INSIDE STANFORD MEDICINE

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Ami Bhatt is mobilizing medical faculty and trainees to collaborate on projects to combat cancer in the developing world.

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Sugar-gobbling cells may drive heart disease

By Bruce Goldman

Hyper-aggressive immune cells parked in arterial plaque and bingeing on glucose appear to be major drivers of coronary artery disease, School of Medicine investigators have found.

The discovery, detailed in a study published online Feb. 29 in *The Journal of Experimental Medicine*, could lead to new therapeutic interventions that provide some protection from the disease, which is the No. 1 cause of death in America.

"We've pinpointed a defect in glucose metabolism by a class of arterial-plaque-associated immune cells as a key factor driving those cells into a hyper-inflammatory state," said Cornelia Weyand, MD, professor and chief of immunology and rheumatology, who is the study's senior author. The lead author is postdoctoral scholar Tsuyoshi Shirai, MD, PhD.

Blocking that glucose overconsumption or, for that matter, a couple of other downstream links in the chain of ensuing biochemical events prevented this hyper-inflammatory activation, the researchers discovered.

The findings support a growing recognition that it's not just arterial deposition of fatty materials called lipids that causes coronary heart disease, but also underlying chronic inflammation. "It's been unclear where the inflammation comes from," Weyand said.

The puzzle of heart attacks

Coronary artery disease, which accounts for nearly half of all deaths in the United States, arises when blood flow through the arteries that supply oxygen-rich blood to the heart is impaired. The underlying process — the buildup of plaque inside the arteries — is called atherosclerosis.

"Most of us develop arterial plaque over the course of our lifetimes," Weyand said. Plaque accumulation can begin early in life, with deposits sometimes evident in individuals as young as 15 to 20 years old, and progresses steadily with advancing age.

When these deposits become severe enough, they can restrict blood flow. It used to be thought that this occlusion triggered heart attacks. But a puzzle remained: If this process is so gradual, why are heart attacks so sudden?

While lipids are a prime constituent of arterial plaque, it's now understood that plaque also contains immune cells — chiefly, a type called macrophages. These cells wear many hats. They attack and ingest invading bacteria, repair tissue, clean up debris left behind after injury or infection, and more.

"We can't live without them," said Weyand.

Macrophages generally fall into two broad categories: The kinder, gentler ones — so-called M2 macrophages — are like construction engineers, nibbling cellular detritus left behind from a wound or infection, releasing factors that encourage new cell growth and stimulate blood flow, and otherwise overseeing tissue repair.

See MACROPHAGES, page 6

NORBERT VON DER GROEBEN

Ryu Watanabe, Cornelia Weyand and Tsuyoshi Shirai are co-authors of a study that identified how immune cells may contribute to coronary artery disease.

Protein controls expression of molecules that protect cancer cells, study finds

By Krista Conger

A cancer-associated protein called Myc directly controls the expression of two molecules known to protect tumor cells from the host's immune system, according to a study by researchers at the School of Medicine.

The finding is the first to link two critical steps in the development of a successful tumor: uncontrolled cell growth — when mutated or misregulated, Myc causes an increase in the levels of proteins that promote cell division — and an ability to outwit the immune molecules meant to stop it.

STEVE FISCH

Dean Felsher and his team have identified a link between the expression of a cancer-related gene and cell-surface molecules that protect tumors from the immune system.

The study was published online March 10 in *Science*. Dean Felsher, MD, PhD, a professor of oncology and of pathology, is the senior author. The lead author is postdoctoral scholar Stephanie Casey, PhD. The work was conducted in collaboration with researchers at the University of Wurzburg.

"Our findings describe an intimate, causal connection between how oncogenes like Myc cause cancer and how those cancer cells manage to evade the immune system," Felsher said.

'Don't eat me' and 'don't find me'

One of the molecules is the CD47 protein, which researchers in the Stanford laboratory of Irving Weissman, MD, have discovered serves as a "don't eat me" signal to ward off cancer-gobbling immune cells called macrophages. Weissman is the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research and the director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine.

Nearly all human cancers express high levels of CD47 on their surfaces, and an antibody targeting the CD47 protein is currently in phase-1 clinical trials for a variety of human cancers.

The other molecule is a "don't find me" protein called PD-L1, known to suppress the immune system during cancer and

See MYC, page 7

Vitamin D deficiency contributes to spread of breast cancer in mice

By Krista Conger

Breast tumors in laboratory mice deficient in vitamin D grow faster and are more likely to metastasize than those in mice with adequate levels of vitamin D, according to a preliminary study by researchers at the School of Medicine.

The research highlights a direct link between circulating vitamin D levels and the expression of a gene called ID1, known to be as-

See VITAMIN D, page 7

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OBITUARY

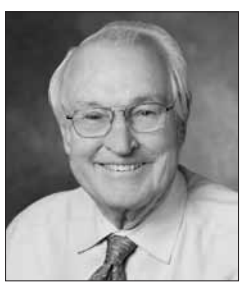
Harry Oberhelman, longtime surgeon and mentor, dies at 92

By Sara Wykes

Harry Oberhelman Jr., MD, professor emeritus of surgery and former chief of general surgery and gastrointestinal surgery at the School of Medicine, died Feb. 10 at his home on the Stanford campus. He was 92.

For more than 50 years, Oberhelman, known to many as Dr. O, was untiringly committed to his Stanford patients. Many people who never saw him operate knew him only as "the sweetest, mildest person you could imagine," said James B.D. Mark, MD, professor emeritus of cardiothoracic surgery and the Johnson and Johnson Professor of Surgery, Emeritus. But once inside the operating room, Mark said, "he was a tiger. He hated cancer, and he wanted to get rid of it no matter what it took."

Oberhelman was as fiercely devoted to teaching young surgeons. He trained more than 160 general surgery residents in his 31 years as director of that residency program. In 1980, M. Ellen Mahoney, the first woman ever selected by Stanford as a general surgery resident, knew that being accepted in the male-dominated field would not be easy. Yet Oberhelman became not only a teacher but a friend and colleague who showed her that understanding patients was as important as knowing surgical technique, Mahoney said. "He taught us to be kind, to pay attention to who each patient was and to know that what a doctor might do in a given situation was not necessarily the correct answer for the patient," she said.



Harry Oberhelman

Fixture of the department

Over his surgery career, Oberhelman worked with 10 medical school deans, five surgery department chairs, five acting chairs and many hospital administrators. He also served as chief of general surgery from 1964-90, chief of gastrointestinal surgery from 1990-97 and acting chief of surgery from 1997-2000.

In 1998, Thomas Krummel, MD, having just been appointed to the Stanford surgery faculty, met Oberhelman when he found himself in an office across the hall from elder surgeon. Krummel was named chair of the department the following year.

"Harry's enormous counsel, wisdom and instinctive sense of how things were organized and what the issues were kept me off the landmines in my early days here," said Krummel, the Susan B. Ford Surgeon-in-Chief at Lucile Packard Children's Hospital Stanford and the Emile Holman Professor in Surgery. "He taught me patience."

Krummel also saw in Oberhelman the courtly and gentle style of doctoring that made him so beloved among his patients and respected by his peers. "He understood bedside manner — the value of a comforting hand on someone's shoulder, of being with a patient," Krummel said. "Surgeons can be imperious, but Harry was very down-to-earth. He was a wonderful match of confidence and competence."

Other colleagues remembered the visits he made to hospitalized patients, even on weekends and holidays.

A patient at Stanford

Oberhelman was actively involved in professional associations. He served as director of the American Board of Surgery from 1972-78; president of the California Board of Medical Quality Assurance in 1979-80; director of the Federation of State Medical Boards from 1979-82; and council member of the National Institutes of Health General Medical Sciences from 1982-85. He was a fellow of the American College of Surgeons and a diplomate of the American Board of Surgeons.

Oberhelman was also a patient at Stanford Hospital. In 1980, he collapsed from a heart attack at the hospital, and his colleague Norman Shumway, MD, the surgeon who performed the first successful adult heart transplant in the United States, repaired Oberhelman's heart with a triple bypass. Legend has it that Oberhelman, while recovering in the intensive care unit, asked a nurse to bring him patient charts so he could continue to work.

