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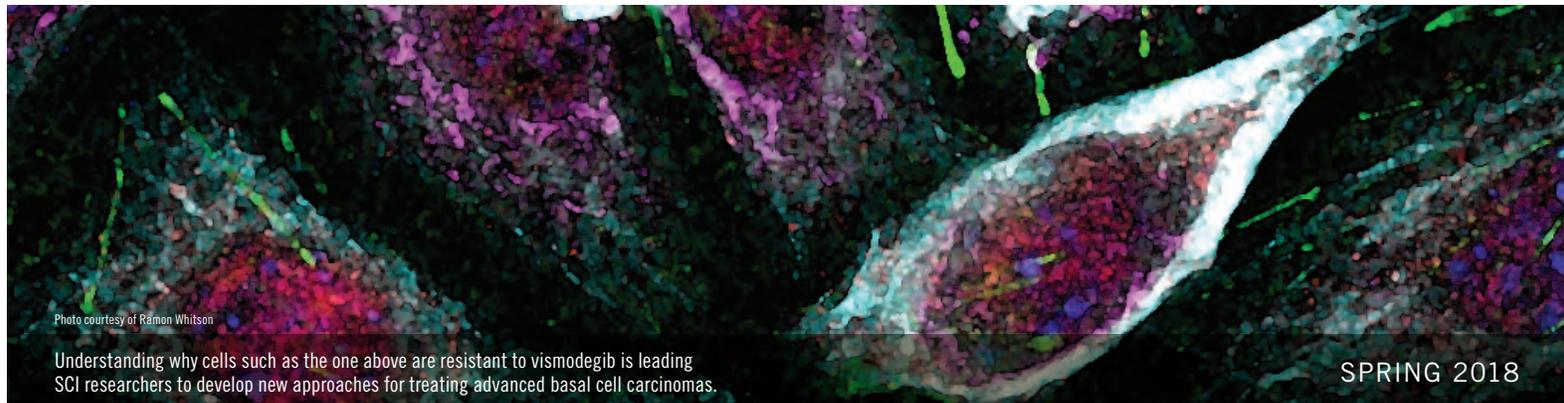


Photo courtesy of Ramon Whitson

Understanding why cells such as the one above are resistant to vismodegib is leading SCI researchers to develop new approaches for treating advanced basal cell carcinomas.

SPRING 2018

Drug Development from Bench to Bedside A Precision Approach to Skin Cancer

Today, if you're one of the millions of Americans a year diagnosed with basal cell carcinoma (BCC), you'll likely get a quick surgery to remove the tumor, which might resemble a shiny bump or reddish patch on your head or neck. If you're one of the unlucky few for whom the cancer returns or spreads, you'll be prescribed a targeted drug that helps shrink the tumor—but it might only be a matter of time before your tumor develops resistance to the drug and starts growing again.

At Stanford, a team of researchers that spans dermatology, basic science, and clinical science is piecing together the molecular details of basal cell carcinomas—not only the most common skin cancer, but the most commonly diagnosed of all cancer types. By revealing the

cancer's strategies for survival, they're assembling new, personalized paradigms to treat the advanced basal cell carcinomas that evade conventional treatment.

“After initial therapy, you can see escapee tumors easily because they reappear on the skin; it provides us with an amazing teaching tool on all the ways cancers can evolve and avoid getting killed,” said Anthony Oro, MD, PhD, a Professor of Dermatology and an SCI member. “This simple and visible tumor really is instructing us and giving us enormous insight into other cancers.”

In the 1990s, Oro was part of the team that discovered the connection between BCC and a cellular pathway called Hedgehog. In embryos, the Hedgehog pathway—a whole cascade of molecules that interact one after

the other like a row of dominoes—directs when and where many types of cells develop. (The pathway was named because fruit fly larva lacking the Hedgehog signaling molecule develop abnormally and resemble spiky hedgehogs). In adults, the Hedgehog pathway helps encourage the proliferation of cells from stem cells, coaxing hair to grow, for instance. But Oro and his colleagues discovered that the pathway was also inappropriately activated in more than 90 percent of BCC cases, spurring the skin's deep layer of basal cells to grow uncontrollably.

