Sugar-gobbling cells may drive heart disease

By Bruce Goldman

Hyper-aggressive immune cells harbored in arterial plaque and binging 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, and 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, nailing 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.

The other molecule 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.

"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'

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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

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 research published online Mar. 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.

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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 associated with the spread of breast cancer.

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Harry Oberhelman, Jr., MD, professor emeritus of surgery and former chief of general surgery and gastroenterological surgery at the School of Medicine, died Feb. 10. He was born in 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 knew him personally knew him only as “the sweetest, mildest person you could imagine,” said James B.D. Mark, MD, professor emeritus of medicine. “Surgeons can be imperious, but Harry was very down-to-earth. He was a wonderful match of compassion and competence.”

Oberhelman was as fiercely devoted to teaching young surgeons. He trained more than 160 general surgery residents in his 50 years at Stanford. “He taught us the art to pay attention to the patient,” said Krummel, the Susan B. Ford Surgeon-in-Chief at Stanford and the Lucile Packard Children’s Hospital Stanford and the associate director of surgery from 1997-2000. “He taught us the art to pay attention to the patient,” said Krummel, the Susan B. Ford Surgeon-in-Chief at Stanford and the Lucile Packard Children’s Hospital Stanford and the associate director of surgery from 1997-2000. “He taught us the art to pay attention to the patient.”

Harry was the model of a general surgeon, said James Mark. “He was a true general surgeon.”

The Obrehelmans came to Stanford for a visit in November 1943. He returned to the Midwest to complete a joint medical degree his junior year. In 1945, he married his high school sweetheart, Betty, the daughter of a surgeon. 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 at UChicago for a research fellowship with Dr. Margaret Draggstedt, 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 1966, 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, Berry 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 members sometimes couldn’t accommodate the Oberhelmans on game days. He also attended the Stanford-Cal game annually for more than 50 years.

There is a little chapel that was always 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 Francisco, 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, PO. Box 20466, Stanford, CA 94309-0466.
A memorial at Stanford will be held at a later date.

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 in an email to 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. More than 224 million 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 focused on providing maternal mortality and major surgical diseases and on maternal and child health. While these still are 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 feasibility and feasibility of providing care in many parts of the world, the said.

Hunting for accurate numbers

The study is an update of research performed by 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).

Data were then adjusted to take into account national gross domestic product per capita and were used to estimate the number of surgical procedures performed in each country.

The number of surgical procedures performed in rich countries was nearly 114.6 percent, from 1,851 to 3,973 operations per 100,000 people per year. In low-expenditure countries, the increase was 114.6 percent, from 1,851 to 3,973 operations per 100,000 people per year. The study was supported by the Stanford University School of Medicine, in an email to other Stanford co-authors of the study are Micaela Esquivel, MD, resident in general surgery and research fellow; research associate Pablo Tarsicio Uribe-Leitz, MD, MPH; graduate student Rui Fu; and medical student Tey Arad.

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

Oncologist Holbrook Kohrt, who suffered from hemophilia, died 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. 22 in Miami, which accounted for 30 percent of the total, suggesting other significant surgical needs, such as traumatic injuries. More than 224 million operations a year, so a lot of patients are at risk. Safety is an important part of a care-delivery strategy.

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.

In his leagues say they will remember Kohrt for his brilliant mind, his thoughtful and impassioned care of cancer patients, and his unique ability to forge 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. Kohrt was determined to give something back to others. As a beneficiary of advances in medical science, and his sincere desire to help others.

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.

Kohrt was the co-principal investigator for many Stanford-based trials exploring whether antinecancer anti-bodies 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 was also a pioneer in developing small pieces of cancer-specific proteins to help the immune system immediately attack any remaining cancer cells.

Huntig for accurate numbers

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 low-income regions, 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 million 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 small 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 under-supported 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."

A ‘true Stanford loyalist’

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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 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 American Cancer Society. And more than 5 million of the 8.2 million reported cancer deaths that year were among patients in these nations.

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, are also 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 and the page 3 of her manuscript.

"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 every time 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 there 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.

“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 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 connect readily with colleagues and share their collective knowledge.

“This is an excellent initiative, and it really brings people together,” said Ann Huang, 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 2011, 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 this drug, which might extend life for five to 10 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 treatment.

Taking on cancer in the developing world

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 overtime with colorful, hand-painted wooden boxes, each one representing a Latin American child with cancer.

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 artist 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 Lahey Packard Children’s Hospital Stanford. An expert in pediatric solid tumors, he volunteers his expertise and advice on behalf of these youngsters.

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 because they are 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 a specific area of the body; neuroblastomas; lymphomas; and brain tumors.