Later, Oberhelman would have surgeries to repair abdominal aneurysms, hernias and spinal stenosis. He was also treated for glaucoma and prostate cancer. "I give my physicians a lot of credit for keeping me going over the years," he said in a 2011 video honoring his 50th year at Stanford. "My experiences as a patient at Stanford have been excellent."

Chicago native

Oberhelman retired from active surgical practice at the age of 78, but he remained "extraordinarily generous with his time," Krummel said. "To me, it was the mark of confident surgeons that they could go and ask Dr. O for an opinion. He was near and dear to all of us."

In 2006, Barbara Ralston, vice president of Stanford Health Care's International Medical Services, recruited Oberhelman to be medical director of the program. "He was like our father, our grandfather," Ralston said. "Anybody who knew Dr. O has a place in their heart for him because he had that kind of place in his heart for everyone. He was an innovator, a gentleman at all times, apolitical and always, always kind."

Oberhelman was born Nov. 15 1923, in Chicago, the eldest son of a surgeon. "Over the years, his compassion and the respect that he was held in by his patients just solidified my desire to become a surgeon," Oberhelman in the 2011 video. He accompanied his father on rounds, but also remembered his reaction to the first operation he watched his father do. "I was standing there, watching him operate, and I fainted."

Oberhelman went to Yale University to begin his college education and lettered in football in 1942 and 1943. He returned to the Midwest to complete a joint bachelor's degree and medical degree in 1946 at the University of Chicago. He also married his high school sweetheart, Betty, that year, and the following year they became the parents of Harry Oberhelman III, the first of their five children.

After graduating, Oberhelman served with the U.S. Air Force Medical Corps before returning to the University of Chicago to complete his surgical training. He stayed on as a research assistant to his mentor, Lester Dragstedt, MD, who was then chair of surgery and a well-known innovator of surgical techniques to treat gastric and duodenal ulcers.

Move to Stanford

By 1960, Oberhelman was an associate professor of surgery at the University of Chicago. A former colleague who had joined the faculty at Stanford asked Oberhelman if he was interested in following suit. The Oberhelmans came to Stanford for a visit in November. The climate, compared to winter in Chicago, was instantly persuasive, Betty Oberhelman recalled: "We said, 'Yes, yes, yes!'" The family moved into a spacious five-bedroom home on the Stanford campus, complete with fruit trees in the backyard.

His loyalty to Stanford football was such that family outings were sometimes rearranged to accommodate the game schedule. He also attended the Stanford-Cal game annually for more than 50 years.

"There is a little place in heaven reserved for Harry," said his former colleague, James Mark. "Because he deserved it."

In addition to his wife, Oberhelman is survived by his brother John Oberhelman of Wheaton, Illinois; sister Barbara Uecker of Minneapolis; daughter Nancy Oberhelman of Colfax, California; sons Harry Oberhelman III of San Jose, California, James Oberhelman of Stanford, California, and Robert Oberhelman of Stanford, California; nine grandchildren; and many nieces and nephews. His son Thomas Oberhelman died in 2011.

A memorial service will be held at 4 p.m. March 16 at Memorial Church on the Stanford campus. In lieu of flowers, donations in memory of Oberhelman may be sent to Stanford University Development Services, P.O. Box 20466, Stanford, CA 94309-0466. ISM

OBITUARY

Robert Swenson, nephrologist who specialized in dialysis, dies at 82

By Tracie White

Robert Swenson, MD, a nephrologist who played a pioneering role in the early days of kidney transplantation and dialysis at Stanford Medicine, died Feb. 12 in Palo Alto of complications from Parkinson's disease. He was 82.

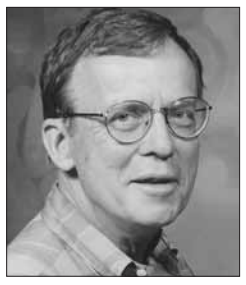
As a research fellow at Stanford in the early 1960s, Swenson administered dialysis to some of the first patients awaiting kidney transplants. These were the early days of kidney transplantation and dialysis, when a diagnosis of kidney disease was often considered a death sentence.

Stanford's kidney transplantation program was the first on the West Coast. In the spring 2000 issue of *Stanford Medicine* magazine, Swenson talked about the patients he cared for in the weeks leading up to their surgeries, administering dialysis as a bridge to help keep them alive.

"The initial recipients were a remarkable group of individuals," said Swenson, an associate professor emeritus of medicine at the School of Medicine. "There was no precedent for the program, but they were highly intelligent and highly motivated. They didn't have to be coaxed into anything in terms of their care. They knew the alternative really was unthinkable. It was death."

Leader in dialysis care

For the next three decades, Swenson would remain a fixture of the nephrology division at Stanford, leading the way in quality clinical care for dialysis patients, teaching medical students and running the dialysis units at the university's teaching hospitals. He retired in 1993. His friends and colleagues said he always remained a clinician first, his patients' care his top priority.



Robert Swenson

"He was a great clinician, a very good doctor," said his friend and colleague Rex Jamison, MD, professor emeritus of medicine. "As a doctor who takes care of patients in dialysis, you have to be a good all-around physician."

In 1972, Swenson became chief of the dialysis unit at what was then called the Veterans Administration Medical Center in Palo Alto. In 1981, he became medical director of Stanford's Hemodialysis Center, and then finished his medical career as chief of staff at Livermore's Veterans Administration Hospital, another teaching hospital of Stanford's.

Minnesota native

Born on April 19, 1933, in Brooten, Minnesota, Swenson graduated from the University of Minnesota in 1955 and earned a medical degree there in 1958. He met his future wife, Carol Conley, during his medical internship at Minneapolis General Hospital, where she was working as a medical technologist. They were married for 56 years.

"He wanted to be a doctor for the reason of helping the patient," she said. "He was very much a people person, very caring, thoughtful."

She added that even toward the end of his long, difficult battle with Parkinson's disease, he remained upbeat and helpful, and kept his well-known sense of humor. "He would do whatever small task he could to help me," she said. "The day before he died, though he hadn't been able to speak, he softly whispered that he loved me."

In addition to his wife, Swenson is survived by daughters Cynthia Swenson and Dana Raphaelson and four grandchildren.

A private burial was held.

Tax-deductible donations may be made in Swenson's name to support the National Institute of Neurological Disorders and Stroke Morris K. Udall Centers for Excellence for Parkinson's Disease Research (NINDS, 31 Center Drive, Rm 8A34, NIH, Bethesda, MD 20892). ISM

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STANFORD MEDICINE

Study underscores huge gap between surgeries available to rich, poor globally

By Ruthann Richter

The number of surgeries performed worldwide has grown steadily, particularly in the developing world, yet there remains an enormous gap in surgical care between rich and poor nations, according to a new study led by a School of Medicine researcher.

Between 2004 and 2012, the estimated annual number of operations around the globe rose 38 percent, from about 224 million to nearly 313 million, the researchers found. The biggest increase, 114 percent, occurred in relatively poor countries.

Yet these developing countries still account for a small percentage of operations overall. Only 6.3 percent of surgical procedures were done in the very poorest nations, which account for nearly 37 percent of the world's population, suggesting a vast unmet need for care, the researchers report.

"Surgery is being provided with increasing frequency in countries with very low expenditure on health care. Yet there is still a huge disparity between what is being offered in high health-expenditure countries versus the low-resourced countries," said Thomas Weiser, MD, an assistant professor of surgery at Stanford and lead author of the study.

Moreover, the most frequently performed operation in poor countries was cesarean section, which accounted for 30 percent of the total, suggesting other significant surgical needs, such as traumatic injuries and cancer care, are being given low priority, Weiser said.

The study was published online March 1 in *Bulletin of the World Health Organization.*

Quality, safety concerns

In addition to issues of access to surgery, Weiser said there is concern about the quality and safety of care provided in developing countries, where inadequate equipment and training, and a lack of sterile environments, can put patients at risk. These concerns are the focus of a separate study, published Feb. 22 online in the *Lancet Global Health*, in which he and his colleagues found high mortality rates and great variability in outcomes among patients undergoing three common procedures — C-section, appendectomy and hernia repair — in low- and middle-income countries.

"Surgery is a high-risk intervention," Weiser said. "We are talking about millions of operations a year, so a lot of patients are at risk. Safety is an important part of a care-delivery strategy."