From there, pharmaceutical companies jumped on the discovery and began developing drugs to block key steps in the Hedgehog. One

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Message from the Director

A Champion for Promising Physician Scientists



One of the most rewarding activities of my job is meeting with our outstanding trainees, many of whom are pursuing a research project after long years of clinical training. One objective of the Stanford Cancer Institute is to help support trainees through this critical period of their careers and enable their success as cancer researchers at a time of markedly diminished funding. This year saw an increase in fellowship applicants despite a decrease in financial support. Therefore, we were extraordinarily pleased that Ellie Guardino, MD, PhD, chose to support three of our fellows with the money donated to the Ellie Guardino Research Fund at this year's Under One Umbrella event.

As outlined in this issue, Ellie is a former Stanford breast medical oncologist who has taken on the mission of raising money for innovative new projects that are frequently being carried out by young researchers. Now at Genentech leading efforts in cancer drug development while herself undergoing cancer treatment, Ellie will have the chance to meet the beneficiaries of her efforts in upcoming months. We are so grateful to all those who have made Under One Umbrella such a success and, of course, to Ellie for all that she will continue to do to support cancer research.

In this issue as well is the remarkable story of Stanford's efforts to develop new approaches to the treatment of advanced basal cell carcinomas. We are the home of a number of researchers focused on the so-called Hedgehog pathway of cancer cell signaling that underlies a number of different cancers. SCI members Tony Oro, MD, PhD, Jean Tang, MD, PhD, and their colleagues have identified novel mechanisms of resistance to initially effective drugs. This team is continuing to push new scientific boundaries by developing ways to circumvent resistance and to test them in clinical trials. The study of the biology of cancer cells frequently contributes to new ideas for therapeutic intervention that lead to the testing of new treatments for cancer patients, which are then carried back to the lab to better understand the biology. This cycle continues to inspire the work of Drs. Oro and Tang, as well as that of many other SCI members. ■

Beverly S. Mitchell, MD

Director

The Stanford Cancer Institute

The Stanford Cancer Institute (SCI) provides support and coordination for the range of cancer-related activities occurring at Stanford University, Stanford Health Care, the Lucile Packard Children's Hospital Stanford and the Cancer Prevention Institute of California. Our nearly 500 faculty members belong to more than 30 academic departments from four schools, and represent the wide array of disciplines involved with comprehensive cancer research, treatment, prevention, education, and outreach.

The SCI is a National Cancer Institute-designated Comprehensive Cancer Center, with a scientific agenda combining laboratory research, clinical study, translational programs and population science. The SCI also provides patient care, community education, clinical trials, as well as support and training for the next generation of cancer physicians and researchers.

Simply put, all of our members and resources are focused on one goal: to reduce the occurrence and impact of cancer.

Give to the Cancer Discovery Fund

The Cancer Discovery Fund gives the Stanford Cancer Institute the flexibility to fund cutting-edge, collaborative and interdisciplinary research that has high potential for translation into new cancer interventions, precise diagnostics and personalized treatment.

Give today at:
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SKIN CANCER, *continued from page 1*

notable development was Genentech's vismodegib as a treatment for BCC, which the Food and Drug Administration approved in 2012.

"The drug is amazing," said Oro. "It really melts away the cancers, but the problem is that these resistant clones re-appear."

So Oro, in collaboration with other Stanford researchers and clinicians including Jean Tang, MD, PhD, an Associate Professor of Dermatology and an SCI member, began isolating samples of the tumors that were resistant to vismodegib and studying how they were managing to survive. The advanced BCC tumors, it turned out, had a variety of ways to turn the Hedgehog pathway back on, even in the presence of the drug. The last step, or final domino, in the Hedgehog pathway—a protein called Gli—needs to be turned on for BCCs to grow. Since vismodegib targets one of the early steps in the Hedgehog pathway, the cancer can activate the pathway again with mutations in proteins that play later roles, flipping Gli back on.

In late 2016, Oro, Tang, and their colleagues reported a collection of mutations in one particular Hedgehog pathway protein that led BCCs to escape treatment with vismodegib. More recently, they've identified a pair of proteins called serum response factor (SRF) and megakaryoblastic leukemia 1 (MLK1) that can directly turn up the cell's production of Gli, even in the presence of vismodegib. In a paper published in the February 2018 issue of *Nature Medicine* the team reported that nearly half of all BCCs take advantage of this SRF/MLK1 duo and that drugs

blocking MLK1 can effectively stop the growth of those cancer cells.