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

Tumor samples, packaged with gratitude, shipped to pathologist

By Ruthann Richter

Edward 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.
Taking on cancer in developing countries

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... to nonprofessionals in the developing world. “The idea would be to discuss cases via the Internet, review radiology and pathology images and other tests and try to reach a consensus on the best treatment options, trying to adapt them to the realities,” said Eduardo Zambrano, MD, professor of pediatrics, 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 clinician, pediatric oncologist, Sandra Luna-Fineman, MD, a professor of pediatrics, is a native of the country and has been in contact with colleagues there.

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 cultural capacity 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.”

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.

Hsing is also conducting gene-wide 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.

By Beverly Mitchell

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, 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.”

With population science experts, cancer institute broadens reach
Researchers test upgraded heart pump device

By Tracie White

Researchers at the School of Medicine have launched 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.

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 patient was the first person on the West Coast to receive one. The 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, MD

"This was the first device that we could envision being used in patients with heart failure 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 from medical centers with LVAD expertise. "Patients would not have to come here as often for visits," Ha said. "Caretakers and others 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.

Dipanjali Banerjee, MD, medical director of the mechanical circulatory support program at Stanford, also sees potential advantages of the new device. "The device has an ultrasonic probe in its body to measure blood flow and generate the device, as opposed to other LVADs, which estimate flow," said Banerjee. "More accurate measurement 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 Koki Bakshi at kbbakshi@stanford.edu.

Researchers test upgraded heart pump device

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 Klingen, 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 "we carry around," said Weyand. "It’s a transformational project.

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

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Researchers test upgraded heart pump device

The primary problem, we learned, is that these macrophages take up glucose at a higher rate than normal cells do. When that happens, glucose breaks down, faster, overheating their mitochondria, which then produce too much IL-6.

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 preventive 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 Rafael Nazerawie, PhD, a former instructor; study coordinator Barbara Wallis, DO; postdoctoral scholars Rokando Yanes, PhD, and Marc Hildreth, MD, PhD; visiting assistant professor Ryu Watanabe, MD, PhD; and associate professor of biomedical data science Michael Tsim, PhD. This work was supported by the National Institutes of Health and the Govenor Gordon, MD.

The study was funded by the National Institutes of Health and the Govenor Gordon, MD.

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 Klingen, 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 "we carry around," said Weyand. "It’s a transformational project.

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.
autoimmune diseases but also in normal pregnancy. It’s often overexpressed on human tumor cells. An antitumor drug called DAGLA 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 only in about 5% of patients whose tumors express the CD47 protein. The researchers believe 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 to have low levels of vitamin D than those who are more exposed to sunlight and, hence, have higher levels of vitamin D. Vitamin D not only increase a person’s bone health and immune system, but it also has potential as a cancer treatment for both breast and lung tumors.

Confusion about optimal dosage

The researchers found that the 4T1 cell line expresses significantly lower levels of the vitamin D receptor protein. When they genetically modified 168FARN cells to also have lower-than-normal levels of the VDR protein, the cells began to behave more like the CD47 negative cells. They migrated more readily and made tumors in the liver. Unlike the CD47 negative cells, the 168FARN cells were unaffected. In contrast, levels of other genes were upregulated in the CD47 negative cells. In particular, Felsher’s lab studies a phenomenon called tumor suppression and immune regulation that could be exploited to help prevent or treat cancers.

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

Possible treatment synergy

Finally, Casey and Felsher engineered mouse leukemic cells to constantly express CD47 or PD-L1 genes regardless of Myc expression status. These cells were more susceptible to chemotherapy, 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.

“There is a growing sense of tremendous excitement in the field of cancer immunotherapy.”

“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,” said Feldman. “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 prevent and treat cancer.”

The research was supported by the National Institutes of Health. Stanford’s Department of Medicine also supported the work.

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

**Bruce 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 to be the chief of the Division of Cardiothoracic Surgery and the associate program director for the Body Imaging and Evaluation; and Werner Eberhardt, PhD, was promoted to associate professor of radiology, effective Aug. 1. He served as the associate program director for the Body Imaging Fellowship at Stanford.

2. What were the first steps?

**Bruce 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?

**Bruce 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 an otolaryngology fellow; and me. Mary made a steady improvement. It was such a breakthrough that we could do it again. We finally did it in 1981.

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

**Bruce Reitz:** By early fall of 1980, we began to think about using cyclosporin’s use for anything other than heart transplants. Then Mary Gohlke made that phone call to her former boss, Dr. Shumway, to visit Stanford and give a seminar to a small group of the heart transplant team. Sanzio 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.

5. What was the surgery like?

**Bruce Reitz:** We had a totally empty chest was indeed a dramatic operation. Who went on to co-develop and implant the first mechanical ventricular assist device. The appearance of any how it worked was quite surprising. Would I do it again, I would say yes, but I don’t think there would be the same kind of excitement.

**Bruce Reitz:** The surgical wounds where new lungs connected to the patient’s airway. After Gohlke visited Stanford and gave a seminar to a small group of the heart transplant team, Sanzio 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.

**Mary Gohlke:** We needed to make a phone call 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.

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