In the past, he said, health systems in low- and middle-income countries have put a priority on managing infectious diseases and on maternal and child health. While these are still significant health issues, industrialization and aging populations have contributed to greater prevalence of other, noncommunicable conditions, such as heart disease and cancer, as well as traumatic injuries, Weiser said. These medical conditions often require surgical intervention, yet little is known about the availability of surgical care in many parts of the world, he said.

Hunting for accurate numbers

The study is an update of research Weiser and his colleagues originally conducted on data from 2004.

For purposes of the study, they categorized countries as very-low-expenditure (less than $100 per capita spent annually on health care); low-expenditure ($100 to $400 per capita annually); middle-expenditure ($400 to $1,000); and high-expenditure (more than $1,000).

They found that the greatest increase in surgical availability occurred in very-low- and low-expenditure countries during the eight-year period since the last analysis was performed. In the poorest nations, the number of operations rose 69 percent, from 394 to 666 procedures per 100,000 people each year. In low-expenditure countries, the increase was 114.6 percent, from 1,851 to 3,973 operations per 100,000 people per year.

ROB BYRON / SHUTTERSTOCK.COM

Focus on high-impact procedures

Still, they found a huge disparity in surgical offerings between rich and poor nations. In 2012, for instance, only 30 percent of surgical procedures were done in very-low- and low-expenditure countries, though these nations comprise 71 percent of the world's population. And the bulk of these procedures were C-sections.

"In resource-poor settings, they don't have the capacity to provide the full repertoire of services," Weiser said. "So they focus on the high-impact services — the ones that are given priority, like maternal health."

The results are in keeping with the 2015 report from Lancet Commission on Global Surgery, which found that some 5 billion people lack access to safe, affordable surgical care and that an additional 143 million operations were needed to meet emergency and essential needs.

Weiser said the latest study reinforces the need to invest in both human and physical capital to help build effective surgical capacity in the developing world.

"One is a skills issue. There aren't enough providers, and there's obviously a brain-drain issue, as trained providers leave their home countries to practice elsewhere," he said. "Surgery is a very unsupported discipline in some parts of the world, in terms of infrastructure, and it's high-risk. … A lot of those fundamental issues need to be addressed."

Other Stanford co-authors of the study are Micaela Esquivel, MD, resident in general surgery and surgical research fellow; research associate Pablo Tarsicio Uribe-Leitz, MD, MPH; graduate student Rui Fu; and medical student Tej Azad.

The study was supported by the Stanford Department of Surgery, Ariadne Laboratories in Boston and the Massachusetts General Hospital Department of Surgery. ISM

■ OBITUARY

Oncologist Holbrook Kohrt, who suffered from hemophilia, dies at 38

By Krista Conger

Holbrook Kohrt, MD, PhD, a noted clinician-researcher at Stanford Medicine dedicated to finding novel ways to arm the immune system to fight cancer, died Feb. 24 in Miami of complications from hemophilia. He was 38.

Kohrt was vacationing in the Bahamas when he became ill. He was flown to Jackson Memorial Hospital in Miami, where he suffered an intracranial hemorrhage on Feb. 22. He died two days later.

His colleagues say they will remember Kohrt for his brilliant mind, his thoughtful and impassioned care of cancer patients, and his unique ability to forge rapid and lasting personal connections with people from all walks of life.

An assistant professor of oncology at the School of Medicine, Kohrt struggled all his life with hemophilia, a disorder that prevents blood from clotting properly. He was open about his disease and how it motivated his research and patient care. In recent years, he had become resistant to the clotting factor used to treat his hemophilia.

"Holbrook knew that his time here on Earth would be short, and he worked tirelessly to accomplish as much as possible," said George Sledge Jr., MD, professor and chief of oncology. "He was an exceptional human being, unparalleled in his brilliance, dedication and persistence. He was passionate about research and making a difference for cancer patients. This is such a loss for his friends, colleagues and the field of medical oncology."

'A true Stanford loyalist'

Kohrt had been a member of the Stanford community since he arrived as a medical student in 2000. He completed his residency and fellowship and a PhD program of his own devising at the university. Described as "a true Stanford loyalist," he touched the lives of colleagues, trainees and patients with his openness about his own disease and his sincere desire to help others.

"A compassionate physician and an innovative investigator, Holbrook exemplified the best of Stanford Medicine," said Lloyd Minor, MD, dean of the School of Medicine, in an email to faculty, staff and students. "Holbrook was among the most brilliant translational researchers of his generation who worked tirelessly to put his findings to work for cancer patients. His bench research on novel therapies to enhance anti-tumor immunity regularly entered the clinic. But to many of us, Holbrook was much more than a brilliant mind; he was a warm and caring friend."

Holbrook Kohrt

Kohrt was born Dec. 14, 1977, in Paupack Township in Pennsylvania. The mutation that caused his hemophilia occurred spontaneously and his parents — pediatrician Alan Kohrt, MD, and nurse MaryLou Kidd — were surprised when their newborn son developed severe, unexplained bruising. But after some adjustment, the family took the diagnosis in stride and set about providing as normal a life as possible for their son, while also navigating the very real possibility that the blood products needed to keep him alive could be contaminated with viruses such as HIV and hepatitis.

'A unique perspective'

"As he grew older, Holbrook had to inject himself, sometimes on a near-daily basis, with blood clotting factor," said Ronald Levy, MD, professor of oncology. "This gave him a unique perspective. He was never able to forget his own mortality. He was acutely aware that he was a beneficiary of advances in medical science, and he was determined to give something back to others."

Kohrt's research focused on the idea that the immune system could be trained to recognize and fight cancer. He was the co-principal investigator for many Stanford-based trials exploring whether anticancer antibodies such as rituximab, which was developed in Levy's lab to treat non-Hodgkin's lymphoma, could synergize with other antibodies to provide an improved immune response.

He also devised clinical trials to learn whether it is possible to prevent the recurrence of solid tumors, such as cervical or ovarian cancers, by vaccinating a patient with small pieces of cancer-specific proteins to help the immune system immediately attack any remaining cancer cells.

Emails of grief and sorrow

In the hours after Kohrt's death, Sledge and Levy received an outpouring of emails from researchers around the world expressing their grief and sorrow.

"Holbrook was widely known and respected," said Sledge. "Even senior researchers in the field of medical oncology have commented that they learned a lot from their interactions with him."

Kohrt is survived by his parents, Mary Louise Kidd and Alan Kohrt; siblings Brandon, Barret and Brie Kohrt; stepmother Lois Kohrt; stepsiblings Jennifer Baldwin, Katherine Czapla and Ryan Baldwin; sisters-in-law Christina Chan and Angie Kohrt; nephew Ceiran Kohrt-Chan; and girlfriend Kendra Cannoy.

A celebration of Kohrt's life was held March 11 in Hawley, Pennsylvania.

A memorial website is at http://www.forevermissed.com/holbrook.

A memorial at Stanford will be held at a later date.

In lieu of flowers, donations in Kohrt's memory may be made to the Holbrook Kidd Kohrt Cancer Immunotherapy Fund at Anticancerfund.org; to a fund at Stanford University being set up to support the training of fellows in medical oncology (contact Ron Levy at levy@stanford.edu); or the Children's Hospital Foundation (contact Julie Taylor at julie.taylor@erlanger.org). ISM

The powerhouse behind Stanford Medicine's global cancer effort

By Ruthann Richter

As a child growing up in the United States, Ami Bhatt would frequently take trips with her parents back to their native country of India, where she saw a world altogether different from her comfortable life in San Jose, where she was born. It was a lesson in global disparity that she would not forget.

"It was impossible not to see the inequity," she said recently. "It seemed like we needed to do better."

Now the director of global oncology at Stanford, Bhatt, MD, PhD, is determined to do just that for patients in the developing world, who are more likely to suffer and die from cancer than those in developed countries. The majority of cancer cases — 57 percent — occur in low- and middle-income countries, and 65 percent of global cancer deaths occur in these parts of the world, according to the American Cancer Society.

"If you ask people, 'What do you think is a bigger problem in the developing world, malaria or cancer?' they will say malaria," said Bhatt, an assistant professor of medicine and of genetics. "But cancer kills more people than HIV, malaria and TB combined worldwide and in the developing world."