"If we can know how a tumor is going to evolve based on some of these common resistance pathways, then we can be ready with second line therapies and third line therapies and fourth line therapies," said Tang. "That means we can convert a deadly killer tumor to one that's handled with chronic treatment where we're always staying one step ahead."

While findings on the basic science of cancer often point toward drug targets for which there are no current remedies, the researchers studying BCC have been lucky to pair many of their discoveries with either drugs that already exist, or small molecules with drug potential. Last year, Oro and Tang collaborated with Atul Butte, MD, PhD, of UC-San Francisco, who has pioneered an approach to combine genetic data on diseases like cancer with large databases of existing drugs. His informatics approach, combined with the knowledge the Stanford team already had on the genetic underpinnings of BCC, pointed them toward another combination of existing drugs—including one that interacts with Gli—which can shut off the Hedgehog pathway in BCC cells.

The progress that the SCI team is making regarding BCC's strategies to activate the Hedgehog pathway are paving the way toward personalized treatment plans for this common cancer, the researchers said. Tang and Oro envision a future where anyone with advanced BCC can have their tumor genetically studied. Then, the



Anthony Oro, MD, PhD



Jean Tang, MD, PhD

right combination of drugs can be selected to shut off their individual cancer. It's a goal that researchers have for many cancer types but is one that seems closer to reality for BCC, they said. That's in part due to how accessible and visible the cancer is—it's easy to biopsy for genetic sequencing—and in part due to vast amounts of research by the Stanford group.

"Basal cell carcinomas are very useful for helping us understand how personalized cancer therapies could work across the board," said Tang.

The team attributes the success of their work to not only a long history studying BCC, but also to a vertically integrated program at Stanford that includes basic scientists, clinicians, and ties to industry.

"It's rare to have this sort of extensive, comprehensive program around a single cancer type, and it's going to teach us how to implement other programs in the future," said Oro.

Other faculty members involved in the BCC Consortium at Stanford include Anne Chang, MD, Associate Professor of Dermatology and SCI member; Kavita Sarin, MD, PhD, Assistant Professor of Dermatology and SCI member; Sumaira Aasi, MD, Clinical Professor of Dermatology and Plastic and Reconstructive Surgery; and Tyler Hollmig, MD, Clinical Associate Professor of Mohs and Dermatologic Surgery. ■

Supporting the Growing Data Needs of Cancer Researchers SCI Research Database Integrates Clinical, Molecular, and Imaging Data

If the wealth of information on patients' medical histories, tumor biopsies, imaging results, and even genetics could be integrated into one database, it could greatly facilitate the performance of large studies spanning multiple cancer types or using many different types of information.

That's the purpose of the Stanford Cancer Institute Research Database (SCIRDB).

"Many cancer centers create databases from their electronic medical systems, but what makes SCIRDB unique is that it's pulling data from multiple sources," said Daniel Rubin, MD, MS, an Associate Professor of Biomedical Data Science, Radiology, and Medicine; and the Director of Biomedical Informatics for the Stanford Cancer Institute.

EPIC, the electronic medical record system used by Stanford Health Care, includes primarily clinical data, Rubin said, and isn't designed for research purposes. Making changes to the EPIC database, to add research data fields or by trying to expand the scope of data that it includes, involves a long and costly process. In the past, this has often led individual investigators who need a research database to design their own. But Rubin and others at the SCI thought it would be most cost and design efficient to have a single all-inclusive database that could be used for SCI research purposes. So they

hired a team of programmers to build the SCIRDB, and then they gathered information from researchers on what data and features they wanted.

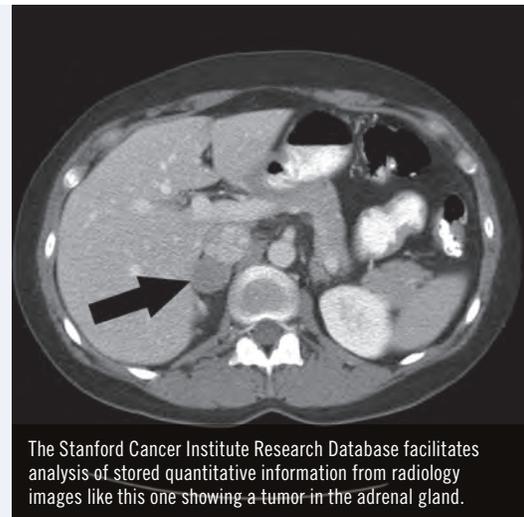
Adding imaging results to the database, for instance, was important to many researchers. Images associated with tumors were already stored in patient records, but studying them involved analyzing each scan one by one. Accordingly, Rubin and his colleagues developed methods to extract quantitative information from radiology images, and those data are now stored in the SCIRDB.

