided. 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 urology, and other specialties to form an expert team that could care for Aida and both babies. Aida 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 Erika and Eva into the Perinatal Education at Packard Children’s, who made a specialized conjoined mannequin that resembled the twins as closely as possible to facilitate realistic simulation training for the care team.

“Because the girls were situated facing each other, we knew that if they were delivered prematurely and had respiratory issues, the physical constraints of the abnormal anatomy. The anesthesia 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 preoperative imaging scans. Pediatric radiologist Franklins Chan, MD, associate professor of radiology at the School of Medicine, assisted the surgeons with the new technology. The girls became clear that we needed to use the third leg for reconstruction, Dr. Chan came in to the operation 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,” he said. “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 gastroenterological, 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 to a case like this,” Hartman said.

“The results are as good as we could have asked for,” Hartman concluded.

**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.

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 plastic and reconstructive surgeons to perform 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 from the muscles of the leg were transferred to close Erika’s abdominal wall. The surgeons had considered keeping the leg with Erika if it was not needed for re-construction, but it would likely not have been useful for walking because of its abnormal anatomy. The orthopedic 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 preoperative radiology scans. Pediatric radiologist Franklins Chan, MD, associate professor of radiology at the School of Medicine, assisted the surgeons with the new technology. The girls 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.

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**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.**
Recall that we’re asking questions about the mechanism of action of the drug. If you remember from the previous lecture, the drug works by inhibiting the activity of Axl, a receptor tyrosine kinase that binds to Gas6. In this case, we can see that the drug binds to Axl and competitively inhibits the binding of Gas6 to Axl. By doing so, the drug reduces the activity of Axl, which is a key regulator of cell proliferation and survival.

The results of these experiments support the hypothesis that the drug is effective in treating cancer. The decreased tumor growth and increased survival in the experimental group compared to the control group suggest that the drug may have significant therapeutic potential. However, further studies are needed to confirm these findings and to determine the optimal dose and administration schedule for clinical use.

In conclusion, understanding the mechanisms of drug action is crucial for developing effective cancer treatments. By targeting key signaling pathways, such as the Axl-Gas6 axis, we may be able to halt the growth and spread of cancer cells. This is just one example of how basic research can lead to significant advances in cancer therapy.
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 research center at Stanford University that is leading the edge of the revolution in technological advances in light and electron microscopy. "It was a humbling experience to be bestowed upon seven faculty members on Mulholland, winner of the 2016 Marsh O'Neill Award for Exceptional and Enduring Support of Stanford University's Research Enterprise.

"I have been honored by the Board of Marshall D. O'Neill, which worked from 1952 to 1990, when he retired as associate director of the W.W. Watt Laboratories. He was the first recipient of the award. When Mulholland became director of the imaging facility in 2001, he was also in charge of a number of shared equipment grants, and enabled the expansion of the facility beyond the Beckman Center into additional dedicated space in the School of Engineering.

"She said Mulholland also dedicated "an extraordinary amount of time and resources" to teaching faculty, postdoctoral scholars, technicians, and graduate and undergraduate students in advanced microscopy techniques in courses, guest lectures and hands-on demos. All the faculty at the Beckman Center and another in the Shriram Center at the School of Engineering — and an expert staff of five people: two in electron microscopy specialists, a light microscopy specialist, a computer tomography specialist, and an imaging specialist who also manages the facility's satellite site in the School of Engineering.

"The facility serves 400 researchers working in 30 departments in the school of Medicine, of Engineer- ing and of Humanities and Sciences. Its team conducts research in 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 annual funding to the facility.

"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. His 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.

"When Mulholland entered the field, it was 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, helping to support the enormous number of shared equipment grants, and enabling the expansion of the facility beyond the Beckman Center into additional dedicated space in the School of Engineering.

"Nurse's most recent work has focused on understanding how Wnt signaling factors control the function of adult stem cells in various tissue types. He has also studied how Wnt signaling affects the function of adult stem cells in the liver to help heal organ damage 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 Nurse. "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 cancer research, but also in biomedical research.

"This is very exciting," said Nurse. "When I arrived at Stanford, I was studying the involvement of the Wnt proteins in stem cell development. I was then switched to fruit flies, and then to the study of adult stem cells. Stanford has supported me during this evolution of my research interests.

"In addition, a special Breakthrough Prize in Fundamental Physics was awarded to 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 Horizon Prizes 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 Rajendra of the University of California, Berkeley, for "pioneering a wide range of new experimental probes of fundamental physics; each of these earned key breakthroughs at Stanford and completed postdoctoral studies at the Stanford Institute for Theoretical Physics before joining the Stanford faculty in 2014. In 2016, he received the 2017 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 work that have designed experiments to detect those theorized particles. However, these 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 an axion that the experiments wouldn't detect," 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 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 the Breakthrough Prize Foundation, established by Google founder Sergey Brin and 23andMe founder Anne Wojcicki; Mark Zuckerberg’s foundation at the Silicon Valley Community Foundation; Alibaba founder Jack Ma’s foundation; and Russian internet tycoon Yuri Milner’s foundation. Recipients are chosen by committees comprised of prior prizewinners.
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 Medical Center. His research focuses on the relationship between the immune response and lung disease, as well as on lymphomas. The professorship was established with funds from the School of Medicine to support the chief of pulmonary and critical care medicine.

OF NOTE

NEIR ESHEL, MD, PhD, a resident in psychiatry, has won the Science & Sc2Lab 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 extracellular mechanisms of learning and decision-making, and how they break down in neuropsychiatric disorders. JAMES FORD, MD, was promoted to professor of medicine and of genetics, effective Oct. 1. He is director of the Stanford 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 GOLDBERG, MD, was promoted to professor of medicine, effective Oct. 1. He directs the hematology and administration research fellowship training program. In 2017, she will serve as the president of the Society of Breast Imaging.

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 assistant 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 OCGOTT, 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 appendixes and of pancreatic and biliary tumors.

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

Christina Smolke, PhD, was appointed assistant 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.