More cancer deaths in developing nations

Of the estimated 14 million new cancer cases reported worldwide in 2012, nearly 8 million were among patients in developing countries, according to the latest figures from the American Cancer Society. And more than 5 million of the 8.2 million reported cancer deaths that year were among patients in these nations.

> **"This is so important, and there aren't enough people doing it."**

Bhatt, who came to the School of Medicine in late 2014, has spent the last year and a half mobilizing dozens of faculty and trainees at the university to collaborate on projects to combat cancer in the developing world, where the disease is on the rise. With longer life expectancies, people are surviving into middle age and beyond — long enough to become prone to conditions such as heart disease and cancer. In Rwanda, for instance, life expectancy in the early 1990s was just 30 years, as many died of uncontrolled HIV. Now, with the wide availability of new life-prolonging antiretroviral drugs, life expectancy in the East African nation is 63, said Shruti Sheth, MD, a Stanford breast cancer specialist collaborating with Bhatt on a project to improve care in Rwanda.

Cancer-causing infections, such as hepatitis B and C, human papilloma virus and *H. pylori*, also are much more prevalent in the developing world. These pathogens can lead to liver, cervical and stomach cancers, respectively, with the highest rates occurring in developing countries, according to a recently published report.

Like most people, Bhatt was unaware of this trend until she started a hematology/oncology fellowship at Harvard in 2009 and began to look more closely at the numbers, which jumped off the page.

Not just a First World problem

"I had fallen victim to the same myth about global cancer — thinking it was only a First World problem," Bhatt said. "I started to look at the data and realized just how misguided that was."

She became passionate about the issue, finding a like-minded colleague in Franklin Huang, MD, PhD, another fellow in her program. "I think we really connected because we felt this strong sense of need for equity in cancer care," said Huang, now an instructor in medicine at Harvard. "We were surrounded by the most advanced treatments in the world, yet both of us knew there was a great distance between that and what less-fortunate people in the world suffer. We connected on day one, as we both believed deeply that that was wrong."

The two decided to form a nonprofit, called Global Oncology Inc., or GO, to build a community of people, both inside and outside academia, to tackle the issue and become advocates in the field. Bhatt's travels to developing countries, such as Botswana and India, brought home the stark disparities in care and reinforced her determination to act.

"When you go to these places, it's heartbreaking," she said. "You see women who come in with a mass of breast cancer that is out of control, causing their bodies to be misshapen."

While in Boston, she and her colleagues hosted the lone oncologist from Malawi, who serves a population of some 16 million. "There are probably more oncologists in the San Francisco Bay Area than in the entire region of sub-Saharan Africa," she said.

Patient-friendly materials

When they asked him how they could help, they learned that many patients drop out of treatment because they don't understand the therapeutic process and what to expect from chemotherapy. Through GO, Bhatt and Huang worked with a design firm and colleagues in sub-Saharan Africa to develop patient-friendly materials with appealing visuals and simple messages about chemotherapy and its potential side effects, as well as a log that patients can use to chart their complications.

The materials have been expanded for use in Rwanda, Botswana and Haiti, where they are distributed in cancer wards. "The feedback is that patients really appreciate them and share them with family members. It's something real that patients can touch and take home with them," Huang said.

The pair also worked with the National Cancer Institute — which has made fighting cancer worldwide a priority — to develop a map of cancer researchers and program managers, a first-of-its-kind resource to help spur collaboration among international experts in the field. The map includes more than 1,500 projects on six continents, with a search mechanism so individuals can readily connect with colleagues and share their collective knowledge.

"This is an excellent initiative, and it really brings people together," said Ann Hsing, PhD, MPH, a professor of medicine, who is co-leader of the Stanford Cancer Institute's Population Sciences Program. "If you want to work in this field, there is no easy way for people to find each other. This network will greatly facilitate that."

Relentless drive

There have been other successes as well. In 2013, while teaching classes on cancer and palliative care in Botswana, Bhatt discovered that patients in the southern African country had lost free access to Gleevec, an expensive, life-prolonging drug used to treat certain kinds of leukemia. Patients were being put on hydroxyurea, which might extend life for three to five years, compared with 20 to 30 years with Gleevec, she said. She and her colleagues persisted for months, lobbying the Ministry of Health, the drug manufacturer and other groups to restore access to the drug — an example of her relentless drive to gain more equitable

Tumor samples, packaged with gratitude, shipped to pathologist

By Ruthann Richter

Eduardo Zambrano's office displays some of the essentials of his pathology practice: a large microscope that dominates his desktop, and a cabinet overflowing with colorful, hand-painted wooden boxes, each one representing a Latin American child with cancer.

NORBERT VON DER GROEBEN

Eduardo Zambrano regularly receives tumor samples sent by pediatric oncologists in Latin America who treat poor, young cancer patients. Volunteering his time and expertise, Zambrano examines the samples and issues diagnoses.

Over the last 12 years, Zambrano, MD, has received as many as 1,000 tumor samples sent by pediatric oncologists in Venezuela and other Latin American countries who treat desperately poor, young patients with various forms of cancer. Each sample is mounted on a glass slide or embedded in wax, then carefully wrapped in tissue paper and lovingly packaged in a wooden box painted by a patient's mother or local artisan as a gesture of gratitude. The boxes are covered in suns, stars, flowers and other images of life and hope.

"To me, behind each one of these boxes is a child with cancer, and to know we've been able to help them is very special to me," said Zambrano, chief of pathology at Lucile Packard Children's Hospital Stanford. An expert in pediatric solid tumors, he volunteers his services on behalf of these youngsters.

> **"Behind each one of these boxes is a child with cancer."**

One or two boxes a week

A professor of pediatrics and of pathology who came to the School of Medicine a year ago, Zambrano said he receives one or two of these boxes a week. He examines the samples under the microscope and then issues diagnoses, some involving rare cancers. Clinicians ship the samples to him because they often don't have the equipment or expertise needed to accurately diagnose the problem.

"Very frequently the diagnosis [from the home country] is either incomplete because they don't have the resources to perform confirmatory tests, or it's wrong because they don't have expertise in pediatric tumors," he said. "It's frequent that I have to give them a significantly different diagnosis."

Among the most common tumors he sees are pediatric sarcomas, which can originate in various parts of the body; neuroblastomas; lymphomas; and brain tumors.

Though he has reviewed cases from Mexico, Bolivia, Brazil and his native country of Ecuador, many of the samples come from Venezuela, where he has a long-standing collaboration with

NORBERT VON DER GROEBEN

Ami Bhatt is mobilizing medical faculty and trainees to collaborate on projects to combat cancer in the developing world.

treatment for patients.

"I'm obsessed. I can't stop," she said. "This is so important, and there aren't enough people doing it."

In 2014, Bhatt was recruited to Stanford on the strength of her research, which focuses on how changes in the microbiome are associated with cancer. Because of her international work, Michele Barry, MD, professor of medicine and director of the Stanford Center for Innovation in Global Health, tapped her to lead the university's global cancer effort.

Since her arrival, Bhatt has been scouring the campus, rallying people who have an interest in the field and an expertise and willingness to work on projects.

Oncology program for Rwanda

Last summer, she introduced Sheth, a clinical assistant professor of medicine, to a Rwandan physician visiting Stanford for a global health training course. The Rwandan doctor, Francois Uwinkindi, MD, had previously led the country's HIV/AIDS effort, but had recently been charged by his government to develop a national oncology program from scratch. Bhatt and Sheth met with him to see what they could do.

He said that because of huge service gaps, "they had to prioritize all cases of cancer and put those people on the plane to Uganda or India," recalled Sheth, who was incredulous. "We just send our patients across the street. … We felt we must do something about this."

She said his initial goals were to create a cancer registry to get a realistic view of how many people are suffering from the disease, and to build the country's first radiation therapy center. The center is a huge undertaking; it means there has to be a stable electrical and water supply, as well as trained personnel to run the machinery, among other things, Sheth noted. She and Bhatt arranged meetings for Uwinkindi at Varian Medical Systems Inc. in Palo Alto, a pioneer in radiation therapy. They hope to travel to Rwanda later this year to get an up-front view of the challenges on the ground.

"It is achievable. Rwanda is absolutely poised to do this," said Sheth. "It's the only country in the region that is far enough ahead to consider these objectives. I stay up at night thinking, 'This is a big deal. It could happen.' It could be overcome but requires serious efforts.