"Many cancer centers create databases from their electronic medical systems, but what makes SCIRDB unique is that it's pulling data from multiple sources."

— Daniel Rubin, MD, MS

"It's key to not only have a text report associated with an image, but also the actual structured measurements," said Rubin. "When we have that, we can use information on how tumors are growing or shrinking to conduct studies at a population level." If a researcher wants to study progression-free survival—how long tumors remain stagnant—after a particular treatment, they can now do that more easily with the measurements included in the database.

The SCIRDB was helpful when Rubin collaborated with Michael



The Stanford Cancer Institute Research Database facilitates analysis of stored quantitative information from radiology images like this one showing a tumor in the adrenal gland.

Gensheimer, MD, a Clinical Assistant Professor of Radiation Oncology and SCI member, to analyze more than 13,000 patients seen at Stanford from 2008 through 2017 who all had metastatic cancer. They mined the database to build a computational model that could predict—using raw medical records data—which patients would survive more than or less than three months, which could help guide clinical care decisions.

As the database grows and expands, Rubin expects it will allow more types of studies and queries to be carried out. For instance, if a patient with a rare cancer is deciding between two treatments, and there is no published clinical trial result that could guide decision making, a physician could search the SCIRDB for the outcomes of similar patients, and he or she could use the information to inform patient care.

"Clinical care is evolving, with the potential of becoming much more data driven, and we're here to help clinicians and researchers leverage that," said Rubin. ■

Get to Know:

Jay Shah, MD, Bladder Cancer Specialist



Though it's the fifth most prevalent form of cancer in the U.S., bladder cancer seems to be out of mainstream conversation. But Jay Shah, MD, an Associate Professor of Urology, has plenty to say about improving outcomes for those with the disease.

A urologic oncologist specializing in bladder cancer who came to Stanford from Houston's MD Anderson Cancer Center in February 2017, Shah now leads the Urologic Oncology Cancer Care Program (CCP) within the Stanford Cancer Center. He takes tremendous pride in getting to know every patient he treats and helping them choose the treatment plan that is right for them.

Shah has a strong interest in outcomes. His research areas of focus include comparative effectiveness, clinical outcomes and population health.

As his first academic endeavor at Stanford, Shah has chosen to focus on a project that lies at the intersection of surgical outcomes and population health. He is currently heading a CELT (Clinical Effectiveness Leadership Training) project studying the role of surgeons in the nationwide opioid epidemic and identifying means to decrease opioid use after surgery. If successful, he hopes to expand the project beyond Stanford to the regional and national levels.

Shah believes that the best chance of a cure for those with invasive bladder cancer is a complex operation that

involves removing the bladder and several other organs in the pelvic region.

"Conventional surgery requires a six-inch incision in the belly, but in the past several years we've started doing this operation robotically. We're able to avoid making that big cut by using advanced instruments to help us do the entire surgery through a few small keyhole incisions in the abdomen," Shah says.

Shah is a huge believer in enhanced recovery, which expands the focus from when the patient is in the operating room to a much broader institutional mindset of preparing the patient for a better outcome after surgery. It includes anesthesiologists, social workers, inpatient nurses, clinical nurse coordinators, advanced practice providers, and many other hospital employees who are involved in managing the patient before, during, and after surgery.

For bladder cancer, enhanced recovery has lowered the rate of complications from around 60 percent to around 30 percent, and it has reduced the average length of stay in the hospital from eight days down to four or five days. With enhanced recovery, patients genuinely feel better and progress more rapidly on their way back to normal activities, and there's a dramatic reduction in costs as well.

As pain management options have evolved, Shah is trying to implement pathways for converting many Stanford

urologic operations so they become fully opioid free.

"Sometimes after surgery people sail through, and other times, even though you've done every single thing by the book, there will still be a very poor recovery. That's why I'm trying to figure out if we can develop a molecular signature for recovery after cystectomy, the surgical removal of the bladder."

He explains that the completion of the Human Genome Project led to a Cancer Genome Atlas, which has yielded new information about the molecular signature of bladder cancer.