"This is where a partnership with an academic institution is helpful," she added. "With a dynamic person like Ami, she can mobilize a lot of people and be really instrumental in overcoming these challenges."

An international tumor board

In another effort, Bhatt has gathered together a team of clinicians, including a radiologist, a radiation oncologist, a pathologist and residents, to serve on Stanford's first international tumor board. Tumor boards are teams of clinicians from diverse subspecialties who meet regularly to discuss difficult cancer cases and decide on the best course of action.

The group would essentially serve as a consulting body for cases in developing countries, using an online platform developed by GO to upload imaging studies and connect with clinicians from distant locales — a system that Bhatt said "throws a lifeline" to nonspecialists in the developing world.

"The idea would be to discuss cases via the Internet, review radiology and pathology images and other tests and come to a consensus on the best treatment options, trying to adapt them to the realities," said Eduardo Zambrano, MD, professor of pediatrics and of pathology, who has agreed to be part of the team.

An expert on bone, soft tissue and pediatric solid tumors, Zambrano serves on the musculoskeletal tumor board at Stanford, participating in reviews of both adult and pediatric cases. But he also has volunteered his expertise for years reading tumors slides and providing cancer diagnoses for very poor pediatric patients in Latin America. (*See story, page 4.*)

He said the fledgling international tumor board would likely focus its initial efforts in Guatemala; one of the participating clinicians, pediatric oncologist Sandra Luna-Fineman, MD, a professor of pediatrics, is a native of the country and has been in contact with colleagues there.

Population scientists

Bhatt also has been connecting with Stanford Cancer Institute faculty in population sciences who are trying to assess the extent of cancer in various parts of the world. Among the 56 countries in Africa, for instance, only a handful have high-quality cancer registries, large databases with patient histories, diagnoses, treatments and outcomes, said Hsing.

Providing reliable data on cancer and supporting research and prevention in the developing world are among the global populationwide initiatives of the Stanford Cancer Institute. (*See story below.*)

Bhatt said Stanford is in a unique position to lead this international effort.

"There are few universities that have the wealth of technical and engineering expertise and the multidisciplinary culture to contribute to solving this problem," she said. "That's why I think this is the year of global oncology at Stanford. I think if we sprinkle a little water on it, it will grow.

"There are so many places where we can make improvements," she added. "We just need to start." **ISM**

Zambrano

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a pediatric oncologist whom he texts or emails every day. She also sends him many photos of children in recovery, as well as notes of thanks: "You are a little angel who helps all of us," reads one in Spanish.

Rewarding work

Zambrano has visited Venezuela and met some of his patients and their families, but in recent years the country, worn down by years of oppressive governance, has become too dangerous for travel, he said.

"It's a tragedy in Venezuela," which is now one of the southern continent's poorest countries, he said. "For me, it's really an obligation to provide this service to them and a way to pay back for what I received in my childhood in South America."

Because some of the cases he diagnoses are rare or advanced forms of cancer not often seen here, they also serve as valuable teaching tools, he said.

"These cases have served me tremendously in teaching my residents," he said.

Zambrano said the work is a particularly rewarding part of his day. "I consider it very valuable, and it's something that really moves me," he said. "A lot of meaning would be lost if I couldn't do this work. And it's important to have meaning."

He said he is now looking for an outside funding source to help support the service. **ISM**

NORBERT VON DER GROEBEN

Each sample is packaged in a wooden box painted by a patient's mother or local artisan as a gesture of gratitude to Zambrano.

With population science experts, cancer institute broadens reach

By Ruthann Richter

The Stanford Cancer Institute is expanding its global reach with the recent addition of two noted population scientists who have major projects in the developing world.

Cancer epidemiologist Ann Hsing, PhD, professor of medicine and co-leader of the population sciences program at the institute, joined Stanford in late 2015 after 26 years at the National Cancer Institute and at the Cancer Prevention Institute of California. She now has an NCI grant for a pilot study in Ghana to develop a hospital cancer registry in the hope of expanding it to become a populationwide database for the West African country.

Beverly Mitchell

Hsing is also conducting genomewide studies on prostate cancer there and in three other African countries with colleagues at the Dana Farber Cancer Institute and Albert Einstein Medical School. Prostate cancer, together with colon and breast cancer, are the three most common causes of cancer deaths in Africa, she said.

Her colleague, Robert Haile, DrPh, professor of medicine and associate director for population sciences at the Stanford Cancer Institute, is focused on Asia and Latin America. He leads the Colon Cancer Family Registry, with centers in the United States, Canada and Australia, and the Latin American Cancer Epidemiology Consortium to coordinate cancer research in the region. In April, Stanford will host a two-day meeting of the LACE behavioral sciences section to discuss a number of initiatives, including programs to promote physical activity as a prevention strategy.

These populationwide initiatives are part of the Stanford Cancer Institute's new emphasis on its international health effort, said Beverly Mitchell, MD, the center's director. "Because we are a relatively new cancer center, a lot of our focus has been on building our clinical research and translational medicine programs," Mitchell said. "But going forward, we will have a much greater focus on global health." **ISM**

Macrophages

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So-called M1 macrophages, on the other hand, are inflammatory: As hard-boiled as traffic cops who've heard every excuse, they blow the whistle on pathogens, recruiting other types of immune cells to the scene. In addition, they attack the invaders themselves by spitting out nasty little clouds of biohazardous chemicals called free radicals. And they squirt out proteins that act both locally and systemically to ramp up the entire immune system to high-alert status.

Testing for inflammation

"Some believe that coronary artery disease patients' macrophages are so preoccupied with their inflammatory power trip they neglect their clean-up tasks," allowing plaque to continue building up in arteries, Weyand said. In any case, the unremitting inflammation renders the plaques increasingly brittle, sometimes culminating in a piece of plaque suddenly breaking off and wounding the artery wall. The ensuing speedy formation of a clot can trigger a heart attack.

The presence of even mildly elevated levels of systemic inflammation can be revealed in laboratory blood tests, such as the one for C-reactive protein, or CRP, now routine in checking cardiovascular health. Statin drugs, which substantially slow the progression of coronary artery disease and prevent heart attacks, are now understood to work not just by lowering lipid levels but also by reducing systemic inflammation. That's why statins reduce heart-related problems among patients who have normal blood-lipid levels but high blood levels of CRP.

The CRP test, in turn, is a good proxy for another protein with a starring role in driving inflammation throughout the body: an immune-signaling protein known as interleukin-6. The body's premier producers of IL-6 are M1 macrophages.

Born in the bone

Macrophages begin life as cells called monocytes that are born in the body's bone marrow. Released into the circulation, monocytes travel through the bloodstream until, responding to chemical "danger signals" that indicate possible injury or infection, they slip into a tissue, take up residence and differentiate into macrophages.

Weyand and her associates commenced their study by comparing monocytes harvested from the blood of 140 patients with coronary artery disease, each of whom had experienced at least one heart attack, with those from 105 healthy, demographically matched control subjects. The blood was obtained by study co-authors John Giacomini, MD, chief of cardiology at the Veterans Affairs Palo Alto Health Care System and professor of medicine at Stanford, and assistant professor of medicine Themistocles Assimes, MD, PhD.

The scientists cultured the monocytes and used standard laboratory methods to differentiate them into macrophages. They observed that the monocytes from patients with coronary artery disease had a pronounced predisposition to develop into inflammatory, IL-6-producing M1 macrophages.

"We also found that macrophages from people with Type 2 diabetes, hyperlipidemia or hypertension — each of these a known risk factor for coronary artery disease — were making more IL-6," said Weyand. The greater the number of these risk factors they had, the more IL-6 their macrophages made, she said.

"Even before taking up residence in arterial plaque and becoming full-fledged macrophages, these patients' monocytes were already leaning toward becoming inflammatory," Weyand said. "If you simply overfeed normal monocytes or macrophages, they do not turn into high IL-6 producers. We wondered why."

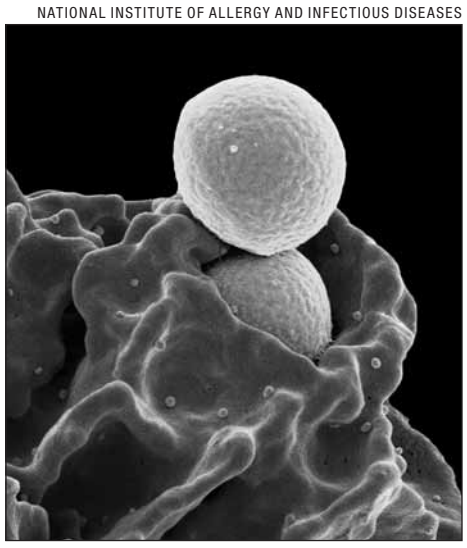
In a series of follow-up experiments, she and her colleagues discovered the reason.

Lots of free radicals

First, they noticed that levels of free radicals inside patient-derived macrophages were double those of macrophages derived from healthy subjects. They traced these free radicals' production to compartments within the patients' macrophages known as mitochondria, which abound in all living cells and serve as their powerhouses, supplying energy by burning sugars and fatty acids.

"This is no easy task," Weyand said. "In doing so, the mitochondria inevitably wind up generating free radicals. The harder they work, the more free radicals they produce."

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES



A macrophage ingests bacteria (whitish objects). A new study indicates that macrophages that take up too much glucose may play a role in coronary artery disease.

When Weyand and her associates used a drug to mop up free radicals in the mitochondria of patient-derived macrophages, their IL-6 production — a major feature of their inflammatory prowess — dropped off considerably.

Blocking glucose metabolism within the mitochondria had the same effect. "Something in there is leading to excessive IL-6 production," said Weyand. "That something is our old friend sugar."

The researchers pinned the excessive free-radical production in the mitochondria of patient-derived macrophages to excessive uptake of glucose by those cells, attributable to a faulty overproduction of proteins responsible for importing glucose into cells.

"The primary problem, we learned, is that these macrophages take up glucose at a higher rate than normal cells do," said Weyand. "That causes them to break it down faster, overheating their mitochondria, which then produce too many free radicals."

Surprising finding

One of the most surprising findings was the discovery that those high levels of free radicals were inducing a change in the status of PKM2, an enzyme that normally busies itself by helping to generate energy from the breakdown of glucose. Under the free-radicals' influence, the scientists learned, PKM2 blows off its day job and instead heads into the cell nucleus, where it activates a protein called STAT3 that proceeds to ramp up the production of pro-inflammatory cytokines, including IL-6.

In the lab, the scientists tested a drug designed to prevent PKM2's status change and succeeded in lowering the IL-6 output of patient-derived M1 macrophages.

The good news, Weyand said, is that several interventions — blocking glucose uptake, sponging up free radicals and preventing PKM2's status change — reduce the macrophages' excess inflammatory activity. This could lead to new therapeutic approaches, she said.

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

Other Stanford co-authors of the study are Rafal Nazarewicz, PhD, a former visiting instructor; study coordinator Barbara Wallis, DO; postdoctoral scholars Rolando Yanes, PhD, and Marc Hilhorst, MD, PhD; visiting assistant professor Ryu Watanabe, MD, PhD; associate professor of biomedical data science Lu Tian, SciD; and professor of immunology and rheumatology Jorg Goronzy, MD.

The study was funded by the National Institutes of Health and the Govenar Discovery Fund.

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

Researchers test upgraded heart pump device

By Tracie White

Researchers at the School of Medicine have launched their portion of a multicenter clinical trial that is evaluating a new version of a mechanical heart pump designed with remote-monitoring capabilities.

As part of that trial, the Stanford team implanted the device Jan. 21 in a patient with heart failure. That patient was the first person on the West Coast to receive it.

Richard Ha

The pump is an upgraded version of a left ventricular assist device, or LVAD, which has been used in the United States since 1984, when a Stanford patient was the first person nationwide to have such a device implanted. The LVAD is used to restore blood flow when the left ventricle fails to pump enough blood to sustain life. Most often, the pumps serve as a bridge to keep patients alive while they wait for a donor heart.

The new version, called the HeartAssist 5, is being evaluated for safety and efficacy. The randomized trial is being conducted at 15-20 sites. The plan is for 192 patients with severe heart failure to participate. Half will be implanted with the new version of the device, and the other half with the regular version. The trial is restricted to patients on the heart transplant list.

Stanford plans to recruit 20 heart failure patients for the study. Ten will receive the new device.

Several features of the experimental device have the potential to improve patient outcomes, said Richard Ha, MD, a clinical assistant professor of cardiovascular medicine who is the principal investigator for Stanford's portion of the trial.

"This would be the first device that we could potentially monitor from a distance," said Ha, who also is a heart and lung transplant surgeon at Stanford Health Care and surgical director of the ventricular assist device program. Built-in wireless monitors are designed to alert clinicians 24/7 if blood-flow problems develop.

The remote-monitoring capabilities could also help patients who live far away from cardiologists with LVAD expertise. "Patients would not have to come here as often for visits," Ha said. Currently, patients are required to make frequent checkup visits in the six months following surgery.

In addition, the new device has a smaller motor, designed to help reduce blood clotting, and a sensor to measure blood-flow speed, Ha said.

Dipanjan Banerjee, MD, medical director of the mechanical circulatory support program at Stanford, also sees potential advantages of the new device. "The device has an ultrasound probe incorporated that directly measures blood flow generated by the device, as opposed to other LVADs, which estimate flow," said Banerjee. "More accurate measurements of flow may allow us to fine-tune the device speed to match the patient's needs."

The trial is expected to run through 2017. It is sponsored by Houston-based ReliantHeart Inc., which makes the device. For more information about the trial, contact Kokil Bakshi at kbakshi@stanford.edu. ISM

Center launched to explore, exploit human microbiome

By Bruce Goldman

The Stanford Institute for Immunity, Transplantation and Infection has launched the Center for Human Microbiome Studies to coordinate research on the myriad microbes that people carry on and inside themselves.

Seeded with a founding gift from investor and venture capitalist Paul Klingenstein, who earned an MBA at Stanford, the center will serve as the hub of an interdisciplinary network of scientists to maximize the use of advanced technologies that enable researchers to learn far more than was previously possible about the microbes with which we humans have co-evolved throughout our evolutionary history.

Co-directors of the center are Justin Sonnenburg, PhD, associate professor of microbiology and immunology, and David Relman, MD, professor of microbiology and immunology and of medicine.

Technological advances spearheaded by Relman, Sonnenburg and others have allowed researchers to conduct "censuses" of the thousands of species of one-celled creatures that inhabit our skin and body cavities, as well as to methodically explore the antagonistic and synergistic interactions among these fellow travelers, trillions of which reside within or upon every healthy person. When faulty diets, antibiotics and numerous other perturbations wreak havoc on an individual's collection of commensal microbes — referred to as the microbiota — the results can range from poor digestion to immune imbalances, obesity and other metabolic disorders, pathogenic infection and more.

One of the center's goals is to speed the translation of findings from such studies to clinically useful therapeutic approaches. Another is to influence medical practice as well as dietary and lifestyle habits.

"We hope to fund studies that will provide the quickest path to realizing the potential of the microbiome to prevent and treat disease," Sonnenburg said. ISM

Myc

continued from page 1

autoimmune diseases but also in normal pregnancy. It's often overexpressed on human tumor cells. An antibody that binds to PD-L1 has been approved by the U.S. Food and Drug Administration to treat bladder and non-small-cell lung cancer, but it has been shown to be effective in the treatment of many cancers.

In cancer, Myc a usual suspect

Researchers in Felsher's laboratory have been studying the Myc protein for more than a decade. It is encoded by a type of gene known as an oncogene. Oncogenes normally perform vital cellular functions, but when mutated or expressed incorrectly they become powerful cancer promoters. The Myc oncogene is mutated or misregulated in over half of all human cancers.

In particular, Felsher's lab studies a phenomenon known as oncogene addiction, in which tumor cells are completely dependent on the expression of the oncogene. Blocking the expression of the Myc gene in these cases causes the complete regression of tumors in animals.

In 2010, Felsher and his colleagues showed that this regression could only occur in animals with an intact immune system, but it wasn't clear why.

"Since then, I've had it in the back of my mind that there must be a relationship between Myc and the immune system," said Felsher.