"People are now trying to figure out if we can break down bladder cancers into subtypes so that we can predict who will respond better to chemotherapy and who will have a better surgical outcome in order to get a better overall sense for how people will do with this disease."

Shah came to Stanford because "it was a chance at a midpoint in my career to move to one of the world's top universities and to help build the urologic oncology program here."

"What really excites me about being at Stanford is the passion that everyone has for their work and the academic firepower all around me. I enjoy learning about the interests of my basic science and clinical medicine colleagues so we can figure out interesting new ways to collaborate!" ■

SCI Shared Resource Is a Boon to Cancer Immunology

Human Immune Monitoring Center Supports Researchers

Cancer immunotherapies—treatments that harness the power of the human immune system to fight cancer—are generating excitement in the world of oncology. But countless questions remain about the interplay between the immune system and each individual cancer type. Researchers want to know how the immune system reacts to cancers and how tumors evade the immune system.

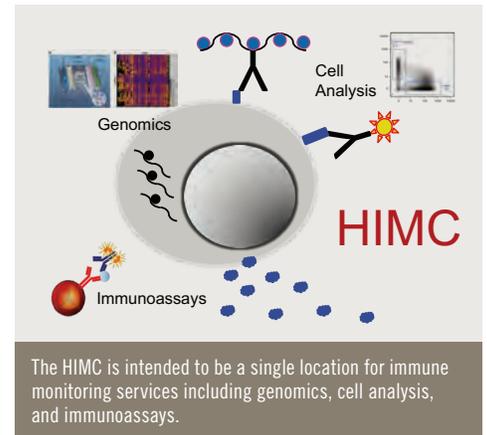
Stanford's Human Immune Monitoring Center (HIMC) is a central shared resource of the Stanford Cancer Institute (SCI) that offers members support in planning immune monitoring experiments, developing assays, and analyzing the results.

“The impetus behind our center is to create a one-stop shop for immune monitoring services,” said Holden Maecker, PhD, a Professor of Microbiology & Immunology and Director of the HIMC. “We don't offer just one platform, but we are ready with a whole range of assays that are applicable for assessing the immune system in humans.”

The technology at the HIMC allows experiments that study the cells of the immune system—their type, frequency, and function—as well as the levels of genes and proteins related to immunity. In one recent study, Susan Knox, MD, PhD, a Professor of Radiation Oncology and SCI member, used the expertise and equipment at the HIMC to study whether the levels of different immune cells in a melanoma patient's body can predict how well the patient responds to a combination of treatments.

In the future, Maecker imagines researchers will ask increasingly complex questions about which immunotherapy drugs are best for which patients.

“Ideally, you don't want to just stratify your patients and say these aren't a good match for immunotherapy, but you want to figure out what you can do to make them better candidates or what other immunotherapy options might be better for them,” said Maecker.



To aid in these types of studies, Maecker and his colleagues are constantly scanning the field for new available technologies. They would like to add the ability to do more comprehensive analyses on single immune cells in the near future.

As the center grows, Maecker hopes that his fellow SCI members take advantage of its presence. Anyone planning immune monitoring studies will benefit from approaching the HIMC during the planning phase so the staff can help optimize sample collection and processing. ■

NCI Grant Helps Expand HIMC Capabilities

In October 2017, Stanford became one of four institutions to receive National Cancer Institute funding to analyze immune function as it relates to cancer. The grant—headed by SCI members Holden Maecker, PhD, a Professor of Microbiology & Immunology, and Sean Bendall, PhD, an Assistant Professor of Pathology—will provide the Stanford HIMC with \$12.5 million over five years.

“It's really going to help support our staff and increase our throughput so that we have a more stable, consistent operation,” said Maecker.

Other institutions to receive the grant are the Dana-Farber Cancer Institute, the Icahn School of Medicine at Mount Sinai, and the University of Texas MD Anderson Cancer Center. The four new Centers for the Immune Monitoring and

Analysis of Cancer will work together to establish best practices for immune profiling and support cancer researchers nationwide in their experiments.

“I think collaborating with these other centers will teach us a lot in terms of analytical methods,” Maecker said. “We're already all communicating about the best kinds of assays to use and how to standardize them.”

Legacy of Hope

A Tribute to Ellie Guardino, MD, PhD

Last fall's ninth annual Under One Umbrella luncheon event to benefit the Stanford Women's Cancer Center paid a particularly moving and meaningful tribute to Ellie Guardino, MD, PhD.

After completing an oncology fellowship at Stanford, Dr. Guardino worked in the lab of Ronald Levy, MD, the Robert K. and Helen K. Summy Professor of Medicine and SCI member, developing a vaccine program for breast cancer and designing Phase 1-2 clinical trials using novel drug combinations. She became a pioneer in cancer immunotherapy, specializing in breast cancer at the Stanford Women's Cancer Center.

While most oncologists genuinely understand and empathize with their patients' struggles during diagnosis and treatment, Dr. Guardino shares first-hand experience. In 2008, she was diagnosed with melanoma, yet she relentlessly pursues her life goals, helping to advance cancer treatment for her patients and the legions of others

who have benefitted from her research.

Midway through her successful career as a faculty member at Stanford, she decided to move to Genentech/Roche because she was eager to expedite the approval process for cancer treatments and prevention techniques that were being developed within the industry environment. At Genentech/Roche, Dr. Guardino's Phase 3 clinical work facilitated the FDA approval of several transformative drugs for early stage and advanced breast cancer. Her efforts improved patient access to breast cancer therapies worldwide.

Dr. Guardino's melanoma has metastasized, but she continues her tireless work to secure funding and approval for the next breast cancer drug trial. Her commitment to these activities, and caring for patients, is what drives her.

Famed actor Tom Hanks, master of ceremonies for the Under One Umbrella luncheon, cited Dr. Guardino's grit and determination as he championed all the women who

have survived cancer, including his wife, actress and singer Rita Wilson, who sang and performed with her band for the nearly 400 supporters at the event.

"Legacy of Hope—Nothing is Worth More Than This Day," a documentary film about Dr. Guardino, directed by Jonathan Berek, MD, MMS, Director of the Stanford Women's Cancer Center and SCI Scientific Advisor, was shown during the luncheon.

The film can be viewed online at underoneumbrella.stanford.edu.

In the film Dr. Guardino says:

"We've been given a gift, don't waste it. Wake up in the morning, look and see what you can do, what you can give, and enjoy the day. Be who you are, love who you are, and have hope and faith. I think there's a lot of good to come."

In honor of that spirit, the Under One Umbrella organizing committee announced the establishment of the Ellie Guardino Research Fund. Dr. Guardino recalled the support she received early on in her career and wants the new fund to support talented cancer physician-scientists as they make a long-term commitment to the research that is essential for understanding, preventing, and curing cancer. This new fund will support innovative cancer research grants and early career fellows as they pursue new treatments for the benefit of cancer patients around the world. ■



From left: Tom Hanks; Ellie Guardino, MD, PhD; Rita Wilson; and Jonathan Berek, MD, MMS.

Photo by Drew Altizer

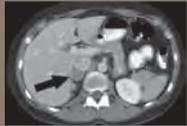


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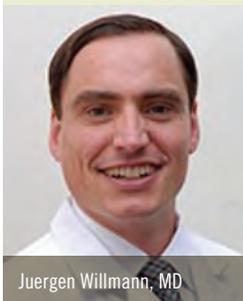
News

Stanford Cancer Institute News

SPRING 2018

In Memoriam: Juergen Willmann, Imaging Expert

The untimely death of Juergen Willmann, MD, a Professor of Radiology and Stanford Cancer Institute (SCI) member who dedicated himself to advancing cancer detection imaging technologies, is a tremendous loss for the SCI and the entire Stanford community.



Juergen Willmann, MD

Willmann died January 8 in a car accident in Palo Alto. He was 45.

“Juergen was poised to make tremendous contributions to our ongoing research efforts in cancer detection, particularly in our newly forming multidisciplinary pancreatic cancer research group,” SCI Director Beverly Mitchell said.

Willmann came to Stanford in 2005 to work on multimodality molecular imaging technologies and early cancer detection. He honed an imaging tool known as targeted contrast microbubbles that, in combination

with ultrasound, could be used to detect early tumors and target the delivery of drugs. His lab performed the first clinical imaging trials of microbubbles in humans, to detect breast and ovarian cancer.

Willmann will be remembered as a brilliant clinician scientist and a devoted family man, with boundless energy and vision. He is survived by his wife, Amelie Lutz, MD, an Assistant Professor of Radiology at Stanford, and their two children. ■