Turning off Myc expression

Casey and Felsher decided to see if there was a link between Myc expression and the levels of CD47 and PD-L1 proteins on the surface of cancer cells. To do so, they investigated what would happen if they actively turned off Myc expression in tumor cells from mice or humans. They found that a reduction in Myc caused a similar reduction in the levels of CD47 and PD-L1 proteins on the surface of mouse and human acute lymphoblastic leukemia cells, mouse and human liver cancer cells, human skin cancer cells, and human non-small-cell lung cancer cells. In contrast, levels of other immune regulatory molecules found on the surface of the cells were unaffected.

> "There is a growing sense of tremendous excitement in the field of cancer immunotherapy."

In publicly available gene expression data on tumor samples from hundreds of patients, they found that the levels of Myc expression correlated strongly with expression levels of CD47 and PD-L1 genes in liver, kidney and colorectal tumors.

The researchers then looked directly at the regulatory regions in the CD47 and PD-L1 genes. They found high levels of the Myc protein bound directly to the promoter regions of both CD47 and PD-L1 in mouse leukemia cells, as well as in a human bone cancer cell line. They were also able to verify that this binding increased the expression of the CD47 gene in a human blood cell line.

Possible treatment synergy

Finally, Casey and Felsher engineered mouse leukemia cells to constantly express CD47 or PD-L1 genes regardless of Myc expression status. These cells were better able than control cells to evade the detection of immune cells like macrophages and T cells, and, unlike in previous experiments from Felsher's laboratory, tumors arising from these cells did not regress when Myc expression was deactivated.

"What we're learning is that if CD47 and PD-L1 are present on the surfaces of cancer cells, even if you shut down a cancer gene, the animal doesn't mount an adequate immune response, and the tumors don't regress," said Felsher.

The work suggests that a combination of therapies targeting the expression of both Myc and CD47 or PD-L1 could possibly have a synergistic effect by slowing or stopping tumor growth, and also waving a red flag at the immune system, Felsher said.

"There is a growing sense of tremendous excitement in the field of cancer immunotherapy," said Felsher. "In many cases, it's working. But it's not been clear why some cancers are more sensitive than others. Our work highlights a direct link between oncogene expression and immune regulation that could be exploited to help patients."

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

Other Stanford co-authors of the paper are oncology instructor Yulin Li, MD, PhD; postdoctoral scholars Ling Tong, PhD, Arvin Gouw, PhD, and Virginie Baylot, PhD; former research assistant Kelly Fitzgerald; and undergraduate student Rachel Do.

The research was supported by the National Institutes of Health.

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

Vitamin D

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sociated with tumor growth and breast cancer metastasis.

The finding builds upon several previous studies suggesting that low levels of vitamin D not only increase a person's risk of developing breast cancer, but are also correlated with more-aggressive tumors and worse prognoses. Although the research was conducted primarily in mice and on mouse cells, the researchers found in a study of 34 breast cancer patients that levels of circulating vitamin D were inversely correlated with the expression levels of ID1 protein in their tumors, and they confirmed that a vitamin D metabolite directly controls the expression of the ID1 gene in a human breast cancer cell line.

"Although much more research needs to be done, research from our lab and others suggests that people at risk for breast cancer should know their vitamin D levels and take steps to correct any deficiencies," said Brian Feldman, MD, PhD, assistant professor of pediatrics.

Feldman, who is a Bechtel Endowed Faculty Scholar, is the senior author of the study, which was published online March 2 in *Endocrinology*. Lead authors of the work are graduate student Jasmaine Williams and postdoctoral scholar Abhishek Aggarwal, PhD.

Confusion about optimal dosage

The researchers emphasize that their findings don't imply that more vitamin D is always better. Correcting a deficiency is very different from taking more than the recommended dosage, which the Institute of Medicine says is 600 international units per day for people age 70 and younger, and 800 IU for older adults. Excess levels, variously estimated to occur at about 4,000 to 10,000 IU per day, have been linked to damage to the kidneys, cardiovascular system and other organs.

Not all medical organizations agree on the optimal amount of vitamin D. The confusion stems in part from the fact that, although it can be ingested via food and nutritional supplements, our bodies can also make vitamin D with the help of ultraviolet rays from the sun. So it's difficult to know exactly how much any individual may need to take as a supplement, and that amount can vary throughout the year. Those who don't get enough sun exposure, or people with darker skin, are more likely than fair-skinned individuals who spend time outdoors each day to be deficient. The use of sunscreen can also affect vitamin D synthesis.

Once ingested or made by the body, vitamin D is converted through a series of steps into its active form, calcitriol. Calcitriol binds to a protein in cells called the vitamin D receptor, which then enters the cell's nucleus to control the expression of a variety of genes, including those involved in calcium absorption and bone health.

A brake on tumor progression?

The link between vitamin D and calcium metabolism is well-known. More recently, however, researchers have begun to suspect that vitamin D may affect many other important biological processes, including tumor progression. However, it's not clear exactly which step in cancer development the vitamin may affect.

In the new study, Williams and Aggarwal investigated whether vitamin D levels affected the metastatic ability of mouse breast cancer cells implanted into the mammary fat pad of laboratory mice. One group of 10 mice was first fed a diet lacking in vitamin D for 10 weeks; the other 10 received a normal dose in their food.

> "This direct association between vitamin D levels and ID1 expression is very interesting to us."

Mice fed a diet deficient in vitamin D developed palpable tumors an average of seven days sooner than their peers, and after six weeks of growth those tumors were significantly larger in size than those in animals with adequate vitamin D levels.

The researchers then examined two well-characterized lines of mouse tumor cells, 168FARN and 4T1. Prior research has shown that cells from either group form tumors when implanted in laboratory mice, but only 4T1 results in aggressive tumors that spread to other parts of the animal's body.

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Brian Feldman and his colleagues found that breast tumors in laboratory mice deficient in vitamin D grow faster and are more likely to metastasize than those in mice with adequate levels of the vitamin.

Vitamin D and ID1 expression

The researchers found that the 4T1 cell line expresses significantly lower levels of the vitamin D receptor protein. When they genetically engineered 168FARN cells to also have lower-than-normal levels of the VDR protein, the cells began to behave much more like the 4T1 cells. They migrated more freely in a laboratory dish and, when injected into 10 mice, they grew aggressively. In six of these mice, the modified cancer cells metastasized to the liver during the course of four weeks. In contrast, none of the tumors in the 10 mice that received unmodified 168FARN cells spread to the liver during the study period.

To identify how vitamin D might be affecting metastasis, the researchers analyzed gene expression in the tumors that developed in mice with varied levels of vitamin D in their diets and in the tumors of mice injected with modified or unmodified 168FARN cells. They found that in cases in which vitamin D was lacking from the diet or in which cells were missing much of the VDR protein, tumor cells expressed more of a gene called ID1, which has been shown to play a role in breast cancer metastasis. Further investigation showed that VDR binds directly to a stretch of DNA near the ID1 gene and suppresses its expression in both mouse and human cells.

Finally, the researchers compared circulating vitamin D levels in 34 breast cancer patients at Stanford with the levels of ID1 in tumor cells that were surgically removed during the course of disease treatment. They found an inverse correlation: Women with lower levels of vitamin D expressed more ID1 in their tumor tissues than did women with higher levels of vitamin D.

"Our study shows that a deficiency in vitamin D levels, or an inability of tumor cells to respond appropriately to the presence of vitamin D, is sufficient to trigger non-metastatic cancer cells to become metastatic," said Feldman. "It's enough to significantly accelerate tumor progression in our mouse model. Further studies are warranted, but this direct association between vitamin D levels and ID1 expression is very interesting to us."

Other Stanford co-authors of the paper are research associate Srilatha Swami, PhD, senior research scientist Aruna Krishnan, PhD, postdoctoral scholar Lijuan Ji, PhD, and assistant professor of comparative medicine Megan Albertelli, PhD.

The research was supported by the Stanford Cancer Institute, the California Breast Cancer Research Program and a National Institutes of Health Director's New Innovator Award. **ISM**

5 QUESTIONS

an occasional feature in which an expert answers five questions on a science or policy topic

Bruce Reitz on first successful heart-lung transplant

On March 9, 1981, just minutes past midnight, Mary Gohlke, a 45-year-old Arizona woman dying of primary pulmonary hypertension, was wheeled into a Stanford Hospital operating room for a heart-lung transplant surgery that would become a medical milestone.

For many months, as her health failed, Gohlke had waited, stuck: Lung transplants were technically feasible, but no human lung transplant patient had survived more than 23 days. The only antirejection drugs then approved for use interfered with the healing of the surgical wounds where new lungs connected to the patient's airway. After Gohlke read a newspaper story about the successful heart-lung transplants Stanford cardiothoracic surgeon Bruce Reitz, MD, had done on rhesus monkeys, she telephoned him. Reitz took the call. She asked him how many heart-lung transplants he planned to do that year on humans. He said 10. She told him she'd like to be the tenth so she "could see how the rest of them turn out," and Reitz responded with a chuckle.

The holdup, however, was the U.S. Food and Drug Administration. It had approved a better antirejection drug, cyclosporin A, for heart-transplant patients, but not for other transplant patients. Stanford had asked the FDA to approve cyclosporin A for heart-lung transplant patients, too — and then waited and waited. Gohlke, increasingly desperate, asked her former boss, the executive editor of the Mesa Tribune*, to help. He made calls to then-U.S. Sen. Dennis DeConcini, D-Arizona, and about an hour later the FDA approved the drug for use in heart-lung transplantation at all qualified hospitals. Gohlke received her new heart and lungs — becoming the first patient in the world to undergo a successful heart-lung transplant — and lived for five years with her new organs.*

Reitz, the Norman E. Shumway Professor, Emeritus, talked with writer Sara Wykes, about that first surgery 35 years ago— and the work that came before it.

1 How did you become involved in doing heart-lung transplants?

REITZ: As an undergraduate physiology major at Stanford, I had done research with a professor studying the immunological reactions of the heart. Then, in 1969, when I was still a medical student, I asked about working in the research lab run by Dr. Norman Shumway, chief of the Division of Cardiothoracic Surgery and the father of heart transplantation. Eighteen months earlier, he and his team did the first successful adult heart transplant in the United States. He said yes. After I finished my residency in cardiac surgery, I came back to the lab. I asked Dr. Shumway what needed to be done, and he said he'd like to see if we could make some progress in combining heart transplantation with complete bilateral lung transplantation. There were patients with congenital heart defects and patients with severe lung disease who currently could not be treated by transplantation. Mary Gohlke, whose heart had been damaged by her disease, was exactly that kind of patient. Nor did we have a way to transplant lungs then except as part of a heart-lung package.

2 What were the first steps?

REITZ: We began by doing auto-transplants: Taking the organs out and replacing them in the same animal. We were using rhesus monkeys. That helped us establish the techniques of the surgery without organ rejection. Then we started looking at the antirejection drugs then in use, but they just didn't work.

3 How did you solve that problem?

REITZ: A new immunosuppressive drug known as cyclosporin A had been developed in Europe by Sandoz Inc. This compound, after experimental and clinical work by professors Roy Calne and David White at Cambridge University, seemed to provide much better immunosuppression. In the summer of 1978, White visited Stanford and gave a seminar to a small group of the heart transplant team. Sandoz agreed to give the Stanford laboratory some of the drug. We could see that when we used it on our monkey transplants that it was very effective: It prevented rejection but allowed good healing of the transplant connection at the trachea and quick recovery of the animals to apparently normal pulmonary and heart function.

CHUCK PAINTER

Bruce Reitz (left) and Norman Shumway (right) perform the first successful heart-lung transplant in 1981 at Stanford Hospital.

4 What held you back from its use in heart-lung transplant?

REITZ: By early fall of 1980, we began to think about potential patients. The Food and Drug Administration and the Stanford Institutional Review Board gave approval for a clinical trial with heart transplants. The first heart transplant trial patient to get cyclosporin was operated on in December 1980. He and subsequent patients showed improved postoperative recoveries that were clearly different from those of the previous patients receiving steroids and a different immunosuppressant medication. But the FDA had not approved cyclosporin's use for anything other than heart transplant. Then Mary Gohlke made that phone call to her boss, and the FDA gave a blanket approval for Stanford and other qualified medical centers to use the drug for heart-lung transplant.

Bruce Reitz

5 What was the surgery like?

REITZ: We had a double-sized team of doctors — one for the donor and one for Mary Gohlke. It included Dr. Shumway; Dr. John Wallwork, then a transplant fellow and now chief of cardiothoracic surgery at Papworth Hospital in Cambridge, England; Dr. Edward Stinson, who had partnered with Dr. Shumway for the first heart transplant surgery; and Dr. Philip Oyer, who went on to co-develop and implant the first mechanical ventricular assist device. The appearance of Mary Gohlke's totally empty chest was indeed a dramatic moment. I wondered, "Is this really going to work out?" But the implantation went smoothly, the heart resuscitated quickly, and lung function was adequate immediately. We finished up about six hours later. Mary made a steady improvement. It was such a transformation for her! To take someone back from the brink of death and give them health — that's one of the great things about transplant and about being involved in transplant. ISM

OF NOTE

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

PAUL BOLLYKY, MD, DPhil, assistant professor of medicine, received a Catalyst Award from the Dr. Ralph and Marian Falk Medical Research Trust. The $485,000 award will fund his effort to develop a new therapy for *Pseudomonas aeruginosa* antibiotic-resistant infections, which can cause pneumonia, wound infections or hospital-acquired infections.

DAVID FIORENTINO, MD, PhD, was promoted to professor of dermatology and of medicine, effective Oct. 1. He is the associate program director for the dermatology residency and specializes in autoimmunity-related skin disease. He is co-director of a multidisciplinary dermatology-rheumatology clinic that treats patients with scleroderma, myositis, psoriasis and lupus. His research focuses on the role of auto-antigens and cancer in the pathogenesis of dermatomyositis.

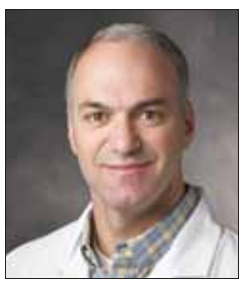
JEREMY GOLDHABER-FIEBERT, PhD, was promoted to associate professor of medicine, effective Sept. 1. He uses computer simulation modeling, cost-effectiveness analyses and econometric techniques to examine policies related to the prevention and management of chronic diseases, including hepatitis C, tuberculosis and Type 2 diabetes.

HANLEE JI, MD, was promoted to associate professor of medicine, effective Dec. 1. His research focuses on using new genomic sequencing technologies to understand cancer metastasis and on developing genetic-based markers for precision cancer medicine.

AYA KAMAYA, MD, was promoted to associate professor of radiology, effective Sept. 1. Her research focuses on abdominal and pelvic imaging, including hepatobiliary cancer and hepatocellular carcinoma imaging, perfusion CT of abdominal tumors, gynecologic and urologic imaging, ultrasound innovations and thyroid cancer ultrasound imaging. She serves as the associate program director for the Body Imaging Fellowship at Stanford.

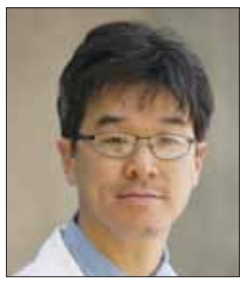
JOHN OGHALAI, MD, was promoted to professor of otolaryngology-head and neck surgery, effective Aug. 1. He directs the Stanford Children's Hearing Center and its pediatric cochlear implant team. He specializes in managing adult skull base tumors and in the evaluation and management of children with hearing loss. ISM

Paul Bollyky



David Fiorentino

Jeremy Goldhaber-Fiebert



Hanlee Ji

Aya Kamaya

John Oghalai

Registration now open for Big Data in Biomedicine 2016

The popular Big Data in Biomedicine conference, now in its fourth year, is open for registration. It will be held May 25-26 at Stanford.

Lloyd Minor, MD, dean of the School of Medicine, will welcome attendees to campus and highlight 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.

Among the dozens of speakers will be Kathy Hudson, PhD, deputy director for science, outreach and policy at the National Institutes of Health; Harlan Krumholz, MD, a cardiologist and director of the Yale-New Haven Hospital Center for Outcomes Research and Evaluation; and Werner Eberhardt, PhD, general manager for personalized medicine at SAP.

The conference will also feature a corporate technical showcase, catered on-site meals and a poster session.

For more information and to register, visit http://bigdata.stanford.edu. ISM

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